The Gut-Brain Connection: Implications for Health

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Consider this: humans have never existed without a symbiotic relationship with microbes. And the brain has never been without signals from the gut and its resident microbes.[1]

These powerful statements underscore the importance of the connections and interactions between our gastrointestinal (GI) system, the microorganisms that reside there, and our brain and central nervous system (CNS). Understanding how microbes in the gut influence brain health and cognitive function is one of the most exciting areas of research in neuroscience and biological psychiatry today.

Much of this research is focused on the gut-brain axis—an intricate series of neural pathways that carry signals between the enteric nervous system (ENS) of the GI tract and the CNS.[2] This dynamic and bidirectional communication network facilitates a complex coordination of neural, hormonal, and immunological interactions that influence various physiological processes beyond digestive function.

The gut-brain axis plays an important role in regulating mood, metabolism, and immune function and may even influence higher cognitive functions such as memory, learning, and decision-making. Emerging evidence also suggests that disturbances in gut-brain communication may contribute to the pathogenesis of a wide range of neurological and psychological disorders, including depression, anxiety, dementia, and irritable bowel syndrome (IBS).

As we dive deeper into an examination of the gut-brain axis, we'll cover the mechanisms underlying this intricate connection and explore its implications for health and disease.

Neural pathways of the gut-brain axis: understanding the communication network

The gut-brain axis's network of neural pathways connects the CNS, the neuroendocrine and neuroimmune systems, the sympathetic and parasympathetic components of the autonomic nervous system, the ENS, and the gut microbiome, coordinating a complex interplay between gut function and brain activity.[3]

The vagus nerve, the longest cranial nerve that extends from the brainstem to the abdomen, is a major pathway for neural communication along the gut-brain axis. Originating in the medulla, it innervates structures in the neck, thorax, and abdomen.[4] The vagus nerve is involved in critical aspects of human physiology, including heart rate, blood pressure, sweating, digestion, and even speaking.[5] It also plays a crucial role in regulating gut motility, secretion, and blood flow through its efferent fibers. Motor signals originating in the brain travel down the vagus nerve to the ENS, modulating GI function and coordinating digestive processes. Sensory (afferent) neurons in the gut mucosa detect conditions such as nutrient availability, gut motility, and microbial metabolites. These neurons transmit these sensory signals to the brainstem, providing the brain with real-time information about gut function and microbial activity. Thus, the vagus nerve is a vital pathway that serves as a direct link between the gut and the brain, conveying sensory information from the gut to the brain and transmitting motor signals from the brain to the gut.[6]

The ENS, consisting of millions of neurons and glial cells organized into interconnected ganglia embedded within the gut wall, supports communication along the vagus nerve. Because it can autonomously control GI tissue dynamics and gut homeostasis without input from the brain or spinal cord, the ENS is sometimes referred to as the "second brain."[7] The vast network of ENS neurons—comprising sensory and motor neurons and interneurons—regulates gut function independently of the CNS. This independence relies on local reflexes that control gut motility, secretion, and blood flow in response to stimuli within the GI tract. These reflexes allow for rapid and coordinated responses to changes in luminal contents, ensuring efficient digestion and absorption of nutrients.[8]

While the ENS operates autonomously, it communicates with the CNS via the vagus nerve and other neural pathways. This bidirectional communication enables the brain to modulate gut function in response to emotional and cognitive cues like stress and arousal.

Neurotransmitters and neuromodulators: mediators of gut-brain communication

The chemical messengers that communicate throughout the gut-brain axis comprise an array of neurotransmitters and neuromodulators that affect synaptic firing and neuronal activity. Studies of these neurotransmitters have mainly revolved around their role in the "fight or flight" response, transmitting signals across a chemical synapse and modulating blood flow throughout the body. However, these compounds can also affect gut motility, nutrient absorption, the GI innate immune system, and the microbiome.[9]

Serotonin, sometimes called the "happy hormone," is mainly synthesized by serotonergic neurons in the raphe nuclei within the CNS. Abnormal expression and function of serotonin in the brain are associated with the pathogenesis of mental health disorders, including depressive and anxiety disorders.[10] Interestingly, approximately 90% of serotonin is synthesized peripherally, mainly by enterochromaffin cells in the intestinal epithelium. There, it regulates gut motility, secretion, and sensation and further acts as a signaling molecule that modulates mood, appetite, and social behavior—highlighting its dual role in gut-brain communication.[11,12]

Gamma-aminobutyric acid (GABA) and glutamate, which are (respectively) the primary inhibitory and excitatory neurotransmitters in the CNS, also play a role in the gut-brain axis. GABAergic and glutamatergic neurons within the ENS modulate gut motility and sensory processing, contributing to the regulation of GI function.[13]

Neuropeptides, such as substance P, vasoactive intestinal peptide, and calcitonin gene-related peptide, are released by enteric neurons and sensory fibers in the gut in response to various stimuli, contributing to neuroimmune interactions, which play an important role in homeostasis in the gut.[14] These neuropeptides act as signaling molecules that mediate pain perception, vasodilation, and immune modulation, influencing gut-brain communication.

Disruption of neural pathways in the gut-brain axis has been implicated in the pathogenesis of various GI and neurological disorders, including IBS, inflammatory bowel disease (IBD), and mood disorders.[15] Altered neural signaling contributes to the development of functional GI disorders, such as IBS, and is characterized by abdominal pain, bloating, and altered bowel habits. These symptoms are the result of visceral hypersensitivity, abnormal gut motility, and altered pain processing.

Inflammation originating in the gut can also impact neural pathways in the gut-brain axis, aggravating symptoms in patients with IBD. This gut-derived inflammation can activate neuroinflammation, which can contribute to the increased visceral pain, fatigue, and mood disturbances commonly reported by individuals with Crohn's disease or ulcerative colitis. Indeed, dysregulation of this axis in patients with IBD has long been associated with mental health conditions such as stress, anxiety, and depression. In some clinical studies, stress, anxiety, and depression have been considered triggers of IBD relapse and clinical deterioration.[16]

Alterations in neurotransmitter signaling, neuroinflammation, and stress-response pathways in the gut-brain axis have been implicated in the pathophysiology of anxiety and depression, as well as Alzheimer disease, dementia, Parkinson disease, autism spectrum disorder, and schizophrenia, highlighting the interconnectedness of gut health and mental well-being.

The gut microbiota—the collection of microorganisms residing in the GI tract—also produces neuroactive metabolites, such as neurotransmitters or their precursors, which can affect the concentrations of either in the brain. This suggests that the neurotransmitter synthesis pathway in the intestine might directly or indirectly affect the brain's neuronal activity and cognitive functions.[17]

Hormone signaling and gut peptides in the gut-brain axis

Recent research on the central role of hormone signaling and gut peptides in the gut-brain axis has provided insight into the intricate communication between the GI system and the CNS. Gut hormones, produced in response to nutrient-related signals and feeding behavior, are secreted by enteroendocrine cells (EECs) and have a wide range of targets, including the CNS.[18] Most gut hormones mainly regulate appetite and food intake. However, they can also regulate other physiological processes, such as inflammation, which is linked to brain disorders including anxiety and depression.[18]

Interestingly, the GI tract and, more specifically, EECs are impacted by the gut microbiota, whose diversity and composition greatly influence a variety of gut hormones and peptides, such as ghrelin, peptide YY, glucagon-like peptide 1 (GLP-1), cholecystokinin (CCK), and neurotensin, hereafter discussed in more detail.[19]

Ghrelin: the hunger hormone. One of the key hormones involved in appetite regulation is ghrelin, often called the "hunger hormone." Ghrelin is primarily synthesized and secreted by the stomach when it is empty, signaling hunger and stimulating appetite. Ghrelin concentration rises before meals and decreases after food intake, reflecting the body's energy status and regulating meal initiation. The current scientific understanding is that ghrelin could be a key signaling molecule governing the communication between the GI tract and the CNS.[18]

Peptide YY and GLP-1: satiety signaling. Peptide YY and GLP-1 are gut-derived peptides that signal meal-ending satiation and inhibit appetite. EECs release peptide YY and GLP-1 in the distal small intestine and colon in response to nutrient intake; particularly to fat and protein in the case of peptide YY. GLP-1 secretion from EECs stimulates insulin secretion and suppresses

glucagon release to regulate blood glucose concentration.[18] GLP-1 receptor agonists have been at the forefront of recent research and medical intervention, having shown promise for weight management and glycemic control in individuals with obesity and patients with type 2 diabetes.

CCK: meal-related signaling. CCK is a gut peptide secreted by EECs in the duodenum and jejunum in response to nutrients—particularly fat and protein. CCK stimulates pancreatic enzyme secretion and gallbladder contraction, produces meal-ending satiation, inhibits gastric emptying, and modulates intestinal motility.[20] CCK receptors are expressed in the brain, where they modulate appetite and food intake. CCK concentration correlates positively with increased anxiety-like behaviors in both humans and mice, and CCK modulates mood disorders through other neurotransmitters, including glutamate, dopamine, acetylcholine, and GABA, all of which play important roles in emotional behaviors.[18]

Neurotensin: role in stress response. Neurotensin is a neuropeptide produced by EECs in the small intestine and colon in response to luminal nutrients and stress. Neurotensin stimulates the growth of intestinal mucosa under basal conditions and during periods of nutrient deprivation,[21] inhibits gastric acid secretion and motility, stimulates pancreatic and intestinal secretions, decreases adipose tissue blood flow, and increases small intestinal blood flow.[22] Dysregulation of neurotensin signaling has been implicated in the pathophysiology of several CNS disorders, such as schizophrenia, drug abuse, Parkinson disease, eating disorders, and cancer, as well as in CNS functions such as inflammation, pain, and central control of blood pressure.[23]

Dysregulation of hormone signaling and gut peptides. Dysregulation of hormone signaling and gut peptides in the gut-brain axis has been implicated in the pathogenesis of various GI and metabolic disorders, including obesity, diabetes, and eating disorders. Consequently, targeting gut hormones and peptides represents a promising approach for developing novel therapeutic interventions aimed at improving GI function, restoring metabolic homeostasis, supporting brain and cognitive function, and promoting health.

The role of gut microbes: exploring the microbiota-gut-brain axis

A revolution in medical research and health care is the growing understanding and awareness of how gut microbes influence systems outside of their immediate influence on the GI tract, including brain function and behavior. This blossoming field of study highlights the intricate relationship between the gut microbiota and the CNS.

The gut microbiota comprises trillions of microorganisms, including bacteria, viruses, fungi, parasites, and archaea, that inhabit the GI tract. Known collectively as the microbiome, these microorganisms have coevolved as integral to human physiology. Various factors, including diet, genetics, environment, and lifestyle, influence the composition of the gut microbiota.

Bacteria are the predominant members of the gut microbiota, with hundreds of different species present in the human gut. The dominant gut microbial phyla are Bacillota (formerly Firmicutes), Bacteroidota (formerly Bacteroidetes), Actinomycetota (formerly Actinobacteria), Pseudomonadota (formerly Proteobacteria),[24] Fusobacteriota, and Verrucomicrobiota, with Bacillota and Bacteroidota representing 90% of gut microbiota.[25]

Beyond taxonomic composition, the functional potential of the gut microbiota is shaped by the metabolic activities and gene expression profiles of its constituent microorganisms. The gut microbiome encodes over 3 million genes, producing thousands of metabolites, whereas the human genome consists of approximately 20 000 protein-coding genes.[26] This vast array of metabolites can be broadly divided into 3 types: (1) metabolites produced by gut microbiota directly from nutrient intake, such as short-chain fatty acids (SCFAs) and indole derivatives; (2) metabolites generated by the host and modified by gut microbiota, such as secondary bile acids; and (3) metabolites produced de novo, such as polysaccharide A. All these metabolites can influence host physiology, including gut and brain function.[27]

Gut microbes produce and metabolize hormones and neuropeptides, such as ghrelin and leptin, which regulate appetite, metabolism, and mood.[28] Microbial metabolites, such as SCFAs and bile acids, can also act as signaling molecules that modulate hormone secretion and energy homeostasis. SCFAs are generated by the fermentation by the gut microbiota of nonhost-digestible dietary fibers, with more than 95% of SCFAs derived from gut microbes being made up of acetate, propionate, and butyrate.[29] SCFAs are perhaps the most extensively studied molecules related to the influence of gut microbiota on host energy metabolism and appetite. However, they are also involved in immunomodulation and the regulation of regulatory T cells and exert crucial physiological effects on several organs, including the brain.[30]

Dysbiosis, or an imbalance in gut microbial composition, can lead to immune dysregulation and neuroinflammation, contributing to the pathogenesis of neurological and psychiatric disorders. Emerging evidence suggests that alterations in the gut microbiota may contribute to the development and progression of neurological disorders, such as Alzheimer disease, Parkinson disease, and multiple sclerosis. Furthermore, the gut microbiota has been implicated in the pathophysiology of psychiatric disorders, including depression, anxiety, and autism spectrum disorder. In addition to its effects on the brain, dysbiosis of the gut microbiota is associated with various GI conditions, such as IBD, IBS, and gastroesophageal reflux disease.

Therapeutic potential: harnessing the power of the microbiota

Microbiota-based therapies include dietary interventions, probiotics, prebiotics, antibiotics, phage therapy, fecal microbiota transplant, live biotherapeutics, and microbiome

mimetics. Each aims to modify the microbiota to treat disease and improve overall health.[31]

Probiotics are live microorganisms that confer health benefits when consumed in adequate amounts, while prebiotics are dietary fibers that selectively stimulate the growth of beneficial bacteria in the gut. Both probiotics and prebiotics modulate the composition and function of the gut microbiota and may have beneficial effects on mood and cognition, as well as GI function.

Diet plays a crucial role in shaping the gut microbiota, with certain foods promoting the growth of beneficial bacteria and others contributing to dysbiosis. The Mediterranean diet, rich in fruits, vegetables, whole grains, and fermented foods, has been associated with a more diverse and resilient gut microbiota and may confer protective effects against neurological and psychiatric disorders.[32] Advances in microbiome science have led to the development of novel microbial-based therapeutics, such as next-generation probiotics, synbiotics (prebiotics and probiotics in combination), and microbial-derived metabolites, or postbiotics. These interventions hold promise for modulating gut microbial composition and activity to improve GI function and, by extension, brain health—mitigating the risk of neurological and psychiatric disorders.

CONCLUSION

In summary, the gut microbiota, composed of trillions of microorganisms residing in the GI tract, plays a profound role in influencing host physiology. Dysbiosis, or imbalance in gut microbial composition, can lead to immune dysregulation, neuroinflammation, and the development of neurological and psychiatric disorders.

Overall, a deeper understanding of the gut-brain connection and the role of the gut microbiota in modulating brain function opens up new avenues for therapeutic interventions, such as dietary interventions, aimed at improving both GI health and mental well-being. By harnessing the power of the microbiota-gut-brain axis, we may be able to develop novel strategies for preventing and treating a wide range of neurological and psychiatric disorders, ultimately improving overall health and quality of life.

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PILOT STUDY

Pilot Study on Therapeutic Horticulture for Chronic Low Back Pain: A Mixed Methods Study

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ABSTRACT

Background • Chronic low back pain (LBP) is common and associated with disability worldwide. Therapists trained in Therapeutic Horticulture (TH) use gardening activities and proximity to nature for therapy and rehabilitation. Patients seeking care for LBP would benefit physically and psychologically from participating in TH.

Primary study objectives • The first aim of this study was to determine if and which patients who were receiving care for chronic LBP were interested in TH to help manage their pain. The second aim of the project was to quantify changes in LBP, functional tasks and anxiety upon completion of a TH session in patients with LBP.

Methods/Design • This was a 2-part study with a mixed methods design: the cross-sectional survey Group and the pilot experimental Group. The Cross-sectional Survey component comprised a total of 170 patients; age 55.9±17.3 years; 58% women. The Pilot Experimental component comprised a total of 9 patients; age 48±14.7 years; 78% women.

Participants Cross-sectional component • patients receiving medical care for LBP with or without additional joint pain sites (n=170; age 55.9 ± 17.3 years; 58% women.

Participants Pilot experimental component • A total of 9 patients (7 women); mean age 48 ± 14.7 years and mean duration of back pain 12.6 ± 8.1 years.

Setting • Patients were receiving medical care at the University of Florida Health Comprehensive Spine Center in the United States, in the tertiary care health system.

Intervention • 1-hour TH session that involved trained therapists using propagating and harvesting herbs planted at various heights in an outdoor setting for therapy and rehabilitation.

Primary outcome measures • A therapeutic horticulture interest survey, PROMIS Pain Interference and Physical Function scores, functional tests (timed-get-up-and-go [TUG], spine range of motion), Roland Morris Disability Questionnaire (RMDQ), 11-point Numerical Pain Rating Scale (NRS_{pain}), 10-item PROMIS Global Health Questionnaire, Tampa Scale of Kinesiophobia-11 and patient enjoyment.

Results • Cross-sectional survey component: A total of 2% of patients had not previously heard of TH and 68% were interested in learning more about it. Patients who expressed interest in TH reported a higher level of agreement that TH could improve mood, improve muscle strength, lower stress level, increase movement and enable patients to perform self-care activities with less pain (all $P < .001$). PROMIS Pain Interference and Physical Function scores did not differ by interest in TH ($P > .05$). Pilot Experimental component: In the pilot session, 44% reported using pain medication to manage their low back pain and 66% believed gardening could provide pain relief. Improvements were observed in anxiety (55.3%; $P = .017$), spine flexion (31.4%; $P = .003$) and spine rotation to the left (26.7%; $P = .005$). All participants believed that gardening improved overall health and spine motion while reducing low back pain. All patients reported having gardening experience at home and none had TH experience.

Conclusion • Patients presenting to an outpatient spine clinic may be receptive to trying TH in conjunction with or in place of conventional medicine to promote health and well-being. The pilot experimental group data suggested that acute TH is enjoyable and may confer the benefits of reducing anxiety and improving spine motion. Future larger studies could use different dose response approaches, explore different TH activity types and involve participants from different geographic locations while controlling for LBP history and psychological status. (*Altern Ther Health Med.* 2024;30(4):10-17).

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INTRODUCTION

Low back pain (LBP) is a condition that affects roughly 40% of the population of the United States.[1] Individuals who have LBP often face more time away from work, leading to lost wages and opportunities compared with their unaffected peers.[2] Current treatment recommendations for LBP include non-steroidal anti-inflammatory medications in conjunction with nonpharmacological treatments such as cognitive behavioral and physical therapy.[3] Additional nonpharmacological alternative treatment modalities have been studied and published in recent years as well, including acupuncture and cognitive behavioral therapy (CBT), each of which focuses on either physical or psychological aspects of pain management.[4-6] While many treatments are available for LBP, clinicians have little information about combining physical and psychologically informed approaches for

managing pain in individual patients or subgroups of patients.[7] One alternative treatment that includes both physical and mindfulness components is therapeutic horticulture (TH).[8]

The use of horticulture and gardening in healing is an ancient practice. The intentional use of plants and plant-based activities to help people heal and rehabilitate emerged during World War I and II, first as a recreational activity for injured and disabled soldiers, and later as a rehabilitative tool. Horticultural Therapy (HT) and Therapeutic Horticulture (TH) are practiced in a variety of clinical, rehabilitative, vocational and community settings in order to help patients increase or regain physical, cognitive, social and psycho-emotional function, as well as for them to learn or regain vocational skills.[9] While individualized goals are designed within an established treatment plan in patients in HT, TH can be applied in broader and more accessible settings and typically involves group goals, making it more suited to a community setting.[10] Both practices involve active participation in gardening and other horticulture-related activities that are intentionally designed to work toward particular goals based on patient needs.

Studies in other patient populations demonstrate that TH has been associated with physiological, psychological, social and cognitive benefits, including reducing stress and anxiety,[11,12] enhancing social connectedness,[13-17] improving physical well-being,[18] lowering cortisol levels[11,19] and increasing life satisfaction.[20]and dose-responses were assessed for exercise intensity and exposure duration. Other subgroup analyses included gender, age group, starting health status, and type of habitat. The overall effect size for improved self-esteem was d = 0.46 (CI 0.34-0.59, $P < .00001$ The American Horticultural Therapy Association (AHTA) indicates that TH can improve brain function (memory, task initiation, socialization) and physical function (balance, endurance, muscle strength, coordination).[8] Gardening activities can be used to encourage patient movement via a range of different postures, all of which could provide health benefits in patients with LBP.[21,22] With respect to physical function and mobility, TH includes tasks that require reaching, grasping, transporting, dynamic balance, stepping-stooping, trunk strength control and sit-to-stand coordination.[23] In patients with chronic joint pain, some of these movements are difficult, fear- or anxiety-inducing or impossible. TH can foster improvements in grip strength, trunk movement coordination, balance and self-reported physical function in aspects of self-care.[23] Individuals who have participated in TH exercise trials have reported both social and physical benefits of reduced pain.[24] A small randomized controlled trial performed in an inpatient rehabilitation setting in people with various types of chronic musculoskeletal pain (fibromyalgia, nonspecific back pain) showed that TH improved self-rated physical health, mental health, anxiety and pain behaviors.[25] Furthermore, passive interaction with restorative natural environments has been linked to decreased perception of pain and the regulation of responses to stress.[9,26] TH as a structured intervention using cost-effective and non-intrusive methods has demonstrated efficacy in other patient groups and may potentially represent a novel, unexplored supplemental treatment option in patients with LBP. However, it is unclear whether TH would be of interest to patients with LBP in a community setting, and what acute effects TH would have on physical function, anxiety and pain severity.

Based on clinical observation patterns, we hypothesized that interested patients who would have more severe pain interference and functional limitations (as assessed by the PROMIS pain Interference and Physical Function surveys), are older, female, do not participate in other physical activities, live alone, are retired and low resourced. We hypothesized that individuals would demonstrate improvements in spine mobility and physical function and reduction in spine pain severity from pre- to post-session.

METHODS

This study was reviewed and approved by the University of Florida Human Ethics Research Committee (Application IDs #202102666 survey component and 202201838 pilot experimental component). Written and informed consent was obtained from each participant using project forms that included the research team's names and professional qualifications.

The 2 initial steps toward the adoption of TH as a more well-accepted treatment option for LBP include: (1) determination of patient interest, perceived health and well-being benefits of TH, and (2) understanding the acute effects of TH on LBP severity, physical function, spine motion and enjoyment of the activity. This 2-part study involved a cross-sectional survey and a pilot TH session with individuals who expressed interest and have LBP. Therefore, the first aim of this study was to determine if and which patients who are receiving care for LBP were interested in TH. The second aim of the study was to quantify changes in back pain, functional tasks and anxiety upon completion of a TH session in a group of individuals with LBP.

Design

This study had a mixed methods design, with cross-sectional survey and pilot experimental components.

Patient Samples and Settings

Cross-sectional component. A consecutive sample of patients ≥18 years of age who were receiving medical care for LBP with or without additional chronic musculoskeletal pain (peripheral joints, axial [spine, neck], pelvis-sacrum) were recruited to participate between January 30, 2022 and July 7, 2023. Patients were receiving medical care at the University of Florida (UF) Health Comprehensive Spine Center, in the tertiary care health system with a catchment of more than 2.5 million individuals. Patients were approached during their clinic visits. A total of 170 patients between age 18 and 84 years agreed to complete the surveys.

Pilot experimental component

For the second part of the study, a subgroup of interested patients agreed to participate in a pilot experimental TH session in April 2023. A total of 9 patients (7 women), mean age 48±14.7 years and mean duration of back pain 12.6 ± 8.1 years participated in the pilot study. A total of 44% reported using pain medications to manage LBP, but the specific medication used varied among the participants. All participants reported having gardening experience and almost all performed gardening at home; however, none had TH experience.

Methods in the Cross-Sectional Study Component

TH Survey. A unique survey was developed specifically for the first part of the research. The study team was comprised of fellowship-trained spine physiatrists, physiologists, therapists and researchers, and they first developed the survey content and then drafted several versions of the survey before piloting it. The survey was piloted with clinical researchers to test the face validity of the questionnaire. A survey guide with standard instructions was developed to ensure that surveys were administered in the same manner to all participants. The survey was piloted in a group of patients with back pain to ensure readability.

The final survey consisted of 4 main domains: (1) social determinants of health (age, race, ethnicity, working status, insurance status, annual income, marital status, home living status); (2) current musculoskeletal pain status (location[s] of musculoskeletal/joint pain, use of medication for pain and number of medications, use of assistive devices for mobility, previous treatments for pain or functional difficulties, current physical activities and frequency of physical activity); (3) awareness, interest level and beliefs about TH; and (4) level of agreement with the impact of TH on well-being. Domains 1-3 used checkboxes or fill-in spaces for answers. A checklist of reasons for interest or disinterest was provided from which respondents could choose their responses. Domain 4 used a Likert scale list of 5 questions and asked about the level of agreement with statements relating TH to health benefits of mood, strength, stress, movement ability and self-care. This survey took about 7 minutes to complete. The survey is in Supplemental File 1.

PROMIS measures

The National Institutes of Health (NIH) invested in the development of the Patient-Reported Outcome Measurement Information System (PROMIS) for clinicians and researchers to measure health status across multiple domains of quality of life (QoL) in various health conditions. A total of 2 paper item banks were provided to characterize the patients: the Pain Interference short form 4a and the Physical Function 10a. Pain Interference was selected to characterize the level of impairment due to pain symptoms on daily functioning (day-to-day activities, work around the home, participation in social activities and household chores). The Physical Function 10a form was selected to characterize the level of difficulty with a variety of physical tasks ranging from athletic (sport engagement, lifting heavy objects), daily life (carrying groceries, vacuuming, yardwork), functional ability (walking more than 1 mile, bending-kneeling-stooping) and self-care (shampooing hair, dressing self, toileting). These PROMIS short-form versions have construct validity and high reliability (r ≥0.9).[27] These 2 surveys took about 4 minutes to complete.

Methods for the Pilot Experimental TH Session

The Experimental session was comprised of pre-TH surveys and functional measures and TH activity and post-session surveys and functional measures.

Surveys. A total of 4 brief surveys were administered before the TH activity to characterize the patients who participated.

Roland Morris Disability Questionnaire (RMDQ). This well-established instrument is comprised of 24 items and is designed to capture the impact of back pain on everyday functioning, with emphasis on physical functioning such as pain intensity, self-care, social life, walking, sitting, standing, sleeping, bending, stairs, general activity, appetite, household chores.[28,29] Scores ranged from 0 (minimum) to 24 points (maximum). This questionnaire has content validity and reliability among individuals with LBP (ICC >.070).[28,30,31]

10-item PROMIS Global Health form. The Global Health 10-item survey (v. 1.0, paper-based) includes questions related to physical, mental and social health, fatigue, pain and overall quality of life (QoL). A T-score of 50 represents the mean of the general population, and higher scores indicate better physical and mental health. This instrument has been used in individuals with LBP in different settings, including outpatient therapy, and validated for use in this population.[32,33]

Tampa Scale of Kinesiophobia 11 (TSK-11). The TSK is a 11-item survey that classifies patients' fear of movement or physical activity as it relates to pain.[34]there is relatively little data to support the psychometric properties of the English version of this scale. This study investigated the psychometric properties of the English version of the TSK in a sample of chronic low back pain patients. Item analysis revealed that four items possessed low item total correlations (4, 8, 12, 16 The TSK can be further categorized into 2 domains: Activity Avoidance (due to potential increase in pain or potential of causing injury) and Somatic Focus (which aims to reflect patients' beliefs about how serious their condition is). The TSK-11 is very responsive to CBP, has good internal consistency (α=0.79), test-retest reliability (α=0.81) and responsiveness in people with back pain.[34,35]there is relatively little data to support the psychometric properties of the English version of this scale. This study investigated the psychometric properties of the English version of the TSK in a sample of chronic low back pain patients. Item analysis revealed that four items possessed low item total correlations (4, 8, 12, 16 Scores range from 11 points (no fear) to 44 points (highest possible fear), with higher scores indicating greater fear of movement.

11-point Numerical Rating Scale for Pain (NRS_{pain}) and Anxiety. This survey includes 3 separate items. Participants self-rated the average intensity of back pain over the "past week" and the current intensity at the time of the TH session on a scale from 0 to 10 points. NRS_{pain} ratings are supported for use in this population as this has minimal recall bias, ease of administration, good test-rest reliability, construct validity and responsiveness.[36,37]describe, and evaluate common outcome measures in patients with chronic low back pain (CLBP The third item also uses an NRS scale for participants to rate their current level of anxiety from 0 to 10 points.

Functional Measures. A total of 2 brief tests were conducted to represent spine movement and potential impairment of pain on mobility.

Timed Up and Go (TUG) test. This test has been used among people with LBP.[38]decreased balance ability, impaired proprioception, and lower strength compared to asymptomatic persons. The aim of this study was to investigate the differences between LBP patients and healthy controls in terms of several physical abilities. Based on the premised that different biomechanical and physiological causes and consequences could be related to different types of LBP, a secondary exploratory attempt of the study was to examine the differences between LBP subgroups based on the pain location (local or referred Participants were instructed to stand up from a chair, walk as fast as possible for 3 meters, turn around and return to a sitting position in the chair as fast as possible. The starting and final positions were with the patient sitting in the chair and touching the backrest. The time for test completion was measured manually with a stopwatch. This test was repeated 3 times, with a 30-second break between the repetitions. The fastest time was taken as the score. This test is responsive to back pain severity.[39]chronic low back pain (CLBP In the clinical setting, patients scoring a TUG test time of >12 seconds can represent functional impairment.[40]

Spine Rotation Range of Motion

This is the spine motion in all 3 planes while participants were seated. Each participant performed trunk rotation (to the left, to the right), lateral bending (to the left, to the right) and spine flexion and extension. The spine exertions were measured using a digital goniometer (WR300 angle gage; Wixey Development, Sanibel, Florida USA).

TH Session

The TH session lasted approximately 1 hour. The content was informed by the physiatrist and structured by the HT practitioners to help patients safely achieve acute improvements in spine mobility. The main objectives were to inspire patients to move the spine in all planes of movement, with motions that may otherwise be avoided in daily life due to pain. The activity was the creation of an herb bowl and involved greenhouse and outdoor gardening activity. The session included greenhouse preparations (gathering materials, reaching and lifting light loads, pushing bins), moving about the garden to collect plant cuttings at different levels (above the head, at ground level, at eye level), digging up roots for planting, standing and working the soil, planting the herbs, emptying compost buckets, washing tools and cleaning the work areas. The physiatrist was present for the session and monitored patients for safety and any adverse responses.

Data was processed to determine the maximum and minimum spine exertion values achieved during the different phases of the herb bowl preparation. A study-specific 5-item survey was utilized to determine patient enjoyment of the TH session. The following statements were provided: (1) I found this horticultural activity to be fun; (2) I felt more relaxed after the activity than before the activity; (3) I feel that this kind of gardening activity can help my back health; (4) I would do more horticultural activities if given the chance; (5) I enjoyed experiencing plants in a social setting with others who have similar back pain. Participants agreed with the statement using the Likert scale: 0=did not agree, 1=agree a little bit, 2=somewhat agree, 3=agree and 4=strongly agree.

STATISTICAL CONSIDERATIONS

Statistical analyses were performed using IBM SPSS software version 28.0 (IBM, Armonk, New York USA). Normality of the cross-sectional data was determined using Shapiro-Wilk tests, and descriptive statistics were calculated for all study variables and demographics. Descriptive statistics were applied to characterize the respondents from the cross-sectional component.

Cross Sectional Survey Component

Respondents were grouped into "interested" and "not interested" in TH. Mann Whitney U tests were applied to determine whether groups differed by baseline categorical characteristics (sociodemographic data, assistive devices and therapies used, physical activity participation, painful sites) and level of agreement with statements relating TH to health benefits. Group differences in continuous variables (age, active days per week, PROMIS scores for Pain Interference and Physical Function) were tested using a one-way analysis of variance. Significance was established at $P < .05$ for all statistical tests.

Pilot Experiment Component

Descriptive statistics were calculated for all patient characteristics, demographics and pre-TH surveys (TSK-11, RMDQ and PROMIS Global Health 10). Pre-post TH values in physical function, pain and anxiety were analyzed using Mann Whitney U tests and paired t tests. Effect sizes of TH on TUG and trunk motion were determined, and size was ranked by the method of Cohen (Cohen's d) as small, moderate and large, where 0.2 was small, 0.5 was moderate and 0.8 was large.[41]Patient Enjoyment Questionnaire scores were characterized using descriptive statistics.

RESULTS

Cross-sectional Component

Upon review, some respondents indicated on the survey that they were not experiencing joint pain at the moment, but

Table 1. Characteristics of the Respondents from the Cross-Sectional Survey Component

Variable	Interested (n=116)	Not Interested (n=44)	*P* value
Female (#, %)	84 (73)	21 (47)	.003
Age (years)	55.4 ± 16.7	56.1 ± 17.7	.030
Race (#, %)			.371
Black/African American	22 (19)	7 (17.1)	
White/Caucasian	85 (75)	30 (73)	
Other	5 (4.4)	3 (7.3)	
Ethnicity (#, %)			.235
Hispanic	10 (11.9)	1(2.8)	
Non-Hispanic	74 (88)	34 (97.1)	
Working status (#, %)			.620
Working	44 (39.3)	14 (34.1)	
Retired	43 (38.4)	13 (31)	
Disabled	13 (11.6)	8 (19.5)	
Not working	12 (10.7)	6 (14.6)	
Insurance status (#, %)			.798
Insured	105 (97.2)	39 (95.5)	
Not insured	3 (2.7)	1 (2.5)	
Annual income (#, %)			.663
<$50,000	47 (45.2)	17 (50)	
>$50,000	55 (52.8)	17 (50)	
Marital status (#, %)			.788
Married	52 (45.6)	22 (51.2)	
Widowed	10 (8.7)	4 (9.3)	
Single	52 (45.6)	17 (39.5)	
Live alone (#, %)	34 (29)	9 (20)	.398
Joint pain >6 months (#, %)	69 (54.8)	49 (52.1)	.345
Other pain sites (#, %)			
Neck	55 (47.8)	16 (39)	.331
Spine	70 (60.1)	23 (56.1)	.593
Knee	44 (38.3)	17 (42.5)	.718
Hip	59 (51.3)	17 (42.5)	.279
Ankle	29 (25.2)	11 (26.8)	.839
Shoulder	41 (35.6)	16 (39)	.700
Elbow	24 (22)	5 (12.2)	.220
Wrist	34 (29.6)	7 (17.1)	.119
Regularly taking pain medication for low back pain (#, % yes)	58 (50.9)	22 (53.6)	.807
Pain medications used on a regular basis (#, %)			.551
None	37 (34.9)	12 (32.4)	
1	29 (27.3)	14 (37.8)	
2	27 (25.5)	6 (16.2)	
≥3	13 (12.3)	5 (13.5)	
Use of assistive device (#, %)			.360
No	91 (81.2)	32 (82)	
Cane	11 (9.8)	5 (12.8)	
Walker	7 (6.2)	0 (0.0)	
Wheelchair/scooter	3 (2.8)	2 (5.1)	
Adjunct therapy obtained (#, %)			
Physical therapy	81 (71)	31 (73.8)	.734
Acupuncture	21 (18.4)	5 (11.9)	.333
Meditation	24 (21)	7 (16.6)	.534
Massage	42 (36.8)	13 (30.9)	.495
Participation in physical activity (# times/week)	4.4 ± 2.2	4.5 ± 2.3	.750
Joint pain prevents participation in enjoyable activities (#, %)	79 (68)	27 (64.3)	.425

Note: Values are number and percentage of the group; values are mean ± SD.

Table 2. Percentage of Patients Who Agreed with the Following Statements Relating Therapeutic Horticulture to Health Benefits

I believe that therapeutic horticulture might:	Interested	Not interested	*P* value
Put me in a better mood	113 (99)	29 (82.8)	<.001
Help me get stronger muscles	109 (96.5)	31 (86)	<.001
Lower my stress level	111 (99.1)	32 (88.8)	<.001
Help me move my body around with less joint pain	108 (92.5)	25 (71.4)	<.001
Help me do my self-care activities with less pain (washing, dressing, brushing teeth, combing hair)	95 (86.4)	26 (74.3)	<.001

Note: Values are number of "yes" responses and percentage of the group.

Table 3. Functional Measures and Numerical Rating Scales for Pain and Anxiety Before and After the TH Pilot Session.

Outcomes	Pre-TH	Post-TH	*P* value	Cohen's *d*
Physical Function Tests				
Timed up and go (s)	8.1 ±3.8	8.4 ±4.9	.311	.6
Spine extension (°)	20.9 ± 12.8	30.5 ± 14.4	.003	.7
Spine flexion (°)	45.7 ± 24.6	52.7 ± 25.8	.116	.3
Rotation, right (°)	21.9 ± 20.3	24.0 ± 13.7	.385	.1
Rotation, left (°)	18.6 ± 9.4	25.4 ± 11.0	.008	.5
Lateral bend, right (°)	35.6 ± 10.4	37.1 ± 18.4	.403	.1
Lateral bend, left (°)	40.0 ± 18.2	38.6 ± 22.2	.311	.1
11-point NRS Rating Scales				
Over the last week, on average, how severe has your back pain been? (points)	5.1 ± 2.1	5.4 ± 2.3	.178	.8
Right now, how severe is your back pain? (points)	4.7 ± 2.4	4.7 ± 1.6	.500	.0
Right now, how high is your level of anxiety? (points)	4.7 ± 3.3	2.1 ± 1.7	.017	1.0

Note: Values are means ± SD.

Abbreviations: °, degrees; NRS, Numerical Rating Scale; s, seconds; TH, Therapeutic Horticulture.

Table 4. Responses to the Enjoyment Questionnaire Post-Therapeutic Horticulture Session

Question	Mean ± SD	Range
I found this horticultural therapy activity to be fun.	3.9 ± 0.4	3-4
I felt more relaxed after the activity than before the activity.	3.1 ± 1.5	0-4
I feel that this kind of gardening activity can help with my back health.	3.3 ± 0.9	2-4
I would do more horticultural therapy if given the chance.	3.9 ± 0.4	3-4
I enjoyed experiencing plants in a social setting with others who have similar back pain.	3.7 ± 0.5	3-4

Note: Answers were in Likert form with the following choices: 0=do not agree, 1=agree a little bit, 2=somewhat agree, 3=agree and 4=strongly agree

they listed pain in at least 1 joint or specified the duration of their joint pain symptoms. This was noted as patients' pain being well-managed at this visit and included in the statistical analysis. A total of 170 survey sets were completed. Overall, the respondent pool (N=170) was 58% female, 68% white and age 55.9±17.3 years. A total of 82% of patients had not previously heard of TH and 68% indicated they would be interested in learning more about it. Supplementary Table 1 provides the breakdown of reasons related to interest and disinterest in TH as an option to help manage pain and functional difficulties.

Table 1 provides the characteristics of the participants by interest in TH. Participants who reported interest in TH had an average of 3.5 years longer duration of LBP symptoms than patients who were not interested (P =.093). A total of 37% more women than men were interested in TH (P <.001). There were no group differences in preferred physical activities; the 5 most common regular physical activities in both groups were walking (72.4-76.2%), weight-lifting (12.1-19.0%), yoga (11.9-13.8%), jogging (9.5-1.3%) and cycling (6.9-7.1%). PROMIS Pain Interference and Physical Function scores did not differ by interest in TH (Pain Interference: 12.8±4.7 points [interested] and 13.0±5.0 points [not interested]; Physical Function: 35.9±7.9 points [interested] and 35.0±8.3 points [not interested]; P >.05).

Table 2 provides the percentage of patients who agreed with statements about possible positive benefits of TH. For all statements, interested patients reported a higher level of agreement that TH could improve mood, improve muscle strength, lower stress level and enable them to move about and perform self-care activities with less pain (all P <.001).

Pilot Experiment Component

A total of 9 patients (48 ± 14.7 years; 78% female) participated in the pilot experiment. A total of 44% reported using pain medication to manage their LBP. All participants reported having gardening experience and almost all performed gardening at home; however, none had TH experience. All participants also believed that gardening improves overall health and spine motion while reducing LBP. A majority (66%) believed gardening can provide pain relief.

Pre-TH Surveys and Physical Function

A group mean PMDQ score of 11 ± 6.7 points out of 24 indicated high impact of back pain on everyday functioning. The group mean PROMIS Score indicated lower physical and mental health among our participants compared with the general population (32.7±6.7 points, range 22-44 points), which typically averages around 50 points. The group mean TSK-11 score was 27.7 ±7.7 points out of 44 possible points (range 13-41 points). TSK Activity Avoidance scores were 14.6 ± 5.0 points (range 6-23 points) and for Somatic Focus were 12.4 ± 3.5 points (range 8 to 18 points).

Post-TH Surveys and Physical Function

Table 3 provides the physical function (spine motion, TUG) and NRS ratings for pain and anxiety. Improvements were detected from pre- to post-TH for some but not all measures. Moderate to large TH effects were found on NRS scores for anxiety (P =.017), back extension excursion (P =.003) and spine rotation to the left (P =.005). Patient Enjoyment Questionnaire scores (Table 4) show that on a 4-point scale, patients average enjoyment scores were 3.1 to 3.9 points for all 5 items (Found TH to be fun; Felt more relaxed after the activity; This kind of gardening activity can help with my back health; Would do more TH if given the chance; Enjoyed experiencing plants in a social setting with others who have similar back pain).

DISCUSSION

The first aim of this project was to determine if and which patients were interested in TH. As we hypothesized, some but not all patients, and more women, were interested in TH, but PROMIS Pain Interference and Physical function scores were not different based on TH interest. The second aim of the study was to quantify changes in back pain, functional tasks and anxiety upon completion of a TH session in a group of individuals with LBP. We detected changes in a few markers of physical function, including spine extension, and spine rotation movement and perceived anxiety after completion of the TH session. Effect sizes for these specific significant changes were moderate to large.

Cross-sectional study component

The majority of patients in the cross-sectional study component were not aware of TH, but 68% indicated interest in the therapy to manage LBP. Exploring the interest in and enjoyment of this therapy was performed in other studies with small samples of patients (n=16-22) with psychological diagnoses[42] and pre-frail and frail elders in nursing homes.[43] The context of TH deployment for other populations has largely focused on psychological outcomes and mental well-being in institutional settings with the elderly. In our study, we assessed the interest level of TH in patients receiving care for chronic LBP. Despite very different health conditions, the level of interest in our study is comparable with the high interest rates previously reported.[42] Aside from the "interested" group consisting of more women, there were no other distinguishing sociodemographic traits. Self-reported pain interference or physical function did not differ according to interest in TH. This is an important finding, in that women may be more receptive to trying TH as part of LBP management, independent of other individual characteristics or LBP history and perceived pain interference and functional status. An unexpected finding was that even among patients initially disinterested in TH, 71% to 88% agreed that TH might provide multiple health benefits (Table 2) These findings show that providers may have a large and unrealized opportunity to inform patients about this therapy option.

Directly comparable data of the benefits of TH on anxiety, musculoskeletal pain and physical function in the patient population with LBP are limited. However, a 6-month study comparing the benefits of TH to social activities on anxiety in adults age 61 to 77 years did not detect differences in this outcome[44]with 29 randomly assigned to the HT intervention and 30 to the waitlist control group. The participants attended weekly intervention sessions for the first 3 months and monthly sessions for the subsequent 3 months. Biological and psychosocial data were collected. Biomarkers included IL-1β, IL-6, sgp-130, CXCL12/SDF-1α, CCL-5/RANTES, BDNF (brain-derived neurotrophic factor; the weekly and monthly 1-hour instructor-led sessions involved a variety of activities from growing, maintaining, harvesting and cooking vegetables to guided walks in parks and flower pressing. These participants were not characterized by chronic pain, which may explain the lack of a significant effect on anxiety compared with our acute effects in people with LBP. One prospective study focused TH effects on various functional, health and physical activity outcomes in patients with cancer diagnoses.[21,45] The impact of master gardeners mentoring the planning, planting and maintaining of 3 seasonal gardens over the course of 1 year was examined in relation to a variety of outcomes; participants interfaced bimonthly with the gardeners and received materials for garden growing. After the intervention, participants' 2-minute step scores and TUG scores were improved by 39% and 13%, respectively, with no difference in perceived emotional well-being (waitlist controls improved 11% and 13%, respectively, in these functional scores).[21]

Using a different set of TH activities in our pilot session, we did not show a significant improvement in TUG test time despite moderate effect size, but we did find moderate improvement in spine extension and rotation. Wahnefred, et al.[45] found that cancer survivors participating in a home gardening intervention reported 15.5% lower physical pain scores, but no other significant changes in mental well-being. It is possible that the different diagnoses (cancer vs LBP) may have differentially affected anxiety responses. This study may have included active participants who had already been doing some gardening and the intensity of movement may not have been challenging enough to induce significant changes in some of the functional metrics or LBP severity. Alternatively, with additional sessions, higher dose exposure or additional lateral bending and flexion movements, TH may have induced improvements in function. Subsequent studies of TH frequency, dose and activities performed are needed to address this issue.

It is important to note that the herb bowl activity in the pilot session is only one of many TH options that can be designed for this population. TH can involve a variety of activities such as sensory stimulation, plant propagation and maintenance, plant art, garden design, garden bed production, harvesting and cooking, among other nature- and horticulture-related activities. Because growing plants has inherent meaning and purpose, participants may feel more motivated to participate in physical activity because it is enjoyable and involves social interaction.[46]older adults are vulnerable to physical deterioration and psychological problems. There is evidence that horticultural therapy (HT Based on the variable responses to the TSK-11, RMDQ and PROMIS Global Health 10, our participants were experiencing variable levels of kinesiophobia, back disability and health impacts from LBP. An important point to note is that all participants performed all herb bowl-related activities and no one experienced a worsening of LBP severity. There is the strong possibility, as with other interventions in chronic musculoskeletal pain, that there are "responders" and "non-responders" to this intervention. Thus, some participants may have responded more favorably to the herb bowl activity than others based on their disability perceptions and fear of movement.

STUDY Limitations and Strengths

There are limitations to this study that deserve comment. First, our cross-sectional survey component involved only 1 outpatient spine center and included only patients who agreed to complete the survey. We are unable to account for the interest level among patients who did not agree to participate, and therefore non-response bias may exist in these results. However, all consecutive patients were approached during the data collection period, and the respondents represented a wide age range, gender and ethnicity distribution, returning and new patients and socioeconomic profiles, which overall represented the composition of our institutional clinic. Second, in our pilot TH session, we did have a small sample size, but we were able to obtain effect sizes for powering subsequent interventions. Moreover, the pilot session involved 1 type of TH activity; while the activity was designed to encourage spine movement in all 3 planes, it is possible that future sessions could be comprised of movements requiring more spine exertion (reaching up and over, flexion and bilateral rotation). Future larger studies could use dose response approaches (single, multiple, long-term or periodic sessions), different TH activity types and involve participants from different geographic locations (rural, suburban, urban), while controlling for LBP history and psychological status.

CONCLUSIONS

Among patients treated for LBP in an outpatient spine clinic, there is considerable interest in TH to help manage pain, independent of current perceptions of pain interference and physical function. The pilot data suggests that acute TH was enjoyable and may confer benefits of reducing anxiety levels and improving spine motion.

FUNDING

The funding source was the University of Florida Health Sports Performance Center.

Supplementary File 1. Horticultural survey provided to patients receiving care in the institutional outpatient spine care center.

Horticultural Therapy for Your Health: A Survey of Patient Interest

What is it? Horticulture is the art and science of growing plants. Horticultural therapy uses plants and gardening to improve bodies, minds and spirits by connecting with nature. A therapist that uses horticultural therapy helps others participate in plant-based activities to help reach specific goals, heal and rehabilitate. By helping to care for plants in a garden, science suggests that there are possible health benefits.

By completing this survey, you can help The Department of Physical Medicine and Rehabilitation find out how this therapy may serve our patients in the UF Health system. Thank you!

About You Survey #: _____

Your age: _____

I am: male; female; prefer not to answer

Race: black/ African American; Asian; white/ Caucasian; Indian; Pacific Islander; Alaskan; More than one; Other

Ethnicity: Hispanic; Not Hispanic

Working status: working; retired; disabled; volunteer; not working

Insurance status: Insured; Medicare; Medicaid; Not insured

Annual income: <$50,000; >$50,000

Marital status: Married; Widowed; Single

Living status: Lives with spouse/partner; Lives alone; Lives with family/ support; Other

Your Health

Do you currently suffer from joint pain? Yes; No

If yes, where? Neck; Spine; Knee; Hip; Ankle/ foot; Shoulder; Elbow; Wrist/ Hand

How many years have you suffered from joint pain? _____

Do you take medicines regularly for your pain? Yes; No

How many pain medicines do you use on a regular basis? 0; 1; 2; 3 or more

Do you use an assistive device? No; Cane; Walker; Wheelchair/ scooter

Have you tried any of the following treatments for your pain or functional difficulties?

Physical therapy; Acupuncture; Meditation; Massage

What physical activities do you do regularly?

Walking; Jogging; Dancing

Walking briskly or hiking; Bowling; Yoga

Yardwork; Kayaking/ canoeing; Team sports

Gardening; Cycling; Pickleball

Golf; Tennis; Lift weights, use weight machines

Other: _____

On average, how many times a week do you do some physical activity? _____

Does joint pain often stop you from participating in the physical activities you enjoy? Yes; No

Horticultural Therapy

Have you heard of horticultural therapy before today? Yes; No

Would you be interested in hearing more about this kind of therapy to help manage your pain or functional difficulties? Yes; No

If yes, why might this therapy be interesting to you? *Check all that apply*

_____ I enjoy handling plants and being outdoors
_____ I believe that nature can have healing benefits
_____ It may be relaxing
_____ It may be a form of exercise I can tolerate
_____ I may feel a sense of accomplishment and purpose
_____ I might get to meet different people socially
_____ It might help my joints move more easily
_____ It might be fun

If no, why not? *Check all that apply*

_____ I am not interested in working with plants
_____ It would be messy and a lot of work to clean up
_____ It would be too hot outside
_____ I don't think this therapy would help my health issues
_____ I don't think I could do it based on my pain level or pain location on my body
_____ I don't think I could move around outside well with my assistive devices
_____ This activity would not give me the same benefits as regular physical therapy for my joint pain, strength or functional difficulties

Please rate your agreement in the following statements using the following answers, where 1 = "do not agree at all" and 5 = "strongly agree".

Horticultural therapy might:	1	2	3	4	5
Put me in a better mood	☐	☐	☐	☐	☐
Help me get stronger muscles	☐	☐	☐	☐	☐
Lower my stress level	☐	☐	☐	☐	☐
Help me move my body around with less joint pain	☐	☐	☐	☐	☐
Help me do my self-care activities with less pain (washing, dressing, brushing teeth, combing hair)	☐	☐	☐	☐	☐

If offered at UF, would you participate in horticultural therapy research to learn more about benefits to physical health and pain? Yes; No

If offered at UF, would you participate in horticultural therapy as part of your health management plan? Yes; No

Supplementary Table 1. Responses to Reasons for Interest and Disinterest in Therapeutic Horticulture to Manage Low Back Pain

I am interested in TH because:	**Interested**	**Not interested**	***P* value**
I enjoy handling plants and being outside.	86 (74.1)	3 (7.3)	<.001
I believe that nature can have healing benefits.	83 (71.5)	2 (4.9)	<.001
It may be relaxing	92 (49.3)	2 (4.9)	<.001
It may be a form of exercise I can tolerate.	76 (65.5)	0 (0.0)	<.001
I may feel a sense of accomplishment and purpose.	67 (57.7)	0 (0.0)	<.001
I might get to meet different people socially.	41 (35.3)	0 (0.0)	<.001
It might help my joints move more easily.	72 (62.1)	0 (0.0)	<.001
It might be fun.	81 (69.8)	0 (0.0)	<.001
I am not interested in TH because:	**Interested**	**Not interested**	***P* value**
I am not interested in working with plants.	0	16 (39)	<.001
It would be messy and a lot of work to clean up.	2 (1.7)	4 (9.7)	<.001
It would be too hot outside.	9 (7.7)	12 (29.3)	<.001
I don't think this therapy would help my health issues.	0 (0.0)	14 (34.1)	<.001
I don't think I could do it based on my pain level or pain location.	4 (3.4)	7 (17.7)	<.001
I don't think I could move around outside well with my assistive devices.	1 (0.8)	6 (14.6)	<.001
This activity would not give me the same benefits as regular physical therapy for my joint pain, strength or functional difficulties.	3 (2.6)	11 (26.8)	<.001

Note: Values are positive agreement answers and percentage of the group.

Abbreviations: NRS, 11-point Numerical Rating Scale for Pain and Anxiety

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ORIGINAL RESEARCH

Comparative Pharmacokinetics of Curcuminoids from Water-Dispersible Turmeric Extract Against a Curcuminoids-Piperine Combination: An Open-Label, Randomized, Balanced, 2-Treatment, 2-Sequence, 2-Period Crossover Study

Shefali Thanawala, BAMS; Rajat Shah, MBA; Lynda Doyle, MS, MBA; Vivek Upadhyay, PhD

ABSTRACT

Objective • Curcuminoids, the major component of which is curcumin, are natural polyphenolic compounds from the rhizome of *Curcuma longa* Linn. and possess extensive biopharmacological properties that are limited in humans due to poor bioavailability. Currently, most commercial bioavailable turmeric extracts use synthetic excipients or the addition of piperine to enhance bioavailability, and are needed in multiple daily doses to achieve clinical efficacy. This study was conducted to compare the bioavailability of a natural, water-dispersible turmeric extract containing 60% natural curcuminoids, the test product, WDTE60N (1 × 250 mg per day), with the reference product, turmeric extract capsules (500 mg curcuminoids and 5 mg piperine, CPC; 3 × 500 mg per day).

Methods • Sixteen healthy adult male subjects fasted overnight for 10 hours and then were dosed with either one capsule of the test product WDTE60N or three capsules of reference product CPC orally (One capsule administered at every 6 hours interval i.e. at 0.00 hrs, 6.00 hrs and at 12.00 hrs) in each study period. Blood sampling before and after dosing was carried out at defined time points at -12.00, -02.00, 00.00 (within 10 minutes prior to dosing) hours in morning before dosing and post-dose (First dose) at 00.50, 01.00, 02.00, 03.00, 04.00, 05.00, 06.50, 07.00, 08.00, 09.00, 10.00, 11.00, 12.50, 13.00, 14.00, 16.00, 18.00, 20.00 and 24.00 hours in each period. Plasma concentration of curcuminoids was determined using a validated liquid chromatography with tandem mass spectrometry bioanalytical method.

Results • The Cmax (GLSM) for the test product WDTE60N was observed to be 74.56 ng/mL; and same for the reference CPC was 22.75 ng/mL. AUC0-t (GLSM) for test WDTE60N was 419.00 h·ng/mL; and for reference CPC it was 359.86 h·ng/mL for total curcuminoids.

Conclusion • The test formulation WDTE60N showed improved relative absorption and equivalent exposure at a 10-fold-lower dose of actives than the reference formulation CPC. (*Altern Ther Health Med.* 2024;30(4):18-23)

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INTRODUCTION

Curcumin is the major biologically active polyphenolic constituent in turmeric rhizomes and is also called diferuloylmethane or (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione). Curcuminoids exhibit a broad spectrum of pharmacological actions, including antineoplastic, antidepressant, antioxidant, anti-inflammatory, immunoprotective, antimicrobial, antidiabetic, and cognitive actions, as demonstrated in several in vitro, preclinical, and clinical studies.[1-9] The mechanisms underlying the beneficial effects of curcuminoids are complex and involve several pathways, including inhibition of proinflammatory factors; activation of peroxisome proliferator–activated receptor gamma cell signaling pathways; downregulation of interleukin 6, resistin, leptin, and monocyte chemotactic protein-1; and upregulation of adiponectin and modulation of expression of host enzymes and other gene products.[2] The clinical data regarding the pharmacokinetic characteristics and metabolism of curcuminoids have established their limited absorption, quick metabolism, and poor bioavailability.

It is well accepted that curcumin itself displays poor solubility in water, chemical instability, and a poor pharmacokinetic profile. Curcumin exhibits various pharmacologic effects such as anti-inflammatory, antiangiogenic, antioxidant, and antiproliferative activities; however, the therapeutic potential of curcumin is hampered due to poor bioavailability in humans, even when administered at a high dosage (12 g/day).[10] Generally, the oral bioavailability of curcumin is low due to relatively low absorption by the

small intestine coupled with an extensive reductive and conjugative metabolism in the liver and biliary elimination. The poor bioavailability is exacerbated by curcumin binding to enterocyte proteins that can modify its structure.[11]

Low absorption, rapid metabolism, and quick elimination of curcuminoids in the body limits their efficacy when orally ingested as a supplement.[10] Therefore, a very large dose of approximately 6 to 8 g turmeric powder or 1500 to 2000 mg turmeric extract standardized to 95% of curcuminoids is required to achieve therapeutic benefits. Such high doses might be associated with poor compliance, particularly when used long term. Overall acceptability of curcumin is reduced with an increase in dose, as this invariably results in an increase in capsule size and/or number required to deliver the optimum dose.[12] Clinical studies have proven that simpler, less frequent dosing regimens result in better compliance in a variety of therapeutic areas.[13] Thus, there is an unmet need to develop a turmeric formulation that may provide health benefits at relatively lower doses and at low dosing frequency. Efforts to enhance the bioavailability of curcuminoids mainly focus on either blocking the curcumin metabolic pathway or improving absorption by changing the formulation to nanoparticles, emulsions, liposomes, or cyclodextrin complexes.[14] Piperine, the bioactive compound found in the fruits of the black pepper plant (*Piper nigrum*), is routinely used to enhance the bioavailability of curcuminoids.[2] However, there are hardly any pharmacokinetic studies evaluating the bioavailability enhancing effect of piperine on curcuminoids or comparing the pharmacokinetics of bioavailable curcuminoid products designed using formulation technologies.

To overcome these limitations and to provide optimum benefit of the therapeutic effect of curcuminoids at a single daily dose, the novel formulation TurmXTRA 60N (WDTE60N; containing 60% curcuminoids from water-dispersible turmeric extract) has been developed using a patented manufacturing technology. In this study, the pharmacokinetics of WDTE60N was compared with a commercially available product of a combination of curcuminoids and piperine, CPC.

MATERIALS AND METHODS

Study approvals

This study was conducted at Enem Nostrum Remedies Pvt Ltd, India, in accordance with the protocol approved by the Human Care Independent Ethics Committee and with the pertinent requirements of the Declaration of Helsinki (Brazil, October 2013), Good Clinical Practices for Clinical Research in India 2005, New Drugs and Clinical Trials Rules 2019, International Council for Harmonisation E6 (R2), and Guidance on Good Clinical Practice, and with all applicable requirements of the Principles of Good Laboratory Practice (Organisation for Economic Co-operation and Development, and Schedule L-I of the Drugs and Cosmetics Rules, 1945) and the New Drugs and Clinical Trials Rules 2019 GSR 227 (E) by the Central Drugs Standard Control Organisation. All subjects were thoroughly informed about the study, given an opportunity to ask questions, and signed informed consent forms before participating in the study. The whole study-specific informed consent process was carried out under recorded audiovisual surveillance.

Study participants

We enrolled 16 healthy adult male subjects 18 to 45 years with a body mass index (calculated as weight in kilograms divided by height in meters squared) between 18.50 and 29.99 and weighing at least 50 kg.

Inclusion criteria. The subjects underwent screening procedures not more than 21 days before the first day of dosing. Subjects were selected based on clinically acceptable laboratory evaluations and electrocardiogram recordings, medical history, clinical examination (general examination and systemic examination), and a chest x-ray (posteroanterior view) within 180 days prior to the first dosing. A COVID-19 antigen test, urine alcohol test, and a urine screen for drugs of abuse were performed on the admission day of each period for all subjects and were required to be negative.

Exclusion criteria. Key exclusion criteria included hypersensitivity to study products or inactive components; history or presence of significant cardiovascular, pulmonary, hepatic, renal, gastrointestinal, endocrine, immunological, dermatological, or neurological disease or disorder; asthma, urticaria, or other significant allergic reaction; significant gastric or duodenal ulceration; drug abuse in the past year; significant smoking habit; or alcohol abuse in the past year. Other exclusion criteria were difficulty with donating blood or swallowing tablets or capsules; use of any treatment which could bring about induction or inhibition of the hepatic microsomal enzyme system within 1 month prior to the dosing of the first period; use of any prescribed medication or over-the-counter medication, including vitamins and herbal products, during the 14 days prior to the dosing of the first period; or major illness or hospitalization within the past 3 months. Subjects were also excluded if they had donated at least 1 unit of blood (≥300 mL) or participated in a clinical study involving blood sampling within 90 days prior to the first dose of the study product; consumed grapefruit juice or xanthine-containing products within 72 hours prior to dosing; used tobacco-containing products or any alcoholic products within 48 hours prior to dosing; or had a positive screening test for human immunodeficiency virus, hepatitis B, or hepatitis C.

Study design

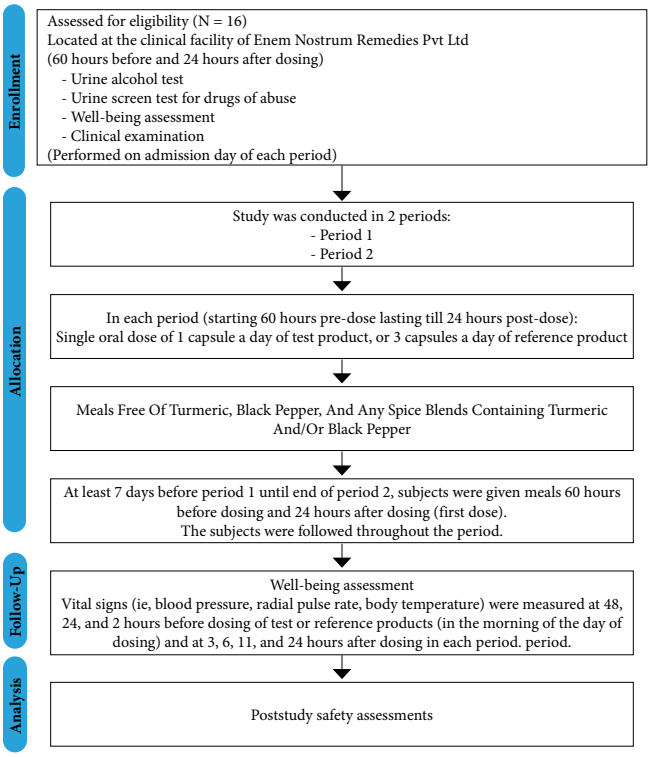
This was an open-label, randomized, balanced, 2-treatment, 2-sequence, 2-period, crossover, oral dose, comparative pharmacokinetic study in 16 normal healthy adult male human subjects under fasting conditions.

The study was conducted in 2 periods; subjects received each of the products in 2 sequences in accordance with balanced block randomization carried out using PROC PLAN of SAS software, version 9.4 (SAS Institute Inc) (ie, one group of subjects were given the test product WDTE60N

followed by the reference product CPC; the other group were given the reference product CPC followed by the test product WDTE60N). Study product compliance was ensured throughout the 2 periods.

The total duration of the study was 16 days, from the day of admission of the first period, the washout period, the admission for the second period and discharge from second period which marked the end of the clinical phase.

Figure 1. Study Design Flowchart



Study procedure

The subjects committed to follow diets free of turmeric and black pepper and any spice mixtures containing turmeric or black pepper, starting at least 7 days before period 1 check-in until the end of period 2. Subjects were instructed during screening to refrain from smoking; refrain from chewing tobacco, pan or pan masala, gutkha, or masala (containing beetle nut and tobacco); and refrain from consuming any alcoholic products or xanthine-containing foods or beverages (such as chocolate, tea, coffee, or cola drinks) for 48 hours prior to dosing and grapefruit juice for 72 hours prior to dosing until the completion of the study.

Enrolled subjects were housed at the clinical facility from 60 hours prior to the day of dosing for each period to ensure strict adherence to meals free of turmeric, black pepper, and any spice blends containing turmeric or black pepper, as well as to ensure 10 hours supervised overnight fasting prior to the scheduled time of dosing. Subjects continued to be housed in the clinical facility until 24 hours after the first dose in each period.

For the second and third doses of reference product CPC, all subjects abstained from food approximately 2 hours prior to the scheduled time of dosing and for at least 4 hours after dosing. Subjects were given standardized meals (free of turmeric and black pepper) during the check-in night and at 48, 44, 40, 36, 24, 20, 16, and 12 hours before dosing (to maintain 10 hours fasting before dosing) and at approximately 4 and 10 hours after the first dose in each period. All in-house meal plans were identical for both periods of study.

If the meal, vital sign measurement, and blood sample collection time points coincided, blood samples were collected before the measurement of vital signs and meals. Drinking water was not allowed from 1 hour before dosing until 1 hour after dosing (except for 240 mL water at room temperature given during dosing).

Subjects were asked to remain in a sitting or semirecumbent posture and were not allowed to lie down for at least 2 hours after administration of the test product WDTE60N or reference product CPC (except for any procedural requirements and for using the restroom), unless clinically indicated. Thereafter, the subjects were allowed to engage in normal activities while avoiding severe physical exertion.

Study products

The test product was TurmXTRA 60N 250 mg capsules (WDTE60N; containing 150 mg curcuminoids from water-dispersible turmeric extract) manufactured by Nutriventia Limited, India. The reference product was turmeric extract capsules (CPC; containing 500 mg Curcumin C3 Complex and 5 mg BioPerine) manufactured by Sami-Sabinsa Group Ltd, India. C3 complex is a standardized turmeric extract having three curcuminoids (curcumin, bisdemethoxycurcumin, and demethoxycurcumin).

Study product dosing

The test product WDTE60N was given as a single oral dose of 1 capsule once in the morning, while the reference product CPC was given as 1 capsule 3 times at 6 hour intervals. Both products were given with 240 mL water at room temperature under fasting conditions.

Period 1 and period 2 doses were staggered with a gap of 2 minutes between each subject to maintain the dosing and sampling time evenly for each subject.

A washout period of 11 days was kept between period 1 and period 2.

All study activities, including dispensing, dosing, sample collection, sample handling, sample processing, bioanalysis, and accountability, were carried out under yellow monochromatic light conditions.

Subject assessments

Well-being and vital signs (blood pressure, radial pulse rate, and body temperature) were measured as safety assessment in each study period before dosing of WDTE60N or CPC at 48, 24, and 2 hours before dosing and at 3, 6, 11, and 24 hours after the first dose in each period. The vital signs were measured within 60 minutes before or after each scheduled time.

Safety assessments were also carried out at the end of the study, including well-being assessment, general clinical

Table 1. Subject Characteristics at Screening Visit

Parameter	Median (range) (N = 16)
Age, y	33.5 (24.0-43.0)
Weight, kg	67.25 (51.50-83.00)
Height, cm	165.0 (156.0-174.0)
BMI[a]	23.99 (19.71-28.26)

[a]BMI, calculated as weight in kilograms divided by height in meters squared.

Abbreviation: BMI, body mass index.

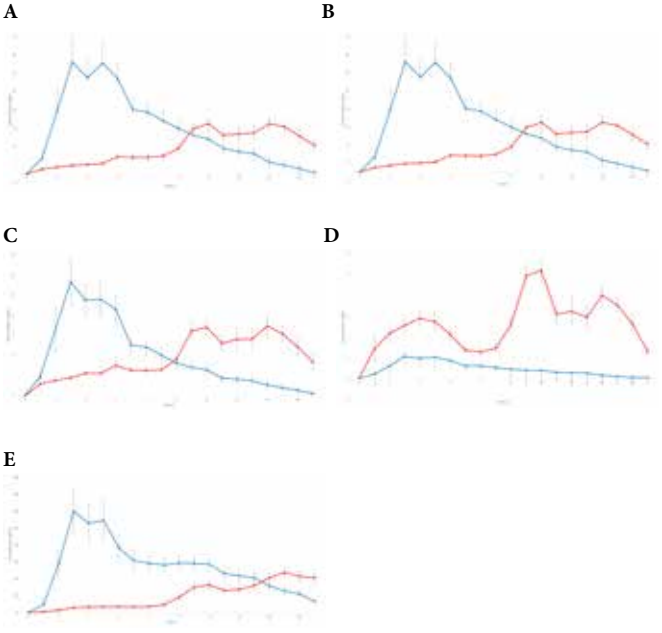
Table 2. Pharmacokinetic parameters of the test (WDTE60N) and reference (CPC) products

PK parameter, unit	Geometric least square mean		Test/ Reference, %	ISCV, %	90% CI
	Test	Reference			
Total curcuminoids					
Cmax, ng/mL	74.56	22.75[a]	327.76	37.31	262.06-409.94
AUC0-t, h·ng/mL	419.00	359.86	116.43	26.74	98.94-137.03
Total curcumin					
Cmax, ng/mL	59.89	11.80[a]	507.50	39.75	400.25-643.50
AUC0-t, h·ng/mL	337.09	194.02	173.74	36.73	139.36-216.60
Demethoxycurcumin					
Cmax, ng/mL	13.75	6.04[a]	227.73	33.02	186.57-277.98
AUC0-t, h·ng/mL	68.46	92.99	73.62	22.49	64.15-84.49
Bisdemethoxycurcumin					
Cmax, ng/mL	1.37	5.12[a]	26.79	17.49	24.05-29.83
AUC0-t, h·ng/mL	7.98	62.65	12.74	14.12	11.68-13.90
Tetrahydrocurcumin					
Cmax, ng/mL	126.52	31.65[a]	399.68	45.69	305.14-23.52
AUC0-t, h·ng/mL	970.84	544.13	178.42	35.31	144.27-220.65

[a]Average of 3 consecutive doses.

Abbreviations: AUC, area under the curve; ISCV, intrasubject coefficient of variation; PK, pharmacokinetic.

Figure 2. Mean Plasma Concentration Versus Time of the Test product WDTE60N and Reference Product CPC. Mean plasma concentration (ng/mL) versus time (hours) of the test WDTE60N and reference CPC with error bars for (A) total curcuminoids, (B) total curcumin, (C) demethoxycurcumin, (D) bisdemethoxycurcumin, and (E) tetrahydrocurcumin.



examination, systemic clinical examination, vital signs (blood pressure, radial pulse rate, respiratory rate, and body temperature), hemogram, and biochemical analysis (aspartate aminotransferase, alanine aminotransferase, bilirubin, creatinine, and urea).

Pharmacokinetic measurements

Plasma concentrations of total curcuminoids, total curcumin, demethoxycurcumin, bisdemethoxycurcumin, and tetrahydrocurcumin were estimated using a validated liquid chromatography with tandem mass spectrometry method.[15]

Calculations of pharmacokinetic parameters (Cmax; area under the curve [AUC] 0-t; AUC0-inf; Tmax; elimination rate constant, kel; half-life, $t_{1/2}$; and extrapolated AUC) using the plasma concentration vs time profiles of the active compounds were carried out using a noncompartmental model of the Phoenix WinNonlin Software, version 8.3.4 (Certara USA, Inc).

Statistical analysis

Statistical comparisons of the pharmacokinetic parameters of 1 test and 1 reference formulation of turmeric extract were carried out using SAS software, version 9.4 (SAS Institute Inc).

Analysis of variance was carried out using PROC GLM of SAS software, version 9.4 (SAS Institute Inc) for ln-transformed Cmax and AUC0-t. The least square means, differences, intrasubject variability, and power of the test and reference formulations were computed for ln-transformed Cmax and AUC0-t. The geometric least square mean ratio and its 90% CI were also computed for the pharmacokinetic parameters Cmax and AUC0-t.

RESULTS

Subject characteristics

The age, weight, height, and body mass index of each subject were recorded during screening (Table 1). Subject weights and body mass indexes were within the clinically acceptable normal ranges.

Pharmacokinetic data

The geometric least square means of the test product and the reference product, geometric least square mean ratio percentage of the test and reference products, intrasubject variability, and 90% CIs of the geometric least square mean ratio percentage were obtained from the analysis of ln-transformed Cmax and AUC0-t data (Table 2).

The mean plasma concentration (ng/mL) versus time (hours) of the test and reference products are displayed in Figure 2.

Safety assessment results: No adverse events were reported by the subjects during the study periods and post study safety assessment.

DISCUSSION

The consumption of curcumin is claimed to convey several health benefits through its antioxidant, anti-inflammatory, antidiabetic, hepatoprotective, anti-allergic,

and neuroprotective effects.[1] Issues which greatly limit the effectiveness of curcumin are its low bioavailability, attributed to water insolubility, and its rapid metabolism to inactive metabolites. Curcumin is an oil-soluble compound, practically insoluble at room temperature in water and at acidic pH. While it is soluble at alkali pH, it is very susceptible to autodegradation. The water solubility of curcumin is estimated to be 11 ng/mL. Therefore, various formulations have been developed to enhance its solubility or dispersibility with the goal of enhancing bioavailability and consequent bioefficacy.[16] These formulations include nanoparticulate preparations; formulations with micelles, liposomes, or gelatin; and polysaccharide complexes alone or in combination with other herbal extracts, such as piperine, the active compound in black pepper.[3,17-19] While most of the bioavailable curcuminoids products show relative superiority through pharmacokinetic evaluation, most of these products are observed to use a higher dose in clinical trials. Thus, the correlation between the dose used in the evaluation of the pharmacokinetics and the dose used in evaluation of the clinical outcomes is often missing.

In a previous study, the pharmacokinetic characteristics of the test product, WDTE60N were compared with a standard 95% curcuminoid product, STE95; subjects received 10-fold-lower quantities of curcuminoids in WDTE60N compared with STE95.[20] Peak plasma concentrations of free curcumin, total curcuminoids, tetrahydrocurcumin, and demethoxycurcumin were statistically similar for WDTE60N at a 10-fold-lower dose compared with STE95. Tmax of WDTE60N was shorter than that of STE95 for total curcuminoids, indicating rapid absorption of active compounds.

Considering these observations from the previous pharmacokinetic study[20], we decided to compare, in the current study, the pharmacokinetic characteristics of 150 mg curcuminoids (test product WDTE60N) with a combination product of 500 mg curcuminoids and 5 mg piperine (reference product CPC). Although the subjects received approximately 10-fold-lower quantities of curcuminoids through WDTE60N in comparison with the curcuminoids-piperine combination, CPC; higher absorption and equivalent exposure were observed for total curcuminoids for WDTE60N than for CPC. Thus, the findings of the present study are in line with our previous study, in which WDTE60N had a better pharmacokinetic profile than STE95.

The available clinical evidence shows that the therapeutic benefits of turmeric formulations are attained by administration of curcuminoids.[19,21,22] Therefore, to gain maximum health benefit, it is prudent to select a turmeric formulation with established bioavailability of total curcuminoids.

As the AUC of total curcuminoids for WDTE60N was equivalent to the curcuminoids-piperine combination, CPC at a 10-fold-lower dose, WDTE60N should also be clinically efficacious at the dose of 150 mg curcuminoids that we used in this study. This efficacy has been established in 2 clinical trials that we conducted for WDTE60N for delayed-onset muscle soreness and for chronic knee-joint pain.[23,24] Thanawala et al[23] demonstrated that intake of 250 mg WDTE60N containing 150 mg curcuminoids for 33 days (with a pre-exercise period of 29 days and a postexercise period of 4 days) significantly reduced subjective perception of muscle soreness and serum lactate dehydrogenase levels and increased the psychological well-being in healthy, recreationally active adult subjects as measured by the Hooper Mackinnon Questionnaire[23]. In another study that we conducted on healthy subjects experiencing chronic knee pain following physical exertion, subjects received 250 mg WDTE60N once daily for 3 months.[24] The visual analog scale, 80 m fast-paced walk test, and 9-step stair-climb test scores, as well as inflammatory biomarkers, significantly improved in subjects who received WDTE60N in comparison with subjects who received a placebo. WDTE60N was well tolerated and safe in both studies.[23,24]

The present study has strengths and limitations. A crossover randomized trial design was used to minimize interindividual variability, as the same subject served as their own control. However, only healthy male, not female, subjects were enrolled. This was a single-dose pharmacokinetic study for the test product WDTE60N, and further studies with a steady-state design would help further elucidate the pharmacokinetic profile of WDTE60N.

CONCLUSIONS

In this study, the test product, 250 mg WDTE60N containing 150 mg curcuminoids, was found to have a better pharmacokinetic profile at a 10-fold-lower single dose than a curcuminoids-piperine combination product CPC administered as per the standard thrice-daily recommendation. WDTE60N had higher absorption and equivalent exposure for total curcuminoids than CPC. Both the study products were well tolerated, and no adverse events were reported. Considering the safety and pharmacokinetic profile as well as the safety of the test product , WDTE60N is expected to have higher compliance when administered for longer periods in a daily single dose.

DATA AVAILABILITY

The data presented in this study are available on request from the corresponding author. The data are not publicly available as per the data privacy policies of the sponsors.

CONFLICTS OF INTEREST

The study was sponsored by Nutriventia Ltd, India, and Laila Nutraceuticals Pvt Ltd, India. The authors have no other conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Conceptualization, Rajat Shah and Lynda Doyle; methodology, Shefali Thanawala; validation, Vivek Upadhyay; formal analysis, Vivek Upadhyay; investigation, Shefali Thanawala; resources, Rajat Shah; writing—original draft preparation, Shefali Thanawala; writing—review and editing, Rajat Shah and Lynda Doyle; visualization, Rajat Shah; supervision, Lynda Doyle; project administration, Shefali Thanawala; funding acquisition, Rajat Shah. All authors have read and agreed to the published version of the manuscript.

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ORIGINAL RESEARCH

The Effect of Graston Technique on Pain, Proprioception, Flexibility, and Disability in Patients with Chronic Non-specific Low Back Pain

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ABSTRACT

Background • Chronic non-specific low back pain (CNLBP) causes significant dysfunction in patients. The Graston Technique (GT) is a new intervention in pain management but there is a lack of evidence in the literature regarding its effectiveness in low back pain.

Study Objective • This study aims to investigate the effect of GT added to exercise on pain, proprioception, disability, flexibility, and quality of life in individuals with CNLBP.

Methods • This was a randomized controlled trial with a total of 30 CNLBP patients.

Setting • Karabük University Training and Research Hospital, Turkey.

Participants • Thirty patients (mean age = 38.46 ± 9.03 years) with CNLBP for at least 12 weeks were included in the study. The patients were randomly divided into two groups intervention and control.

Intervention • Graston was applied three times a week for four weeks in addition to the exercise program in the intervention group, while only the exercise program was applied to the control group.

Outcome measures • Pain intensity, pressure pain threshold, proprioception, flexibility, disability, and quality of life were evaluated at the beginning and end of the study.

Results • Significant improvements in pain, disability, and quality of life were found in both the control and intervention groups ($P < .05$). There was an increase in flexibility and a decrease in proprioception deviation angles of 15° and 30° in the GT group ($P < .05$). The improvement in pain and disability in the intervention group was significant compared to the control group ($P < .05$). However, there was no significant difference between the groups regarding pressure pain threshold, flexibility, proprioception, and quality of life ($P > .05$).

Conclusion • GT added to exercise in patients with CNLBP better reduces pain and disability, improves proprioceptive sense, and increases mobility and quality of life. GT may be used as a supportive treatment during the rehabilitation of CNLBP patients. (*Altern Ther Health Med.* 2024;30(4):24-30).

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INTRODUCTION

Non-specific low back pain (NLBP) is defined as low back pain that cannot be attributed to a recognizable, known specific pathology (infection, tumor, osteoporosis, fracture, radicular syndrome, etc.).[1] It is a problem that 80% of healthy individuals encounter at least once in any period of their lives and has a very high prevalence in the whole population.[2] With the prolongation of the process that starts as acute pain, the pain becomes chronic. Chronic pain restricts physical function and negatively affects the quality of life, causing loss of workforce and increased health care expenses.[2,3]

Within the skeletal system, the most load-bearing region of the spine is the lumbar region. Therefore, it is the region most affected by mechanical stresses, functional loads, and occupational and sports traumas.[4] Instability in the lumbar region leads to insufficient motor control system and causes low back pain.[5] Impaired lumbar proprioception can also cause low back pain.[6] As lumbar proprioception is impaired, it becomes more challenging to maintain the neutral position of the spine, and neuromuscular control is interrupted.[5] This situation causes low back pain to increase and become chronic. As a result, the ability to detect changes in body position is affected, thereby impairing proprioception, and creating a vicious circle.[5,6]

According to the current literature, various methods are used in treating low back pain based on the time and

symptoms. Exercise therapy has an important contribution to the treatment of chronic lower back pain and can prevent the recurrence of pain.[7] Recent studies show that manual therapy is a viable treatment option for reducing chronic low back pain. Instrument Assisted Soft Tissue Mobilization (IASTM) is a popular treatment modality that can be used for myofascial restriction. IASTM is used to reduce pain in the pathology region, increase range of motion (ROM), restore function, and offer a mobilizing effect.[9-11] Graston technique (GT) is a widely used IASTM technique for this purpose.[12]

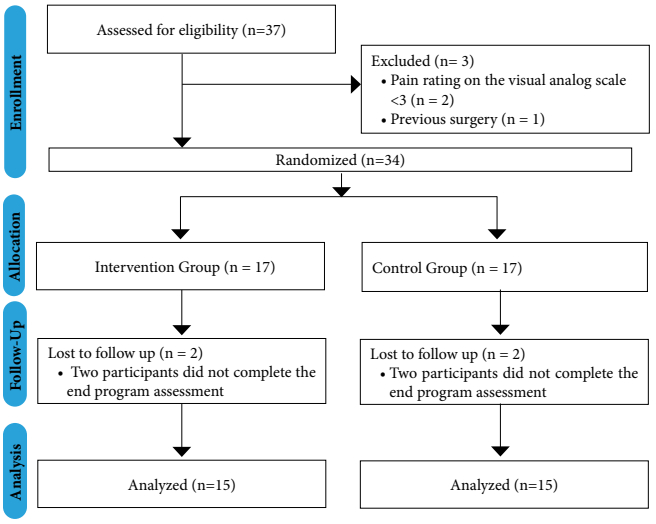
Studies show that the Graston technique can effectively reduce pain and improve soft tissue mobilization.[12,13] It also improves the quality of daily life by reducing the disability caused by pain.[12,14] Studies in the literature focused on the effect of Graston on pain and reported that it could be used in practice.[12,15] An additional systematic review suggests that Graston is an effective therapeutic intervention to reduce pain and improve function in less than three months.[16] A study by Lee et al.[13] showed that the Graston technique applied for four weeks in individuals with chronic low back pain was effective in reducing pain and improving joint range of motion.[13] However, a meta-analysis study does not support the effectiveness of IASTM on function, pain, and range of motion in the treatment of spine disorders, thus contrasting the findings of other researchers. Therefore, the evidence is not clear.[17] Since pain is a significant problem affecting patients' quality of life, it is important to investigate it. However, the lack of studies examining the long-term effectiveness of Graston on pain severity in individuals with chronic non-specific low back pain (CNLBP) draws attention. In addition, there is no study examining the effectiveness of Graston on proprioception, which plays a vital role in the healing mechanism. Based on the existing evidence on the efficacy of the Graston technique, we hypothesize that the Graston technique added to exercise will have a positive effect on pain, flexibility, proprioception, disability, and quality of life in individuals with CNLBP. Therefore, this study aimed to investigate the effect of the Graston technique added to exercise on pain, flexibility, proprioception, disability, and quality of life in individuals with CNLBP.

METHODS

Participants

Thirty volunteer patients who visited the Neurosurgery outpatient clinic and were diagnosed with CNLBP were included in this study. Inclusion criteria for this study were: between the ages of 18-65 years; being diagnosed with CNLBP by a neurosurgeon (pain that persists for at least 12 weeks and no known pathoanatomical cause in between gluteal folds and 12th ribs); pain rating of >3 on the visual analog scale (VAS); volunteering to participate in the study; and those who signed informed consent. Exclusion criteria for this study were: signs of neurological deficit, history of spondylosis or spondylolisthesis, psychological disorder, mental disorder, cancer, and severe depression; primary or metastatic spinal malignancy; diagnosis of advanced osteoporosis; surgery or acute infection of the lumbar region; regular use of analgesics.

Figure 1. Flow Diagram of Participants



The sample size was calculated using G*Power analysis software Version 3.0.10 (G*Power, Franz Faul, Universitat Kiel, Germany). Based on a previous study (effect size = 1.62), it was determined that the sample size should be at least 8 people for a significant change in pain intensity (pain pressure threshold) for 95% power ($\alpha = 0.05$).[18] Due to data loss that may occur during the study process, a total of 30 individuals, 15 for each group, were included in the study.

The study was approved by the ethics committee of the University (No: 2021/598) and conducted following the Declaration of Helsinki. All subjects gave written informed consent to participate in this study after being informed about the content, purpose, and associated benefits and risks of this study.

Study design

A randomized controlled trial was conducted to examine the efficacy of IASTM on CNLBP. The individuals included in the study were divided into two groups by simple randomization using a number random table and the closed envelope technique: intervention and control. All parameters outlined in outcome measures section were evaluatedin both groups at baseline and immediately after the four-week study period. The consolidated standards of reporting trials (CONSORT) diagram of patient flow throughout the study is shown in Figure 1.

The same exercise program was applied to the patients in both groups, three days a week, for four weeks. The exercise program included exercises for stretching the lower back muscles, strengthening the back and abdominal muscles, and postural correction (Table 1).[19] The exercise program was given and supervised by a physiotherapist, and the program was adapted according to the patient's tolerance. Strengthening and postural correction exercises were prescribed for three sets, ten repetitions, three times a day, each repetition for 5-7

Table 1. Exercise Program

Exercise Types	Frequency	Duration
Stretching Exercises	3 sets x 10 repetitions	15 to 30 sec
Knee to chest		
Double knee to chest		
Straight leg raise		
Cat and camel		
Quadratus Lumborum Stretch		
Strengthening exercises	3 sets x 10 repetitions	5-7 sec
Curl ups		
Diagonal curl ups		
Back extension		
Postural correction	3 sets x 10 repetitions	5-7 sec
Pelvic tilt		
Bird dog		

seconds. The repetitions were checked weekly and gradually increased until they reached 15 seconds according to tolerance. The stretching exercise was prescribed three times a day, three sets and ten repetitions, each lasting for 15 to 30 seconds. The number of repetitions was checked weekly and gradually increased according to tolerance.[12,19]

To treat the affected area of the patients in the intervention group, a Graston instrument was applied to the superficial and deep fascia on the erector spines, gluteus maximus, gluteus medius, and hamstrings by the physiotherapist. At first, patients were asked to kneel directly on the bed and lie forward. In this position, the superficial and deep fascia of the erector spinae was applied. Then, Graston was applied to the gluteus maximus and gluteus medius in the hip and knee flexion position, with the patient in the side-lying position. It was applied in the prone position for the hamstring muscles. The largest Graston instrument (GT1), used to treat soft tissue restrictions over large surface areas, was chosen for the treatment.[20] Lubricating cream was used to facilitate the gliding of the Graston instrument over the tissues. The Graston technique was applied for 20 seconds at a 45° angle in a direction parallel to the muscle fibers for each treated muscle. Immediately afterward, an additional 20 seconds of application was made at a 45° angle perpendicular to the muscle fibers, and the total treatment time was approximately 40 seconds for each muscle. Patients were informed that they may have painful, bruised, or small red spots called petechiae in the treated area. If there was severe pain after the treatment, ice was applied for 15-20 minutes.[12,13] Graston was applied 3 times a week for a total of 4 weeks.

Outcome measures

After the demographic and clinical characteristics of the patients were recorded, the following evaluations were made at the beginning of the study and after four weeks:

Pain intensity: Low back pain severity was measured using VAS. The VAS is a 10-point scale, where 0 represents no pain and 10 represents unbearable pain. The patients' pain intensity at rest was determined from the VAS score obtained between 0 and 10 points.[21]

Pressure pain threshold: Pressure pain threshold (PPT) was measured using an algometer (Baseline®, US). Algometer is a device that measures sensitivity to pain caused by pressure or force applied to any part of the body. The subjects were required to lie prone on the examination table with both forearms over the sides. The algometer was placed vertically 2 cm lateral to the 3rd lumbar vertebra, and then the pressure was applied to the area at a rate of 1 kg/s. The point at which the patient felt an unpleasant sensation or pain was accepted as the pressure pain threshold. Three short consecutive PPT measurements with 10 seconds between them were performed at each of the selected regions for the right and left sides. It was then recorded by averaging the values obtained for the right and left sides.[22,23]

Flexibility: Sit and Reach Flexibility Test was used to evaluate trunk and hamstring muscle flexibility. Patients rested their feet on the sit-and-reach table with their knees extended. Then, they were asked to lie forward with their hands together without lifting their knees. The test was repeated 3 times and the maximum distance the patient reached was recorded.[24]

Proprioception: The sense of position, known as the sense of repositioning of the trunk, was evaluated with a digital inclinometer (Baseline®, USA). Patients were asked to stand comfortably with their heels shoulder-width apart and their hands hanging freely at their sides. The inclinometer was placed parallel to the spinous processes of the T12-L5 vertebrae, with the patients standing upright. The digital inclinometer was reset before evaluation. The patient was asked to lean forward. The evaluator reminded the patient when the inclinometer showed an angle of 15° and 30°. Then, for trial and learning, they were asked to bend forward three times at 15° and 30° with their eyes closed and stop there for 3 seconds. The same procedure was applied after the trial, and the patients repeated the test 3 times. Deviation angles were recorded for 15° and 30° trunk flexion.[25]

Disability: The Oswestry Disability Index (ODI) was used to evaluate the level of functional disability caused by chronic low back pain.[24] The scale has ten subgroups. Subgroups of the scale: severity of pain, lifting, carrying, walking, sitting, standing, sleep, sexual life, traveling, and social life. Each subgroup has six options, and the first statement is scored as "0" and the sixth statement as "5". As the total score increases, the level of disability also increases.[26]

Quality of life: The Short Form-36 (SF-36) was used to measure changes in quality of life (QoL) levels due to chronic low back pain. This scale consists of 36 items and includes physical function, physical role, bodily pain, general health, emotional role, social function, mental health, and vitality sub-parameters. The score of the Short Form 36 range from 0 (worst) to 100 (best).[27,28]

Statistical analysis

Statistical analysis was performed using SPSS version 23 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation; categorical data were expressed as numbers and percentages. It was determined whether the variables were normally distributed using visual (histograms) and analytical methods (Shapiro Wilk). Independent *t* test and Chi-Squared Pearson Test were used to compare demographic variables between groups. Normally distributed variables were compared using the Independent *t* test, and non-normally distributed variables were compared using the

Table 2. Sociodemographic Characteristics of Participants

	Intervention (n = 15)	Control (n = 15)	*P* value
Age, years, X ± SD	37.13 ± 8.87	39.8 ± 9.30	.429[a]
Gender, n (%)			.705[b]
Male	10 (66.7)	9 (60.0)	
Female	5 (33.3)	6 (40.0)	
Weight, kg, X ± SD	74.26 ± 12.90	80.0 ± 16.72	.302[a]
Height, cm, X ± SD	166.06 ± 10.05	169.8 ± 10.79	.335[a]
BMI, kg/m^2, X ± SD	26.95 ± 4.29	27.61 ± 4.20	.673[a]
Civil status, n (%)			.195[b]
Married	10 (66.7)	13 (86.7)	
Unmarried	5 (33.3)	2 (13.3)	
Educational status, n (%)			.007[b]
Primary school	5 (33.3)	1 (6.7)	
High school	4 (26.7)	0 (0.0)	
University degree	6 (40.0)	14 (93.3)	
Occupational status, n (%)			.019[b]
Housewife	7 (46.7)	0 (0.0)	
Student	1 (6.6)	0 (0.0)	
Working	7 (46.7)	14 (80.0)	
Unemployed	0 (0.0)	0 (0.0)	
Retired	0 (0.0)	1 (20.0)	
Smoking			.896[b]
Never smoked	7 (46.7)	6 (40.0)	
Currently smoking	5 (33.3)	5 (33.3)	
Has smoked before	3 (20.0)	4 (26.7)	

[a]Independent *t* test,
[b]Chi-Squared–Pearson test

Abbreviations: X, Mean; SD, Standard Deviation; BMI, Body Mass Index;

Table 3. Changes in VAS, Pain Pressure Threshold, Flexibility, and Proprioception

Variables	Groups	Before	After	Effect size	Group difference *P* value	Between groups *P* value
VAS	Intervention	6.94 ± 1.84	3.41 ± 1.99	1.842	0.001[c]	.002[a]
	Control	5.52 ± 1.83	4.38 ± 2.13	0.574	0.003[c]	
	P value	0.043[b]	0.210[b]			
Pressure pain threshold	Intervention	6.03 ± 1.68	7.73 ± 1.85	0.962	0.001[c]	.074[a]
	Control	8.81 ± 3.08	9.93 ±3.50	0.339	0.025[c]	
	P value	0.004[a]	0.233[a]			
Flexibility	Intervention	-5.53 ± 11.91	-1.93 ± 10.28	0.323	0.001[d]	.174[b]
	Control	0.86 ± 8.62	2.70 ± 7.26	0.230	0.077[d]	
	P value	0.056[a]	0.126[a]			
Proprioception						
15°	Intervention	4.54 ± 3.59	2.20 ± 1.85	0.819	0.003[c]	.567[a]
	Control	5.24 ± 3.40	3.36 ± 2.44	0.635	0.099[c]	
	P value	0.588[b]	0.174[a]			
30°	Intervention	5.66 ± 4.37	2.69 ± 1.92	0.879	0.011[d]	.073[b]
	Control	4.38 ± 2.85	3.76 ± 2.64	0.225	0.416[d]	
	P value	0.567[a]	0.217[a]			

[a]Mann Whitney U test
[b]Independent *t* test
[c]Wilcoxon test
[d]Paired *t* test

Abbreviation: VAS, Visual Analog Scale.

Mann–Whitney U test. Changes occurring after treatment were determined using the Paired Sample *t* test for normally distributed data and the Wilcoxon test for non-normally distributed data. Effect sizes were calculated using Cohen's d and categorized as trivial (≤0.20), small (0.21–0.49), moderate (0.50–0.79), or large (≥0.80).[29] Data were evaluated over a 95% confidence interval and considered statistically significant at $P < .05$.

RESULTS

This study was reported using the CONSORT guidelines. Thirty-seven patients with CNLBP were screened. Three patients did not meet the inclusion criteria. A total of 34 participants were randomly assigned to one of the two groups. Two participants from both groups did not complete the programs and did not participate in the final assessments. Finally, the data of 30 participants were analyzed.

The demographic characteristics of the participants according to the groups are shown in Table 2. The mean age of all participants was 38.46 ± 9.03 years. There was no statistically significant difference between the two groups regarding age, gender, body mass index, smoking, and marital status ($P > .05$, Table 2).

A significant decrease in pain severity was observed after the intervention program in both groups ($P < .05$), and a significant difference in pain severity was found between the two groups ($P < .05$). In VAS, while the effect size was large for the intervention group (d = 1.84), it was medium for the control group (d = 0.57). Pressure pain threshold increased significantly in both groups compared to baseline ($P < .05$) after the treatment but there was no significant difference between the groups ($P > .05$). The effect size in post-intervention and pre-intervention comparisons for each group is given in Table 3.

The participants' flexibility increased significantly only in the intervention group at the end of the treatment, and the effect size was small ($P < .05$ d = 0.32). At the end of the treatment, proprioception angular errors at 15 and 30 degrees of trunk flexion decreased significantly only in the intervention group ($P < .05$). In addition, the effect size was large for 15° and 30° of proprioception (d = 0.819 and d = 0.879, respectively). Changes in VAS, pressure pain thresholds, flexibility, and proprioception outcome measures, and effect size are shown in Table 3.

A significant decrease was observed in ODI scores according to both in-group and between-group analyses ($P < .05$). In ODI, the effect size was large (d = 0.99) and moderate (d = 0.53) for the intervention and control groups, respectively. The improvement in ODI scores was higher in favor of the intervention group ($P < .05$). After the intervention program, there were significant improvements from baseline in all QoL levels in the intervention group, except for the 'social function' subgroup of SF-36 ($P < .05$). In the control group, there were significant improvements from baseline only in the 'physical role' and 'body pain' subgroups ($P < .05$). The difference between the two groups was significant in the physical function, general health, and emotional role subgroups ($P < .05$). The effect size for the SF-36 sub-parameters was between 0.42 and 0.93 in the intervention group, while these were between 0.07 and 0.47 in the control group. Changes in ODI and SF-36 outcome measures and effect size are shown in Table 4. There were no adverse effects associated with the interventions.

DISCUSSION

This study showed that the Graston Technique (GT) added to the exercise program significantly reduced pain and increased the pressure pain threshold. Although GT added to the exercise improved proprioception, it was not superior to exercise. In addition, the GT improved physical function and general health, reducing the level of disability.

Table 4. Changes in Disability and Quality of Life

Variables	Groups	Before	After	Effect size	Group difference *P* value	Between Groups *P* value
ODI	Intervention	45.20 ± 21.52	24.80 ±19.50	0.993	.000[d]	.002[b]
	Control	28.26 ± 13.60	20.53 ± 15.48	0.530	.021[d]	
	P value	0.029[a]	0.624[a]			
SF-PF	Intervention	55.33 ± 21.99	75.33 ± 20.65	0.937	.002[c]	.005[a]
	Control	78.33 ± 17.07	80.66 ± 17.71	0.133	.559[c]	
	P value	0.003[b]	0.454[b]			
SF-RP	Intervention	40.00 ± 39.86	65.00 ± 38.72	0.636	.016[c]	.567[a]
	Control	63.33 ± 38.80	80.00 ± 31.62	0.471	.031[c]	
	P value	0.126[a]	0.345[a]			
SF-BP	Intervention	37.33 ± 22.48	56.00 ± 24.97	0.785	.002[c]	.089[a]
	Control	60.00 ± 21.85	70.00 ± 20.48	0.472	.031[c]	
	P value	0.009[b]	0.104[b]			
SF-GH	Intervention	47.66 ± 20.86	60.66 ± 26.24	0.548	.007[d]	.047[b]
	Control	59.33 ± 21.45	61.00 ± 20.37	0.079	.648[d]	
	P value	0.142[b]	0.902[b]			
SF-VT	Intervention	36.83 ± 22.31	56.50 ± 23.31	0.862	.018[d]	.126[b]
	Control	53.16 ± 28.99	58.16 ± 24.33	0.186	.394[d]	
	P value	0.095[b]	0.850[b]			
SF-SF	Intervention	56.66 ± 25.38	67.50 ± 25.35	0.427	.066[d]	.099[b]
	Control	79.16 ± 19.28	75.83 ± 21.37	0.163	.604[d]	
	P value	0.015[a]	0.436[a]			
SF-RE	Intervention	20.00 ± 35.18	75.55 ± 38.76	1.500	.040[c]	.013[a]
	Control	68.88 ± 44.48	75.55 ± 36.65	0.163	.257[c]	
	P value	0.013[a]	0.870[a]			
SF-MH	Intervention	54.13 ± 24.61	68.00 ± 20.81	0.608	.038[d]	.243[b]
	Control	61.20 ± 25.85	65.73 ± 20.51	0.194	.375[d]	
	P value	0.450[b]	0.766[b]			

[a]Mann Whitney U test
[b]Independent *t* test
[c]Wilcoxon signed rank
[d]Paired *t* test

Abbreviations: ODI, Oswestry Disability Index; SF, Short Form 36; PF, Physical Functioning; RP, Role Physical; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role Emotional; MH, Mental Health.

In our study, pain was reduced by 30% more in the intervention group compared to the control group, and the effect size was large. A 30% change compared with the pre-test is considered a clinically meaningful improvement for individuals with low back pain.[30] Pressure pain threshold improved in both groups and although this effect was greater in the intervention group, no significant difference was found between the groups. The decrease in pain intensity may have been caused by Graston's increased flexibility in the muscles. The GT applied to the erector spinae, gluteus maximus/medius, and hamstring muscles are thought to increase muscle flexibility. Any shortening of the muscles surrounding the lumbar region and the deep fascia limits hip flexion, causes lumbar hyperextension and increases pain by affecting the biomechanics in the region.[31,32] It is assumed that the GT relieves pain by stimulating mechanoreceptors in soft tissues, reduces the activity of neurons and provides an additional analgesic response to skin deformations.[32] For this reason, it is thought that it is important to treat the muscle and fascia in chronic lower back pain. Similar to the results of our study, it was reported that chronic low back pain decreased and lumbar flexion, extension, right/left trunk flexion, and hip flexion ROM increased after four weeks of intervention of the GT.[13] In another study investigating the effect of the GT, it was reported that the technique applied in addition to the routine treatment of patients with NLBP, increased hamstring flexibility and thus decreased pain intensity.[15] In addition to the stimulation of mechanoreceptors with the Graston technique, increased tissue temperature increases the pressure pain threshold.[18] In our study, these effects of Graston improved the pressure pain threshold by 15% more in the intervention group than in the control group and provided a large effect size. Although Graston has a good penetration depth,[16] its effect on the deep group muscles in the lumbar region, which consists of a deep tissue layer, may be limited. Since more deep tissue was evaluated with pressure at the pressure pain threshold, the lack of difference between the groups may be because the effect of Graston was a little more superficial.

It has been reported that the angle of deviation increases with the deterioration of proprioception in patients with chronic low back pain.[33] Therefore, it is stated that proprioceptive sense should be considered during the treatment process to stimulate recovery by providing motor control.[5] However, the long-term effect of soft tissue mobilization on proprioceptive sensation in patients with chronic low back pain is unclear. This study showed that Graston added to exercise improved 15° and 30° of proprioception in patients with CNLBP by 51% and 52%, respectively, and the effect size was large. However, no difference was observed between the groups. Problems in afferent signals from muscle spindles and central regulation in patients with low back pain may lead to impaired proprioception.[34] The significant increase in proprioception may have been due to functional recovery in muscle memory due to soft tissue mobilization with the GT. In addition, the flexibility obtained in the muscles may have increased the sense of joint position by providing biomechanical improvement. It is suggested that pressure applied to the tissue increases position sensitivity by activating mechanoreceptors.[35,36] Therefore, it is rationalized that GT can be used in developing proprioceptive sense, which plays an important role in the effectiveness of rehabilitation.

Decreased flexibility limits the joint range of motion, causes abnormal load on the musculoskeletal system, and leaves the body vulnerable to injury.[37] The GT, applied in correct and appropriate doses, may reduce pain and increase muscle flexibility and ROM within a few weeks after treatment.[38] In a study, the knee range of motion of a patient who developed a complication of knee arthrofibrosis after patellar tendon rupture surgery was limited, and muscle activation was impaired. It has been observed that the GT, which was applied to the patient in addition to joint mobilization, flexion ROM exercise, strengthening, and home exercise program for a total of 5 times for four weeks, increased the range of motion and improved physical function.[39] In patients with plantar heel pain, it has been reported that a home stretching exercise program including triceps surae muscles and calcaneal tubercle and applying the GT for up to 8 sessions reduce pain and provide a significant improvement in lower extremity function.[40] Similar to previous studies, in our study, it was observed that flexibility increased due to soft tissue mobilization with the application of GT in patients with CNLBP. However, no difference was found between the groups. The GT creates a controlled local inflammation by increasing fibroblast production. With the

onset of the inflammatory response, the load on the muscle-tendon complex with exercise may play a role in muscle elasticity and strength.[36] These results support the physiological effects of the GT in tissue. The increase in blood flow, decrease in tissue viscosity, myofascial relaxation, increase in deep tissue flexibility, and interruption of transmission in pain receptors may have improved function.[16] Therefore, the use of GT is recommended to improve restricted mobility in patients with chronic low back pain.

Pain causes fear in patients during activities of daily living, leading to the development of avoidance behavior and an increase in disability. Disability is a significant problem affecting physical performance and work efficiency in patients with chronic low back pain.[41] This study showed that both exercise and GT added to exercise reduced disability by 27% and 45%, respectively. In addition, it was observed that GT was more effective in reducing disability compared to exercise alone, while the effect size was large and medium, respectively. The change in disability level is above the minimal clinically significant difference for ODI after Graston intervention in individuals with low back pain.[30] Similar to our study, Abdel-Aal et al.[12] reported that four weeks, three sessions of exercise per week, and GT added to exercise reduced pain and disability in both groups in patients with cervicogenic headaches. In addition, it has been reported that the GT is more effective in reducing disability, headache frequency, and duration.[11] Crothers et al. showed that ten sessions of chiropractic and Graston intervention in individuals with thoracic spine pain reduced pain and disability within three months after treatment; however, this effect was not statistically significant.[14] Literature has reported that clinically important developments will be achieved when the GT is combined with exercises.[42] In our study, it is thought that the combination with exercise was also effective in observing significant improvements in the intervention group.

It is stated that soft tissue mobilization improves the quality of life in patients with chronic pain, but there is insufficient evidence on this subject.[43] In the present study, it was observed that Graston improved patients' quality of life with CNLBP but it was not superior to exercise. Also, the GT improved more effectively sub-parameters of quality of life such as physical health, general health, and mental and emotional role. However, for the quality of life sub-parameters, the effect size was large and medium in the GT group, whereas it was small or trivial in the control group. Since combining GT with exercise improves pain and disability parameters, the improvement observed in the intervention group in quality of life sub-parameters may be due to this. Similar to our study, Ozsoy et al.[44] showed that soft tissue mobilization added core stabilization exercises reduce pain and disability and improve the quality of life in patients with NLBP. However, no difference was observed between the groups in terms of the improvement in quality of life.[44]

This study has several limitations. Although the individuals participating in our study were randomly included in the groups, the severity of pain and disability at the beginning seemed higher in the intervention group. This may have led to a more significant improvement in pain and disability after the Graston treatment. Finally, reassessment three and six months after the GT would help explain the long-term effects of the technique.

CONCLUSION

GT added to exercise reduces pain and disability, increases mobility and proprioception, and plays an important role in improving quality of life compared to exercise alone. Considering these results, it is suggested that GT can be added to rehabilitation programs to improve pain control, mobility, and quality of life in patients with CNLBP.

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The authors declare that they have no competing interests.

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ORIGINAL RESEARCH

The Initial Efficacy of Comprehensive Treatment of External Treatment of Traditional Chinese Medicine on Acute Mastitis During Lactation and its Influence on Patients' Symptoms

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ABSTRACT

Objective • To evaluate the initial efficacy of comprehensive treatment of external treatment of traditional Chinese medicine in the therapy of acute mastitis during lactation and its influence on sufferers' symptoms.

Methods • From January 2021 to January 2023, a retrospective analysis was performed on 100 sufferers with acute mastitis during lactation who were received in our hospital as the study objects. Divided them into a control group (n = 50) and an observation group (n = 50). Among them, the control one was received in 50% magnesium sulfate for moist heat compress, and the observation one was treated with comprehensive external therapy of traditional Chinese medicine. After different treatment measures were carried out in the 2 groups, the total effective ratio of clinical therapy, excellent and good rates of lactation, quality of life measurements, pain scores before and after treatment, and TCM symptom points at pre-therapy and post-therapy, negative emotion scores at pre-therapy and post-therapy related to patients were analyzed.

Results • (1) In the data comparison of the total effective ratio of clinical therapy between the 2 groups of sufferers after therapy, the data in the observation one were greater than the control one, and the distinction was obvious, with $P < .05$. (2) In the data comparison of the excellent and good lactation rate between the 2 groups of sufferers at post-therapy, the data in observation one were greater than the control one, and the distinction was obvious, with $P < .05$. (3) In the data comparison of quality of life measurements between the 2 groups of sufferers at post-therapy, the data in the observation one were greater than the control one, and the distinction was obvious, with $P < .05$. (4) Before treatment, it had no obvious distinction in the pain scores between the 2 groups, with $P > .05$; in the data comparison of the pain points between the 2 groups after therapy, the data in observation one were less than the control one, and the distinction was obvious, with $P < .05$. (5) Before therapy, it had no obvious distinction in TCM symptom points between the 2 groups, with $P > .05$; in the data comparison of TCM symptom points between the 2 groups after therapy, the data in the observation one were less than the control one, and the distinction was obvious, with $P < .05$. (6) Before therapy, it had no obvious distinction in negative emotion points between the 2 groups, with $P > .05$; in the data comparison of negative emotion scores between the 2 groups of sufferers at post-therapy, the data in the observation one were less than those in the control one, and the distinction was obvious, with $P < .05$.

Conclusion • The comprehensive therapy of TCM external treatment for acute mastitis during lactation has a significant therapeutic effect, which is conducive to improving the clinical symptoms of sufferers as soon as possible and at the same time, greatly improving the life quality of sufferers and improving their negative emotions, which can relieve the pain of sufferers and promote the recovery of the sufferers. (*Altern Ther Health Med.* 2024;30(4):31-37)

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INTRODUCTION

According to the data of the World Health Organization, about 1.5 million women worldwide are affected by acute mastitis every year. However, this figure may be underestimated, because many women may not be correctly diagnosed and reported. In addition, mastitis is more common among women in developing countries.Acute mastitis during lactation is a purulent infection of the mammary gland, which is a common and frequently-

occurring disease in lactating women, especially primipara,[1-2] mostly caused by the invasion of staphylococcus aureus, streptococcus, escherichia coli along the Milk ducts.[3-4] The decline of the immune system may make the breast more vulnerable to bacterial infection. For example, during breastfeeding, women's immune system may be affected by some factors, such as fatigue, stress, malnutrition and so on. These factors may lead to the decline of immune system function, making the breast more vulnerable to bacterial infection.The clinical manifestations of acute mastitis during early lactation are mainly local redness and swelling, fever, pain in the breast, poor milk discharge, and systemic symptoms such as chills and high fever.[5-6] It may cause abscess formation and even sepsis in late stages, which not only cause physical pain and psychological burden to the mother but also hinder breastfeeding,[7-8] and affect the health of the baby. Acute mastitis during lactation belongs to the "milk carbuncle" category in traditional Chinese medicine[9-10] . According to the theory of traditional Chinese medicine, breast redness refers to a kind of disease with symptoms such as breast redness and pain. The causes of breast red are mainly related to qi stagnation, blood stasis, damp heat and other factors. The occurrence of acute mastitis during lactation is often related to factors such as milk deposition, breast duct blockage, bacterial infection, etc. These factors lead to pathological changes such as qi stagnation, blood stasis, damp heat and so on in the breast, which in turn leads to the symptoms of milky red.About 10% of acute mastitis will develop into breast abscess if not treated in time and effectively. It can be seen that early treatment is the key to ensuring the normal breastfeeding of patients. In order to prevent breast stiffness and pain, premature delivery and excessive use of antibiotics are not recommended.[11-12] In treating traditional Chinese medicine, it is advocated to take effective measures as early as possible, mainly to dredge accumulated milk, promote the disappearance of lumps to control infection, and avoid or reduce the impact on pregnant women and babies.[13-14] Many clinical studies have shown that[15-16] comprehensive Chinese medicine exogenous treatment of acute mastitis in lactation period has good curative effect and less side effects. It is of great significance to study the external comprehensive treatment of acute mastitis in lactation with traditional Chinese medicine. First of all, this study can explore a non-drug treatment method to provide more treatment options for lactating women and reduce their dependence on antibiotics and other drugs. Secondly, the external comprehensive treatment of traditional Chinese medicine is relatively simple and can be carried out at home, which reduces the treatment cost and burden of patients. Finally, this study can further verify the efficacy and safety of external comprehensive treatment of traditional Chinese medicine, provide scientific basis for clinical practice, and promote its application to more lactating women. Therefore, based on the above background, this paper mainly evaluates the preliminary curative effect of TCM comprehensive treatment of acute mastitis during lactation and its influence on patients' symptoms, which gives more theoretical basis for treating patients with acute mastitis during lactation.

PATIENT DATA AND METHODS

Patient data

From January 2021 to January 2023, a retrospective analysis was performed on 100 sufferers with acute mastitis during lactation who were received in our hospital as the study objects. To divide them into a control one (n = 50) and an observation one (n = 50).

Among them, among the sufferers in control one, the youngest one was 20 years old, while the oldest one was 35 years old, and the mean measured data was (25.66±3.51) years old; there were 30 instances of primipara and 20 instances of multiparae; the illness course was 3-7 days, and the mean illness course was (5.55±1.11) days; there were 40 instances with unilateral breast lesions and 10 instances with bilateral breast lesions; the average tumor diameter was (5.55±1.13) cm. Among the sufferers in observation one, the age was between 20 and 36 years old, and the measured data was (25.67±3.52) years old; there were 31 instances of primipara and 19 instances of multiparae; the course of disease was 3-7 days, and the average (5.57±1.12) days; there were 41 cases with unilateral breast lesions, and 9 cases with bilateral breast lesions; the average tumor diameter was (5.57±1.12) cm. Statistical software was used for evaluating the above data among the groups, and it had no distinction, with $P > .05$.

Data analysis

group	age	Primipara/ multipara	course of a disease	Unilateral breast lesions/bilateral breast lesions	Average diameter of tumor
Observation group	25.67±3.52	31/19	5.57±1.12	41/9	5.57±1.12
control group	25.66±3.51	30/20	5.55±1.11	40/10	5.55±1.13

Inclusion criteria for these patients: (1) Patients who were in the lactation stage; (2) Patients who were in the early stage of acute mastitis during lactation; (3) Patients who had not received other relevant clinical treatments recently. Exclusion criteria: (1) Clinical data is incomplete.; (2) Sufferers with a history of mental illness; (3) Patients with acute mastitis in pus stage.

Methods

The control group received 50% magnesium sulfate for moist and hot compress treatment: 3~4 layers of gauze was soaked in 50% magnesium sulfate solution at 50~60, and then wet compress and hot compress were applied to the affected breast. During hot compress, the gauze was changed appropriately according to the temperature. Moist and hot compress should carried out for 30 min each time, with 3 times a day. Antibiotics could be used when necessary.

The observation group received comprehensive therapy of external treatment of traditional Chinese medicine: (1) External application of Chinese medicine Jinhuang powder.

Drug composition: 160 g rhubarb, 160 g phellodendron, 320 g radices trichosanthis, 160 g white peony root, 160 g radix curcumae, 64 g atractylodes, 64 g unprocessed rhizoma arisaematis, 64 g tangerine peel, and 64 g licorice. The above-mentioned traditional Chinese medicine was weighed according to the amount, then crushed into fine powder, sieved, and mixed evenly, and then it was mixed with vegetable oil or honey to form a paste and applied evenly on gauze every time. After proper heating, take the photon therapy instrument Chongqing Mingxi Medical Equipment Co., Ltd. provided to irradiate the affected area. The range of external irradiation was about 2 cm outside the edge of the mammary gland so that the nipples were exposed and milk was discharged easily. It was treated twice a day, about 30 minutes each time. (2) Grasping, kneading, and draining milk: The patients took a sitting position, and the nurse took an appropriate amount of lubricant and applied it to the affected breast to protect the skin; the nurse held the breast with her left hand and gently supported the nipple and areola with five fingers towards the end of the nipple, so as to reduce the pressure on the milk duct and dredge the stagnant milk; then used the five fingers of the right hand to rub and massage the breast hard nodules, and then rubbed the breasts radially from the base of the breast to the areola with both hands; finally, held the nipple and areola with the thumb of the right hand, gently pulled and continued to lift until the hard nodules shrank or disappeared, the breast was soft, and the exosmotic milk was drained. Then, the nurse asked the patients whether the pain was obviously relieved. Based on the actual situation of the sufferer, the treatment could be performed 3 to 4 times a day, 30 minutes to 1 hour each time. When operating, the nurse should pay attention to the force of milk discharge that should not be too large, and the massage should be gentle with fingertips so as not to scratch the skin and nipples; the milk discharge time should not be too long each time; and the milk discharge frequency should not be too less. At the same time, patients were required to continue breastfeeding adequately and regularly, and the unfinished milk should be drained in time after breastfeeding. (3) Acupoint massage: The Tanzhong, Rugen, Neiguan, Taichong and other acupoints were located on the affected area. When the patients were comfortable and relaxed, the operator disinfected his hands applied lubricant, and pressed and rubbed the thumbs of both hands regularly on the above-mentioned acupoints in sequence, with even force, and gradually increased the pressure according to the patients' tolerance, so that the acupoints could generate a sense of heat. Each acupuncture point lasted 4-5 minutes, about 30 minutes each time, once daily.

Patients were treated for 2 weeks to observe the changes of indexes.

Evaluation criteria

After different treatment measures were carried out in the 2 groups, the total effective ratio of clinical therapy, excellent and good rate of lactation, quality of life measurements (psychological function scores, material life status scores, social function scores), pain scores before and after treatment, and TCM symptom points at pre-therapy and post-therapy, negative emotion scores (anxiety and depression) before and after treatment related to sufferers were analyzed.

The total effective ratio of clinical therapy (markedly effective rate + effective rate): It was divided into obviously effective, effective, and invalid; markedly effective meant that the clinically relevant symptoms such as the patients' mass had been significantly improved; effective meant that the patients' mass and other clinically relevant symptoms had been improved; invalid means that the patients' mass and the other related symptoms had been improved have not been improved, and even worsened.

Excellent and good rate of lactation (excellent rate + good rate): It was divided into excellent, good, and poor: excellent: indicating normal milk excretion; good: indicating relatively smooth of milk excretion; poor: indicating that milk could not be excreted.

Measurements of quality of life (psychological function scores, material life status scores, social function scores): After treatment, the test personnel evaluated their life quality through the life quality scale, with a comprehensive point of 0-100 points, and the greater scores of sufferers were, the higher standard of living was.

Pain degree scores: The pain degree was evaluated by a visual analog scale, ranging from 0-10 scores, and the score was greater, the pain was more severe.

TCM symptom score: The symptoms were scored based on the patients' breasts' redness, swelling and pain, ranging from 0 to 10 scores. The scores were greater, the symptoms were more severe.

Negative emotion scores (anxiety and depression): The scores were determined by the anxiety and depression self-rating scales, with 100 points for the total score. The higher the scores were, the more serious the negative emotion was.

Statistical methods

All indicator data were included in SPSS23.0. χ^2 and t value were used separately to verify the counting and measurement data expressed in the form of % and $\bar{x} \pm s$, respectively, and $P < .05$ was the test standard.

RESULTS

The total effective ratios of clinical therapy compared between the 2 groups

In the data comparison of the total effective ratios of clinical therapy between the 2 groups of sufferers at post-therapy, the data in the observation one were greater than the control one, and the distinction was obvious, with $P < .05$. See Table 1 and Figure 1.

Comparison of the excellent and good rates of lactation between the 2 groups

In the data comparison of the excellent and good lactation rate between the two groups of patients after treatment, the data in observation one were greater than the

Table 1. The total effective ratios of clinical therapy compared between the 2 groups

Group	Number of cases	Markedly effective	Effective	Invalid	Total effective rate (%)
Observation group	50	28	20	2	96.00
Control group	50	28	20	9	82.00
χ^2	-	-	-	-	5.005
P value	-	-	-	-	0.025

Figure 1. The total effective ratios of clinical therapy compared between the 2 groups

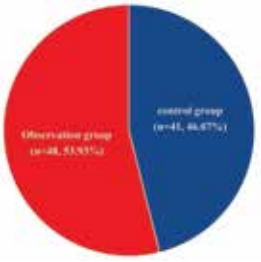
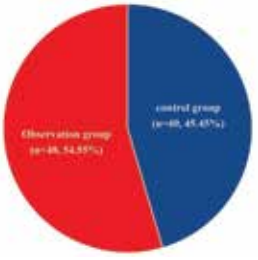


Table 2 The excellent and good rates of lactation between the 2 groups of sufferers

Group	Number of cases	Excellent	Good	Poor	Excellent and good rate of lactation (%)
Observation group	50	28	20	2	96.00
Control group	50	20	20	10	80.00
χ^2	-	-	-	-	6.061
P value	-	-	-	-	0.014

Figure 2. Comparison of excellent and good rates of lactation between the two groups



control one, and the distinction was obvious, with $P < .05$. See Table 2 and Figure 2.

Comparison of quality of life measurements (psychological function scores, material life status scores, social function points) between the 2 groups.

In the data comparison of the quality of life measurements (psychological function scores, material life status scores, and social function points) between the 2 groups of sufferers, the data in the observation one were greater than the control one, and the distinction was obvious, with $P < .05$. See Table 3 and Figure 3.

The pain degree points compared between the 2 groups before and after therapy

The pain score of the observation group decreased more obviously than that of the control group, $P < .05$. See Table 4 and Figure 4.

Table 3. The life quality measurements (psychological function scores, material life status scores, social function points) between the 2 groups

Group	Number of cases	Mental function scores	Material status scores	social function scores
Observation group	50	88.43±4.33	84.63±7.55	85.43±4.44
Control group	50	75.53±5.55	76.63±8.66	71.77±5.66
t value	-	12.958	4.924	13.427
P value	-	.000	.000	.000

Figure 3. The life quality measurements (psychological function scores, material life status scores, social function points) between the 2 groups

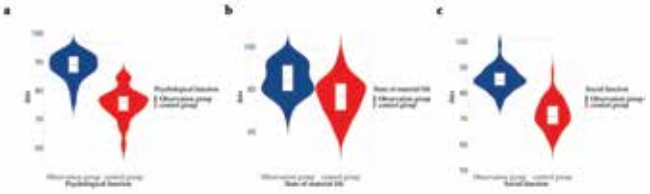


Table 4. The pain degree points at pre-therapy and post-therapy compared between the 2 groups(points)

Group	Number of cases	Before treatment	After treatment
Observation group	50	6.56±0.32	2.88±0.44
Control group	50	6.53±0.31	4.15±0.35
t value	-	0.476	15.973
P value	-	.635	.000

Figure 4. The pain scores at pre-therapy and post-therapy compared between the 2 groups

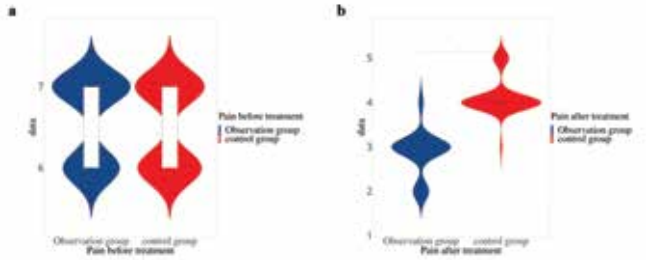


Table 5 The TCM symptom scores before and after therapy compared between the 2 groups

Group	Number of cases	Before treatment	After treatment
Observation group	50	5.55±1.66	2.44±0.55
Control group	50	5.57±1.67	4.77±1.55
t value	-	0.060	10.017
P value	-	.952	.000

The TCM symptom points before and after therapy compared between the 2 groups

Before therapy, it had no obvious distinction in TCM symptom points between the 2 groups, with $P > .05$; in the data comparison of TCM symptom scores between the 2 groups at post-therapy, the data in the observation one were less than the control one, and the distinction was obvious, with $P < .05$. See Table 5 and Figure 5.

Comparison of the negative emotion scores (anxiety and depression) between the 2 groups of sufferers at pre-therapy and post-therapy

Before therapy, it had no obvious distinction in negative emotion scores (anxiety and depression) between the 2 groups, with $P > .05$; in the data comparison of negative emotion scores (anxiety and depression) between the 2 groups of sufferers after therapy, the data in the observation one were less than the control one, and the distinction was obvious, with $P < .05$. See Table 6 and Figure 6.

DISCUSSION

Acute mastitis during lactation can be divided into initial and abscess formation stages.[17-18] In the initial stage, the main manifestations are redness, swelling, heat, and pain. Because patients are afraid of pain, they cannot breastfeed in time, and the milk cannot be emptied, forming a vicious circle and aggravating inflammation.[19-20] Western medicine mainly uses antibiotics to treat bacterial infections in treating acute mastitis during lactation. However, most patients do not accept antibiotics because antibiotics will have adverse effects on infants and hinder breastfeeding.[21-22] Magnesium sulfate for hot compress is also a commonly used method in clinical practice. 50% magnesium sulfate solution is a hypertonic solution, and local hot compress can generate high osmotic pressure.[23-24] Under the dual impacts of temperature and drugs, the vessels of mammary ducts and local breast blood are expanded, and the circulation is accelerated, which is conducive to promoting the dissipation of inflammation and produces detumescence, analgesia, and lactation effects,[25-26] but the degree of effects varies from person to person, and individual patients have little effect, and the effect is slower, which increases the possibility of abscess formation.[27-28] During the course of treatment, some patients have allergic reactions to magnesium sulfate and have to stop taking the medicine. Therefore, magnesium sulfate has certain limitations in treating acute mastitis during lactation.Compared with antibiotics, external treatment of traditional Chinese medicine has the following advantages: First, mastitis is usually caused by bacterial infection, and antibiotics are commonly used as treatment methods. However, the abuse of antibiotics may lead to the emergence of bacterial resistance, making treatment more difficult. External treatment of traditional Chinese medicine can be used as an alternative method to avoid the abuse of antibiotics. Second, antibiotics can only kill bacteria, but can't regulate the balance of the whole body. External treatment of traditional Chinese medicine can promote the self-healing ability of the body by regulating qi and blood, so as to achieve the purpose of treating mastitis. Third, antibiotics usually need to be used continuously in a short period of time, and external treatment of traditional Chinese medicine can be used as a long-term treatment. External treatment of traditional Chinese medicine can regulate the overall balance of the body and enhance the immunity of the body, thus reducing the recurrence rate of mastitis.

Figure 5. The TCM symptom scores before and after therapy compared between the 2 groups

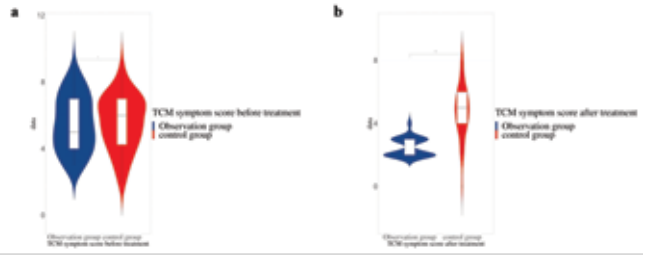
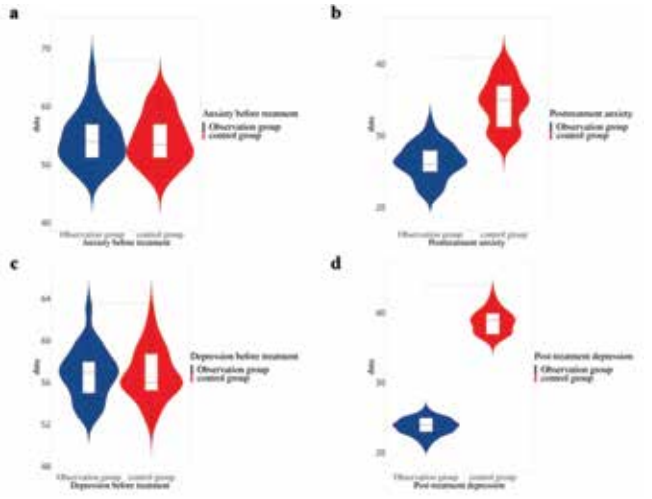


Table 6. The negative emotion scores (anxiety and depression) compared between the 2 groups of sufferers before and after therapy

Group	Number of cases	Anxiety before therapy	Anxiety after therapy	Depression before treatment	Depression after treatment
Observation group	50	54.41±4.32	26.39±2.41	56.85±2.46	23.69±1.14
Control group	50	54.44±4.33	34.57±3.23	56.89±2.47	38.73±1.65
t value	-	0.035	14.353	0.081	53.028
P value	-	.972	.000	.935	.000

Figure 6 Comparison of negative emotion scores (anxiety and depression) before and after treatment between the two groups



Traditional Chinese medicine believes that acute mastitis during lactation can be closely related to liver and stomach stagnation, milk stagnation, and exogenous pathogenic factors. The timing of this disease's treatment is critical, and early treatment can eliminate it. Abscesses can be easily formed if not handled properly or delayed.[29-30] The composition, dosage, and curative impact of external application of Chinese medicine Jinhuang powder have been affirmed and recognized through many years of clinical practice. Golden powder is a Chinese herbal medicine, and its main components include Scutellaria baicalensis Georgi, Coptidis Rhizoma, Cortex Phellodendri, etc. These ingredients have antibacterial, anti-inflammatory and detumescence effects, which can help relieve the symptoms of mastitis. Massage technique is a very effective method to relieve mastitis symptoms and improve lactation rate. For

example, gently massaging the breasts with warm wet towels or hot water bottles can promote smooth mammary glands and relieve the symptoms of mastitis. Gently kneading the breast with your fingers and massaging it from the periphery of the breast to the nipple can promote the blood circulation of the breast and relieve the symptoms of mastitis. Pushing up from under the breast with the palm of your hand can promote lymph circulation of the breast and relieve the symptoms of mastitis. Massage the nipple gently with your fingertips can stimulate the mammary gland to secrete milk and improve the lactation rate.The radice trichosanthis in the prescription has the effects of clearing heat and purging fire, draining pus, and reducing swelling, and is the most prominent drug in the prescription. Rhubarb clears away heat, purifies fire, and detoxifies; Phellodendron purifies fire and detoxifies, clears heat and eliminates dampness; Atractylodes is fragrant and dry, expelling wind and dampness; Rhizoma arisaematisis used for external application can dissipate stagnation, reduce swelling and relieve pain; Tangerine peel regulates Qi, eliminates dampness and reduces phlegm. Licorice root is a kind of auxiliary drug that has detoxification, antidrug properties, and mediates the effects of various drugs. Looking at the whole prescription, it clears heat and detoxification, eliminates dampness and reduces phlegm, promotes blood circulation and removes blood stasis, reduces swelling and relieves pain. After heating, the local blood vessels of the mammary duct and mammary gland can be expanded under the dual stimulation of drugs and temperature, and the blood flow accelerates, which can relieve local symptoms and relieve pain. In addition, Chinese medicine believes that "if there is no flow, there will be pain", so ensuring the smooth flow of milk is the key to successful treatment. Grasping, kneading, and milk discharge directly act on the affected area to achieve the purposes of "regulating Qi and dispelling stagnation, promoting blood circulation and unblocking milk". On the basis of grasping, kneading, and milk drainage, supplemented by acupoint massage, it can achieve the therapeutic effects of dredging meridians, dissipating blood stasis, and reducing swelling. Massaging the acupoints is beneficial to dredge breast collaterals and reduce swelling. The results of this data could also show that in the data comparison of the total effective ratio of clinical therapy, excellent and good lactation rate, and quality of life measurements (psychological function scores, material life status scores, and social function scores) of the 2 groups of sufferers at post-therapy, the data in the observation one were greater than the control one, and the distinction was obvious, with $P < .05$. Moreover, there were no obvious differences in pain severity scores, TCM symptom scores, and negative emotion scores (anxiety, depression) between the 2 groups before therapy, with $P > .05$; after therapy, in the data comparison of the pain degree scores, TCM symptom scores, and negative emotion scores (anxiety and depression) of the 2 groups, the data in the observation one were less than those in the control one, and the distinction was obvious, with $P < .05$. The data suggest that the clinical values of the comprehensive therapy of traditional Chinese medicine external treatment in the treatment of patients with acute mastitis during lactation is significant, and it has very high application safety and feasibility, can significantly relieve the clinical symptoms of sufferers, and improve the pain degree of sufferers.

It can be seen that the comprehensive treatment of TCM external treatment for acute mastitis during lactation has a significant therapeutic effect, which is conducive to improving the patients' clinical symptoms as soon as possible and at the same time, greatly improving the sufferers' life quality and improving their negative emotions, which can relieve pain of the patients and promote their recovery.However, there may be other factors not considered in the study, which may be related to the study variables and may have an impact on the results. In order to reduce the influence of these biases and confounding factors, subsequent researchers can transparently reveal possible biases and confounding factors in the research results and discuss their influence on the results.In addition, the specific aspects of TCM treatment of acute mastitis during lactation are worthy of further study. Although modern medicine has made remarkable progress in treating mastitis, Chinese medicine, as a traditional medical system, has a unique theory and treatment method, which may provide new ideas and methods for the treatment of mastitis. For health care practitioners, studying the specific aspects of TCM treatment of mastitis can increase their selectivity and flexibility in the treatment of mastitis. This will enable doctors to comprehensively use the treatment methods of modern medicine and traditional Chinese medicine according to the specific conditions of patients, and provide more personalized and effective treatment programs. For lactating mothers, the study of TCM treatment of mastitis is of great significance. Mastitis is one of the common complications of lactating mothers, which brings physical discomfort and pain to mothers and also affects breastfeeding. If Chinese medicine can provide effective treatment, it can alleviate the mother's pain, promote the recovery of mastitis and ensure the smooth progress of breastfeeding. The findings may have a positive impact on clinical practice, especially in areas where traditional Chinese medicine is commonly used. There are various methods of treating mastitis in Chinese medicine, including Chinese medicine treatment, acupuncture, massage, etc. These methods are widely used in areas commonly used by Chinese medicine. If the research can prove the effectiveness and safety of TCM in treating mastitis, it will help to popularize and apply TCM treatment methods and improve the therapeutic effect of mastitis.

DATA AVAILABILITY

The experimental data used to support the findings of this study are available from the corresponding author upon request.

CONFLICTS OF INTEREST

The authors declared that they have no conflicts of interest regarding this work.

FUNDING STATEMENT

Yixing Science and Technology Bureau of Jiangsu Province, number: yxsfzd202106 Clinical efficacy of "Lactation Carbuncle Elimination Formula" in the treatment of early Qi stasis and fever in the early stage of lactational acute mastitis.

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REVIEW ARTICLE

The Relevance of Naturopathy as a Therapeutic Tool in the Modern Era: A Narrative Review

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ABSTRACT

Background • There are numerous reports of remarkable recoveries from diseases through drugless healing systems. In an effort to enhance the understanding of naturopathic therapies, the author, a renowned BNYS doctor specializing in naturopathy, yoga, nutrition, and wellness, aims to explain the importance of drugless therapies in various disease conditions.

Objective • To provide a comprehensive overview of the relevance and efficacy of naturopathy as a therapeutic tool in modern healthcare. Drawing on a literature review and the author's expertise, it aims to explore the benefits of drugless healing systems.

Methods • This study adopts a narrative review methodology to synthesize existing literature on the efficacy of naturopathy as a therapeutic tool in modern healthcare settings. A comprehensive search strategy was employed, utilizing databases such as PubMed, with keywords including "naturopathy," "drugless healing," "alternative medicine," "therapeutic modalities," and specific interventions such as "hydrotherapy" and "acupuncture." Boolean operators were used to combine terms to ensure the inclusivity of relevant literature. The intervention under investigation involved the effects of naturopathy, fasting, hydrotherapy, chiropractic, acupuncture, acupressure, magnet therapy, therapeutic manipulation, color healing, and other drugless therapies. The primary focus of the reviewed studies was to evaluate the efficacy of naturopathic interventions in improving health outcomes across diverse disease conditions, including cardiac health, skin diseases, cancers, immunity, and metabolic syndrome.

Results • The review identified a significant body of literature supporting the efficacy of naturopathic interventions in improving health outcomes across various disease conditions. Studies consistently reported positive effects of drugless healing modalities, including improvements in cardiac health, skin diseases, cancers, immunity, and metabolic syndrome.

Conclusion • The findings highlight the relevance and effectiveness of naturopathy as a therapeutic approach in modern healthcare. With its emphasis on lifestyle modifications and non-invasive treatments, naturopathy offers a holistic and cost-effective alternative for addressing lifestyle disorders and enhancing overall well-being. (*Altern Ther Health Med.* 2024;30(4):38-41)

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INTRODUCTION

Naturopathy stands as a distinct primary healthcare system that prioritizes the body's natural capacity for self-healing. Its core principles are rooted in the holistic integration of various elements, including exercise, sunlight exposure, adequate hydration, stress management, and a balanced diet.[1] The scope of naturopathic practices encompasses an array of therapies aimed at fostering health promotion and disease prevention.[1-3] In the early twentieth century, naturopathy emerged in the United States and Canada, integrating principles of nature cure, homeopathy, spinal manipulation, and various other therapeutic modalities.[2] American naturopathic practitioners employ a diverse range of interventions, encompassing dietary and clinical nutrition strategies, behavioral modification techniques, hydrotherapy, homeopathic remedies, herbal medicine, physical therapy, pharmaceuticals, and minor surgical procedures.[3]

Drugless therapy,[4] by definition, prohibits naturopathy practitioners from utilizing pharmacotherapy but instead provides them access to the expansive realm of drugless

healing.[5,6] The foundational principles of naturopathy are deeply rooted in a comprehensive understanding of living organisms. Diagnostic and therapeutic protocols in naturopathy are grounded in the fundamental elements of the universe (Panchamahabhootas). An imbalance among these elements, manifesting as diseases and symptoms, can be rectified through the careful application of five-element treatment methods.

Naturopathic treatment methods involve the thoughtful utilization of the five fundamental elements. With a history spanning approximately two centuries, the practices employed in naturopathy have undergone refinement, definition, and rigorous examination through the lens of modern science. The majority of natural methods have been demonstrated to be cost-effective, safe, and beneficial for individuals, regardless of their health status.[3-6]

The rising prevalence of lifestyle disorders, exacerbated by factors such as pollution, stress, and irregular daily routines, underscores the pressing need for effective therapeutic approaches.[4] Naturopathy's emphasis on lifestyle modifications and dietary interventions presents a promising solution to mitigate the adverse effects of chemical-based treatments.[5] This study aims to explore the efficacy and cost-effectiveness of naturopathic interventions in addressing modern health challenges, providing valuable insights for healthcare practitioners and policymakers.

METHODS

Search Strategy

This study utilized a narrative review methodology to examine current research concerning the effectiveness and cost-effectiveness of naturopathic interventions in managing lifestyle disorders and fostering holistic well-being. A comprehensive search strategy was implemented, utilizing electronic databases such as PubMed, and Google Scholar. Keywords including "naturopathy," "lifestyle disorders," "cost-effectiveness," and "therapeutic interventions" were employed to identify relevant studies published in peer-reviewed journals.

Inclusion and Exclusion Criteria

Inclusion criteria encompass studies conducted within the past two decades, focusing on the effects of naturopathic treatments on lifestyle-related health conditions. Exclusion criteria include non-English studies, case reports, and studies lacking sufficient methodological rigor. Data extraction was performed systematically, with emphasis on key findings related to the efficacy and affordability of naturopathic interventions.

Data Synthesis

The collected information from the included studies was analyzed and integrated to identify overarching patterns and trends within the literature. It involved organizing and summarizing the findings from individual studies to draw comprehensive conclusions. Through thematic analysis, common themes and relationships between different variables were identified, allowing for a deeper understanding of the research landscape.

THERAPEUTIC APPLICATIONS OF NATUROPATHY IN VARIOUS HEALTH CONDITIONS

Enhancing Immunity through Naturopathic Therapies

Enhancing immunity through naturopathic therapies involves a holistic approach aimed at strengthening the body's natural defense mechanisms. Once neglected, immunity is now recognized as the most crucial determinant of health. Naturopathy emphasizes the importance of lifestyle modifications, dietary interventions, and exposure to various natural elements to support immune function. The body's natural defense system can become disruptive when it incorrectly identifies external stimuli, whether they are related to diet or the environment.

Traditional methods to control, restrict, and regulate immunity have yielded unsatisfactory and transient results. Naturopathy emphasizes restoring immunity through clinical doses of exposure to the external environment, such as sunlight, fresh air, mud, and various cold and hot therapeutic applications. By addressing the underlying factors that influence immune health, naturopathic therapies strive to optimize the body's ability to fight off infections and maintain overall well-being.[9-10]

Naturopathic Interventions for Obesity

Fasting emerges as a potent strategy in combating obesity, earning the title of "*the supreme remedy.*" Various fasting protocols, including short-term fasting, alternate-day fasting,[7] intermittent fasting,[8] mono-dieting, and religious fasts like Ramadan fasting,[9] exhibit remarkable effectiveness in weight control. Additionally, fasting demonstrates cardioprotective benefits,[10] enhances insulin sensitivity,[11] inhibits the progression of certain cancers,[12] reduces oxidative stress and inflammation, optimizes biomarker levels, and fosters longevity[13]

Metabolic Syndrome and Naturopathic Interventions

Global research consistently emphasizes the effectiveness of adopting an active lifestyle[14-16] and consuming abundant wholesome natural foods,[17,18] and stress management as the primary, if not the ultimate, solution to the increasing health hazards posed by metabolic syndrome. Naturopathic medicine's promise lies in its ability to correct biological rhythms and modify behaviors, providing the most effective approach to safeguarding against metabolic syndrome.[19]

Naturopathic Holistic Approaches to Managing Musculoskeletal Pain

Various holistic modalities, including acupuncture,[20,21] hydrotherapy,[22-24] magnet therapy,[25] acupressure,[26-28] chiropractic care,[29,30] therapeutic manipulation,[31,32] and color healing,[33,34] have demonstrated efficacy in managing musculoskeletal pain. These interventions enhance

circulation, alleviate congestion, reduce stiffness, improve range of motion, and facilitate recovery with minimal adverse effects. Acupuncture, in particular, has been extensively researched for its potential to regenerate stem cells and reverse degenerative joint conditions.[35]

Promoting Cardiac Wellness through Naturopathic Lifestyle Interventions

Dr. Dean Ornish concluded in his seminal work that a regimen consisting of a plant-based, low-fat, and low-carbohydrate diet, combined with gentle yoga practices, has the potential to reverse chronic and costly coronary artery disease.[36] Naturopathic lifestyle interventions offer a safe, cost-effective, and easily adaptable approach to enhancing overall cardiac efficacy.

Naturopathic Perspectives on Cancer Prevention

Cancer remains one of the most feared diseases worldwide. According to naturopathic principles, our bodies and the environment are intricately connected. Environmental pollutants, industrial emissions, and chemicals disrupt the endocrine system, predisposing individuals to various types of cancers.[37] Studies have shown that individuals living in remote areas, adhering to an active lifestyle, and consuming naturally grown organic foods exhibit a lower incidence of breast cancer.[38,39] Moreover, natural dietary practices and living in natural surroundings have been associated with improvements in various types of cancers.[40]

Naturopathic Approaches to Treating Skin Conditions

Skin diseases often stigmatized, exert a negative impact on the patient's psyche.[41] Evidence suggests that regular application of mud and sunlight exposure, along with natural dietary practices and fasting, produces excellent results in alleviating stubborn skin problems such as psoriasis, dermatitis, and eczema.[42] Furthermore, a higher intake of antioxidant-rich foods demonstrates remarkable anti-aging effects and helps maintain youthful skin.[43,44]

Addressing Inflammation Through Nutritional Intervention

Modern lifestyles, stress, unhealthy dietary habits, and environmental factors weaken the immune system, leading to unresolved inflammation and recurrent infections. A diet rich in fruits and vegetables aids in combating inflammation by stimulating the body's healing pathways.[45] Nutrition plays a pivotal role in managing the financial burden of various new-age diseases, offering a cost-effective and efficient approach to improving health outcomes.[46]

DISCUSSION

Naturopathy, rooted in a holistic philosophy, recognizes the individuality of health needs and acknowledges that responses to therapeutic modalities vary among individuals.[10-15] Mind-body medicine underscores the interconnectedness of the entire body, emphasizing the structural, biochemical, mental, and emotional aspects.[16-18] Disruptions in one area often manifest as dysfunction elsewhere, highlighting the inadequacy of viewing diseases as isolated disturbances in single organs or systems.[20-25] Holistic and drugless therapies offer a comprehensive approach to addressing imbalances on deeper levels. These time-tested and effective interventions provide less invasive means of alleviating chronic lifestyle disorders. By addressing the root causes of illness and promoting overall well-being, naturopathic therapies offer promising avenues for achieving sustainable health outcomes.[26-40]

This review presents compelling findings regarding the efficacy of naturopathic interventions across various health conditions. It highlights the role of naturopathy in enhancing immunity through lifestyle modifications and natural therapies. Additionally, the benefits of fasting in weight management emphasize its cardioprotective effects and potential to improve insulin sensitivity. Naturopathic lifestyle interventions are shown to be effective in mitigating metabolic syndrome by promoting an active lifestyle, wholesome natural foods, and stress management. Furthermore, this review explores the efficacy of holistic modalities such as acupuncture and hydrotherapy in managing musculoskeletal pain with minimal adverse effects. Additionally, naturopathic approaches are highlighted for their potential to promote cardiac health and cancer prevention, emphasizing the holistic nature of naturopathic medicine in addressing underlying imbalances and promoting overall well-being.

Strengths and Limitations of the Study

The strengths of this study include its comprehensive review of naturopathic interventions across various health conditions, which provides valuable insights into the efficacy of these approaches. However, a limitation is the reliance on existing literature, which may not encompass all relevant studies or could introduce bias based on publication trends. Additionally, the heterogeneity of study designs and outcomes across included studies may pose challenges in synthesizing and interpreting the findings. Future research should focus on conducting large-scale, well-designed clinical trials to further reveal the effectiveness of naturopathic interventions across diverse populations. Additionally, exploring the mechanisms underlying the observed therapeutic effects of these interventions could provide valuable insights into their mode of action.

CONCLUSION

In conclusion, holistic health emerges as a pivotal determinant for humanity's prosperity. Health literacy stands out as a robust predictor, surpassing other social or environmental factors. Naturopathy advocates for a holistic and drugless approach, prioritizing the minimization of pharmaceutical interventions while maximizing vitality. While numerous articles extol the benefits of drugless therapies, many lack scientific rigor in terms of sample size, design, and analytic methods. Future studies with larger population bases hold promise in establishing the efficacy of

natural, drugless methods, paving the way for a more comprehensive understanding and integration of holistic health practices into mainstream healthcare.

COMPETING INTERESTS

The authors report no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REVIEW ARTICLE

Effect of Nonpharmacological Methods on Pruritus in Patients with Liver Disease and Liver Cirrhosis: Systematic Review

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ABSTRACT

Background • Pruritus is a symptom that greatly affects the quality of life in patients with liver disease and liver cirrhosis. Since most pharmacological methods for itching have limited efficacy, there is a need to assess the effectiveness of nonpharmacological methods.

Purpose • This systematic review aims to examine the effects of nonpharmacological methods on itching in individuals with liver disease and liver cirrhosis.

Methods • PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) criteria were used as the basis for creating the systematic review protocol and writing the article. Studies were searched in "Scopus, Web of Science, PubMed, Cochrane Library, and CINAHL" databases, and studies from January 1, 2016, to January 1, 2024, were included in this systematic review. Studies were selected based on inclusion and exclusion criteria according to the PICOS method, and these studies included in the review were evaluated using the revised Joanna Briggs Institute (JBI) critical evaluation lists according to their types.

Results • Five randomized controlled trials with a total of 257 participants were included in this systematic review. While one of the studies was published in 2016, the others were published after 2016. The nonpharmacological interventions used in the studies consisted of baby oil, peppermint oil, clove oil, curcumin capsules, and ultraviolet light. In all five studies included in the review, it was found that nonpharmacological methods significantly reduced itching, with advantages such as being non-invasive, easy application, cheap, and very low toxicity and side effects.

Conclusions • Based on the findings, nonpharmacological methods have a positive effect on itching in individuals with liver disease and liver cirrhosis. It is recommended to conduct more studies with higher methodological quality, using larger sample groups, different interventions, randomization, and blinding methods, to examine the effectiveness of nonpharmacological methods in patients with liver disease and liver cirrhosis. (*Altern Ther Health Med.* 2024;30(4):42-46)

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INTRODUCTION

Liver cirrhosis is a chronic and progressive liver disease in which healthy liver cells turn into nodules and fibrous structures. [1,2] It is a global health problem due to its complications requiring hospitalization, deterioration in quality of life, and high mortality, and it is encountered more frequently today with the increase in the prevalence of obesity and alcohol consumption.[1,2] It is stated that 42% of patients with cirrhosis worldwide are due to Hepatitis B virus infection, 21% to Hepatitis C virus infection, and then excessive alcohol use. The highest prevalences are: it is stated that Hepatitis B virus infection occurs in the Western Pacific Region; Hepatitis C virus infection occurs in the Eastern Mediterranean; and for those who consume excessive alcohol, it occurs in Europe and America.[2]

It is clinically classified as compensated or decompensated. While non-obvious symptoms may be observed in compensated cirrhosis, major complications such as variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatopulmonary syndrome, and hepatic encephalopathy may develop as liver damage progresses in decompensated cirrhosis.[2,3] Therefore, it is important to prevent complications and improve prognosis with early diagnosis.[4] Individuals with liver cirrhosis may

experience different symptoms, such as pain, shortness of breath, muscle cramps, erectile dysfunction, insomnia, daytime sleepiness, fatigue, itching, anxiety, and depression. Due to the diversity of symptoms and the fact that these symptoms affect people's quality of life, timely intervention and approaches to alleviate symptoms are very important.[5]

Itching is a condition that occurs due to multiple etiologies and affects the quality of life of patients.[6,7] It is a common symptom, occurring in about 40.3% of liver cirrhosis patients.[5,8-10] The physiopathology of itching in individuals with cirrhosis is quite complex, and it is stated that many substances such as histamine, substance P, bile acids, and endogenous opioids accumulate in the blood and tissue and stimulate the neurons that cause itching.[11]

Currently, there are no medications that can completely cure itching in patients with liver cirrhosis, and this highlights the importance and need for nonpharmacological interventions.[10-12]

There is a lack of systematic review of nonpharmacological methods for addressing itching associated with liver disease and liver cirrhosis in the literature. It is envisaged that a systematic review can guide healthcare professionals to integrate nonpharmacological methods used in the management of itching associated with liver diseases and liver cirrhosis, and this fact motivates the current study. The main purpose of this study is to systematically examine the effects of nonpharmacological methods on the management of itching, which is one of the common symptoms of liver diseases such as liver cirrhosis.

METHODS

PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) was used as the basis for creating the systematic review protocol and writing the article.[13] To reduce the risk of potential bias, the literature search, article selection, data extraction, and study quality assessment were performed independently by two researchers. Thereafter, the independent evaluations made by the researchers were compared, and a consensus was reached by the third researcher.

Scanning Strategy

The searches were carried out through Pubmed, Scopus, Web of Science, CINAHL, and Cochrane Library databases in line with the English keywords determined by MeSH (Medical Subject Headings) terms. The screening was carried out between December 1 and December 31, 2023, using combinations of words and word groups such as "liver cirrhosis or cirrhosis or liver diseases," "pruritus or itch," "complementary therapy or complementary and alternative therapy," and "randomized controlled." Studies from January 1, 2016, to January 1, 2024, were included in this study. 5 studies were finally included in the systematic review from a total of 641 studies and the process of selection of studies is shown using the PRISMA flow diagram (Figure 1).

Figure 1. PRISMA Flow Chart of the Screening Process

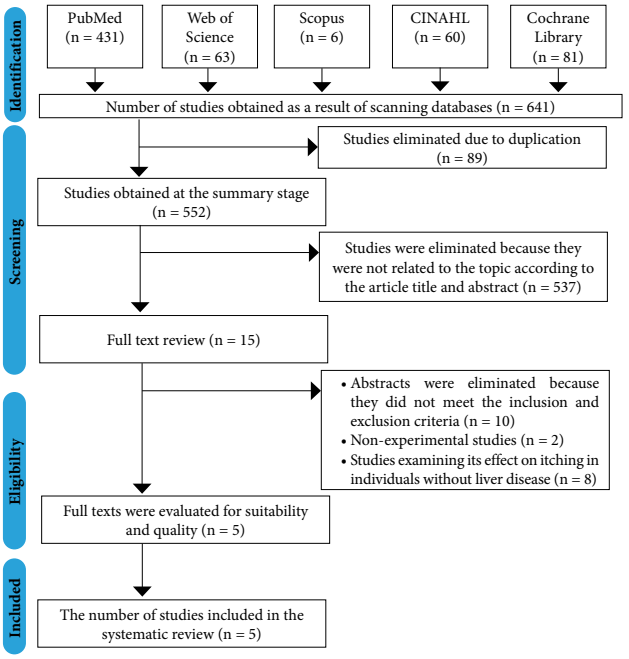

Table 1. Inclusion and Exclusion Criteria

	Inclusion criteria	Exclusion criteria
P	Patients with liver disease and liver cirrhosis	Patients without liver disease and liver cirrhosis
I	Patients to whom nonpharmacological methods were applied	Patients to whom pharmacological methods are applied
C	Studies where routine maintenance or a different intervention is applied	Studies where routine maintenance or comparison with a different method are not applied
O	Studies evaluating the results related to itching	Studies that did not report results regarding pruritus
S	Experimental studies in English with full text available	Non-experimental studies whose full text is not available, not in English

Inclusion and Exclusion Criteria

The selection of studies included in this systematic review was determined according to the inclusion criteria created by the PICOS (P = Population, I = Implementation, C = Comparison group, O = Outcome, S = Study design) method. Inclusion and exclusion criteria are detailed in Table 1.

Selection of Studies

In this systematic review, a total of 641 studies were found after scanning the databases. 89 of these studies were eliminated due to duplication. Upon title and abstract review, 537 studies were eliminated because they were irrelevant to the subject. After the full-text review, 10 studies were eliminated because they did not meet the inclusion and exclusion criteria. The choices made independently by two researchers were compared, and a consensus was reached by the third researcher. Finally, it was determined that only five experimental studies were conducted to determine the effect of nonpharmacological methods on itching in liver cirrhosis and liver diseases. The PRISMA flow diagram showing the selection process for studies is given in Figure 1.

Data Extraction and Analysis

A standard data extraction form was developed by the authors to summarize the data, and the data were evaluated

accordingly. With the data extraction form, data were collected about the authors of the studies included in the systematic review, the year, the place where the study was conducted, its design and methodology, context, sample size, and characteristics, the frequency of application of nonpharmacological methods, its duration, and the measurement tool.

Evaluation of Methodological Quality

The quality assessment of the studies was made independently by the first and second researchers. Then, the evaluations made by the researchers independently were compared, and a consensus was reached by the third researcher. Additionally, to evaluate the methodological quality of the studies in this review, the Joanna Briggs Institute (JBI) critical appraisal tool, revised by Barker and Stone for assessing the risk of bias in randomized controlled trials, was used.[14] This assessment tool consists of 13 items, and the total score varies between 0-13. For each item, the answer "yes" is evaluated as 1 point, and the answers "no," "unspecified," and "not appropriate" are evaluated as 0 points. A high score indicates high methodological quality in the research.[14]

RESULTS

Methodological Quality Assessment Results

Five studies[15-19] were selected for the systematic review and their methodological quality was assessed using the revised Joanna Briggs Institute (JBI) critical appraisal tool. From the evaluation of the studies, it was determined that the lowest score was six and the highest score was 12 (Table 2).

Table 2. Methodological Evaluation of Randomized Controlled Studies

Materials	Karadağ et al. 2022	Ibrahim et al. 2017	Nouri-Vaskeh et al. 2020	Kupsa et al. 2023	Elsaie et al. 2016
1. Was true randomization used to assign participants to treatment groups?	1	0	1	1	0
2. Were assignments to treatment groups hidden?	1	0	1	1	0
3. Were the experimental and control groups similar in terms of basic characteristics at the beginning of the study?	0	1	1	0	0
4. Were participants blinded to the treatment assignment?	1	0	1	1	0
5. Were the treatment providers blind to treatment assignment?	1	0	1	0	0
6. Were the outcome reviewers blinded to the treatment assignment?	0	0	0	0	0
7. Were the treatment groups treated the same except for the intervention?	1	1	1	1	1
8. Was follow-up completed, and if not, were there differences between groups? Have the tracking conditions been adequately defined and analyzed?	1	1	1	1	1
9. Were the participants analyzed in randomly selected groups?	1	1	1	1	1
10. Were outcomes measured in the same way for treatment groups?	1	1	1	1	1
11. Were the results measured reliably?	1	1	1	1	1
12. Was appropriate statistical analysis used?	1	1	1	1	1
13. Was the trial design appropriate, and were deviations from standard RCT design (individual randomization, parallel groups) taken into account in the conduct and analysis of the trial?	1	0	1	1	0
Total score	11	7	12	10	6

General Characteristics of Studies and Participants

In the systematic review, five studies with a sample size of 39-60 and a total of 257 participants were found suitable for review. Since the samples of three of these studies included diseases whose itching may develop due to more than one etiology (dermatological, hepatic, renal, diabetic problems, etc.), while our study was aimed at patients with liver disease and diagnosed with liver cirrhosis, so the relevant diseases were included, but not the entire sample. The sample size of two of the studies was 50 and that from the other studies was 39, 15, 16, and 6 people, were included based on the inclusion criteria of our study. All five of the studies included in the systematic review were randomized controlled trials. One of the studies included in the analysis was published in 2016, and the others were published after 2016. Studies were conducted in Iran (1), Turkey (1), Egypt (2), and Austria (1). In two of the included studies, the 5-Dimensional Itch Scale (5D-IS) was used alone to evaluate the severity of itching, while in another study, the 5-Dimensional Itch Scale (5D-IS) and the Visual Analogue Scale (VAS) were used together to accurately assess the level of itching; the Fatigue Severity Scale to measure fatigue; Four different measurement tools, including the Beck Anxiety Inventory, were used to evaluate the level of anxiety. Another study includes the Chronic Liver Disease Questionnaire (CLDQ), which evaluates chronic liver disease; the Liver Disease Symptom Index 2.0 (LDSI 2.0), which evaluates itching, one of the symptoms of liver disease; and the Short Form-36 Quality of Life (SF-36), which evaluates the quality of life. In the fifth study, itching and itch-related sleep disorders and subjective data were evaluated using the Visual Analogue Scale (VAS) (Table 3).

Features of Nonpharmacological Methods

In the studies included in the systematic review, information was provided about the application methods of nonpharmacological methods. In one of the studies, cooled baby oil (10-15°C) was applied to the itchy area once a day for 15 days at 15-minute intervals,[15] while in another study, patients were asked to apply topical clove oil to the itchy areas by hand after moisturizing their skin twice a day for 2 weeks, as per the instructions provided.[16] In one study, a total oral dose of 1000 mg/day capsule curcumin was taken twice a day for 12 weeks,[17] while in another study, the whole body was exposed to ultraviolet rays three times a week for 6 weeks.[18] In another study, patients were instructed to manually apply topical peppermint oil to the itchy areas twice a day for 2 weeks, after moisturizing their skin.[19] In one study, it was informed that the application should be done in the afternoon when itching is intense,[15] while in another study, information was given about taking curcumin with breakfast and dinner.[17] However, in other studies, no information was provided about when the practices were applied (Table 3).[16,18,19]

Comparison Group

In one of the studies examined, the control group received standard care,[15] while in two of the studies, the skin was moistened with vaseline.[16,19] In another study, the control group received a capsule similar to the curcumin capsule in terms of shape and color,[17] while in the fifth study, there was no control group.[18]

Table 3. Characteristics of Studies Examining the Effects of Nonpharmacological Methods on Itching Associated with Liver Disease and Liver Cirrhosis

Writer, publication year, country	Study pattern	Nonpharmacological Methods	Sample group and features	Intervention			Measurement Tool	Main findings
				Duration/ Amount	Frequency	Period		
Karadağ et al. (2022) Turkey	RCT	Baby oil	Intervention group: 30 Average age: 61.26 ± 8.95 years Female: 17 Male: 13 Control group: 30 Average age: 54.20 ± 51.85 years Female: 10 Male: 20	15 minutes	1 time/day	15 days	5D-IS VAS	At the end of the study, it was determined that there was a significant decrease in the average score of itching in the intervention group starting from the end of the 15th day. Itching – Pre-test average: Intervention 17.80 (2.52); Control 17.36 (2.18) Itching – Post-test average: Intervention 8.63 (1.03); Control 17.40 (1.92) Itching – *P* value: Intervention <.001; Control .393
Ibrahim et al. (2017) Egypt	RCT	Clove oil	Group 1: 25 Average age: 48.04 ± 11.46 years Female: 12 Male: 13 Group 2: 25 Average age: 50.76 ± 7.80 years Female: 12 Male: 13 Of these 50 people, 16 had liver disease, and 8 of these patients were assigned to Group 1 and the other 8 to Group 2.	-	2 times/day	2 weeks	5D-IS	In group 1, it was found that there was a significant decrease in the total 5D-IS score of patients with liver disease and pruritus after treatment. Itching – Before treatment: Group 1 24.8 ± 4.42; Group 2 23.67 ± 5.09 Itching – After treatment: Group 1 15.8 ± 8.02; Group 2 22.20 ± 6.73 Itching – *P* value: Group 1 .001; Group 2 0.02
Nouri-Vaskeh et al. (2020) Iran	RCT	Curcumin capsule	Curcumin group: 28 Average age: 46.00 ± 12.99 years Female: 14 Male: 14 Placebo group: 30 Average age: 46.40 ± 10.62 years Female: 14 Male: 16	1000 mg/day	2 times/day	12 weeks	LDSI 2.0 CLDQ SF-36	After the intervention, a significant reduction in itching was found in the curcumin group compared to the placebo group. Itching – Before treatment: Curcumin 1.48 ± 0.93; Placebo 1.45 ± 0.72 Itching – After treatment: Curcumin 1.07 ± 1.02; Placebo 1.82 ± 0.56 Itching – *P* value: Curcumin .003; Placebo <.001
Kupsa et al. (2023) Austria	RCT	Ultraviolet rays	NB-UVB group:20 Average age: 60.5 ± 16.6 years Female: 13 Male: 7 BB-UVB group:19 Average age: 64.9 ± 16.1 years Female: 11 Male: 8 Of these 39 people, six had liver disease, and it is unclear how these patients were assigned to the groups.	-	3 times/week	6 weeks	VAS	It has been determined that phototherapy is effective in reducing itching, and the reduction in itching is greater in NB-UVB than in BB-UVB. Itching – Before application: NB-UVB group 6.09 ± 2.81; BB-UVB group 6.13 ± 2.35 Itching – After application: NB-UVB group 2.42 ± 2.93; BB-UVB group 2.75 ± 2.28 Itching – *P* value: NB-UVB group NA; BB-UVB group NA
Elsaie et al. (2016) Egypt	RCT	Peppermint oil	Group 1: 25 Average age: 47.76 ± 8.23 years Female: 15 Male: 10 Group 2: 25 Average age: 50.76 ± 7.80 years Female: 12 Male: 13 Of these 50 people, 15 had liver disease, and 7 of these patients were assigned to Group 1 and the other 8 to Group 2.	-	2 times/day	2 weeks	5D-IS	In group 1, a significant improvement was detected in patients with liver disease and pruritus after treatment. Itching – Before treatment: Group 1 15.18 ± 3.55; Group 2 14.54 ± 2.09 Itching – After treatment: Group 1 7.94 ± 3.28; Group 2 13.47 ± 3.73 Itching – *P* value: Group 1 <.05; Group 2 >.05

Abbreviations: RCT, Randomized Controlled Study; 5D-IS, 5-D Itch Scale; VAS, Visual Analog Scale; LDSI 2.0, Liver Disease Symptom Index 2.0; CLDQ, Chronic Liver Disease Questionnaire; BB-UVB, Broadband-ultraviolet B; NB-UVB, Narrowband-ultraviolet B; NA, Not Available

Effect of Nonpharmacological Methods on Itching

In five of the five studies reviewed, it was found that nonpharmacological methods significantly reduced itching in liver cirrhosis and liver patients (Table 3).

DISCUSSION

In this systematic review, the effects of nonpharmacological methods applied to liver cirrhosis and liver patients on itching were examined. Five studies that met the inclusion criteria were included in the research.[15-19] The studies examined within the scope of the research included patients with different sample sizes and different evaluation scales. Thus, the samples of the studies included in the systematic review were heterogeneous. All of these may have affected the outcome of the study.

In all five of the studies included in the study, it was observed that nonpharmacological methods applied to liver cirrhosis and liver patients contributed positively to the management of itching. When the results obtained from the systematic review were compared with the literature, it was determined that nonpharmacological methods reduced itching in some studies conducted in different sample groups. Karadağ et al. (2014) reported that baby oil had a positive effect on itching, sleep quality, and quality of life in hemodialysis patients. It is thought that dry skin triggers itching, and the paraffin contained in baby oil moisturizes

the skin by creating a thin layer on the skin, thus reducing the itching symptom. It has also been emphasized that the application of cold may have a vasoconstrictor effect on blood vessels, reducing cell metabolism and nerve conduction speed, and thus interrupting the transmission of receptors that cause itching.[20] Portincasa et al. (2016) found that symptoms and quality of life were significantly improved in patients with Irritable Bowel Syndrome after a 1-month curcumin and fennel essential oil combination intervention.[21] It is stated that curcumin may also reduce liver damage and prevent the progression of liver cirrhosis with its anti-inflammatory effect.[17,22,23] Amjadi et al. (2012) concluded in their study that the combination of peppermint oil with sesame oil was effective in reducing the severity of itching in female patients with pruritus gravidarum.[24] Asih et al. (2021) emphasized in their study that the combination of peppermint, lavender, and turmeric oil can be used safely to treat itching in pregnant women.[25] It is thought that peppermint may relieve the itching sensation by activating the c-opioid receptor and A-delta fibers.[19] Regarding the use of clove oil as a topical agent alone or in combination with other agents in the treatment of itching, Ibrahim et al. (2017) in their study state that clove oil has a nerve conduction-blocking effect of 10-25% and can also prevent itching.[16] Wang et al. (2014) concluded in their study that narrow-band ultraviolet B phototherapy was effective in relieving kidney disease-related itching.[26] Phototherapy can be used as an effective method in treating chronic itching due to its anti-inflammatory effect.

The number of studies evaluating the effect of nonpharmacological methods in the management of itching associated with liver disease and liver cirrhosis is quite limited in the literature. Compared to pharmacological methods, nonpharmacological methods used to control itching associated with liver disease and liver cirrhosis have various advantages, such as being non-invasive, easy to use, safe, cheap, and having very low toxicity and side effects. In summary, current studies show that nonpharmacological methods can be applied by healthcare professionals to address itching problems in patients.

Limitations

A limitation of this systematic review is that only studies conducted in English and pertinent to our topic were included, while studies conducted in other languages were excluded. Additionally, the sample sizes and evaluation tools used in the studies included in our systematic review varied.

CONCLUSION

Based on the studies included in the systematic review, nonpharmacological methods have been found to have a positive effect on itching in individuals with liver disease and liver cirrhosis. However, since the number of studies evaluating the effect of nonpharmacological methods in the management of itching associated with liver disease and liver cirrhosis is limited, it is recommended to conduct more studies on the topic with higher methodological quality, using larger sample groups, different interventions, randomization, and blinding methods. In addition, based on the included studies, it is recommended that nurses include nonpharmacological methods in their care interventions to manage itching symptoms in patients with liver disease and liver cirrhosis.

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AUTHOR DISCLOSURE STATEMENT

The authors declare that they have no competing interests.

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ORIGINAL RESEARCH

Minimally Invasive Surgery for Spontaneous Intracerebral Hemorrhage With or Without Intraventricular Hemorrhage

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ABSTRACT

Objective • The treatment effect of minimally invasive surgery (MIS) for spontaneous intracerebral hemorrhage (sICH) remains controversial. Intracerebral hemorrhage patients with intraventricular hemorrhage (IVH) seemingly have a worse prognosis. So we aim to verify the efficacy of MIS for small and medium cerebral hemorrhage (15-30ml) using the propensity score matching (PSM) method which could reduce the heterogeneity, and further analyze the different treatment effects of MIS for sICH with or without IVH.

Methods • We collected the data of patients with sICH from January 2016 to March 2021 retrospectively. The propensity score matching method was used to compare the clinical outcomes of surgery and conservative treatments. The primary outcome was neurological prognosis. The second outcomes were the rate of complications, length of stay, and hospitalization expenses. Furthermore, we use the binary logistic regression analysis to explore the influence of MIS on patients' prognosis.

Results • For all sICH patients, the Modified Rankin Scale (MRS) and Glasgow Outcome Scale (GOS) of the surgery group were worse than those of the conservative group. The length of stay (P = .001), hospitalization expenses (P < .01), pneumonia incidence (P < 0.01), and history of tracheotomy (P = .002) of the surgery group were higher than those of the conservative group. For sICH patients without IVH, the GOS and MRS of surgery patients were statistically better than those of conservative patients at 3 months. The length of stay (P = .046), hospitalization expenses (P < .001), and pneumonia incidence (P < .001) of the surgery group were also higher than the conservative group. Binary logistic analysis showed that MIS is the protective factor for patients' neurological function, especially for intracerebral hemorrhage patients without IVH (OR = 66.636).

Conclusions • For small and medium cerebral hemorrhage, stereotactic puncture drainage minimally invasive surgery could result in better functional outcomes, especially for the sICH patients without IVH.Nevertheless, surgery cannot reduce the occurrence of complications, hospitalization length, and expenses. (*Altern Ther Health Med.* 2024;30(4):47-53)

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INTRODUCTION

Over 1 million people are suffering from spontaneous intracerebral hemorrhage (sICH) worldwide yearly. Approximately 30% to 55% of patients die within 1 month after onset, and the people who survive largely have different degrees of neurological sequelae.[1,2] Theoretically, removing the hematoma from the brain can relieve the mass effect of hematoma and the brain edema that results from the blood product breakdown. Both of these factors result in neurological function impairment.[3,4]

Surgical treatment for sICH is controversial. The findings from the STICH(surgical trial in intracranial hemorrhage) I and STICH II tests[5,6] suggest that when compared with conservative treatment, surgical treatment cannot improve the prognosis of patients with neurological function and mortality. However, in the STICH II study, the patients who have a superficial hematoma without intraventricular hemorrhage would own a survival advantageThe conventional craniotomy can help remove the hematoma, however, the brain may be damaged. The surgery benefits may outweigh the risks of surgery.[7,8] Minimally invasive surgery for sICH including stereotactic aspiration, endoscopic surgery, craniopuncture, etc. may bring more benefits for sICH patients. In these procedures, blood is eliminated, and there is less brain injury.[9]

However, it remains unclear which MIS or conservative treatment is better. MIS cannot result in the absolute removal of the hematoma. Furthermore, MIS, especially when the drainage pipe is used, may cause intracranial infection.[10] At present, the Minimally Invasive Surgery Plus rt-PA for ICH Evacuation (MISTIE) II study has proved that the MIS+rt-PA (alteplase) was safe with an apparent better neurological functional outcome at 180 days with ICH ≥ 20 ml. However, asymptomatic rebleeding is the major cautionary finding. The MISTIE III study proved that MIS couldn't bring better outcomes for ICH ≥ 30 ml while it could improve the mortality obviously.[11,12] Clinically, we have performed many stereotactic aspiration surgical procedures for patients with sICH. From what we have observed, the infection and the rebleeding of the drainage pipe are less likely due to the pipe's small size and the shortened rentention time. In addition, the blood can be cleared away effectively. Nevertheless, the heterogeneity of subjects in previous experiments may have influenced the treatment effect of MIS.

PSM is a statistical method primarily used for subgroup analysis of observational clinical studies or clinical trial research data. It can effectively reduce confounding bias and achieve similar effects as randomized controlled trials throughout the entire study design phase. In subgroup analysis of observational clinical studies and RCT research, due to various reasons, biases and confounding variables are more prevalent. PSM can effectively reduce the impact of these biases and confounding variables, enabling a more reasonable comparison between the observation group and the control group.Therefore, we sought to further explore the treatment effect of stereotactic aspiration surgery in a retrospective observational study using the propensity score matching (PSM) method which could reduce the heterogeneity between the surgery and conservative group.[13] We aimed to compare the treatment effect of MIS and conservative treatment for patients with small to medium sICH (15–30 mL). Furthermore,the IVH could result in an inflammatory response in subepidermal and epidermal tissue layers, which could influence the circulation of cerebralspinal fluid and result in hydrocephalus.[14-16] In view of this, the sICH patients with IVH may have worse outcomes than these patients without IVH. So, we want to further explore the difference in treatment effect of MIS for the sICH patients with or without IVH. Our reserach is the study in the real world, and it is the supplement of the Randomized controlled trial. We aims to compare the treatment effect of MIS and conservative treatment for patients with small to medium sICH and investigate whether IVH has a differential impact on these treatments.

MATERIALS AND METHODS

Study Design

This retrospective cohort study aimed to compare the clinical outcomes of surgery and conservative treatment for sICH patients using PSM. This study has two parts. In the first part, we collected the data of sICH patients with or without intraventricular hemorrhage (IVH) from the electronic medical records of the hospital neurosurgery department. Patients who were treated between January 2016 and March 2021 were included. In the second part, we excluded the data of patients who had IVH, which was determined based on computed tomography (CT) findings. Patients were divided into surgery and conservative groups depending on the operating records.

In addition, we collected data on age; sex; admission time; hematoma volume and location; Glasgow coma scale (GCS) score, presence of IVH, re-hemorrhage, and complications; history of tracheotomy; history of hypertension, diabetes, cerebral infarction; hematoma volume, edema, and the total mass effect at 3, 7 and, 14 days after onset; length of stay; hospitalization expenses; Glasgow outcome scale (GOS) and modified rankin scale (MRS) at 2weeks,1 month and 3months after onset.

Patients

The inclusion criteria were as follows: (1) diagnosis of spontaneous hemorrhage in the basal ganglion with or without IVH of the brain, as detected via CT; (2) presence of hemorrhage with a volume of 15 to 30 mL; (3) age ranging from 18 to 80 years; (4) hemorrhagic duration from the onset of the stroke to arrival at the hospital ≤ 24 h; (6) a GCS of 7 to 15 upon arrival at the hospital.

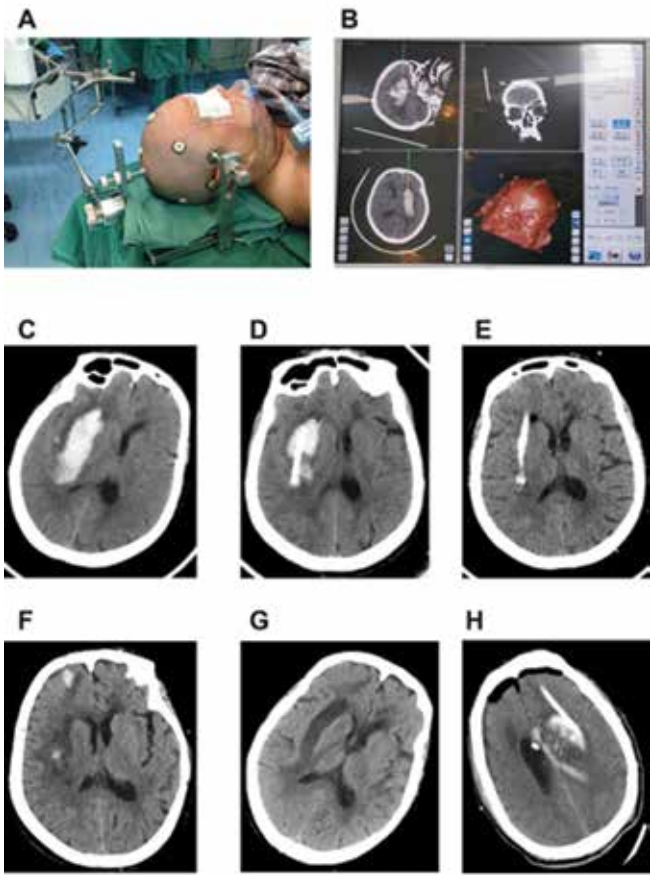
Contrastingly, the following were the exclusion criteria: (1) a previous history of stroke with obvious neurological dysfunctions; (2) hematoma caused by secondary causes, such as an arteriovenous malformation, intracranial tumor, or aneurysm,etc; and (3) surgical contraindications ; (4) severe renal or hepatic dysfunction and terminal brain hernia, which was manifested by bilateral pupil dilation and central respiratory circulatory failure; and (5) incomplete data.

Treatment

All sICH patients received standard medical treatment, which aimed to decrease intracranial pressure, control blood pressure, and prevent complications. Dehydrating drug was administered based on the clinical conditions of these patients. The medical management provided was in accordance with the recommendations of the American Heart Association and American Stroke Association (AHA/ASA) guidelines and clinical experience.[17]

In each case, most of the ICH was cleared using the puncture needle. The needle had small holes at the end to allow lysis fluid infusion and the drainage of the hematoma. The puncture site was based on the patients' three-dimensional reconstruction of CT scans to avoid important functional domains and blood vessels. The puncture needle was fixed onto the skull after the needle was located in the center of the hematoma (Figures 1A and 1B).[18] Lysis fluid was then injected to dissolve the residual hematoma. The main component of the lysis fluid was urokinase (10 000–50 000 U everyday based on the volume of the hemorrhage). A CT scan was performed

Figure 1. (A) The device of the stereotactic puncture drainage. (B) The navigation picture during the surgery. (C) The head CT before surgery. (D) The head CT on the first day after surgery. (E) The head CT on the third day after surgery. (F) The head CT on the Seventh day after surgery. (G) The head CT on the Fourteenth day after surgery. (H) The sICH with IVH patients accept hematoma drainage and external ventricular drainage

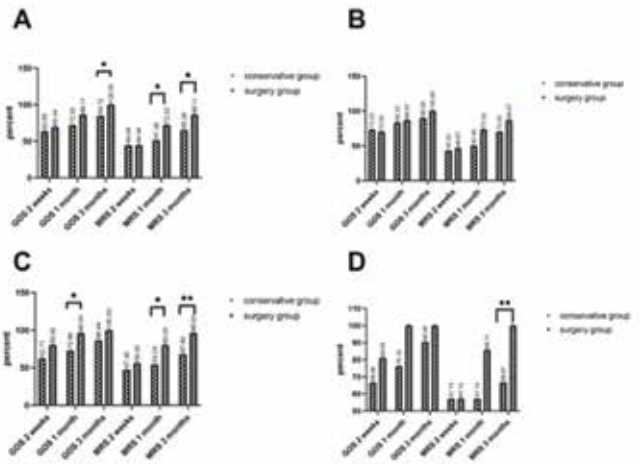


immediately after the procedure and again1,3,7 and 14 days thereafter to ascertain the location of the puncture needle and to evaluate the volume of the remaining blood. The drainage needle was retained in the brain for 3 to 5 days and then removed to reduce the chance of infection. For sICH patients with IVH, we would do the external ventricular drainage depending on the amount of bleeding in the cerebral ventricles and the degree of ventricles obstruction (Figure 1H). Patients who received MIS were provided with routine medical treatment and the medical treatment between the two groups is identical.

Outcomes and Data Collection

All relevant clinical information about admission, hospitalization, and discharge, including clinical signs and symptoms, medical history, and CT scans, which showed the volume of hematoma before surgery (Figure 1C), the volume of the residual hematoma, edema, and total mass effect at 1, 3, 7, and 14 days after surgery, (Figures 1D, 1E, 1F, and 1G), were extracted from emergency and hospitalization charts.

Figure 2. (A) The percent of the MRS (0-2) and GOS (4-5)in the unmatched Conservative Versus Surgery Cohort of all sICH patients at two weeks, one month, and three months. (B) The percent of the MRS (0-2) and GOS (4-5) in the matched Conservative Versus Surgery Cohort of all sICH patients at two weeks, one month, and three months. (C) The percent of the MRS (0-2) and GOS (4-5) in the unmatched Conservative Versus Surgery Cohort of sICH patients without IVH at two weeks, one month, and three months. (D) The percent of the MRS (0-2) and GOS (4-5) in the matched Conservative Versus Surgery Cohort of sICH patients without IVH at two weeks, one month, and three months.



The hematoma volume was measured depending on the CT scan. The formula ABC*0.8/2 was used, in which A was the greatest diameter of the hemorrhage measured on CT, B was the diameter perpendicular to A, and C was the approximate number of 8 mm CT slices with hemorrhage.[19] The total mass effect was calculated by the same formula including the volume of the hematoma and the edema around the hematoma. The edema volume is the difference value between the total mass effect volume and the hematoma volume. The patients' conscious disturbances were evaluated using the GCS on admission. The primary outcomes were neurological functional status, including the GOS and MRS scores of the survivors at 14 days, 1, and 3 months post-ictus. We defined GOS (4–5) and MRS (0–2) as favorable neurological functions, and we collected the percentage of favorable neurological function in the four different groups (Figures 2A, 2B, 2C, and 2D). The secondary outcomes included the occurrence of complications, length of stay, and hospitalization costs. In addition, we also explore the different neurological prognosis improvements of MIS for all sICH patients, sICH patients with IVH, and sICH patients without IVH.

Statistical Analyses

The Statistic Package for Social Science (SPSS) statistics version 22.0 (IBM Corporation, Armonk, New York, USA) was used to analyze the data. Parts of the figures were created using GraphPad Prism 9.0 (GraphPad Software, La Jolla, CA, USA). One-to-one matching analysis was performed between

Table 1. Characteristics and outcomes of all the sICH patients in the conservative and surgery groups before PSM

Variables	Conservative group (n = 72)	Surgery group (n = 36)	statistics	*P* value
male (1/0)	52/20	24/12	0.355 (χ^2)	.551
Age,y, (SD)	59.21 (12.15)	52.53 (10.86)		.006
Time ictus,h, (SD)	6.25 (4.38)	5.14 (5.33)		.25
GCS, (mean rank) (z)	58.52	46.46	z=-1.927	.054
Hematoma location (left)	33/39	15/21	0.169 (χ^2)	.681
Hematoma volume, (SD)	20.06 (5.15)	23.81 (5.79)		.001
With IVH	13/59	11/25	2.17 (χ^2)	.141
History				
Hypertension	65/7	35/1	1.68 (χ^2)	.194
Diabetes mellitus	3/69	1/35	0.13 (χ^2)	.719
Previous stroke	6/66	2/34	0.27	.603
Hematoma 3th day	19.74 (9.76)	13.51 (8.14)		.001
Edema 3th day	14.23 (19.41)	9.90 (5.88)		.085
Total mass effect 3th day	33.97 (28.16)	23.41 (8.69)		.004
Hematoma 7th day	14.88 (11.31)	10.14 (9.06)		.031
Edema 7th day	20.19 (20.83)	13.79 (9.46)		.03
Total mass effect 7th day	35.08 (29.18)	23.93 (11.89)		.006
Hematoma 14th day	7.53 (5.86)	5.29 (4.79)		.049
Edema 14th day	24.70 (23.98)	17.40 (9.66)		.027
Total mass effect 14th day	32.23 (27.84)	22.69 (11.73)		.014
Rebleeding	3/33	8/64	0.202 (χ^2)	.653
Complication				
Pneumonia	5/67	23/13	40.524 (χ^2)	<.001
Need for tracheotomy	0/72	10/26	20.041 (χ^2)	<.001
Neurological function status				
GOS (mean rank, two weeks)	51.42	60.65	z=1.549	.121
GOS (mean rank, one month)	47.97	67.56	z=3.289	.001
GSO (mean rank, three months)	46.89	69.72	z=3.981	<.001
MRS (mean rank, two weeks)	55.68	52.14	z=-0.57	.569
MRS (mean rank, one month)	60.44	42.46	z=-2.843	.004
MRS (mean rank, three months)	61.62	40.25	z=-3.442	.001
GOS (4-5 two weeks)	46/26	25/11	0.329 (χ^2)	.566
GOS (4-5 one month)	52/20	31/5	2.602 (χ^2)	.107
GOS (4-5 three months)	61/11	36/0	6.124 (χ^2)	.015
MRS (0-2 two weeks)	32/40	16/20	0 (χ^2)	1
MRS (0-2 one month)	37/35	26/10	4.286 (χ^2)	.038
MRS (0-2 three months)	47/25	31/5	5.192 (χ^2)	.024
Length of stay, day, (SD)	17.85 (5.55)	30.17 (17.72)		<.001
Hospitalization expenses	49327.08 (5813.2)	57753.17 (9625.5)		<.001

Abbreviations: SD, Standard Deviation; Time ictus means the time from the onset to admission; Hematoma location (left) means the hematoma is in the left hemisphere; IVH, Intraventricular Hemorrhage; mean rank was calculated by the rank sum test; GOS 4-5 and MRS 0-2 were reckoned the favorable neurological function.

Table 2. Characteristics and outcomes of all the sICH patients in the conservative and surgery groups after PSM

variables	Conservative group (n = 30)	Surgery group (n = 30)	statistics	*P* value
male (1/0)	23/7	20/10	0.739 (χ^2)	.39
Age,y, (SD)[a]	52.07 (8.19)	54.83 (10.14)		.25
Time ictus,h, (SD)	6.17 (4.65)	5.43 (5.78)		.59
GCS, (mean rank) (z)	34.07	26.93	z=1.622	.105
Hematoma location (left)	13/17	13/17	0 (χ^2)	1
Hematoma volume, (SD)[a]	20.93 (6.09)	22.53 (5.51)		.29
With IVH	6/24	9/21	0.8 (χ^2)	.371
History				
Hypertension	27/3	29/1	1.071 (χ^2)	.612
Diabetes mellitus	2/28	1/29	0.351 (χ^2)	1
Previous stroke	2/28	2/28	0 (χ^2)	1
Hematoma 3th day	19.37 (7.08)	12.53 (7.24)		<.001
Edema 3th day	12.37 (14.96)	10.09 (5.86)		.442
Total mass effect 3th day	31.74 (20.88)	22.62 (8.54)		.033
Hematoma 7th day	14.21 (7.00)	9.77 (8.25)		.028
Edema 7th day	18.62 (19.41)	14.00 (9.91)		.252
Total mass effect 7th day	32.83 (25.05)	23.77 (11.91)		.008
Hematoma 14th day	7.14 (4.37)	5.31 (4.57)		.119
Edema 14th day	25.36 (24.95)	17.11 (9.27)		.098
Total mass effect 14th day	32.50 (28.00)	22.42 (11.06)		.007
Rebleeding	3/30	3/30	0 (χ^2)	1
Complication				
pneumonia	0/30	19/11	27.81	<.001
Need for tracheotomy	0/30	8/22	9.231	.002
Neurological function status				
GOS (mean rank, two weeks)	28.57	32.43	z=0.919	.358
GOS (mean rank, one month)	25.03	35.97	z=2.641	.008
GOS (mean rank, three months)	23.7	37.3	Z=3.477	.001
MRS (mean rank, two weeks)	31.35	29.65	Z=-0.39	.697
MRS (mean rank, one month)	35.82	25.18	Z=-2.412	.016
MRS (mean rank, three months)	37.05	23.95	Z=-2.998	.003
GOS (4-5 two weeks)	22/8	21/9	0.082	.774
GOS (4-5 one month)	25/5	26/4	0.131	1
GOS (4-5 three months)	27/3	30/0	3.158	.237
MRS (0-2 two weeks)	13/17	14/16	0.067	.795
MRS (0-2 one month)	15/15	22/8	3.455	.063
MRS (0-2 three months)	21/9	26/4	2.455	.209
Length of stay, day, (SD)	17.57 (4.76)	30.10 (17.99)		.001
Hospitalization expenses	24390 (10605.7)	81894.87 (61924.6)		<.001

[a]Data were matched between the two groups with the Propensity Score Matching Method

the surgical and conservative groups based on the estimated propensity scores of each patient to reduce the selection bias of the retrospective observational studies.

To adjust for baseline differences, the two cohorts were matched without replacement in a 1:1 ratio with a caliper of 0.03 using propensity scores derived from the baseline characteristic comparisons using the method of maximizing execution performance. A secondary analysis involving the ICH patients without IVH was subsequently performed. Patients with IVH were excluded from this secondary analysis, and the surgery and conservative cohorts were matched without replacement in a 1:1 ratio also with a caliper of 0.03. Statistical significance was defined as $P < .05$, and all tests were two-tailed. Binary logistic regression analysis was performed to explore the influence of MIS on patients' prognosis, including all the sICH patients, sICH patients with IVH, and sICH patients without IVH. The MRS and GOS were assessed by neurosurgeons working in the same department who don't know patients' baseline information. Student's *t* test or Wilcoxon's ranked sum test was used to compare continuous variables. Pearson's chi-square test or Fisher's exact test was used to compare categorical variables.

RESULTS

Characteristics and outcomes of ICH Patients before and after PSM

Before PSM, a total of 108 sICH patients were enrolled in our study. The surgery group included 36 patients and the conservative group included 72 patients. Table 1 shows the comparison of the baseline demographic, clinical, and radiographic characteristics of the unmatched surgery group versus the conservative group.

The PSM was done using the covariate of age and hematoma volume with a matching tolerance of 0.03. The matched covariates were well-balanced between the two cohorts. After PSM, a total of 60 sICH patients were enrolled in our study. The surgery group included 30 patients and the conservative group included 30 patients.

Table 2 shows the comparison of the baseline information of the matched surgery group versus the conservative group.

Second Analysis of the ICH Patients without IVH

After excluding 24 patients with IVH, the secondary analysis of ICH patients without IVH comprised 59 patients who received conservative treatment and 25 patients who received surgical treatment. Table 3 shows the comparison of

Table 3. Characteristics and outcomes of the sICH without IVH patients in the conservative and surgery groups before PSM.

Variables	Conservative group (n = 59)	Surgery group (n = 25)	statistics	*P* value
male (1/0)	43/16	18/7	0.007 (χ^2)	0.934
Age,y, (SD)	59.34 (12.18)	50.24 (10.71)		0.002
Time ictus,h, (SD)	6.24 (4.36)	5.76 (6.05)		0.685
GCS, (mean rank) (z)	43.33	40.54	Z=-0.49	0.624
Hematoma location (left)	27/32	10/15	0.237 (χ^2)	0.627
Hematoma volume, (SD)	20.54 (5.07)	23.84 (6.05)		0.012
History				
Hypertension	54/59	24/25	0.53 (χ^2)	.664
Diabetes mellitus	2/57	0/25	0.868 (χ^2)	1
Previous stroke	5/54	1/24	0.530 (χ^2)	.664
Hematoma 3th day	20.04 (9.80)	10.89 (6.69)		<.001
Edema 3th day	14.56 (19.52)	10.82 (5.75)		.184
Total mass effect 3th day	34.60 (28.19)	21.70 (8.78)		.002
Hematoma 7th day	14.23 (8.56)	8.72 (8.46)		.008
Edema 7th day	20.90 (20.34)	15.50 (10.63)		.116
Total mass effect 7th day	35.14 (26.11)	24.22 (12.60)		.012
Hematoma 14th day	7.31 (4.39)	4.57 (4.56)		.012
Edema 14th day	24.82 (21.79)	18.74 (10.45)		.088
Total mass effect 14th day	32.13 (23.98)	23.31 (12.87)		.032
Rebleeding	7/52	3/22	0 (χ^2)	1
Complication				
pneumonia	0/59	14/11	39.648 (χ^2)	<.001
Need for tracheotomy	0/59	4/21	9.912 (χ^2)	.001
Neurological function status				
GOS (mean rank, two weeks)	38.37	52.24	Z=2.552	.011
GOS (mean rank, one month)	35.85	58.2	Z=4.142	<.001
GSO (mean rank, three months)	37.03	55.4	Z=3.518	<.001
MRS (mean rank, two weeks)	44.86	36.92	z=-1.407	.159
MRS (mean rank, one month)	48.28	28.86	z=-3.405	.001
MRS (mean rank, three months)	49.08	26.96	z=-3.922	<.001
GOS (4-5 two weeks)	37/22	20/5	2.406 (χ^2)	.135
GOS (4-5 one month)	43/16	24/1	5.814 (χ^2)	.017
GOS (4-5 three months)	51/8	25/0	3.747 (χ^2)	.098
MRS (0-2 two weeks)	28/31	14/11	0.513 (χ^2)	.474
MRS (0-2 one month)	32/27	20/5	4.942 (χ^2)	.03
MRS (0-2 three months)	40/19	24/1	7.70 (χ^2)	.005
Length of stay, day, (SD)	17.81 (5.16)	24.20 (13.98)		.035
Hospitalization expenses	32744. (54180.0)	53074.4 (45634.56)		.016

the baseline information between the unmatched conservative group and the surgery group without IVH.

Table 4 shows the comparison of the baseline demographics and clinical and radiographic characteristics between the matched conservative group and the surgery cohorts using the covariates of hematoma volume and age with a caliper of 0.03. The matched covariates were well-balanced between the two cohorts.

Binary logistic regression analysis for prognosis of ICH patients

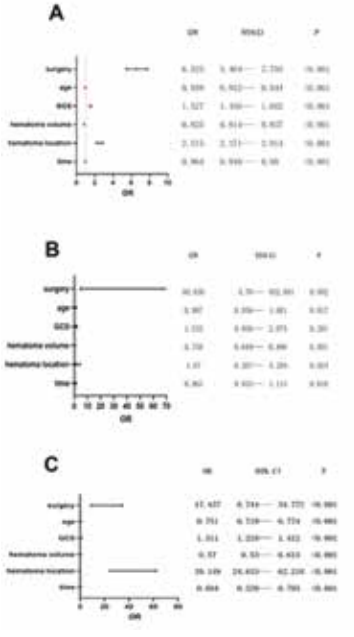
A binary logistics regression model was formulated to evaluate the value of surgery for the ICH patients' neurological prognosis. The outcome indicator was patients' MRS (0-2) at 3 rd month after onset. We made the model in all sICH patients, sICH patients without IVH, and sICH patients with IVH. We found that, for all sICH patients, patients' age, hematoma volume, and the time from onset to the hospital were the disadvantage factors for patients' prognosis while Surgery was the protective factor for patients' outcome (OR=6.525 95% CI 5.464- 7.793). For sICH patients without IVH, hematoma volume was the hazard for patients' prognosis while surgery was the protective factor for patients' neurological function (OR=66.636 95% CI 4.76-932.881). For sICH patients with IVH, surgery was also the protective factor with OR=17.437 95% CI 8.744-34.772 (Figure 3).

Table 4. Characteristics and outcomes of sICH patients without IVH in the conservative and surgery groups after PSM

variables	Conservative group (n = 21)	Surgery group (n=21)	statistics	*P* value
male (1/0)	15/6	15/6	0 (χ^2)	1
Age,y, (SD)[a]	49.67 (7.01)	52.62 (9.73)		.266
Time ictus,h, (SD)	5.81 (4.76)	5.10 (5.14)		.643
GCS, (mean rank) (z)	20.62	22.38	Z=0.476	.634
Hematoma location (left)	8/13	9/12	0.099 (χ^2)	1
Hematoma volume, (SD)[a]	20.29 (5.69)	22.57 (5.78)		.204
History				
Hypertension	18/3	21/0	3.231 (χ^2)	.232
Diabetes mellitus	0/21	0/21	0 (χ^2)	1
Previous stroke	0/21	1/20	1.024 (χ^2)	1
Hematoma 3th day	18.18 (7.18)	11.24 (6.89)		.002
Edema 3th day	11 (13.97)	10.52 (5.96)		.089
Total mass effect 3th day	29.43 (19.84)	21.76 (8.79)		.012
Hematoma 7th day	13.52 (6.42)	9.38 (8.94)		.092
Edema 7th day	17 (18.32)	15.38 (11.36)		.073
Total mass effect 7th day	30.52 (23.52)	24.76 (13.13)		.033
Hematoma 14th day	7.57 (4.83)	4.90 (4.71)		.078
Edema 14th day	25.76 (24.19)	19.33 (10.75)		.028
Total mass effect 14th day	33.33 (27.17)	22.57 (5.78)		.009
Rebleeding	2/19	3/18	0.227 (χ^2)	1
Complication				
pneumonia	0/21	13/8	18.82 (χ^2)	<.001
Need for tracheotomy	0/21	3/18	3.231 (χ^2)	.232
Neurologicalfunctionstatus				
GOS (mean rank, two weeks)	18.93	24.07	1.445 (χ^2)	.148
GOS (mean rank, one month)	16.79	26.21	2.767 (χ^2)	.006
GSO (mean rank, three months)	16.86	26.14	2.921 (χ^2)	.003
MRS (mean rank, two weeks)	22.62	20.38	-0.618	.537
MRS (mean rank, one month)	25.86	17.14	-2.359	.018
MRS (mean rank, three months)	26.67	16.33	-2.855	.004
GOS (4-5 two weeks)	14/7	17/4	1.109 (χ^2)	.484
GOS (4-5 one month)	16/5	21/0	5.676 (χ^2)	.48
GOS (4-5 three months)	19/2	21/0	2.1 (χ^2)	.488
MRS (0-2 two weeks)	12/9	12/9	0 (χ^2)	1
MRS (0-2 one month)	12/9	18/3	4.2 (χ^2)	.085
MRS (0-2 three months)	14/7	21/0	8.4 (χ^2)	.009
Length of stay, day, (SD)	18.14 (5.40)	25.29 (14.93)		.046
Hospitalization expenses	23499.24 (10975.2)	66145.24 (48491.6)		<.001

[a]Data were matched between the two groups with the Propensity Score Matching Method

Figure 3. (A)The hazard of all sICH patients' baseline information for neurological prognosis. (B) The hazard of sICH without IVH patients' baseline information for neurological prognosis. (C) The hazard of sICH with IVH patients' baseline information for neurological prognosis.



DISCUSSION

Our study focused on the treatment effect of stereotactic hematoma aspiration for intracranial hemorrhage. In the present study, we found that patients with hematoma of 15–30 mL who received MIS had better neurological outcomes, especially the ICH patients without IVH.

Although surgical treatment can result in the removal of the hematoma and reduction of the toxicity of the blood-breaking product, many previous studies showed that sICH patients receiving surgical treatment did not have better outcomes.[5,6] Most neurosurgeons attributed these results to the additional brain injury caused by the surgery.[7] Except for additional brain injury and complications caused by surgery, unbalanced factors such as hematoma volume or coma scale between the two groups may also undervalue the surgical effect because patients in the surgery group always had a larger hematoma volume and a more severe coma.[19] Considering these results, we adopted the PSM method to reduce the confounding factors between the surgery and conservative groups. To date, few studies have used the PSM method to evaluate the surgical treatment for sICH. Zheng et al. performed a PSM study to observe the treatment effect of surgery for sICH patients; however, they used craniotomy or neuro-endoscopy in their study.[19] Hence, in our study, the PSM method was employed to observe the treatment effect of MIS.

For all sICH Patients with or without IVH, before data were matched, we found that the surgery group had a larger hematoma volume, was younger than the conservative group, and had a worse coma scale calculated by GCS (though the $P = .054$). After the data matched, the hematoma volume, age, and GCS were balanced between the two groups. Based on the volume of the 3rd-day hematoma, we found that the MIS surgery could effectively remove the hematoma. Furthermore, the drainage tube might have released some toxicants, including iron ions and oxygen free radicals, which induced brain edema.[20] We found that, before and after the PSM, the total mass effect of the surgery group on days 3, 7, and 14 after onset was smaller than those in the conservative group.

Before the PSM, we found that the surgery group had a better outcome at one month (MRS 0-2) and three months (MRS 0-2, GOS4-5). However, after PSM, the MIS surgery didn't appear the improvemet effect on patients' prognosis (MRS 0-2 ,GOS 4-5) (figure 2A and 2B). When we used the Wilcoxon rank sum test to compare the neurological function between the two groups, we found that the neurological function of the surgery group was better than the conservative group at one month, and three months before or after PSM. We think that the difference was due to the different statistical methods. The Pearson χ^2 test results mainly reflected the proportion of favorable neurological function, while the Wilcoxon rank sum test reflected the overall distribution of the neurological function. Therefore, we believe that, for all sICH Patients with or without IVH, the favorable outcome (MRS 0–2 or GOS 4–5) in the surgery group was not better than that in the conservative group. However, the overall neurological function outcomes of the surgery group were better than those of the conservative group at 1rd and 3rd month after onset and the improvement in neurological function may be attributed to the eliminated mass effect by surgery which is related to patient's prognosis.[21,22]

Previous studies[6,16,22] showed that sICH patients with IVH may have worse outcomes due to the following mechanisms: acute obstructive hydrocephalus, delayed chronic hydrocephalus, and toxicity of the blood-breaking product. Considering the extra brain impairment of the IVH, so, we further deleted the data of sICH patients with IVH to merely explore the treatment effect of stereotactic hematoma extra-drainage surgery for cerebral parenchymal hemorrhage. For ICH without IVH, the hematoma volume and age were matched between the conservative and surgery groups. We observed that the total mass effect at 3 rd, 7th and 14rd in the surgery group was less than the conservative group before or after PSM. Furthermore, before PSM, our study found that the neurological function of the surgery group at 1rd month (MRS 0-2, GOS 4-5) and 3rd month (MRS 0-2) were better than the conservative group. After PSM, the surgery group also had a better outcome at 3rd month (MRS 0-2) (figure 2C and 2D). Then, we made a further binary logistic analysis to explore the hazard related to patients' neurological function. We found that MIS is the protectative factor for the neurological function of all ICH patients (OR=6.525), ICH patients with IVH (OR=17.437) and ICH patients without IVH (OR=66.636) (figure 3). That is to say, the MIS surgery appears more curative effect for ICH patients without IVH than all the ICH patients with or without IVH. Previous studies have shown that patients with intraventricular bleeding presented an increased number of clinical and neurological complications, worse outcome, higher mortality rates, and longer hospitalization.[24,25] So, we think that the IVH might cover up the treatment effect of MIS and the MIS could bring better neurological prognosis for ICH patients without IVH.

Some studies indicated that the use of a drainage tube may increase the risk of infection and urokinase usage may increase the risk of re-bleeding.[10,26] However, in our study, we found that the rate of intracranial infection and the rate of rebleeding between the two groups were not significantly different. We believe that strict aseptic operation and a suitable dosage of urokinase can prevent infection and rebleeding.

While MIS may offer benefits in terms of functional outcomes, it does not reduce complications, hospitalization length, or expenses because of the complications.

CONCLUSIONS

For small and medium cerebral hemorrhage, stereotactic puncture drainage minimally invasive surgery could result in better functional outcomes, especially for the sICH patients without IVH. Nevertheless, surgery cannot reduce the occurrence of complications, hospitalization length, and expenses.MIS may be a beneficial choice for some spontaneous hemorrhage patients without IVH. However, further detailed research is still needed especially for the IVH patients. More

effective surgery treatment is needed to explore to improve the prognosis of sICH patients with or without IVH.

Limitations

First, this article was a single-center retrospective cohort study that used propensity score matching. A potential selective bias still existed, although it was greatly reduced and future prospective trials are needed to confirm the present conclusions.

Second, the sample size was not large enough to provide compelling evidence. Especially, we didn't make the comparison between the surgery and the conservative group of the ICH patients with IVH because of the limited number of these patients.

Third, our follow-up time was short. Further longer follow-up periods are needed. Besides, the cases that were lost to follow-up would also bring bias.

ETHICAL COMPLIANCE

We only collected the medical information of patients, and our study had no adverse effects on the patients. Therefore, our study's protocol was approved by the ethics committee of the Jinshan Hospital, Fudan University. The ethical approval number is JIEC 2022-S95.

CONFLICT OF INTEREST STATEMENT

We haven't submitted this article elsewhere for publication, in whole or in part, and all the authors listed have approved the manuscript that is enclosed. We declare that this article has not been submitted to other journals and the content of this article was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

YuFeng Yan was the leader of this study, mainly involved in experimental design and manuscript writing. Meng Liu and Lijun Fan were mainly involved in the data collection and draft writing. Xu Zhang and Xuhui Fan mainly took part in the data analysis and paper revision.

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ORIGINAL RESEARCH

Correlation Analysis of Serum 3-NT, NPASDP-4, and S100β Protein Levels with Cognitive Function in Patients Diagnosed with Cerebral Infarction

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ABSTRACT

Objective • To observe the levels of serum 3-nitrotyrosine (3-NT), neuronal PAS domain protein 4 (NPASDP-4), and S100β protein in patients diagnosed with cerebral infarction and analyze their correlation with cognitive dysfunction in these patients.

Methods • The study included a cohort of 158 patients suffering from cerebral infarction who were admitted to the Liwan District Hospital of Traditional Chinese Medicine between January 2021 and December 2022. After stabilizing vital signs, all patients underwent the Montreal Cognitive Assessment (MoCA) to assess their cognitive function. Based on the assessment results, they were divided into two groups: the cognitive dysfunction group (121 cases) and the normal cognitive function group (37 cases). The baseline characteristics and serum levels of 3-NT, neuronal PAS domain protein 4 (NPASDP-4), and S100β protein were compared in the patient cohorts. Furthermore, the correlation between these three indicators and cognitive function in patients suffering from cerebral infarction was analyzed. A logistic regression model was constructed to analyze how serum levels of 3-NT, NPASDP-4, and S100β protein levels affected cognitive function in patients suffering from cerebral infarction. ROC curve analysis was conducted to assess the predictive value of serum 3-NT, NPASDP-4, and S100β protein levels for cognitive function in patients suffering from cerebral infarction.

Results • Among the 158 patients with cerebral infarction, 121 (76.58%) had cognitive dysfunction, while 37 (23.42%) had normal cognitive function. The levels of 3-NT, NPASDP-4, and S100β protein were found to be significantly higher in the cognitive dysfunction group compared to the normal cognitive function group (t = 5.788, 7.774, 6.460; P = .000, .000, .000). The point-biserial correlation analysis results showed a positive correlation between serum levels of 3-NT, NPASDP-4, and S100β protein and the occurrence of cognitive dysfunction in patients suffering from cerebral infarction (r=0.420, 0.529, 0.424; P = .000, .000, .000). The logistic regression model demonstrated that serum levels of 3-NT(95%*CI*: 1.299-2.603), NPASDP-4(95%*CI*: 1.487-3.386), and S100β protein(95%*CI*: 1.153-8.746) were risk factors for cognitive dysfunction in patients suffering from cerebral infarction (*OR*=1.839, 2.244, 1.429; P = .001, .000, .240). ROC curve analysis demonstrated that serum 3-NT, NPASDP-4, and S100β protein levels exhibited a certain predictive value for cognitive function in patients with cerebral infarction (AUC = 0.789, 0.881, 0.820).

Conclusion • Serum levels of 3-NT, NPASDP-4, and S100β protein are closely related to the cognitive function of patients with cerebral infarction, and abnormal changes in these levels may exacerbate cognitive dysfunction in these patients. (*Altern Ther Health Med.* 2024;30(4):54-59)

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INTRODUCTION

Cerebral infarction is a common clinical cerebrovascular disorder characterized by a high incidence rate, disability rate, and mortality rate. Its main clinical manifestations include facial paralysis, language impairments, sensory deficits, etc., which can lead to varying degrees of cognitive

dysfunction in patients.[1,2] Studies have indicated that cognitive function affects limb function, social activities, and overall well-being in patients with cerebral infarction.[3] Therefore, accurate assessment of cognitive function in such patients and the timely implementation of corresponding interventions are of great significance for improving the prognosis. 3-nitrotyrosine (3-NT) is a protein oxidation product and serves as an important marker for evaluating oxidative stress levels in clinical settings.[3] Relevant research has highlighted the critical role of 3-NT in the occurrence and progression of unstable atherosclerotic plaques and is also one of the key contributing factors in the progression of ischemic brain diseases.[4] Neuronal PAS domain protein 4 (NPASDP-4) is a transcription factor that regulates neuronal growth and development, particularly playing a crucial role in inhibitory synapse development and participating in stress-induced hippocampal damage, leading to cognitive impairment.[5,6] S100β protein belongs to calcium-binding acidic proteins and is widely distributed in glial cells of the central nervous system, capable of reflecting early brain injury conditions.[7] Based on the above research, it is inferred that serum levels of 3-NT, NPASDP-4, and S100β protein may play a certain role in cognitive impairment in patients with cerebral infarction. Therefore, this study aimed to examine the levels of serum 3-NT, NPASDP-4, and S100β protein in patients suffering from cerebral infarction and analyze their correlation with cognitive dysfunction. The purpose is to provide a reference for the early evaluation of cognitive function and the formulation of treatment plans for patients with this condition. The results of the study are presented below.

MATERIALS AND METHODS

Study Subjects

A cohort of 158 patients with cerebral infarction were admitted to the Liwan District Hospital of Traditional Chinese Medicine between January 2021 and December 2022 were included in the study. Inclusion criteria were as follows: (1) Patients with cerebral infarction meeting the relevant diagnostic criteria outlined in *Diagnostic Essentials of Various Cerebrovascular Diseases*[8] and confirmed by imaging examination; (2) First onset of cerebral infarction; (3) Patients with clear consciousness and normal cognitive function before the onset of the disease; (4) Patients whose vital signs stabilized after acute-phase treatment; (5) Patients or their family members provided informed consent and were willing to cooperate in the study. Exclusion criteria were as follows: (1) History of cranial or brain trauma; (2) Concomitant central nervous system infections, hydrocephalus, intracranial tumors, or subarachnoid hemorrhage; (3) Coexisting psychiatric disorders such as mental retardation, bipolar disorder, schizophrenia, anxiety disorder, or depression; (4) Coexisting thyroid dysfunction or other endocrine system disorders; (5) History of abuse of antipsychotic drugs; (6) Coexisting malignant tumors or other severe diseases.

Methods

Cognitive Function Assessment. After stabilizing the vital signs of the patients, the cognitive function of the patients was evaluated using the Montreal Cognitive Assessment (MoCA).[9] The MoCA consists of seven domains: naming (3 points), orientation (6 points), delayed recall (5 points), language (3 points), attention (6 points), visuospatial and executive abilities (5 points), and abstraction (2 points), resulting in a total score of 30 points. A higher score reflects better cognitive function. Following the study by Gong Juan et al.,[10] individuals with a score of less than 26 points will be considered to have cognitive impairment, while those with a score of 26 points or higher will be considered to have normal cognitive function. Out of the 158 patients with cerebral infarction, 121 cases (76.58%) experienced cognitive dysfunction, while 37 cases (23.42%) had normal cognitive function.

Detection of Serum Levels of 3-NT, NPASDP-4, and S100β Protein

Upon admission, each patient underwent venipuncture to collect a 4ml blood sample and then subjected to centrifugation at 3500 rpm for 15 minutes to isolate the upper layer, which contains the serum. The levels of 3-NT, NPASDP-4, and S100β protein were determined using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA). The test kits used were from Wuhan Huamei Biotech Co., Ltd., and all relevant procedures were strictly carried out according to the instructions provided with the test kits.

Outcome Measures

(1) The cognitive function status in patients with cerebral infarction was observed after stabilizing their vital signs. (2) Patients who developed cognitive dysfunction were included in the cognitive dysfunction group, while patients with normal cognitive function were included in the normal cognitive function group. Baseline data were compared within the two groups, including gender (male, female), age, body mass index (BMI), underlying conditions (diabetes, hypertension, hyperlipidemia), smoking history (yes, no), alcohol consumption history (yes, no), and blood lipid levels [total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C)]. Blood samples for lipid level measurements were collected in sterile tubes containing anticoagulants, inverted 5-10 times to mix thoroughly, and then analyzed using an automated biochemistry analyzer (Beckman Coulter, AU5800) to measure TC, TG, LDL-C, and HDL-C levels. (3) Comparison of serum levels of 3-NT, NPASDP-4, and S100β protein between the two groups.

Statistical analysis

Data processing was conducted using Statistic Package for Social Science (SPSS) version 23.0 software (IBM, Armonk, NY, USA). Measurement data were presented as $\bar{x} \pm s$ and analyzed using *t* tests. Count data were presented as n (%) and

Table 1. Comparison of Baseline Characteristics between the Cognitive Dysfunction Group and Normal Cognitive Function Group

Indicators		Cognitive Dysfunction Group (n = 121)	Normal Cognitive Function Group (n = 37)	Statistical values	*P* value
Gender(%)	Male	63 (52.07)	20 (54.05)	χ^2=0.045	.832
	Female	58 (47.93)	17 (45.95)		
Age ($\bar{x} \pm s$, year)		64.86±5.73	65.12±6.08	t=0.238	.812
BMI ($\bar{x} \pm s$, kg/m^2)		25.78±2.13	25.89±2.21	t=0.273	.786
Underlying conditions (%)	Diabetes	17 (14.05)	3 (8.11)	χ^2=0.447	.504
	Hypertension	39 (32.23)	8 (21.62)	χ^2=1.526	.217
	Hyperlipidemia	21 (17.36)	5 (13.51)	χ^2=0.304	.581
Smoking history(%)	Yes	32 (26.45)	7 (18.92)	χ^2=0.864	.353
	No	89 (73.55)	30 (81.08)		
Alcohol consumption history(%)	Yes	28 (23.14)	6 (16.22)	χ^2=0.804	.370
	No	93 (76.86)	31 (83.78)		
TC ($\bar{x} \pm s$, mmol/L)		4.94±0.87	4.86±0.82	t =0.496	.621
TG ($\bar{x} \pm s$, mmol/L)		1.61±0.63	1.58±0.60	t =0.256	.798
LDL-C ($\bar{x} \pm s$, mmol/L)		3.02±0.75	2.97±0.71	t =0.359	.720
HDL-C ($\bar{x} \pm s$, mmol/L)		1.38±0.48	1.43±0.53	t =0.541	.589

analyzed using the χ^2 test. The correlation between categorical variables and continuous variables was analyzed using point-biserial correlation analysis. A logistic regression model was constructed to assess the influence of serum levels of 3-NT, NPASDP-4, and S100β protein on cognitive function in patients suffering from cerebral infarction. ROC curve analysis was conducted to assess the predictive value of serum levels of 3-NT, NPASDP-4, and S100β protein for cognitive function in patients suffering from cerebral infarction. Statistical significance was set at $P < .05$ for all analyses.

RESULTS

Comparison of Baseline Characteristics between the Cognitive Dysfunction Group and Normal Cognitive Function Group

No statistically significant differences were observed in baseline characteristics, including gender, age, body mass index (BMI), underlying conditions, smoking history, alcohol consumption history, TC, TG, LDL-C, and HDL-C between the normal cognitive function group and the cognitive dysfunction group ($P > .05$). (Table 1)

Comparison of Serum Levels of 3-NT, NPASDP-4, and S100β Protein between the Cognitive Dysfunction Group and Normal Cognitive Function Group

The cognitive dysfunction group had significantly higher levels of 3-NT, NPASDP-4, and S100β protein compared to the normal cognitive function group ($P < .05$). (Table 2 and Figure 1)

Correlation between Serum Levels of 3-NT, NPASDP-4, and S100β Protein and Cognitive Function in Patients Suffering from Cerebral Infarction

The point-biserial correlation analysis results indicated that serum levels of 3-NT, NPASDP-4, and S100β protein showed a positive correlation with the occurrence of cognitive dysfunction in patients suffering from cerebral infarction ($r > 0$, $P < .05$). (Table 3 and Figure 2)

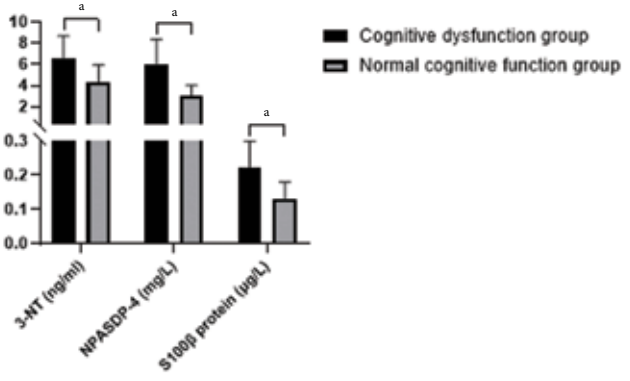
Table 2. Comparison of Serum Levels of 3-NT, NPASDP-4, and S100β Protein between the Cognitive Dysfunction Group and Normal Cognitive Function Group ($\bar{x} \pm s$)

Groups	3-NT (ng/ml)	NPASDP-4 (mg/L)	S100β Protein (μg/L)
Cognitive Dysfunction Group (n=121)	6.51±2.17	6.04±2.32	0.22±0.08
Normal Cognitive Function Group (n=37)	4.26±1.69	2.98±1.04	0.13±0.05
t	5.788	7.774	6.460
P value	.000	.000	.000

Indicators	Cognitive Dysfunction Group (n = 121)	Normal Cognitive Function Group (n = 37)	t	*P* value
3-NT (ng/ml)	6.51±2.17	4.26±1.69[a]	5.788	.000
NPASDP-4	6.04±2.32	2.98±1.04[a]	7.774	.000
S100β Protein (μg/L)	0.22±0.08	0.13±0.05[a]	6.460	.000

[a]Compared to the cognitive dysfunction group, $P < .05$

Figure 1. Comparison of Serum Levels of 3-NT, NPASDP-4, and S100β Protein between the Cognitive Dysfunction Group and Normal Cognitive Function Group.



[a]$P < .001$

Table 3. Correlation between Serum Levels of 3-NT, NPASDP-4, and S100β Protein and Cognitive Function in Patients Suffering from Cerebral Infarction (r/P).

Indicators	r	*P* value
3-NT	0.420	.000
NPASDP-4	0.529	.000
S100β Protein	0.424	.000

Figure 2. Correlation between Serum Levels of 3-NT, NPASDP-4, and S100β Protein and Cognitive Function in Patients Suffering from Cerebral Infarction.

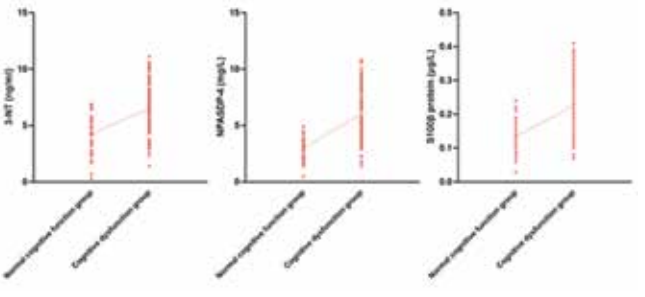


Table 4. Impact of Serum Levels of 3-NT, NPASDP-4, and S100β Protein on Cognitive Function in Patients with Cerebral Infarction

Independent variables	*β*	Standard error	*Wald* χ^2	*P* value	*OR*	95%*CI*
3-NT	0.609	0.177	11.789	.001	1.839	1.299-2.603
NPASDP-4	0.808	0.210	14.809	.000	2.244	1.487-3.386
S100β Protein	16.195	3.386	22.879	.000	1.429	1.153-8.746
Constant	-1.656	1.409	1.382	.240	0.191	-

Figure 3. Clinical Feature Forest Plot Based on Multivariate Logistic Regression Analysis.

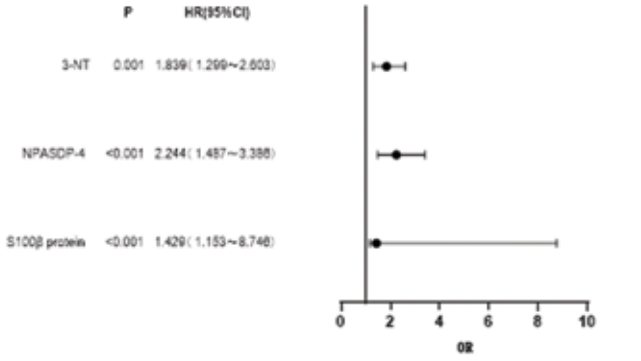


Figure 4. ROC Curve of Serum Levels of 3-NT, NPASDP-4, and S100β Protein for Predicting Cognitive Function in Patients Suffering from Cerebral Infarction.

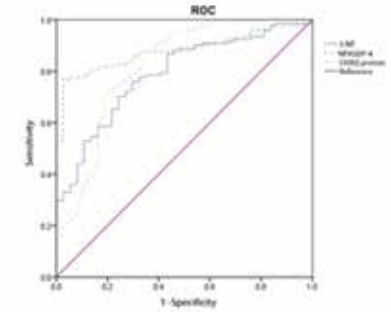


Table 5. Predictive Value of Serum Levels of 3-NT, NPASDP-4, and S100β Protein for Cognitive Function in Patients with Cerebral Infarction.

Test variables	AUC	Standard error	*P* value	95%*CI*	cut-off value	Sensitivity	Specificity	Jaccard Index
3-NT	0.789	0.040	.000	0.711-0.867	4.820 ng/ml	0.785	0.649	0.434
NPASDP-4	0.881	0.027	.000	0.828-0.933	3.660 mg/L	0.860	0.703	0.563
S100β Protein	0.820	0.045	.000	0.732-0.908	0.165 μg/L	0.802	0.676	0.478

Impact of Serum Levels of 3-NT, NPASDP-4, and S100β Protein on Cognitive Function in Patients Suffering from Cerebral Infarction

Using serum levels of 3-NT, NPASDP-4, and S100β protein as independent variables (all considered as continuous data) and the cognitive function status of patients with cerebral infarction as the dependent variable (1 = cognitive dysfunction, 0 = normal cognitive function), a logistic regression model was established. The results showed that serum levels of 3-NT(95%*CI*: 1.299-2.603), NPASDP-4(95%*CI*: 1.487-3.386), and S100β protein (95%*CI*: 1.153-8.746) were risk factors for cognitive dysfunction in patients with cerebral infarction (*OR* >1, *P* < .05). (Table 4 and Figure 3)

Predictive Value of Serum Levels of 3-NT, NPASDP-4, and S100β Protein for Cognitive Function in Patients Suffering from Cerebral Infarction

Using serum levels of 3-NT, NPASDP-4, and S100β protein as test variables and the cognitive function status of patients with cerebral infarction as the state variable (1=cognitive dysfunction, 0=normal cognitive function), ROC curves were generated (Figure 4). The results showed that serum levels of 3-NT, NPASDP-4, and S100β protein had certain predictive value for cognitive function in patients with cerebral infarction (AUC=0.789, 0.881, 0.820). (Table 5)

DISCUSSION

Mechanisms of Cognitive Dysfunction in Patients Suffering from Cerebral Infarction

Cognitive function refers to an individual's ability to perceive, acquire, store, and intelligently process information, including language comprehension, calculation, memory, executive functions, and so on. Cognitive dysfunction, on the other hand, refers to the pathological process in which the above functions are impaired, resulting in a single or a series of functional changes.[10] After the occurrence of cerebral infarction, a large area of infarction can lead to abnormal brain cortical structure and function. The cerebral cortex is the higher center of consciousness in the brain, and damage to the cortex will inevitably lead to impairment of consciousness, thereby causing varying degrees of cognitive dysfunction.[11] In recent years, advancements in medical technology have led to a reduction in the mortality rate of patients with cerebral infarction. However, the number of patients with cognitive dysfunction has gradually increased. If effective intervention measures are not taken promptly, cognitive dysfunction can progress to dementia. Therefore, early assessment of cognitive function in patients suffering from cerebral infarction is of great significance in guiding subsequent treatment.

Relationship between Serum 3-NT Levels and Cognitive Function in Patients Suffering from Cerebral Infarction

Oxidative stress plays an important role in cerebral amyloid angiopathy, cerebral dysfunction, and cerebral arteriosclerosis. Oxidative stress can disrupt the metabolism of nitric oxide, which is dependent on vascular endothelial cells, thereby affecting cerebral vascular relaxation function and disrupting the balance between pro-inflammatory and anti-inflammatory responses, as well as oxidative and antioxidative processes, leading to cerebral vascular damage.[12,13] 3-NT is a relatively stable marker used in clinical assessment of oxidative stress, and it accurately reflects the level of oxidative stress in the body.[14] Previous studies have suggested that 3-NT promotes atherosclerosis and is involved in the formation of unstable plaques.[15] The study findings demonstrated that patients with cerebral infarction and

cognitive dysfunction had significantly elevated serum levels of 3-NT compared to those with normal cognitive function. Furthermore, the findings of point-biserial correlation analysis confirmed a positive correlation between 3-NT levels and the occurrence of cognitive dysfunction in patients with cerebral infarction. In other words, higher serum 3-NT concentrations were associated with more severe cognitive dysfunction in patients. As a product of oxidative stress, 3-NT can directly affect the denaturation of intracellular proteins and proteinases, damage DNA, induce chronic inflammatory reactions, disrupt the blood-brain barrier, aggravate cerebral vascular dysfunction, and lead to the necrosis and apoptosis of cholinergic neurons and other intracranial neurons, ultimately affecting cognitive function in patients.

Relationship between Serum NPASDP-4 Levels and Cognitive Function in Patients Suffering from Cerebral Infarction

NPASDP-4 is mainly present in the hippocampal tissue as an activity-dependent transcription factor. It plays a vital regulatory role in various processes, including synaptic plasticity transcriptional regulation, dendritic cell skeleton formation, and neuronal cell survival in the hippocampal tissue, exhibiting certain neuroprotective effects.[16] Under the action of intracellular calcium ions (Ca2+), NPASDP-4 can selectively induce inhibitory synapse formation and regulate function-dependent genes, promoting the restoration of inhibitory synapses under pathological conditions.[17] An animal study conducted by Laurence[18] suggested that the level of NPASDP-4 in neurons is related to cognitive function in mice. The study findings indicated that the serum levels of NPASDP-4 were elevated in the cognitive dysfunction group compared to the normal cognitive function group. Moreover, the logistic regression analysis indicated that elevated serum NPASDP-4 levels were a risk factor for the occurrence of cognitive dysfunction in patients with cerebral infarction. After cerebral infarction, the brain tissue experiences severe hypoxia and ischemia, leading to the release of a large amount of excitatory amino acids at abnormal concentrations, causing ion influx into neurons and neuronal damage, thereby triggering the expression of NPASDP-4. However, NPASDP-4 can further aggravate brain hypoxia and ischemia in patients with cerebral infarction, severely disrupting the physiological and psychological balance of the body, inhibiting the generation of neuronal cells, causing morphological changes in the hippocampal tissue, and consequently resulting in cognitive dysfunction.

Relationship between Serum S100β Protein Levels and Cognitive Function in Patients Suffering from Cerebral Infarction

S100β protein is primarily produced by astrocytes in the central nervous system and is a major component of glial cell cytoplasm. It participates in the regulation of various biological functions, accurately reflecting glial cell function, and has an impact on the interaction between glial cells and neurons. Additionally, the S100β protein can regulate the levels of inflammatory cytokines and nitric oxide synthase, thereby modulating neuronal inflammatory damage.[19,20] A study by Ozturk et al.[21] demonstrated a significant association between S100β protein levels and cognitive dysfunction following robot-assisted laparoscopic radical prostatectomy. Other research also indicated that serum S100β protein levels in patients suffering from cognitive dysfunction following cerebral infarction when compared to those with normal cognitive function, and these studies also established a strong correlation between serum S100β protein levels and cognitive function in these patients.[22] The study findings indicated that the cognitive dysfunction group exhibited significantly higher serum S100β protein levels than the normal cognitive function group. Moreover, elevated serum S100β protein levels were identified as a risk factor for cognitive dysfunction in patients suffering from cerebral infarction, which aligns with the findings of the aforementioned studies. Under normal physiological concentrations, S100β protein has inhibitory effects on glutamate toxicity and acts as an antioxidant, promoting axonal growth and repair in neurons and exerting neuroprotective effects. However, when S100β protein levels are abnormally elevated, it can become neurotoxic, exacerbate oxidative stress and inflammatory responses, and cause neuronal death and cell apoptosis. During the occurrence of cerebral infarction, the disruption of the blood-brain barrier, central nervous system demyelination, activation and proliferation of brain glial cells, neuronal damage, and spontaneous inflammatory reactions may lead to an increase in S100β protein content in cerebrospinal fluid, which then enters the bloodstream. This process triggers a cascade of events, including the release of a large amount of calcium ions (Ca2+), elevated nitric oxide levels, and the generation of free radicals and other harmful substances, ultimately leading to neuronal apoptosis and cognitive dysfunction. Finally, the ROC curve analysis confirmed that serum levels of 3-NT, NPASDP-4, and S100β protein can serve as predictors for cognitive function in patients suffering from cerebral infarction. The mechanism underlying cognitive impairment in patients with cerebral infarction is complex. Clinically, early prediction of the risk of cognitive dysfunction can be achieved by observing serum markers such as 3-NT, NPASDP-4, and S100β protein. High-risk patients can then be actively treated with neurotrophic drugs and neuroprotective agents to prevent the occurrence of cognitive dysfunction.

In conclusion, serum levels of 3-NT, NPASDP-4, and S100β protein are closely related to the cognitive status of patients with cerebral infarction. Abnormal changes in the levels of these markers can exacerbate cognitive dysfunction in patients. Clinically, the observation of serum 3-NT, NPASDP-4, and S100β protein levels can serve as a predictive indicator for patients' cognitive function and take early intervention measures to improve patient prognosis.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

ZX, XW, and MG designed the study and performed the experiments, LC, DL, and FZ collected the data, SC, YZ, and HH analyzed the data, and ZX, XW, and MG prepared the manuscript. All authors read and approved the final manuscript.

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This study did not receive any funding in any form.

ETHICAL COMPLIANCE

This study was approved by the ethics committee of Fifth Clinical Medical College, Guangzhou University of Chinese Medicine. Signed written informed consent was obtained from the patients and/or guardians.

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META-ANALYSIS

Meta-Analysis of Metformin on Recurrence Risk and Long-Term Survival in Patients with Diabetes and Renal Cell Carcinoma

Kai Xu, MM; Yinyin Ying, MM

ABSTRACT

Objective • To evaluate the effect of metformin on the survival of patients with diabetes mellitus complicated with renal cell carcinoma by Meta-analysis.

Methods • To collect the required data, we looked through the databases of the Cochrane Library, PubMed, and EMBASE, as well as the network for querying registration data from clinical trials (https://clinicaltrials.gov). Retrieve relevant ongoing or closed clinical trials. To avoid publication bias, the search process is limited to randomized controlled trials, and the search results are not limited to language, publication time, or other restrictions. All included studies need to be evaluated according to the quality evaluation standard of the Cochran system evaluation manual. The relevant data were statistically analyzed by Revman 5.3 software. In the evaluation of overall survival (OS) and progression-free survival (PFS), the index of hazard risk (HR) was selected in this paper.

Results • Eight cohort studies were included in the analysis. Partial and metastatic subgroup analysis of renal cell carcinoma demonstrated no significant effect of metformin on PFS, CSS, or OS. There was no evidence of publication bias, according to the findings.

Conclusion • This systematic review and meta-analysis found that metformin did not improve survival rates for diabetic patients with renal cell carcinoma. (*Altern Ther Health Med.* 2024;30(4):60-65)

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INTRODUCTION

Renal cell carcinoma is a highly malignant and most common tumor in the urinary system. It is a malignant tumor originating from the renal parenchyma and ureteral epithelial system, also known as renal adenocarcinoma, which accounts for roughly 80% to 90% of all kidney cancers.[1] Renal cell carcinoma accounts for 2%-3% of adult malignant tumors and about 20% of genitourinary malignant tumors in China, according to relevant surveys, ranking just behind bladder tumors as the most common genitourinary tumor.[2] The prevalence of renal cell carcinoma is twice as high in men as in women and increases with age, according to available data.[3] According to statistics, the peak age for developing renal cell carcinoma is between 40 and 55. On the other hand, the prevalence of diabetes has grown over time, paralleling the rise of modern society and modern ways of living. It has become another non-infectious chronic disease that endangers human health. At present, the prevalence rate of diabetes is about 11% in China. The effects of diabetes and its complications on patients' health and longevity are tragic. Although the mechanism is unclear, several studies have revealed that people with diabetes have a higher-than-average prevalence of cancer and a poorer-than-average prognosis for their malignancy.[4] It may be related to hyperglycemia, hyperinsulinemia, application of some hypoglycemic agents, or chronic inflammation in diabetic patients. The commonly used hypoglycemic drugs in the clinic include insulin and its analogs; Biguanides, such as metformin; Insulin-secreting agents, such as glibenclamide; α- Glucosidase inhibitors, such as acarbose; Insulin sensitizers, such as pioglitazone.[5] Metformin's favorable hypoglycemic effect, low rate of side effects, and its affordable price have led to its widespread use as a sound therapy for type 2 diabetes.[6]

Many studies have highlighted that the kidney is a targeted organ in patients with diabetes mellitus (DM), which is a common chronic disease in patients with renal cell carcinoma. The prevalence of DM was found to be high in the early-stage renal cell cancer population analyzed by surveillance and SEER (11 190 individuals).[7] At the same

time, the diagnosis of DM is also related to the high probability of renal cell carcinoma. A recent meta-analysis of 97 studies showed that 820 900 patients reported a moderate association between renal cancer mortality and DM diagnosis. Several indicators of poor overall survival of renal cell carcinoma in patients with DM, including tumor recurrence, were found in the Surveillance, Epidemiology, and End Results (SEER) Program database analysis. In contrast, other studies have found that people with DM and renal cell cancer have lengthy lifetimes. It is unclear how DM affects individuals with renal cell carcinoma's long-term prognosis. Some studies have shown that high glucose (Hg) can significantly enhance the proliferation and migration of renal cell carcinoma cells.[8] Metformin is now widely accepted as a first-line therapy option for people with type 2 diabetes (T2DM) and it has even gained international recognition. Evans et al proposed metformin can reduce the incidence of cancer in diabetic patients. The potential antitumor effect of metformin has attracted the attention of researchers at home and abroad. Metformin is a well-tolerated derivative of bi-guanide, which can regulate blood glucose levels and reduce the risk of DM complications.[9] Population-based studies have shown that diabetic patients who take metformin have a better prognosis for cancer treatment and a lower risk of developing cancer. Some in vitro and ex vivo studies have demonstrated the ability of metformin to fight tumor breast, colorectal, and prostate cancer and other tumor cells. The mechanism is that metformin can act on the cell cycle, activate apoptotic signaling pathways, promote apoptosis of cancer cells, or make the cell cycle stagnate, thereby inhibiting the proliferation of tumor cells.[10] Compared with other hypoglycemic drugs, metformin can delay or even reverse the drug resistance of tumors and improve the prognosis of tumor patients. Metformin affected the prognosis of patients with stage II–IV renal cell carcinoma treated with first-line chemotherapy, according to retrospective research. The prognosis of individuals with renal cell carcinoma is still dismal despite advancements in surgical techniques, radiotherapeutic approaches, and novel chemotherapy medicines.[11] Therefore, it is necessary to emphasize the development of new methods to improve the effectiveness of current treatment. Some published studies have reported that metformin treatment can improve the survival of patients with DM; However, many inconsistencies have been found in the existing literature.[12] Therefore, we did a systematic assessment and meta-analysis to offer trustworthy and up-to-date evidence of the effect of metformin treatment on the survival of patients with renal cell carcinoma and further examine its association based on histological subgroups.

METHODS

literature retrieval strategy

We searched the Cochrane Library, PubMed, and EMBASE. Two researchers searched independently from the establishment of the database to September 2016. The retrieval words include metformin, renal cell carcinoma, diabetes mellitus, survival rate, and prognosis. English search terms include "metformin", "renal cell carcinoma", "kidney carcinoma", "survival", and "diagnosis". Subject words and free words work together in the retrieval approach. To avoid publication bias, the search process is limited to randomized controlled trials, and the search results are not limited to language, publication time, or other restrictions. At the same time, we also searched the clinical trial data query registration website (https://clinicaltrials.gov)To retrieve relevant ongoing or closed clinical trials. For the retrieved review literature, further consult the references to avoid missing literature as much as possible.

literature selection and inclusion

Independently, our two researchers screened all the literature. The inclusion criteria were as follows: (1) All patients were untreated patients with renal cell carcinoma; (2) The exposure factor was Metformin; (3) All included studies were randomized controlled prospective studies; (4) The endpoint was the prognosis or mortality of renal cell carcinoma; (5) The literature provides hazard ratio (HR) or other information that can calculate HR, such as Cox regression curve. Before entering the full-text screening link, the two researchers performed a preliminary screening based on the titles, abstracts, and types of studies contained in the aforementioned literature. If the retrieved research does not meet the above requirements, it will be excluded, and the corresponding exclusion reasons will be given. Specific exclusion criteria: (1) Inclusion of randomized controlled prospective clinical studies in patients with non-renal cell carcinoma; (2) Clinical studies that are in progress or whose results have not been published; (3) Clinical studies with repeated publication of research data. If there is any dispute in the process of literature inclusion or exclusion, it shall be judged and decided again after discussion and consultation with a third party.

Data extraction and literature evaluation

Cochrane's Handbook for Systematic Reviews of Interventions states that when assessing the quality of included studies, researchers should look for things like randomization, allocation concealment, blinding, data integrity, selective reporting of results, and other types of bias (such as premature study termination, obvious imbalance of baseline level, etc.). When evaluating each standard, "low risk", "high risk" and "unknown" are adopted. In case of any dispute during the evaluation, it shall be judged and decided again after discussion and consultation with a third party. The data were extracted by two researchers using pre-designed tables. The extracted contents include the first author of the study, publication year, study design type, sample size, average age, renal cancer type, tissue type, treatment plan, etc. The New Castle Ottawa standard is adopted for literature quality evaluation. If there is any inconsistency in the evaluation, it shall be decided through discussion.

Figure 1. The literature search process

Figure 2. Risk of bias plot for quality evaluation according to various criteria

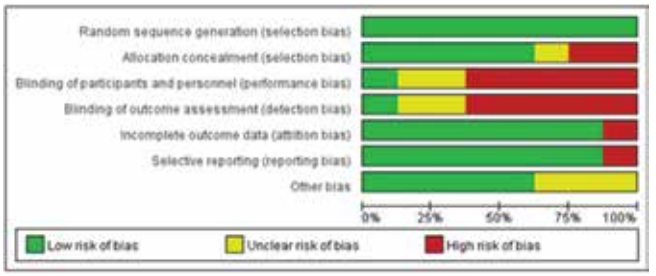
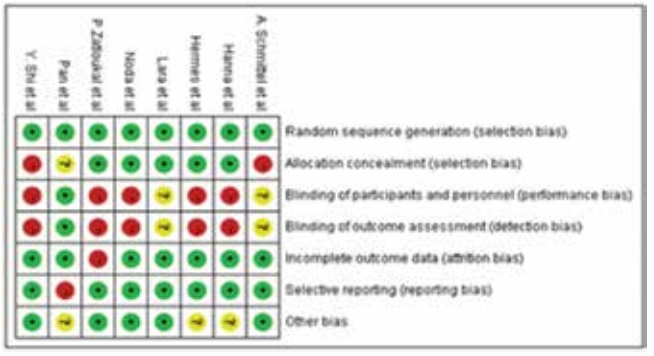


Figure 3. A detailed diagram depicting the outcomes of the quality assessment of the included studies



Definition of outcome indicators

Time to disease recurrence, death, or loss of follow-up after nephrectomy is called progression-free survival (PFS). Chronological survival (CSS) measures how long someone lives after receiving a diagnosis of renal cell carcinoma. OS measures how long it takes from when metformin treatment begins until the patient either dies or is lost to follow-up.

Statistical analysis

We pooled the HR values obtained after adjusting for the most influential confounders across studies to determine the overall HR and 95% CI. The I^2 test was employed to assess the degree of variation between studies. When the degree of heterogeneity was high enough to warrant its use ($I^2 > 50\%$), a random-effects model was employed. Otherwise, a model with fixed effects was employed. Overall effect values were also assessed using sensitivity analysis. For time event data such as PFS and OS, we use HR as the evaluation index; For binary variables such as disease control rate (DCR), we use risk ratio (RR) as the effect scale index. If the risk ratio of OS and PFS in the study cannot be obtained directly from the literature, relevant important data shall be extracted from the given survival curve, and the HR shall be calculated by using Engauge Digitizer version 4.1 software. We believe that when HR > 1, more death or disease progression occurred in the IP group; RR > 1 indicates that more related events have occurred in the IP group. Use Review Manager 5.3 to complete the above analysis.

RESULTS

literature search results

A total of 1060 articles as well as 7 clinical trials were retrieved. Duplicate studies were excluded based on the inclusion and exclusion criteria, and then those that were not relevant to the study were excluded by crisping the title and abstract, and then those that were in the study or whose status and results were unknown were also excluded. The remaining 39 articles were read in full. Finally, a total of 2089 patients were included in 8 articles, which had been published from 2002 to 2015. The flow chart of literature searches and screening is shown in Figure 1.

Characteristics of our study subjects

The median follow-up time was about 8 ~ 120 months. Volumes varied from 283 and 4468 in the sample. Participants' average ages differed from 59 to 67. Most studies corrected for the effects of common confounding factors, including gender, age, tumor stage, and so on. Two studies were aimed at patients with local renal cancer, one study was aimed at patients with metastatic renal cancer. More, there was one study that involved both types of patients, while the type of kidney carcinoma was not specified in one study. The full score of literature quality evaluation is 9, and the score of each study is 7 or more.

Quality evaluation results included in the study

As for the above research methods, according to the requirements of Cochran's system evaluation manual, we assessed how well the studies generated random sequences, hid distributions, used blinded settings, and reported their findings. Two researchers agreed that the overall quality of the included studies matched that of the systematic review and meta-analysis. The generation of random sequences in the included studies was evaluated as "low risk"; Two studies were rated as "high risk", one study was "unknown", and the rest were rated as "low risk". In terms of blind setting, four studies were served as "high risk", while there being two studies were evaluated as "unknown", and the rest were "low risk"; Only one study was rated as "high risk" in terms of completeness of outcome data and selective reporting of results, and the rest as "low risk"; Three studies had "unknown" other biases.

Effect of metformin upon progression-free survival in patients who had kidney cancer

A random-effects model was used because of significant inter-study heterogeneity. After summarizing the full HR values, it was found that metformin did not significantly

Figure 4. Effect of metformin upon progression-free survival in patients who had kidney cancer

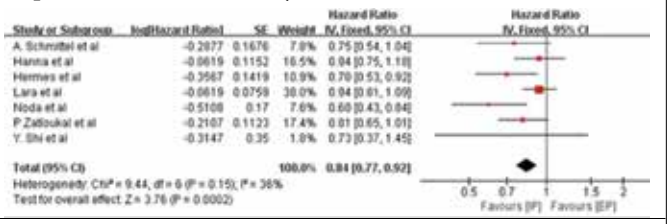


Figure 5. Effect of Metformin on cancer-related Survival in patients suffering from Kidney Cancer

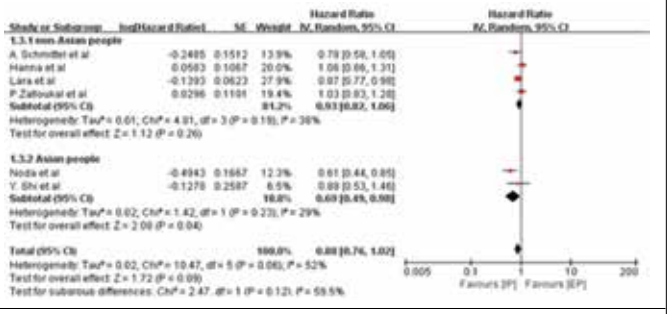
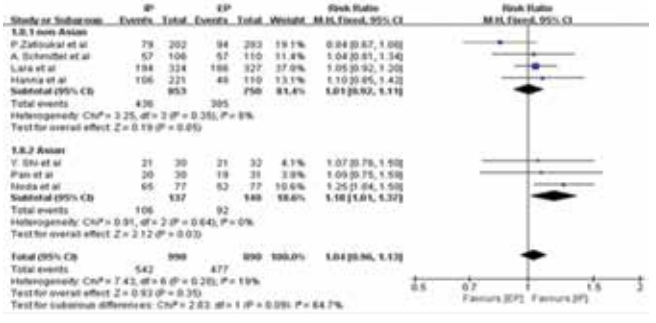


Figure 6. Metformin's impact on overall survival for kidney cancer patients



improve progression-free survival in patients with kidney cancer, regardless of metastasis or not. Sensitivity analysis found that the combined effect was still not statistically significant after excluding four studies.

Effect of Metformin on cancer-related Survival in patients suffering from Kidney Cancer

When analyzing CSS, five studies were included and divided into local and metastatic subgroups. The random effect model was utilized because of the substantial heterogeneity among the investigations. After summarizing all HR values, metformin did not significantly improve the cancer-related survival rate of patients with renal cancer, regardless of metastasis or not. Sensitivity analysis found that after excluding Psutka SP, there was a statistically significant aggregate effect. The overall effect was not statistically significant once the other four trials were removed.

Metformin's impact on overall survival for kidney cancer patients

Three studies were included in the analysis of OS, and the data were split into local and metastatic subgroups. The fixed effect model was utilized due to the lack of heterogeneity between trials. The overall survival rate of patients with kidney carcinoma, regardless of metastasis, was not significantly improved by metformin after summing all HR values. After excluding the influence of Psutka SP, the overall effect was still shown to be statistically significant. When the other three trials were taken out, the overall effect was not significant.

DISCUSSION

Metformin is a widely used first-line treatment for type 2 diabetes. However, as a multidrug, it can also modulate many diseases, including cancer, in addition to its hypoglycemic effect. Metformin has been linked to potential cancer-fighting effects in several studies, and the return visit survey also found that metformin can benefit some cancer patients. Researchers explored the effect of metformin on the survival rate of breast cancer and analyzed the clinical outcomes of 1215 breast cancer patients who underwent surgery from 1997 to 2013. 97 of them used metformin before being diagnosed, and 97 patients began using metformin after being diagnosed. Patients who used metformin before diagnosis had a 50% higher risk of dying compared to those who had never taken metformin, whereas those who started metformin after diagnosis had a 25% higher chance of surviving.[13] The use of metformin as a cancer prevention strategy has been controversial, and the relevant research results are inconsistent, but more analysis shows that the use of metformin is time-dependent. Some breast cancer patients may benefit from metformin, but those with breast cancer who use metformin before diagnosis may have more aggressive subtypes of cancer. This indicates the complexity of the interaction between basal metabolic risk and breast cancer outcomes and highlights the importance of multi-system cancer treatment. The results also showed that patients who used metformin were more likely to be diagnosed with cancer after the age of 50. However, in all the experimental groups, tumor size and disease progression were similar. Patients who took metformin after diagnosis were more likely to develop ER/PR-positive tumors, while those with metformin before diagnosis had a higher probability of having Her2+ and three negative breast cancers.[14] The study authors feel more investigation into metformin's impact on cancer recurrence is warranted. However, researchers believe that there is convincing biological evidence that the difference in tumor markers between breast cancer is related to the difference in tumor initiation mechanism in patients taking metformin.

Renal cell carcinoma is becoming more common every year in the global population. Although early detection is possible, there has been little improvement in survival rates. Multiple studies have also demonstrated that diabetes is a negative prognostic factor in renal cell carcinoma patients. Therefore, the treatment of diabetes may improve the survival of patients with renal cell carcinoma. Metformin is a first-line treatment for diabetes and has been shown to increase the

survival rate of several malignancies.[15] There is evidence that both insulin-dependent and insulin-independent mechanisms contribute to metformin's anticancer effect, but the precise mechanism is still unclear. Metformin inhibited cell proliferation in a time- and concentration-dependent manner, inhibited cell clone formation in a concentration-dependent manner, and induced cell cycle arrest in in vitro studies of renal cell carcinoma. In addition, the study also found that mice transplanted with metformin significantly reduced the size of the tumor. Although laboratory data indicate that metformin may have a potential therapeutic benefit for renal cell carcinoma, observational studies assessing the impact of metformin application upon survival have yielded conflicting results.[16]

The first published study was conducted by Hakimi AA and others to evaluate the relationship between the application of metformin and the survival results of 784 patients with renal cancer, of which 55 patients were treated with metformin. In this study, the patients involved fell within the categories of pT2 and pT3. The results showed that the application of metformin during surgery had a bad effect on DFS, but was beneficial to CSS.[17] However, there was no statistical significance between these associations. So it is very important to point out that this group of people is not limited to diabetes. Metformin users include all people with diabetes, while non-diabetic users include both people with and without diabetes; this suggests that diabetes may affect how long people with kidney carcinoma live. Psutka SP explored the correlation between metformin and survival outcomes in patients with renal cell carcinoma. The results expressed that metformin was more effective in renal cancer, but did not prolong survival. The number of patients treated with metformin reached 83. Two prospective randomized trials were conducted in these patients to assess changes in renal function and the occurrence of serious complications after treatment. Similar to the first study, the use of metformin did not exhibit statistically significant differences with DFS, CSS, and OS. The multifactor model variables in this investigation were chosen sequentially. So this result may be due to the lack of sample size. There are several problems with the choice of independent variables, which limits the comprehensive interpretation of the results shown by metformin users. A recent study by Cheng s et al. suggests that metformin showed significant efficacy in treating DFS and CSS in patients with localized renal cell carcinoma, yet in those with metastases, its efficacy was not as good. This study was adjusted for the karakiewicz score only. Although this assessment metric covers critical predictive variables, it does not take into account other predictive factors such as age and gender.[18]

The study conducted by Madhur Nayan et al. was not the first study to assess the relationship between metformin and renal cell carcinoma outcomes, but it was the first to apply a propensity score. The propensity score approach reduces the effect of confounding factors. Of course, this study has several limitations: first, it is an observational study, so it cannot prove causality; second, the study will have limitations due to its small sample size. Therefore, considering the prevalence of diabetes in treated renal cell carcinoma patients and the prevalence of metformin use in these patients as well, a multicenter or multi-population-based study may result in a larger population. Third, the exposure group was divided into different groups depending on whether metformin was administered after surgery.[19] Maybe some patients did not use metformin continuously after the operation, while those who were divided into non-metformin groups began to use metformin after the operation. But these problems are difficult for us to avoid. Despite the many limitations, however, the propensity to use score is consistent with previous studies indicating that the use of metformin is not effective in improving survival in diabetic patients after nephrectomy for nephrocalcinoma.

The lack of a beneficial therapeutic benefit of metformin in individuals with renal cell carcinoma is consistent with the majority of research. Perhaps the lack of sample size is the main reason, but at the same time, in the process of grouping, the random dressing change or intermittent withdrawal of patients may also be the factor affecting the difference between groups. Therefore, if we want to get results consistent with laboratory data, we may need a more rigorous clinical design and a larger sample of multi-center clinical research.

CONCLUSION

This systematic review and meta-analysis found that metformin did not improve survival rates for patients with renal cell carcinoma.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

DATA AVAILABILITY

The simulation experiment data used to support the findings of this study are available from the corresponding author upon request.

FUNDING SOURCES

There are no funding sources to declare.

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META-ANALYSIS

A Meta-Analysis of Differences in Thyroid and Cardiac Function Between Women with Normal Pregnancies and Gestational Diabetes Mellitus

Juan Guo, MM; Yinjian Zhou, MM; Qiongshan Li, MM; Ping Zhang, MD

ABSTRACT

Objective • This is a meta-analysis of thyroid function (TF) and cardiac function (CF) differences between women with normal pregnancies and gestational diabetes mellitus (GDM), in order to provide more reliable reference and guidance for the future clinical prevention and treatment of GDM.

Methods • Studies on the correlation of GDM with TF and CF were searched in PubMed, Cochrane Library, and other literature databases, and the literature for final analysis was confirmed after screening according to the eligibility criteria. Authors, publication time, research subjects, and endpoints were extracted for meta-analysis using Review 5.3 software.

Results • After screening, 10 studies with a total of 2554 subjects were selected, including 1125 GDM patients (GDM group) and 1429 normal pregnant women (control group). All the included papers scored 6-7 points on the Newcastle-Ottawa Scale used for literature quality evaluation, implying high-quality research. In the meta-analysis, the relationship between GDM and TF, TSH, and FT3 increased evidently in the GDM group, while FT4 decreased ($P < .05$). The meta-analysis of GDM and CF revealed lower LVEF and E/A while higher E/E' in GDM patients compared to the controls ($P < .05$). The funnel plot showed that the graphs of all the endpoints were basically symmetrical, indicating low publication bias.

Conclusion • Given the obvious thyroid dysfunction and cardiac dysfunction in GDM patients, symptomatic intervention measures should be taken actively and timely to improve the safety of GDM patients during pregnancy. (*Altern Ther Health Med.* 2024;30(4):66-70)

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INTRODUCTION

Gestational diabetes mellitus (GDM), defined as diabetes with normal glucose metabolism or underlying impaired glucose tolerance before pregnancy, only appears or is diagnosed during pregnancy, which is one of the most common medical complications during pregnancy.[1] The World Health Organization (WHO) reported a GDM incidence of about 1-14% worldwide, and in populous countries like China and India, the incidence can reach more than 5%.[2,3] Unlike simple diabetes mellitus, the glycometabolism of GDM patients mostly returns to normal after delivery.[4] Nevertheless, GDM patients are still at an increased risk of type 2 diabetes mellitus, with some patients hyperglycemic even remaining after childbirth.[5] For mothers, GDM may lead to macrosomia, significantly elevating the risk of dystocia and postpartum massive bleeding, and predisposing patients to various infections.[6] As far as the newborns are concerned, maternal hyperglycemic status may cause neonatal organ hypoplasia, endocrine disorders, and susceptibility to congenital diseases.[7]

On the other hand, thyroid diseases rank second among the endocrine diseases that women of childbearing age are susceptible to after GDM.[8] Thyroid function (TF) during pregnancy is influenced by the body's immune status and endocrine levels, resulting in a vicious circle of interaction between glycometabolism and hypothyroidism.[9] In most cases, GDM or thyroid diseases are treatable, but without proper evaluation and management, they can adversely affect mothers and fetuses, leading to multi-system metabolic abnormalities and even multiple adverse pregnancy outcomes.[10] GDM has also been reported to influence the structural and functional changes of the heart in pregnant women and newborns, and increase the occurrence of cardiovascular risk events.[11] However, at this stage, the clinical concern for GDM patients mainly focuses on glycometabolism, ignoring TF and cardiac function (CF) alterations, which also leads to the awkward situation that the incidence of GDM has been constantly rising while the

treatment efficiency has not been significantly improved.[12] Therefore, this study will systematically evaluate and meta-analyze TF and CF in GDM patients, aiming at providing a more reliable and comprehensive reference for future clinical interventions to prevent and treat GDM.

MATERIALS AND METHODS

Document retrieval

By searching keywords "Gestational Diabetes" and "Cardiac Function", or "Gestational Diabetes" and "Thyroid Function" in the PubMed (URL: https://pubmed.ncbi.nlm.nih.gov/), Cochrane library (URL: https://www.cochranelibrary.com/), and Web of Science (URL: www.webofscience.com), related studies on TF and CF in GDM were screened. Then, the relevant journals and the references of the included studies were searched manually. After the retrieval, the documents with the same title, author(s), and publication years were checked and de-duplicated by using the document management software. The de-duplicated documents were screened for the first time according to the title and abstract to remove the irrelevant ones, followed by a second screening through reading the full text. In addition, literature types such as reviews, systematic reviews, and case reports were excluded.

Eligibility criteria

Inclusion criteria: (1) published papers whose research years were from 2010 to now; (2) articles with the main research content involving the correlation of GDM with TF and CF; (3) randomized controlled studies or cohort studies; (4) papers with clear and correct standards for the included research subjects; (5) papers with complete original data. Exclusion criteria: (1) duplicate or suspected duplicate articles; (2) documents with possible conflicts of interest among researchers; (3) literature with selective reporting risks; (4) literature with obvious defects or logical errors in the research design.

Literature screening

The literature, centrally managed by EndNoteX9, was independently screened by two research members. After removing the duplicate literature, the final judgment was made after reading the title, abstract, and full text. The literature agreed by two research members to meet the requirements was included in the final analysis, and in case of disagreement, a third research member would help to make the final decision. In order to prevent subjective factors from affecting literature evaluation, the information of all authors was blinded during the screening.

Literature quality evaluation

The quality of the included literature was evaluated with reference to the Newcastle-Ottawa Scale (NOS),[13] a document quality evaluation tool, from the domains of adequate with independent validation, representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of controls, compatibility of cohorts on the basis of the design or analysis, ascertainment of exposure, determination of exposure of cases and controls by the same method, and non-response rate. On a scale ranging from 0 to 9 points, a score above 6 points indicated good literature quality, while a score below 5 suggested poor quality, in which case the literature would be excluded.

Figure 1. Flow Chart of Literature Screening

Data Extraction

The author(s), publication years, and basic data (age, gestational age, etc.) of research participant were extracted from the literature, and the endpoints mainly included thyroid function [thyroid stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4)] and cardiac function [left ventricular ejection fraction (LVEF), E/E', and E/A].

Statistical processing

Meta-analysis was performed using Review 5.3 software, and the significance threshold was $P < .05$. The included data were first tested for heterogeneity ($\alpha = 0.1$). When $I^2 < 50\%$, it was considered that there was no heterogeneity among papers, in which case the fixed-effects model would be adopted for analysis. The presence of heterogeneity among documents was indicated by $I^2 > 50\%$; in this case, analysis would be first carried out using a fixed-effects model, and validation analysis using the fixed-effects model would be further performed on indexes with differences. Finally, publication bias was observed by drawing the funnel plot. The publication bias was considered small if the two ends of the plot were basically symmetric; while little or no symmetry suggested large bias and no reference value.

RESULTS

Search results

According to the keyword-based search results, 68 related papers were initially found, 41 of which selected for further evaluation, after checking and de-duplication by EndNote. After reading the full text and screening according to the eligibility criteria, 10 papers were finally included for this meta-analysis.[14-23] See Figure 1 for literature screening process.

Table 1. NOS Scores of Literature Used

Author	Domains of adequate with independent validation	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of controls	Compatibility of cohorts on the basis of the design or analysis	Ascertainment of exposure	Determination of exposure of cases and controls by the same method	Non-response rate	Total Score
Demiral Sezer S 2022	1	1	1	1	1	1	1	0	7
Raets L 2022	1	1	0	1	1	1	1	0	6
Rawal S 2018	1	1	0	1	1	1	1	0	6
Xu C 2018	1	1	0	1	1	1	1	1	7
Yanachkova V 2021	1	1	0	1	1	1	1	1	7
Aguilera J 2020	1	1	0	1	1	1	1	0	6
Calabuig AM 2021	1	1	0	1	1	1	1	1	7
Meera SJ 2017	1	1	0	1	1	1	1	0	6
Sonaglioni A 2022	1	1	0	1	1	1	1	1	7
Winhofer Y 2014	1	1	0	1	1	1	1	0	6

Evaluation of literature quality

The NOS scores of the included studies were all 6-7 points, indicating that they were high-quality studies with high reference value and therefore suitable for meta-analysis. See Table 1 for detailed scoring results.

Basic information about the literature

A total of 2554 subjects were studied in all these papers, among which 1125 GDM patients were considered as GDM group, and the rest 1429 normal pregnancies were considered as the control group. Detailed information of all subjects is shown in Table 2. Five of the articles observed differences in TF between GDM patients and normal pregnant women and 5 observed differences in CF.

Meta-analysis

Correlation of GDM with TSH. By testing the heterogeneity among the five articles reporting the comparison of TSH, it was found that the I^2 value was not less than 50%, implying heterogeneity among the papers. The analysis results using the random-effects model revealed a 0.28 elevation in TSH in GMD patients compared to controls, with statistical significance ($P < .05$). Further, when the analysis model was replaced with a fixed-effects model, it also showed higher TSH levels in GDM group ($P < .05$), confirming the accuracy of the above results (Figure 2).

Correlation of GDM with FT3. Analysis of the results showed that FT3 was higher in the GDM group than in the control group ($P < .05$). After validation of the fixed-effect model, the same showed that FT3 was higher in the GDM group than in the control group ($P < .05$) (Figure 3).

Correlation of GDM with FT4. The analysis results using the random-effects model revealed 0.24 decrease in FT4 in GMD patients compared to controls, with statistical significance ($P < .05$). Further, the analysis model was replaced with a fixed-effects model, which also showed lower FT4 levels in GDM group ($P < .05$), confirming the accuracy of the above results (Figure 4).

Correlation of GDM with LVEF. Similarly, five studies on cardiac function were first analyzed for heterogeneity among the literature ($I^2 \geq 50\%$), using a random effects model. After analysis, it was seen that LVEF was lower in the GDM group compared to the control group, by approximately 2.70 ($P < .05$). The results of the fixed-effects model validation analysis were also consistent with the results above ($P < .05$) (Figure 5)

Table 2. Evaluation of Literature Quality

Authors	Main study content	Pregnant women with GDM (GDM group)	Normal pregnant women (control group)
Demiral Sezer S 2022	thyroid function	78	82
Raets L 2022	thyroid function	199	398
Rawal S 2018	thyroid function	107	214
Xu C 2018	thyroid function	50	50
Yanachkova V 2021	thyroid function	412	250
Aguilera J 2020	cardiac function	73	73
Calabuig AM 2021	cardiac function	123	246
Meera SJ 2017	cardiac function	18	72
Sonaglioni A 2022	cardiac function	30	30
Winhofer Y 2014	cardiac function	35	14

Abbreviations: GDM, Gestational diabetes mellitus.

Figure 2. Correlation of GDM with TSH

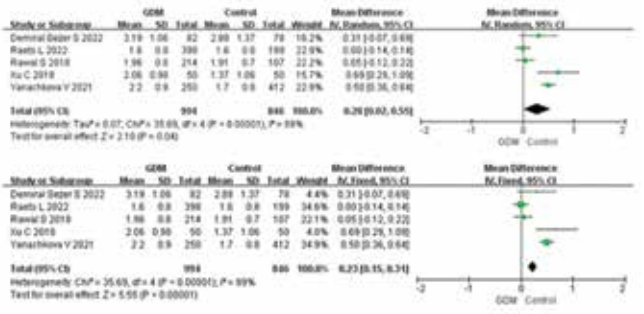


Figure 3. Correlation of GDM with FT3

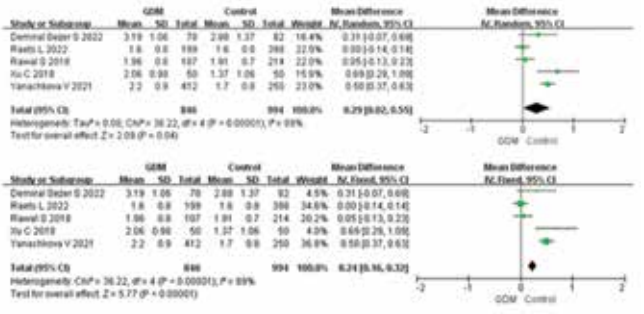


Figure 4. Correlation of GDM with FT4

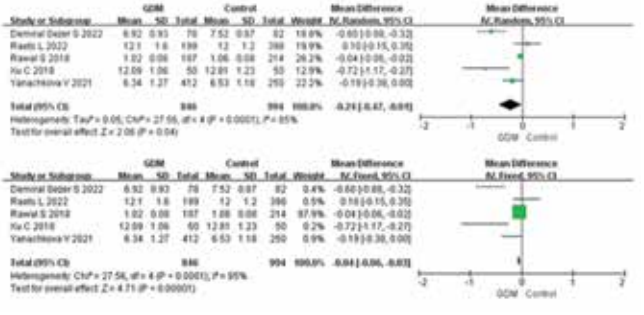


Figure 5. Correlation of GDM with LVEF

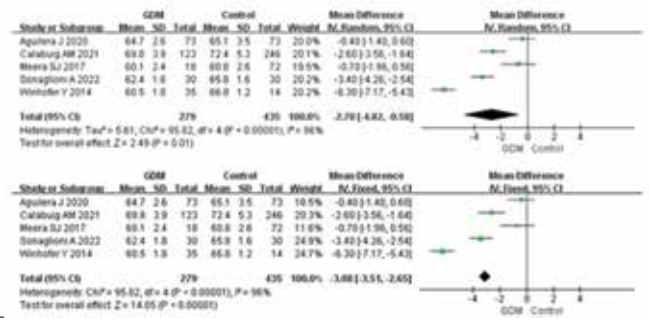


Figure 6. Correlation of GDM with E/A

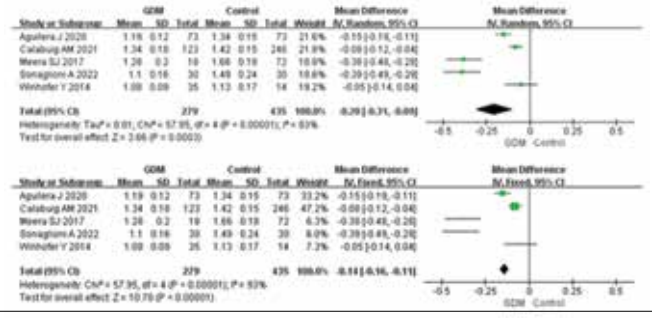


Figure 7. Correlation of GDM with E/E'

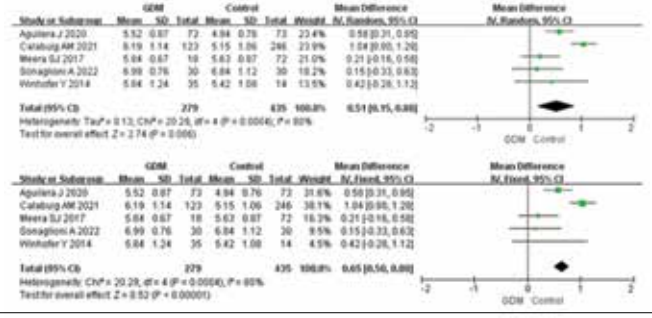
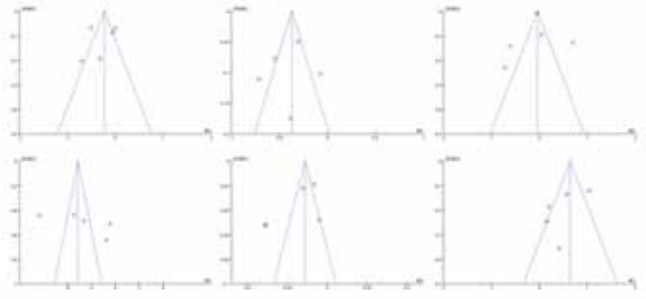


Figure 8. Publication Bias (The First Row from Left to Right is TSH, FT3, and FT4, the Second Row from Left to Right is LVEF, E/A, and E/E')



Correlation of GDM with E/A. The results of the random-effects model analysis showed that E/A was lower in the GDM group compared to the control group, by approximately 0.20 ($P < .05$). The results of the validation of the fixed-effects model analysis also showed lower E/A in the GDM group ($P < .05$) (Figure 6).

Correlation of GDM with E/E'. The analysis showed that E/E' was higher in the GDM group by approximately 0.51 compared to the control group ($P < .05$). The results of the fixed-effects model analysis also showed that E/E' was higher in the GDM group than in the control group ($P < .05$), verifying the results of the above analysis (Figure 7).

Publication bias

Funnel plots of all endpoints were drawn, and it can be seen that both sides of the funnel plots were basically symmetric, which indicates that the literature included in this analysis has low publication bias and high reference value (Figure 8).

DISCUSSION

The WHO defines GDM as any degree of glucose intolerance during pregnancy. For pregnant women, GDM may cause convulsions, premature delivery and stillbirth, in addition to increasing the possibility of reproductive system infections.[24,25] Statistics show that preterm birth occurs in approximately 10% of patients diagnosed with GDM and puerperal infection in more than 20%.[26] In the long run, GDM not only adversely influences pregnancy, but also increases prognostic metabolic syndrome and cardiovascular diseases in patients that may eventually evolve into lifelong type 2 diabetes, thus requiring lifelong maintenance treatment.[27,28] For newborns, GDM may increase the likelihood of developing congenital diseases, cause developmental deformities, and reduce the quality of life of newborns.[29] Currently, the pathogenesis of GDM has not been fully defined, and an in-depth understanding and summary of the pathological characteristics of GDM will be of great significance for future clinical development of prevention and treatment strategies for GDM. At the present stage, there is still much clinical controversy about the correlation of GDM with TF and CF. By screening the related literature in recent years and conducting a meta-analysis, the current relationship between GDM and TF and CF can be preliminarily summarized, so as to lay a reliable foundation for subsequent studies.

We finally selected 10 articles for analysis after screening based on the eligibility criteria. There were 2554 subjects participating in these studies, including 1125 GDM patients. Through meta-analysis, we found markedly elevated TSH while reduced FT3 and FT4 in GDM patients versus normal pregnant women, confirming obvious alterations in TF in GDM patients. Many scholars have conducted studies on the correlation between GDM and thyroid dysfunction, pointing out that the association between the two is very likely to be caused by insulin resistance in the body, which leads to abnormal glycometabolism, and thus adverse effects.[30] Giannakou et al. also proposed a link between GDM and the occurrence of hyperthyroidism from two perspectives. On the one hand, hyperthyroidism not only affects insulin sensitivity, but also accelerates insulin degradation, which directly interrupts the normal operation of the islet function in pregnant women. On the other hand, GDM influences normal TF through autoimmune abnormalities and glucose toxicity of the thyroid, thereby further increasing the risk of hyperthyroidism or hypothyroidism.[31] Therefore, the

interaction between GDM and TF mainly lies in the fact that TF further affects the normal endocrine function of pregnant women by regulating hormone secretion, which promotes the occurrence of GDM. Meanwhile, TF affects normal fat metabolism, which in turn influences glucose-lipid metabolism, thus accelerating the development of GDM.[32]

In terms of CF, we observed lower LVEF and E/A while higher E/E' in GDM patients compared to controls, which also suggests that GDM causes cardiac dysfunction. We believe that this may be related to the fact that GDM enhances the sensitivity of the heart to oxidative stress and affects vascular contraction, causing dysfunction of intracellular mitochondria and DNA, promoting the generation of hydroxyl, carboxyl, hydrogen peroxide, and other oxygen free radicals and aggravate myocardial cell damage, thereby inducing cardiac dysfunction.[33] Based on the above results, we can further speculate that the influence of GDM on CF may also be related to GDM-induced TF changes, which aggravates abnormal blood lipid metabolism or triggers inflammatory reactions, thus affecting myocardial contraction and heart rate. Previous studies have also shown that patients with GDM combined with hypothyroidism have a significantly increased risk of cardiovascular adverse events,[34] which can also preliminarily support our view.

Glycolipid metabolism has been repeatedly mentioned as one of the key indicators in the exploration of the correlation of GDM with TF and CF. A number of studies have also fully demonstrated that the primary pathogenic mechanism of GDM is through the modulation of glycolipid metabolism.[35] But due to the limited information reported in the included literature, patients' glycolipid metabolism was not discussed in this analysis, which requires further research and analysis. Besides, we should further explore the association between TF and CF in GDM patients, as well as the relationship among the three. Finally, regional differences in iodine intake due to different sources of the literature samples included in this study, as well as variations in test results caused by the difference in testing instruments and kits for TF, all contribute to the heterogeneity to a large extent. So, in addition to expanding the included literature for a more comprehensive analysis, we should also conduct clinical trials to analyze the relationship between GDM and TF and CF, so as to provide more reliable reference for subsequent research.

CONCLUSION

There is significant thyroid dysfunction and cardiac dysfunction in GDM patients, and these three clinical conditions interact with each other, further increasing the risk of adverse events during pregnancy. In future clinical practice, it is necessary to closely monitor TF and CF changes in GDM patients, to improve their pregnancy safety.

AUTHOR DISCLOSURE STATEMENT

The authors report no conflict of interest.

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ORIGINAL RESEARCH

Observation on the Therapeutic Safety of Pulsatile Intravenous Insulin Therapy Combined with Critical Value Early Warning Nursing for Diabetic Ketoacidosis Patients

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ABSTRACT

Objective • To observe the therapeutic effect of pulsatile intravenous insulin therapy (PIVIT) combined with critical value early warning nursing on diabetic ketoacidosis (DKA).

Methods • Ninety-six DKA patients treated in our hospital between May 2021 and February 2023 were selected as the research subjects, of which 53 cases received PIVIT (research group) and the other 43 cases received insulin intravenous infusion therapy (control group). The blood glucose (BG), condition, pH control time and the incidence of adverse reactions were analyzed in the two groups. Changes in pre- and post-treatment BG, cardiac function, β-Hydroxybutyric acid (β-HBA), lactate (Lac), and blood ketone body (BKB) were determined before and after treatment. In addition, patients' psychological status was assessed using the Self-rating Depression/Anxiety Scale (SDS/SAS) and their satisfaction with the nursing services was investigated.

Results • The research group took less time to control BG, condition, and pH value than control group, with lower BG, β-HBA, Lac, and BKB levels and better cardiac function after treatment ($P < .05$). No notable differences were identified between groups in terms of adverse reactions, SAS and SDS scores, and nursing satisfaction ($P > .05$).

Conclusions • PIVIT combined with critical value early warning nursing can alleviate the acidosis of DKA patients more quickly and effectively. (*Altern Ther Health Med.* 2024;30(4):71-75)

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INTRODUCTION

Diabetic ketoacidosis (DKA) is one of the most common severe acute complications of diabetes mellitus (DM), which is caused by severe metabolic disorders due to insulin deficiency and inappropriate increase of glycogenic hormones, with hyperglycemia, ketosis and acidosis as the main manifestations.[1] DKA is most prevalent in people under the age of 20, with a mortality as high as 5-10%.[2] Epidemiological statistics show that the global incidence of DKA in 2020 is about 3-56/1000, an increase of about 4.3 times compared with ten years ago, which is also related to the rising incidence of DM in recent years.[3] For DKA, a condition with an increasing prevalence, a timely and effective treatment plan is the key to ensuring the life safety of patients, which also underlies the importance of sufficient attention from the patients and doctors.[4]

DKA is known to be primarily caused by insulin deficiency, so supplementing exogenous insulin is the most direct treatment for DKA.[5] The traditional insulin supplementation program is based on intravenous drip, but due to the rapid onset of DKA, intravenous insulin may not be able to achieve the ideal insulin regulation within a short period of time, and thus patients may still suffer from more serious critical complications.[6,7] For this reason, clinical attempts have been made to improve the slow response time of intravenous drips with pulsatile intravenous insulin therapy (PIVIT). Currently, some studies have preliminarily confirmed that PIVIT can also achieve excellent DKA treatment effects.[8,9] However, the specific differences between PIVIT and intravenous infusion are still unclear, and there are few studies on the subject.

In addition, as a high-risk disease with extremely high mortality, targeted nursing measures for DKA are also one of the focuses worthy of our attention.[10] Traditional emergency nursing often adopts measures such as monitoring the patient's condition and vital signs according to the doctor's advice, with some clinical limitations such as single nursing mode and lack of comprehensiveness, which is difficult to meet the nursing needs of patients' rehabilitation.[11] Critical value warning is to dynamically assess the risk level of patients according to the changes of some biochemical

Table 1. Patient's information

Group	n	Age	Gender male/female	BMI (kg/m^2)	Duration of diabetes mellitus (years)	Triggers infection/stress/diet
Control group	43	53.8±3.9	23 (53.59)/20 (46.51)	22.5±1.5	4.6±1.3	38 (71.70)/3 (5.66)/12 (22.64)
Research group	53	53.6±4.1	31 (58.49)/22 (41.51)	22.7±1.5	4.4±1.3	32 (74.42)/4 (9.30)/7 (16.28)
χ^2/t		0.243	0.241	0.650	0.455	0.942
P value		.809	.623	.518	.750	.625

indicators, and implement targeted nursing interventions according to the risk level, so as to promote the decline of critical value and improve the prognosis of patients.[12]

Therefore, this study conducts observation and analysis on the effect of PIVIT for DKA under critical value early warning nursing, aiming at providing more reliable reference and guidance for future treatment of DKA patients.

Materials and methods

Patient data

Ninety-six DKA patients treated in our hospital between May 2021 and February 2023 were selected as the research subjects, of which 53 cases received PIVIT (research group) and the other 43 cases received insulin intravenous infusion therapy (control group). This study was conducted after the approval of the Ethics Committee of our hospital, and the patients and their families gave informed consent to participate in this study. The clinical data of the two groups are shown in Table 1, and no statistical difference was identified between them ($P > .05$, Table 1).

Criteria for patient enrollment and exclusion

Inclusion criteria: Patients meeting the diagnostic criteria for DKA (13), with first episode, clear consciousness, and normal communication ability were included. Exclusion criteria: ketoacidosis caused by other reasons; female patients during pregnancy and lactation; severe organ dysfunction; incomplete clinical baseline data; other major diseases.

Treatment methods

Insulin intravenous infusion: Continuous intravenous infusion of insulin was given at a dose of 0.1U/kg/h, and insulin solution (insulin: glucose = 1: 4) was administered intravenously after the blood glucose (BG) dropped to 13.9 mmol/L. PIVIT: Before intravenous drip therapy (same protocol as above), 0.1 U/kg insulin was given via an intravenous bolus in a pulsatile manner. The total amount of insulin infusion in both groups was 50U.

Nursing methods

A critical value early warning report form was established, with the contents covering the pH value, total bilirubin, arterial partial pressure of oxygen, hemoglobin, white blood cells, platelets, fibrinogen, urea nitrogen, prothrombin time, etc. Each item was assigned 0-3 points, with 0 being normal, 1 being slightly higher, 2 being moderate, and 3 being high-risk; the higher the total score, the more serious the condition. Then the nursing measures corresponding to the risk level were implemented according to the critical value warning report form: < 11 points: The nursing staff made regular rounds and implemented routine nursing intervention; 11-22 points: The nursing staff made ward rounds at least every 2 hours, paid close attention to the patient's blood pressure, BG, and vital signs, and adjusted the dosage of insulin drips according to the patient's condition; > 22 points: The head nurse made regular visits every half an hour, continuously monitored the patient's BG and vital signs, kept the respiratory tract and venous access unblocked, and actively cooperated with the attending doctor to complete relevant treatment. During the treatment of all patients, the nursing staff timely adjusted the insulin dose according to the changes in BG to prevent hypoglycemia. In case of any abnormalities, nurses gave feedback to the doctor in time to take active intervention measures. Patients with different levels of risk were scored repeatedly after different care measures until the risk score dropped to normal.

Outcome measures

The BG, condition, and pH control time (that is, the time for BG, vital signs, and pH to return to normal) and the incidence of adverse reactions during treatment were counted. In addition, fasting venous blood was collected before and after treatment, and enzyme linked immunosorbent assay (ELISA) was used for the determination of β-Hydroxybutyric acid (β-HB), lactate (Lac) and blood ketone body (BKB) in the serum, and the kits were purchased from Beijing Sobalite Biotechnology Co. The kits were purchased from Beijing Sobalite Biotechnology Co. Enzyme kinetic assay for the determination of creatine kinase (CK), creatine kinase-MB (CK-MB) and aspartate transaminase (AST) in serum was purchased from Beijing Ita Biotechnology Co. Furthermore, BG analysis was performed to detect fasting blood glucose (FBG), 2h postprandial blood glucose (2hPG) and glycated hemoglobin (HbA_{1c}). Furthermore, we employed the Self-rating Depression/Anxiety Scale (SDS/SAS) (14) to evaluate patients' anxiety and depression before and after intervention. With a score ranging from 20 to 80, high scores were associated with more serious negative emotions. Finally, the self-made questionnaire was used to evaluate patients' satisfaction with nursing intervention. Finally, a self-administered questionnaire was used to assess the satisfaction of the two groups of patients with the nursing interventions, which included four items: service attitude, communication skills, nursing responsibility and professional competence, and each item was scored out of 100 points, with the higher the score, the higher the nursing satisfaction.

Statistical methods

Data were statistically analyzed by the SPSS23.0 statistical software (International Business Machines Corporation). Categorical variables were represented by [n(%)], and chi-square test was used for comparisons. Continuous variables were expressed by ($\bar{x} \pm s$) and analyzed by the independent sample *t* test and paired *t* test. A significance level of $P < .05$ was used in all analyses.

Figure 1. clinical indexes. A) the control time of BG, B) the control time of condition, C) the control time of pH.

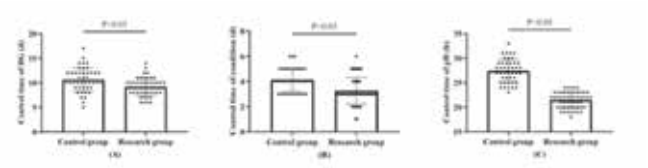
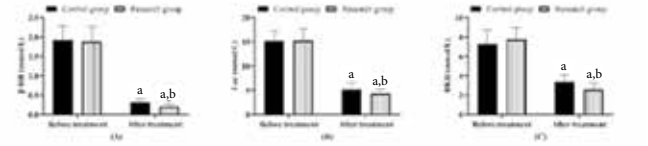


Figure 2. Comparison of acidosis. A) β-HBA, B) Lac, C) BKB.



[a]vs. before treatment, $P < .05$
[b]vs. control group, $P < .05$

RESULTS

Comparison of clinical indexes

According to statistics, the control time of BG, condition, and pH value in research group were (9.17±1.73)d, (3.26±1.06)d and (21.45±1.62)h, respectively, all of which were significantly reduced compared with control group ($P < .05$, Figure 1).

Comparison of acidosis

The detection results revealed no statistical differences in pre-treatment β-HBA, Lac, and BKB between research group and control group ($P > .05$). The three indexes reduced markedly in both cohorts after treatment, with even lower levels in research group ($P < .05$, Figure 2).

Comparison of BG

The two groups did not differ significantly in pre-treatment FPG, 2hPG, and HbA_{1c} ($P > .05$). The intra-group comparison showed that FPG, 2hPG, and HbA_{1c} decreased obviously in both groups after treatment ($P < .05$, Figure 3).

Comparison of cardiac function

Before treatment,there was no significant difference in CK,CK-MB and AST between the two groups ($P > .05$). After treatment,CK and AST were lower in both groups,while CK-MB was higher than before treatment ($P < .05$). CK and AST in the research group were even lower than that in the control group after treatment, while CK-MB was higher than that in the control group ($P < .05$, Figure 4).

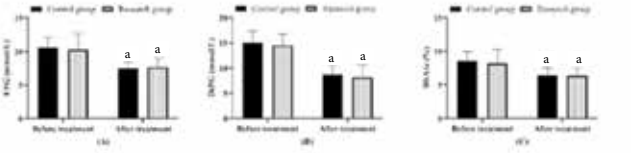
Comparison of adverse reactions

According to the statistics of adverse reactions during treatment, both groups of patients developed hypoglycemia, hyperchloric acidosis and respiratory failure; the total incidence was 13.95% in research group and 11.32% in control group, with no statistical difference ($P > .05$, Table 2).

Comparison of negative emotions

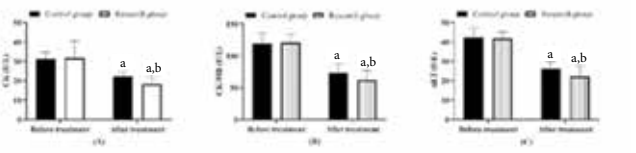
Both groups had high SAS and SDS scores before treatment, with no statistical inter-group difference ($P > .05$).

Figure 3. Comparison of BG. A) FPG, B) 2hPG, C) HbA_{1c}.



*: vs. before treatment, $P < .05$

Figure 4. Comparison of cardiac function. A) CK, B) CK-MB, C) AST.

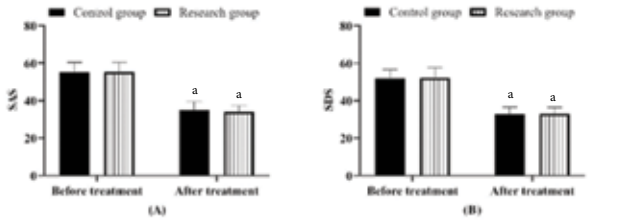


[a]vs. before treatment, $P < .05$.
[b]vs. control group, $P < .05$.

Table 2. Comparison of adverse reactions

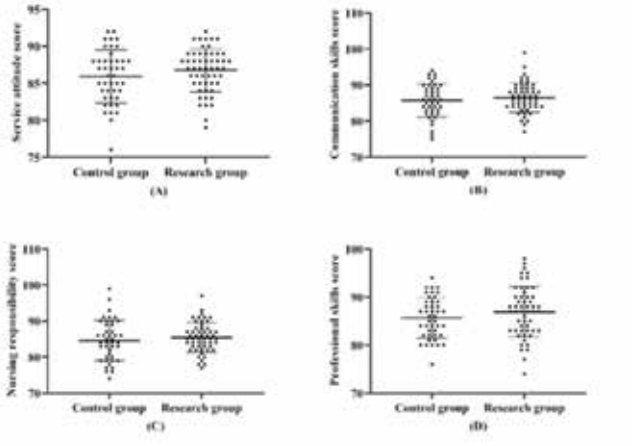
Group	n	Hypoglycemia	Hyperchloric acidosis	Respiratory failure	Pressure injuries	Ulcers	Total incidence
Control group	43	3 (6.98)	1 (2.33)	1 (2.33)	1 (2.33)	0 (0.0)	13.95
Research group	53	3 (6.98)	1 (2.33)	1 (2.33)	0 (0.0)	1 (2.33)	11.32
χ^2							0.150
P value							0.698

Figure 5. Comparison of negative emotions. A) SAS, B) SDS.



[a]vs. before treatment, $P < .05$.

Figure 6. Comparison of nursing satisfaction. A) service attitude score, B) communication skills score, C) nursing responsibility score, D) professional skills score.



Evident reductions in SAS and SDS scores were found in both research group and control group after the intervention ($P < .05$), but no significant difference was identified between groups ($P > .05$, Figure 5).

Comparison of nursing satisfaction

Finally, in the survey of nursing satisfaction, we found no marked difference in service attitude, communication skills, nursing responsibility, and professional skills between research group and control group ($P > .05$, Figure 6), which proves that both groups have high nursing satisfaction.

DISCUSSION

In this study, the symptom improvement was more pronounced in research group, confirming that PIVIT has a better therapeutic effect on DKA and is more recommended for clinical use. In addition, the critical value early warning nursing shows excellent application potential in the treatment of DKA, which will also provide a more reliable safety guarantee for future treatment of DKA.

First of all, the inter-group comparison of clinical indicators showed less time it took to control BG, condition, and pH value in research group, indicating that PIVIT can alleviate DKA symptoms more rapidly. The subsequent comparison of acidosis after treatment also revealed lower β-HBA, Lac, and BKB in research group than in control group, which also suggests that PIVIT can relieve the acidosis of patients more effectively. We also found similar conclusions in previous studies,[15,16] which can also support our experimental results. The reason may be that insulin, as an anabolic hormone, can effectively inhibit the process of ketone body formation in patients, reduce the level of hepatic glycogenolysis, and maintain muscle activity by promoting the uptake of glucose by corresponding tissues.[17] In DKA patients, because of dehydration and acidosis, the sensitivity to exogenous insulin is reduced, and small-dose insulin can not achieve the effect of inhibiting ketone body production in a short period of time, while the one-time shock treatment program of insulin can maintain higher insulin levels in the body, and has better effect on the improvement of patients' indexes such as β-HB.[18] However, in the comparison of BG indexes, no significant difference was identified between groups in post-treatment FPG, 2hPG, and HbA1c, which indicates that the two methods have basically the same effect on patients' BG. As we all know, insulin is one of the direct means to control the progression of DM, which can effectively maintain the continuous rise of BG level and reduce the threat of DM under the action of insulin in vitro.[19] We hypothesized that the reason for the no difference in BG indexes between the two groups was that the dose used by research group in PIVIT was the same as that used by control group. Therefore, it is possible that the drop in BG in research group will be more pronounced in the early stages of treatment, but the BG change between the two groups will show a more similar state as the dose of insulin is gradually stabilized. On the other hand, infection of various organs is one of the inducements of the onset and development of DKA. Being in a high glucose state for a long time will induce glycosylation and vascular inflammation, damage myocardial cells, and trigger serious vascular complications.[20,21] Therefore, the cardiac function changes in DKA patients are also worthy of our attention. The comparison of cardiac function showed that CK and AST were lower in research group after treatment, while CK-MB was higher, confirming better heart function of research group compared with control group. This may be due to the rapid reduction of BG levels in research group after the pulsatile intravenous insulin, which alleviates the damage of cardiomyocytes and promotes the recovery of cardiac function in patients. Farzadfar D et al. also found that PIVIT was more conducive to improving the heart function of DM patients,[22] which can support our findings.

Subsequently, we found no significant differences in the comparison of adverse reactions, psychological status, and nursing satisfaction. But compared with other previous studies on DKA treatment.[23,24] the incidence of adverse reactions, SAS and SDS scores of patients in this study were found to be more significantly reduced, and the nursing satisfaction reached more than 95%, presumably due to the positive role of critical value early warning nursing. The basis of the critical value early warning nursing model is to establish a critical value early warning report form and form a unified evaluation system, through which the risk degree of patients can be effectively identified and targeted nursing intervention can be implemented. Moreover, the establishment of critical value early warning report form is based on the dynamic changes of patients' blood biochemical indicators, enabling strengthened patrol and nursing after risk classification.[25] This nursing model can dynamically evaluate and reflect the change of the patient's condition, reasonably arrange the nursing workload according to the patient's condition, provide precise nursing for the patient, and avoid the increase in workload.[26] Moreover, the step-by-step precision nursing according to the degree of the patient's condition makes it possible to provide more targeted nursing services for patients, so the treatment safety can be enhanced and the negative psychology be mitigated.[27]

However, there are still many limitations in this study. For example, this study only detected the changes of various indicators before and after treatment, and lacked more accurate time points, resulting in the inability to dynamically assess the changes in patients' conditions. Besides, there may be room for optimization and improvement of nursing measures for DKA, which is worthy of more in-depth and comprehensive experimental analysis.

CONCLUSION

PIVIT can alleviate acidosis in DKA patients more quickly and effectively, while maintaining the health of patients' heart function, which has high clinical application value. Meanwhile, carrying out critical value early warning nursing in the process of insulin treatment of DKA is more conducive to promoting patients' comprehensive recovery,

improving treatment safety and alleviating negative psychological state. In the future clinical treatment of DKA patients, it is recommended to use PIVIT combined with critical value early warning nursing, so as to provide more reliable guarantee for patients' rehabilitation.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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META-ANALYSIS

Assessing the Impact of Prone Positioning on Mortality and Adverse Events Among Patients with Acute Respiratory Distress Syndrome: A Meta-Analysis

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ABSTRACT

Background • Prone positioning has evolved as a therapeutic intervention for patients with acute respiratory distress syndrome (ARDS). ARDS remains a critical condition, with a mortality rate of approximately 40%. Prone positioning, which involves placing patients in a face-down position, has the potential to enhance gas exchange and improve lung mechanics, possibly leading to better patient outcomes.

Objectives • This comprehensive review aims to evaluate the impact of prone positioning on mortality (primary outcome) and the occurrence of adverse events (secondary outcome) in patients with ARDS compared to conventional supine positioning.

Methods • We conducted an extensive systematic review, including studies published from 2000 to 2022. We searched databases including PUBMED, MEDLINE, EMBASE, CENTRAL, and WEB OF SCIENCE. Only randomized controlled trials (RCTs) that compared the outcomes of patients with ARDS in prone and supine positions were included. We employed the Cochrane risk of bias instrument to assess the methodological quality of the included RCTs.

Results • Our review included a total of twelve RCTs involving 2736 patients, with 1401 patients in the prone position. The meta-analysis demonstrated a lower mortality rate among patients in the prone position compared to those in the supine position (odds ratio [OR], 0.71; 95% confidence interval [CI], 0.52-0.98; $P = .04$). Notably, there was a higher incidence of pressure sores in patients placed in the prone position (OR, 0.15; 95% CI, 0.09-0.20) compared to those in the supine position. However, there were no statistically significant differences in the occurrence of arrhythmias, unplanned extubation, or pneumothorax between the two positioning strategies.

Conclusions • Prone positioning offers potential benefits for patients with ARDS by reducing mortality rates. However, it is important to note that there is an associated risk of pressure sores. Further research and clinical consideration are needed to optimize the use of prone positioning in ARDS management. (*Altern Ther Health Med.* 2024;30(4):76-81)

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INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) is a medical condition characterized by respiratory failure due to decreased lung compliance, impaired oxygenation, and pulmonary congestion. This condition typically manifests in severely ill patients, often resulting from lung injuries such as pulmonary viral infections or because of systemic inflammatory responses, such as those seen in polytrauma or sepsis.[1]

The prone position induces changes in alveolar ventilation distribution, enhances ventilation-perfusion matching at a local level, decreases the prevalence of regions with low ventilation-perfusion ratios influenced by gravitational effects, and reduces the risk of ventilator-induced lung injury.[2] Numerous studies have demonstrated that placing patients with ARDS in a prone position can lead to improvements in gas exchange and disease progression.[3]

In a study conducted by Valter et al.,[4] four awake hypoxemic patients were placed in a prone position without the need for sedation or intubation. This maneuver led to a rapid improvement in PaO_2 levels in all patients, and it was well-tolerated. In recent years, there has been a noticeable rise in patients undergoing prone positioning and noninvasive respiratory support.[5,6] Adopting the prone position in patients with ARDS improved oxygenation levels and reduced intubation rates.

Additionally, during the COVID-19 outbreak, this approach contributed to delayed or decreased hospital admissions.[7] These studies collectively suggest that prone positioning may offer significant benefits to patients with

ARDS, particularly in reducing the need for invasive mechanical ventilation.

Currently, research in patients with ARDS placed in the prone position primarily consists of observational studies, cohort studies, and case reports. There is a notable shortage of large-sample randomized controlled trials (RCTs), and the existing findings are marked by inconsistency. This meta-analysis examined the impact of prone positioning on mortality and adverse events in patients with ARDS. This study aimed to offer valuable insights for optimizing the management of ARDS patients.

METHODS

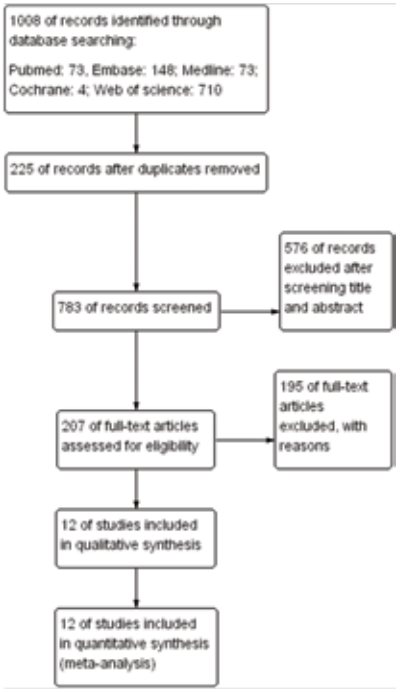
Study Design

We employed a systematic review and meta-analysis study design. This approach allowed us to systematically gather and critically evaluate a wide range of existing studies on prone positioning in patients with ARDS. This study adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines to ensure a comprehensive and structured review process.

Search Strategy

Our search strategy involved entering the following terms: ("prone position" OR "prone positioning") AND ("acute respiratory distress syndrome" OR "ARDS"), with a specific focus on randomized controlled trials. This comprehensive search yielded a total of 1008 references. These references were carefully organized and stored using EndNote. Subsequently, we identified and removed 225 duplicate references from the database. Following this initial screening, the remaining 783 original references were thoroughly reviewed, guided by our predefined inclusion criteria (as illustrated in Figure 1).

Figure 1. Selection of Studies for the Meta-Analysis



Note: This figure illustrates the process of study selection for the meta-analysis, including the initial identification of relevant studies, screening, eligibility assessment, and the final inclusion of studies in the analysis. It provides a visual representation of the study selection flowchart.

Inclusion and Exclusion Criteria

Two independent researchers thoroughly reviewed the full texts of all studies. Each reviewer independently assessed the relevance of the studies and determined their eligibility for inclusion. In disagreements, consensus was reached among the researchers through discussion and mutual agreement.

The inclusion criteria for study selection encompassed the following: (1) randomized controlled trials (RCTs); (2) studies comparing prone positioning to supine positioning in patients with ARDS; and (3) studies reporting data on mortality rates and adverse events. The exclusion criteria were as follows: (1) Studies not published in English, including commentaries, reviews, and duplicate publications from the same study; (2) Studies where data could not be extracted through statistical methods; and (3) Studies that did not address the specific outcomes of interest.

Data Extraction and Assessment of Study Quality

Data were independently extracted and recorded in an Excel spreadsheet, focusing on key aspects such as the study details, groupings, interventions, and outcomes. We utilised the Cochrane Collaboration risk of bias instrument to evaluate the quality and potential bias within each study. This comprehensive instrument facilitated the assessment of various elements, including random sequence generation, allocation concealment, blinding of caregivers, outcome assessment, handling of incomplete outcome data, and selective reporting.[8]

Selected Outcomes for Evaluation

We carefully selected a set of outcomes established through consensus among our content experts. These outcomes were deemed critical and substantial in assessing the impact of prone positioning. Our primary focus was on mortality, recognizing its utmost significance. In addition, we also examined adverse events, which included unplanned extubation or catheter displacement, arrhythmias, pressure sores, and pneumothorax.

Statistical Analysis

We employed odds ratios (OR) for the analysis of dichotomous outcomes. Qualitative and quantitative heterogeneity were assessed using the I^2 measure to evaluate clinical heterogeneity across studies. Statistical significance was established with a $P < .05$. Additionally, we examined funnel plots, plotting treatment effects against study quality, to assess the potential presence of publication bias.

All statistical analyses were conducted using RevMan 5.2, a software tool from the Cochrane Collaboration based

Table 1. Baseline Characteristics of Included Studies

Study	Sample (T/C)	Grouping (T/C)	Intervention	Mortality	Adverse events
Alhazzani et al. 2022[9]	205/195	awake prone positioning/usual care	8 h/d to 10 h/d with 2 to 3 breaks (1-2 hours each)	46/46	Unintentional removal of intravenous access:1/0
Beuret et al. 2002[10]	25/26	prone position/ supine position	positioned prone for 4 h once daily	7/12	NA
Chiumello et al. 2012[11]	13/13	Prone position/ Supine position	Prone position	8/7	NA
Fernandez et al. 2008[12]	21/19	Prone/Supine	Prone/Supine	8/10	Pneumothorax: 0/1; Unplanned extubation:1/1;
Gattinoni et al. 2001[13]	152/152	Prone/Supine	prone group: kept prone for at least six hours per day for a period of 10 days;	32/38	Pressure ulcers:54/42; Displacement of tracheal tube:12/15
Guerin et al. 2013[14]	237/229	Prone/ Supine	prone position: at least 16 consecutive hours	38/75	Non-scheduled extubation: 31/25; Cardiac arrest: 16/31
Guerin et al. 2004[15]	413/378	Prone/Supine	Prone: at least 8 hours per day; Supine: a 30° angle semi-recumbent position	134/119	Unplanned extubation: 44/47; Cardiac arrest: 87/88; Pressure sores: 208/157; Pneumothorax: 22/28
Jayakumar et al. 2021[16]	30/30	Prone/ Standard care	Prone: more than 6 hours in a day; Standard care: As per their comfort, they may change their position	3/2	Intubated: 4/4
Lu et al. 2021[17]	40/40	PPV/SPV	Prone; Supine: mechanical ventilation in a semi-supine position with the head of the bed raised 30-40°	5/9	NA
Mancebo et al. 2006[18]	76/60	Prone/Supine	Prone/Supine	33/35	Pneumothorax: 7/4; Unplanned tracheal extubation: 6/1
Taccone et al. 2009[19]	168/174	Prone/ Supine	Prone positioning was applied using a rotational bed	52/57;	Hypotension, arrhythmias, increased vasopressors:121/95 Displacement of endotracheal tube:18/8
Voggenreiter et al. 2005[20]	21/19	Prone/ Supine	Prone positioning: During nighttime. Supine group: positioned according to standard care guidelines	5/16	Pressure sores and skin lesions: 19/12; Displacement of an endotracheal tube: 1/1; Brady- or tachyarrhythmias: 8/3

Note: This table provides an overview of the baseline characteristics of the included studies, including the study name, sample size, grouping, intervention, mortality rates, and adverse events observed in both the prone and supine positions. "T/C" denotes the patient count in the treatment and control groups. Adverse events are listed with corresponding occurrences in the prone (T) and supine (C) groups. "NA" signifies data not available for certain studies.

in Oxford, UK. The results were analyzed, and forest plots were generated, utilizing either a fixed-effect or random-effect model, depending on the level of heterogeneity. A fixed-effect model was chosen for values of I^2 less than 50%, indicating low heterogeneity, while values exceeding 50% were considered moderate heterogeneity and thus required a random-effects model. Furthermore, we utilized funnel plots to aid in assessing publication bias. A significant difference was determined to exist when the $P < .05$.

RESULTS

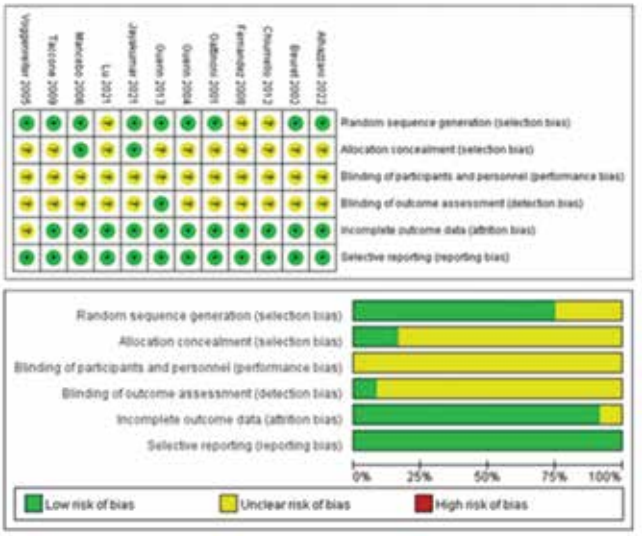
Search Outcomes

Our search across various databases initially yielded a total of 1008 publications that were considered relevant to our study's focus. Subsequently, these publications underwent careful screening, resulting in the identification of 12 articles from the year 2000 to 2023. These 12 articles collectively comprised data from 2736 patients with ARDS, of which 1401 were placed in the prone position. A comprehensive summary of all the articles included in this study is presented in Table 1, providing key insights into their main characteristics ($P = .05$).

Risk of Bias in Included Studies

A comprehensive evaluation of each study's risk of bias was conducted, and the findings are presented in Figure 2, providing a graphical summary of assessments. Our analysis revealed that most studies demonstrated a low risk of bias in terms of "selective reporting," "incomplete outcome data," and "random sequence generation." However, it is worth noting that our assessment of "blinding of participants and personnel" across all studies resulted in an outcome of "unclear risk." Furthermore, a total of ten studies fell into this category due to the absence of clear descriptions regarding allocation concealment.

Figure 2. Risk of Bias Graph and Bias Summary

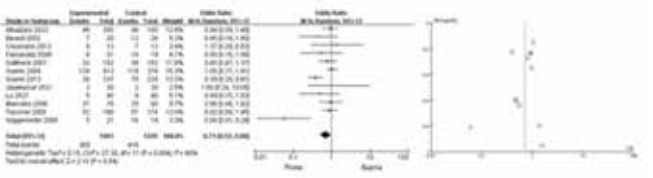


Note: This figure presents a graphical representation of the risk of bias assessment for the included studies. It provides an overview of the assessment results, indicating the potential sources of bias in each study. Additionally, it includes a bias summary, presenting a concise summary of the overall risk of bias in the included studies.

Primary Outcome: Mortality

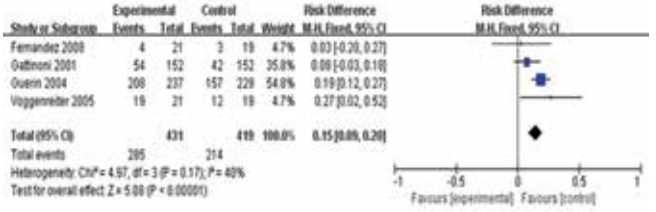
A total of twelve studies involving 2736 participants contributed data on mortality. The analysis resulted in an odds ratio (OR) of 0.71 (95% CI: 0.50 to 0.98; $P = .04$), signifying a lower mortality rate among patients in the prone positioning group, see Figure. 3. This study's findings provide compelling evidence that prone positioning holds the potential to mitigate the risk of mortality in individuals afflicted with ARDS.

Figure 3. Primary Outcome: Mortality Comparison between Prone and Supine Positions



Note: This figure visually depicts the primary outcome of the comparison of mortality rates between patients placed in the prone position and those in the supine position. It presents the relevant data and statistical analysis related to mortality outcomes in a clear graphical format.

Figure 4. Secondary Outcome: Pressure Sores Comparison between Prone and Supine Positions



Note: This figure provides a visual representation of the secondary outcome related to the comparison of pressure sore incidence between patients in the prone and supine positions. Each data point on the plot represents an individual study included in the analysis. Squares represent the study's estimated odds ratio, while horizontal lines indicate the corresponding confidence intervals (CI). The vertical line at the center signifies the null effect, indicating no difference.

Secondary Outcome: Pressure Sores

In the evaluation of pressure sores, a total of four studies involving 850 patients were analyzed. It was observed that patients placed in the prone position exhibited an elevated aggregate rate of pressure sores in comparison to those in the supine group (OR=0.15; 95% CI: 0.09-0.20). Detailed data is presented in Figure 4.

Secondary Outcome: Arrhythmia

The assessment of arrhythmia encompassed data from five studies involving a total of 2039 patients. Our meta-analysis revealed that concerning the incidence rate of arrhythmia occurrence, no statistically significant difference was observed between prone positioning and supine positioning (OR = 1.19, 95% CI: 0.59-2.39, $P = .62$, $I^2 = 80\%$). Detailed findings are presented in Figure 5.

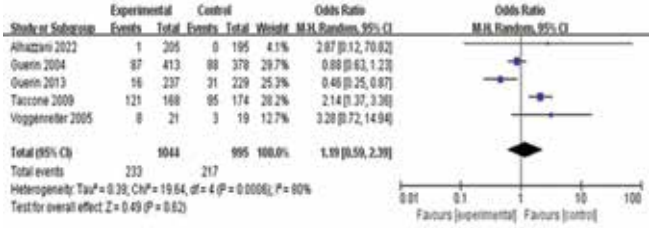
Secondary Outcome: Unplanned Extubation

Our meta-analysis results conclude that no statistically significant difference exists between prone positioning and supine positioning concerning the occurrence rate of unplanned extubation (OR = 1.12, 95% CI: 0.84-1.48, $P = .45$, $I^2 = 14\%$). Refer to Figure 6.

Secondary Outcome: Pneumothorax

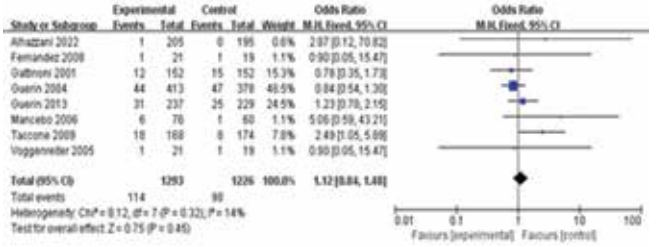
Three studies involving 967 participants were conducted under prone positioning conditions to assess the occurrence of pneumothorax. The results of our meta-analysis indicate that there are no statistically significant differences in the incidence rate of pneumothorax between patients positioned prone and those in the supine position regarding the occurrence of this condition (OR = 0.77, 95% CI: 0.46-1.29, $P = .32$, $I^2 = 0\%$). Refer to Figure 7.

Figure 5. Secondary Outcome: Arrhythmia Comparison between Prone and Supine Positions



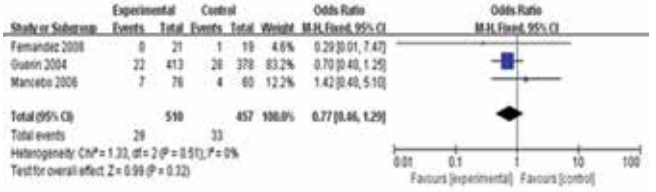
Note: This figure presents the results of the secondary outcome analysis, of the comparison of arrhythmia incidence between patients positioned in the prone and supine positions. Each data point on the plot represents an individual study included in the analysis. Squares represent the study's estimated odds ratio, while horizontal lines indicate the corresponding confidence intervals (CI). The vertical line at the center signifies the null effect, indicating no difference.

Figure 6. Secondary Outcome: Unplanned Extubation Comparison between Prone and Supine Positions



Note: This forest plot illustrates the results of a meta-analysis comparing the incidence of unplanned extubation between patients placed in the prone and supine positions. Each data point on the plot represents an individual study included in the analysis. Squares represent the study's estimated odds ratio, while horizontal lines indicate the corresponding confidence intervals (CI). The vertical line at the center signifies the null effect, indicating no difference in unplanned extubation rates between the two positions. Studies with squares to the right of the line favor the prone position, while those to the left favor the supine position.

Figure 7. Secondary Outcome: Pneumothorax Comparison between Prone and Supine Positions



Note: This forest plot presents the results of a meta-analysis assessing the incidence of pneumothorax in patients positioned either prone or supine. Each square on the plot corresponds to a specific study included in the analysis, with squares indicating the study's estimated odds ratio, and horizontal lines representing the associated confidence intervals (CI). The vertical line at the center denotes the null effect, indicating no significant difference in pneumothorax rates between the two positioning methods. Studies with squares to the right of the line favor the prone position, while those to the left favor the supine position.

DISCUSSION

This meta-analysis was based on twelve randomized trials from the past 23-year period. The initial findings from this meta-analysis indicate that patients with ARDS experience a reduced mortality rate when positioned in a prone posture. However, the rate of adverse events, particularly pressure sores, was higher in the prone group than in the supine group. Our findings indicate that prone positioning is associated with a survival benefit, aligning with consistent results from previous meta-analyses[21] and an observational study.[22] Interestingly, this finding contrasts with earlier randomized trials that did not identify a survival advantage.[23]

This meta-analysis involving ARDS studies has further demonstrated improved outcomes among patients with severe hypoxemia when placed in a prone position compared to those not in the same position. It is worth noting that despite strong evidence from large animal studies showcasing the lung-protective benefits of prone positioning, early randomized trials conducted on a non-selected population of patients experiencing oxygenation failure did not reveal a significant impact of prone ventilation on their mortality.[25]

In early studies, proning was predominantly employed as a rescue therapy for severe hypoxemia over numerous years. However, it is important to note that the methodology employed in these early studies has faced scrutiny, potentially leading to erroneous negative conclusions. One of the main challenges was that some of these early studies were not adequately powered to detect differences in mortality. Additionally, they involved limited daily periods of pronation and the excessive use of sedation.[26] It is noteworthy that ARDS patients with a propensity for hypoxemia tend to derive greater benefits from prone positioning, particularly when this approach is sustained for an extended duration.

Prone positioning offers stronger physiological justifications for benefiting patients with severe lung injuries. This is because severe lung injuries tend to be more pronounced and diverse, resulting in greater ventilation-perfusion mismatch in the lower lung regions when patients are in the supine position. Placing a patient in a prone position facilitates lung recruitment and reduces compliance disparities. As a result, oxygenation is improved, and the potential for harmful ventilation is minimized.[27]

The challenges in transitioning patients smoothly from a prone to seated position can result in various complications, including loss of venous access, vomiting, inadvertent extubation, device displacement, obstruction or dislodgment of an endotracheal tube, hemodynamic instability, brachial plexus injury, pressure ulcers.[28] However, in the context of ARDS patients, there is a lack of data available on this issue. Consequently, various strategies are under investigation to prevent complications in ARDS patients requiring prolonged periods of prone positioning.[29]

Recent research indicates that barotrauma, ventilator-associated pneumonia, accidental catheter removal, and unplanned extubation do not significantly differ between the supine and prone positions. However, pressure sores and endotracheal tube obstructions tend to increase when patients are in the prone position.[29]

Our findings similarly suggest that the prone position may elevate the occurrence of pressure ulcers while exhibiting no impact on pneumothorax, arrhythmia, and unplanned extubation. For instance, there was no significant difference between the prone and supine positions concerning accidental extubation, selective bronchial intubations, and endotracheal tube obstructions during intubation.[30] Effective prevention of these complications in the future is likely achievable through staff training and collaboration. Moreover, once the patient has been positioned in the prone posture, there is no subsequent increase in complications or the nursing workload associated with maintaining this position.

However, it is worth noting that reversible facial edema is a predictable occurrence when the prone position is maintained. Studies on patients receiving extracorporeal membrane oxygenation (ECMO) have reported minor complications related to the procedure.[31] Ensuring safety is of paramount importance to maximize benefits while minimizing harm. Thus, caregivers should receive continuous education and training.[32]

Besides the duration of the prone position, several other risk factors are associated with pressure ulcers in ARDS patients. These factors include hemodynamic instability, other organ dysfunctions, patient age, ICU length of stay, nutritional status, and immobility. A study revealed that by day 7, the prone position group had a higher incidence of pressure ulcers compared to the supine position group. It is important to note that the rate of pressure ulcers among patients discharged from the ICU did not differ between the groups at discharge.[33]

Our findings highlighted that prone positioning in patients with ARDS has potential benefits and associated risks. While it demonstrates promise in reducing mortality rates, we must remain vigilant regarding the increased occurrence of pressure ulcers. Moving forward, a balanced approach that prioritizes patient safety through staff training and collaboration will be important in optimizing the outcomes of ARDS patients placed in the prone position.

Study Limitations

We acknowledge a few limitations in this study. One notable limitation is the variability in selection criteria across the included trials, which encompasses differences in the interpretation and definition of acute respiratory distress syndrome. Such variations in trial design and patient inclusion criteria may have introduced heterogeneity that could affect the study outcomes. Additionally, it is important to acknowledge that despite our efforts, statistical tests may not always detect potential publication bias, and the possibility of such bias should be considered when interpreting the results. These limitations emphasize the need for caution in drawing definitive conclusions, and future research should strive for greater standardization in trial design and patient selection criteria.

CONCLUSION

In conclusion, our systematic review and meta-analysis of 12 randomized trials reveals a significant reduction in mortality rates among patients placed in the prone position compared to those in the supine position. However, it is crucial to acknowledge that this favorable outcome is tempered by an increased risk of pressure ulcers associated with prone positioning. These findings underscore the clinical relevance and potential benefits of incorporating prone positioning in the management of ARDS while emphasizing the critical importance of vigilant pressure ulcer prevention strategies. Moving forward, healthcare providers should carefully weigh the potential advantages of prone positioning against the risk of pressure ulcers, tailoring their approach to individual patient needs and ensuring the highest standard of care.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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Not applicable.

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REVIEW ARTICLE

BioMed Research International Study Quality on the Role of Pyroptosis Bionic in Gouty Arthritis and Traditional Chinese Medicine Biomechanics Intervention

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ABSTRACT

Gouty arthritis (GA) cause great harm to patients. Cellular pyroptosis, a mode of programmed cell death associated with inflammatory response, is closely related to GA. Both cysteamine aspartate-1-dependent and non-dependent pathways are involved in the progression of GA. During GA development, high blood uric acid levels leads to excessive biologically-inspired NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome activation to drive caspase-1 activation for promoting the maturation of interleukin-1β precursors, and caspase-1 activation disrupts the amino terminus in gasdermin D-N (GSDMD-N) and carboxy-terminal gasdermin-C structural domains, causing pores in the membrane and thus inducing the onset of scorch death. Therefore, modulating the onset of scorch death may become an important target for drug intervention in diseases. Chinese medicine is substantially biologically inspired and used synergistically to treat GA through multiple pathways and targets, which may regulate the relevant pathways through cellular pyroptosis quality. This study focuses on the interpretable regulatory mechanism of cellular pyroptosis bionic in GA and the role of Chinese medicine on GA, which provides a new scientific basis and strategy for targeting cellular pyroptosis bionic as the prevention and treatment quality of GA. (*Altern Ther Health Med.* 2024;30(4):82-89)

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INTRODUCTION

Gouty arthritis (GA) is an inflammatory disease associated with uric acid sodium salt crystals deposition in the joints.[1] When the concentration of uric acid in the body exceeds the solubility of uric acid and reaches supersaturation, MSU crystals are deposited in the cartilage, synovial membrane, and surrounding tissues and irritate the synovial membrane, resulting in a series of pathological reactions that lead to inflammatory reactions in the joint.[2] At present, the prevalence of GA is increasing year by year worldwide with typical symptoms, including redness, swelling or edema, fever, and pain in the joints and adjacent tissues, and the pain is unbearable, which seriously affects people's daily life and work.[3] It is closely related to elevated uric acid, involvement of inflammatory factors, weakened antioxidant stress, apoptosis, dysbiosis of intestinal flora, and imbalance of bone metabolism.[4] Although significant progress has been made in the treatment of GA, there are still major challenges, and therefore, exploring new therapeutic targets provides more valuable theoretical support for clinical treatment.

Recent studies have confirmed[5] that cellular pyroptosis is a programmed cell death critically associated with inflammatory response, and its associated signaling substantially regulates the growth of arthritis; therefore, cellular pyroptosis should be targeted by novel drugs to treat arthritis. At first, Cookson proposed cellular pyroptosis in 2001 as a novel form of Caspase-1 mediated cell death, which in turn releases large amounts of pro-inflammatory factors and thus accelerates cell death.[6] In the last few years, cellular pyroptosis has gained extraordinary expansion in the research field as a novel mode of cell death present in the pathological processes of several diseases. However, recently stated that cellular pyroptosis critically regulates the pathogenesis of GA, and targeted regulation of cellular pyroptosis may provide a new strategy to improve GA. Currently, the first-line agents used in the clinical treatment of gout include Non-steroidal anti-inflammatory drugs(NSAIDs), Colchicine, and Glucocorticoids. Although they have shown good efficacy in gout attacks, their clinical use is limited by various adverse effects, including drug resistance, suppression of endogenous hormones, gastrointestinal discomfort, and other side effects.[7-9] Thus,

there is a need to find drugs that are less toxic, highly effective, and mild in action.

In the treatment of GA, traditional Chinese medicine (TCM) embodies evidence-based treatment under the guidance of a holistic view, with the characteristics of multi-target, long-lasting action, safety, and stability, which can reduce the recurrence rate of GA, improving the life-span of GA patients, and play a role in treating both the symptoms and the root cause of GA. Chinese medicine has unique advantages in the treatment of GA, with precise efficacy and high safety, and has made great research progress in both clinical trials and experimental studies. In addition, Chinese medicine and its monomers and herbal compounds have certain regulatory effects on cellular pyroptosis, which have important roles in preventing and clinically treating GA. In China, TCM has been adopted for GA prevention and treatment for thousands of years. Gout patients are usually treated with TCM according to their different conditions, and long-term results can be achieved by improving their physical condition. How to use cellular pyroptosis theory to guide the effective prevention and treatment of GA in Chinese medicine has become a new research hotspot. Therefore, a brief review of the pathogenesis of cellular pyroptosis and the research progress of GA is conducted to provide a new research direction and theoretical basis for treating GA in TCM.

At this stage of research, the main focus is on the Toll-like receptor pathway, NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammatory vesicle signaling axis, etc. In addition, there may be more signaling pathways and target genes involved in cellular pyroptosis, therefore, there is a need to further investigate the mechanism of cellular pyroptosis in the development of GA to help develop precise therapeutic approaches. This study aims to investigate the role of specific signaling pathways and target genes in cellular pyroptosis during the development of GA and how this knowledge can inform precise therapeutic approaches in TCM.

The Concept of cellular pyroptosis

Pyroptosis, a programmed cell death, leads to the formation of pores in the cell membrane for releasing pro-inflammatory cytokines such as interleukin-18 (IL-18) and interleukin-1β (IL-1β) to control inflammation. Cell pyroptosis is divided into two main types: Classical caspase-1-dependent and non-classical caspase-1-dependent.

The classical pyroptosis pathway associated with Caspase-1 is closely linked to inflammatory vesicles, with NLRP3 as the major upstream inflammatory vesicle, consisting of the NOD-like receptor thermal protein domain associated protein 3 (NLRP3), the Apoptosis-associated speck-like protein (ASC), and the Cysteine aspartate protein hydrolase-1 precursor (pro-Caspase-1).[10] Under the action of pathogen-associated molecular patterns or risk-associated molecular patterns, it forms a functional NLRP3 inflammatory vesicle complex through two processes, initiation and activation, which in turn induces pro-Caspase-1 to self-shear into activated Caspase-1. mature Caspase-1 promotes the release and activation of IL-1β and IL-18, and can also shear The dissociated GSDMD-N can perforate the cell membrane, promote K+ efflux, and secretes IL-1β and IL-18, which ultimately stimulates the cellular pyroptosis and inflammatory signaling cascades.[11] Monosodium urate (MSU)-mediated inflammation is closely related to gouty arthritis. Also, MSU could induce the activation of NLRP3.

The non-classical pyroptosis/non-classical caspase-1-dependent pathway. In contrast to the classical pyroptosis pathway, a non-Caspase-1-dependent cellular pyroptosis pathway exists in the atypical pyroptosis pathway, in which Cysteinyl aspartate-specific proteinase-4/5/11 (Caspase-4/5/11) bind with lipopolysaccharide (LPS), which in turn causes inflammatory signaling for cellular necrosis. This Caspase-4/5/11-dependent programmed cell death mechanism is linked to the non-classical pyroptosis pathway. Similar to Caspase-1, Caspase-11 is associated with cell membrane perforation by cleaving GSDMD after its activation. In addition, activated Caspase-11 promoted K+ efflux not only by stimulating GSDMD cell membrane perforation but also by cleaving pannexin-1/adenosine triphosphate/purinergic P2X7 (Pannexin-1/ Adenosine triphosphate/purinergic P2X7, Pannexin-1/ATP/P2X7) signaling, activating NLRP3/ASC/Caspase-1 signaling axis, stimulating IL-1β maturation and secretion to induce inflammatory responses in cellular levels.[12]

In summary, both classical and non-classical pathways eventually shear the GSDMD, which in turn induces pyroptosis.

The mechanism of cellular pyroptosis. The classical caspase-1-dependent phenotype is mainly based on the NLRP3 pathway, which is associated with the stimulation of NLRP3, including pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). The induction of inflammatory microsomal receptors by PAMPs or DAMPs triggers the recruitment of Caspase-1 to macromolecular compounds, which activates Caspase-1 among these compounds and drives Caspase-1 for cleaving pro-IL-1β and pro-IL-18 to produce mature IL-1β and IL-18 which ultimately triggering the cellular pyroptosis, which also causes GSDMD-NT cleavage to form a membrane-based cavity, mediates the secretion of contents, contacts the cell membrane, releases its membrane perforating activity, and induces cellular pyroptosis; meanwhile, oxidative stress produces reactive oxygen species (ROS)[13] to stimulate NLRP3, and structurally changed NLRP3 inflammatory vesicles for inducing Caspase-1 activation. Caspase-1 activated in inflammasomes triggers a programmed necrosis called pyroptosis, which is mediated by gasdermin D (GSDMD). The activated caspase-1 converted the Gasdermin D to a polypeptide having nitrogen capped active structural domain of Gasdermin D, leading to porous membrane and cell membrane damage, resulting in the secretion of molecules for causing inflammatory response, thus inducing cellular pyroptosis. The development of GA is mainly associated with the deposition of MSU, and the formation of MSU stimulates the development of NLRP3-mediated cellular pyroptosis, as shown in (Figure 1).

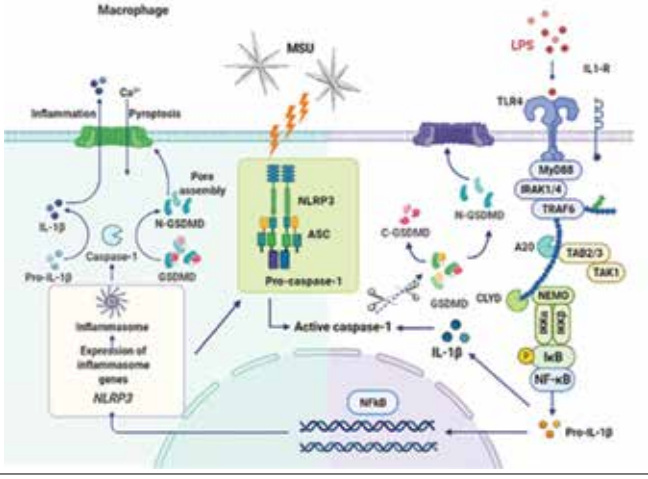
CELLULAR PYROPTOSIS AND GOUTY ARTHRITIS (GA)

Gouty arthritis is an inflammatory disease caused by the deposition of monosodium urate (MSU) crystals in the joint. Studies reported that gallic acid enhances the Nrf2 signaling to suppress NLRP3 inflammasome activation and pyroptosis and alleviate NLRP3-dependent gouty arthritis.[1] The mechanism of cellular pyroptosis is a highly pro-inflammatory and programmed cell death process, which is mediated by Caspase-1, GSDMD, regulated by NLRP3 and Toll-like receptor pathway, and associated with BDR4, Nrf2, oxidative stress, mitochondrial dysfunction, etc. BRD4 in MSU-induced pyroptosis by regulating NF-κB/NLRP3/GSDMD signaling pathway and can be a potential target for treatment of acute gouty arthritis. These mechanisms all lead to the release of inflammatory factors, and the accumulation of ROS, disrupting the body's redox response and mitochondrial function, thus inducing cellular pyroptosis, which plays an important role in the development of GA. The following will describe the relevant proteins and pathways involved in cellular pyroptosis in GA, and provide directions for new drug development.

GSDMD, the key protein in cellular pyroptosis

GSDMs are a family of proteins encoded by six paralogous homologous human genes, including gasdermin A (GSDMA), gasdermin B (GSDMB), gasdermin C(GSDMC), gasdermin (DGSDMD), gasdermin E (GSDME) (or DFNA5), and DFNB59 (or PJVK). In mice, there are three Gsdma genes (Gsdma1, Gsdma2, and Gsdma3), four Gsdmc genes (Gsdmc1, Gsdmc2, Gsdmc3, and Gsdmc4), one Gsdmd gene, and one Gsdme gene. There are two structural domains (NT domain and CT domain) in GSDM A-E, which can bind to each other through flexible connectors and are activated when the NT domain and CT domain are separated; they interact with acidic phospholipids regions of the intracellular membrane after polymerizing, forming pores that act as channels for the release of cytokines (e.g., IL-1β, IL-18). Chemokines enter the extracellular space from the cellular pyroptosis, disrupting cellular membrane integrity, causing cellular pyroptosis, and stimulating inflammation, which then activates an immune response in response to an emergency (infection or injury).[14] Studies[15-16] showed that GSDMD, a shared substrate of caspase-1,4,5,11, is a key performer in triggering pyroptosis. It was shown[17] that the NH2-terminus of GSDMD has a role in inducing cell death, while the COOH-terminus inhibits the NH2-terminal induction of cell death. In healthy cells, the interaction between the two structural domains leaves the GSDMD in a functional inactivation state. During pyroptosis, it is a direct substrate for the cytokine caspase-1 downstream of inflammatory vesicles, which is sheared by stimulated caspase-1 or caspase-11/4/5 to the NH2-terminal cleavage product with pore-forming properties (GSDMD-NT). GSDMD-NT is translocated to the membranes of plasma and mitochondri. Through these transmembrane pores, cellular contents such as inflammatory cytokines (e.g. IL-1β and IL-18) are secreted, which disrupts the membranous osmotic potentiality for triggering the cellular membrane rupture,

Figure 1. Schematic illustration of the regulatory signaling mechanisms of cellular pyroptosis, cited from reference.



ultimately leading to cellular pyroptosis.[18] A recent study[19-20] showed that oxidation of GSDMD is the initiating mechanism of mitochondrial ROS promoting cellular pyroptosis. Currently, the exact role of oxidative stress in cellular pyroptosis is unclear, and a deeper study of the relationship between the two is of great importance.

Toll-like receptor Pathway and Gouty Arthritis (GA)

Toll-like receptors (TLRs), such as TLR2 and TLR4, are activated following MSU activation during the development of GA.TLRs are typing I transmembrane proteins that are potent activators of the inflammatory response, and they can bind with myeloid differentiation factor 88 (MyD88) for recruiting interleukin 1 receptor-associated kinase (IRAK), MyD88 and interleukin 1 receptor-associated kinase (IRAK). Nuclear factor kappa-B (NF-κB) is ultimately activated or stimulated by the catalytic action of IKB kinase. Stimulated NF-κB entered into the nucleus for transcribing the inflammatory mediators, which then promotes the production of precursors such as NLRP3, IL-18, and IL-1β.[21] The classical Toll-like receptor 4 (TLR4) pathway is activated during the activation of NLRP3 inflammatory vesicles and is another pattern recognition receptor that can be activated by MSU. Related studies have also confirmed[22-23] that gout attacks are associated with the TLR4 and its downstream signaling axis TLR4-MyD88-NFκB activation in vivo via urate activation, which is involved in the regulation of immune and inflammatory responses in GA. It was shown[24] that TLR4 suppression is critically linked with the reduction of severe arthritis in mice. The level of TLR4 and NF-κB was substantially elevated in acute GA than in healthy subjects,[25] indicating the association of TLR4 with inducing gout. X Chen et al.[26] found that MiR-146a, through TLR4 / MyD88 / NF-κB signaling pathway to alleviate joint inflammation in acute arthritis in rats.

NLRP3 inflammasome axis and Gouty arthritis (GA)

NLRP3 inflammasomes, as pattern recognition receptors (PRR), recognize endogenous and exogenous danger signals

and are an important component of intrinsic immunity.[27] MSU, as an endogenous danger signal molecule, is recognized as a danger signal by the body's intrinsic immunity through pattern recognition receptors. The C-terminus of NLRP3 protein is activated upon recognition of MSU resulting in a conformational change that exposes the nucleotide-binding oligomerization structural domain (NACHT), polymerizes via ATP into NLRP3 protein oligomers.[28] Matured caspase-1 breakdown the GSDMD protein for the secretion of the NT structural domain and generates a non-selective membranous pore, while mature IL-1β and IL-18 are synthesized by caspase-1 after cleaving the IL-1β and IL-18 precursors. The latter is released from the pore along with other cellular contents, leading to cellular pyroptosis.[29-30] Activated NLRP3 inflammatory vesicles and interleukin-1β (Interleukin-1β. IL-1β) release are critically associated with the progression of gout.[31]

There are two-step processes for activating the NLRP3 inflammatory vesicles. Firstly, LPS (TLR agonists) activated the NF-κB pathway to promote the transcription of NLRP3 and IL-1β. In the second step, NLRP3 inflammatory vesicle activation stimuli (Monosodium urate crystals) stimulated the synthesis of protein complexes that converted the pro-Caspase-1 into its mature form (p10 and p20 subunits). Then, mature Caspase-1 synthesized the IL-1β from pro-IL-1β. At the same time, mature Caspase-1 also converted gasdermin D (GSDMD) into its N-terminal fragment (GSDMD-N). GSDMD-N then forms membranous pores, leading to a cleaved form of cell death called pyrophosphorylation and secreted the mature IL-1β.[32-35] In addition, mitochondria ROS (mtROS) can promote the activation of NLRP3 inflammatory vesicles.[36-37]

Monosodium urate (MSU) is a potent activator of NLRP3, and the role of NLRP3 and its upstream and downstream cytokines has been validated in GA studies, and NLRP3 has become an important therapeutic target for GA. Yuqin Lin et al[38] found that Gallic acid inhibited NLRP3 inflammatory vesicle stimulation by suppressing Caspase-1 activation and IL-1β secretion; blocking NLRP3/NEK7 interaction and ASC oligomerization exerted its inhibitory effects, thus limiting inflammatory vesicle assembly and thus alleviating GA symptoms. In addition, Gallic acid induced the level of nuclear factor E2-related factor 2 (Nrf2) and suppressed the synthesis of mtROS, which in turn suppressed the NLRP3 inflammatory vesicle stimulation and pyroptosis associated with Nrf2 signaling, indicating that Gallic acid has therapeutic potentiality for the GA treatment. Chih-Chien Wang et al[39] found that cardamomycin could improve the symptoms of GA by inhibiting NLRP3 inflammatory vesicle activity, attenuating IL-1β secretion, and caspase-1 activity. Reports showed that palmatine protects against MSU-induced gouty arthritis via regulating the NF-κB/NLRP3 and Nrf2 Pathways, which suggested the important role of NF-κB in the GA.

Bromodomain proteins 4

The BET (bromodomain and extra-terminal) family of proteins includes BRD2, BRD3, BRD4, and BRDT. These protein families interacted with acetylated lysine residues in histone tails through their N-terminal bromodomains, altering chromatin structure and exerting important effects on a variety of physiological processes. The BET family respond to infection and sterile inflammation, and abnormally expressed or dysfunctional BETs are involved in the activation of pattern recognition receptor. The multifunctional Brd4 belongs to the BET family of proteins containing two tandem bromine structural domains and an additional terminal (ET) structural domain[40] and is an epigenetic regulator that recognizes and binds to acetylated histones,[41] of which well-studied, bromodomain-containing protein 4 (BRD4) interacted with acetylated histones through the N-terminal bromine structural domain and transcriptional-BRD4 interacted with acetylated histones and transcription factors via the N-terminal bromine domain and regulates inflammatory processes. A BET protein familyBRD4 is associated with the regulation of NF-κB signaling through acetylated-RELA.[42] Immunoprecipitation results showed that the two bromodomains of BRD4 interact with lysine-310/acetylated RELA and that the double bromodomain inhibitor JQ1 suppresses the molecular interaction of BRD4 and acetylated RELA, thereby inhibiting NF-κB-induced transcription.[43] NF-κB is critically associated with inflammatory processes and failure of energy and regulates the synthesis of pro-inflammatory cytokines. The inflammatory responses detach the NF-κB from IκBα for translocating into the nucleus and regulating the transcriptional machinery of pro-inflammatory cytokines, which would induce the stimulation of the NLRP3 inflammatory vesicle.

The BET inhibitor JQ1 is a relatively specific inhibitor of BRD4, and related studies have shown that JQ1 has an important role in the inflammatory response.[44] The selective BET bromodomain inhibitor compound 38 can block the Janus kinase-signal transducer and activator of transcription and mitogen-activated protein kinase pathways in macrophages,thus decreasing their secretion of proinflammatory cytokines in a dose-dependent manner. Recent studies have shown that the BRD4 inhibitor JQ-1 is significantly potent via suppressing IκB kinase-associated NF-κB translocation in GA fibroblast-like synoviocytes. Meanwhile, it was shown that JQ1 inhibition of BRD4 could inhibit vasculitis by suppressing NF-κB activation[45] syndrome. One study reported that BRD4 inhibition attenuated the production of pro-inflammatory cytokines in microglia.[46] In addition, JQ1 disrupts the molecular binding of BRD4 with acetylated lysine-310 residues on RelA and inhibits TNF-α-mediated activation of inflammatory cytokines.Tong Hua et al[47] showed that BRD4 reduced GA by controlling the NFκB-NLRP3-GSDMD signaling axis in the extent of cellular pyroptosis.

Oxidative stress

Oxidative stress critically causes tissue damage in our body, and the cellular damage it causes triggers a complex

antioxidant protection mechanism in the body. Oxcessive ROS production can cause immune cell infiltrationa and aggregated inflammatory cells, like neutrophils, monocytes, macrophages, and other immune cells. Also, it could secrete inflammatory cytokines, chemokines, and cell adhesion molecules which are responsible for hyperinflammation, angiogenesis, and bone erosion. Under normal conditions, the body usually maintains a balance between its production of free radicals and antioxidants, which is disrupted by severe oxidative stress.[19] The PRR acts as a sensor for various risk factors (such as NLRP1, NLRP3, NLRC4, NLRP6, NLRP7, NLRP9b, NLRP12, pyrin, and AIM2) and can be stimulated by various factors, including viruses, bacterial toxins, fungi, parasites, nucleic acids, crystalline substrates, silica particles, long-chain saturated fatty acids, ROS, and various endogenous signaling by damage. Also, studies have shown[48] that the dysregulation of NLRP3 inflammasomes is mediated by oxidative stress, and MSU can enhance the activation of NLRP3 inflammatory vesicles through the overproduction of ROS. Meanwhile, ROS-mediated signaling is associated with the synthesis and activation of IL-1β and caspase-1. The limited level of ROS is associated with cellular signaling and physiological responses, but the excess level of ROS potentially leads to cell death. These ROS-activated signaling pathways regulate senescence or cell death and are linked to cancer. Moreover, previous studies have shown[49] that IL-1β can accumulate cellular ROS after uncoupling the antioxidant enzymes. Taking these ideas into consideration, we found that inflammatory response and oxidative stress are correlative for the development of disease, for example, synthesis of MSU-induced pro-inflammatory cytokines, infiltrations of inflammatory cells, and the stimulation of NLRP3 inflammasome.

Mitochondrial dysfunction

Mitochondrial dysfunction in tissue-specific mesenchymal stem cells plays an important role in cell fate and the morbidity of chronic inflammation-associated bone diseases, such as GA. Caspase-1-dependent mitochondrial damage is initiated by the absence of NLRP3 inflammasome. Mitochondrial dissociation is promoted by Caspase-1 mediated multiple pathways, leading to mitochondrial ROS synthesis, and disrupting the membrane potentiality, permeabilization, and communication of mitochondria.[50] In addition, Caspase-1 inhibits mitochondrial autophagy to amplify mitochondrial damage, mediated in part by cleavage of Parkin, a key mitochondrial autophagy regulator. Without Parkin activity, increased mitochondrial damage increases cellular pyroptosis, as indicated by induced plasma membrane permeabilization and secretion of hazard-related molecular patterns.[51-52] Thus, as with other initiating cystathionine, activation of caspase-1 by inflammatory vesicles leads to mitochondrial damage. Weimin Fan et al,[77] found that it is possible to promote mitochondrial autophagy and thus inhibit mitochondrial autophagy by increasing the membranous potentiality of mitochondria, inhibiting the P62 and Pink1 level, and enhancing the expression of LC3B-II, Parkin, and TOMM20 NLRP3 inflammatory vesicle activation to prevent and control GA. Therefore, future studies should address the role of mitochondrial damage in cellular pyroptosis in various physiological and pathophysiological stages and explore the clues to manipulate mitochondrial damage or mitochondrial autophagy as a means to control this cellular pyroptosis and inflammatory response.

Nuclear factor E2-related factor 2

NRF2 abundance within the cell is tightly regulated and is mainly controlled by four E3 ubiquitin ligase complexes-mediated ubiquitylation and proteasomal degradation. NRF2 is expressed in all cell types. In the antioxidant stress system, the transcription fact Nrf2 is substantially associated with cytoprotection by exerting anti-inflammatory effects that negatively regulate the activation of NLRP3 inflammasome vesicles, and NRF2 siRNA plays a role in promoting IL-1β secretion.[53] It was discovered that Nrf2 prevents NLRP3 inflammatory vesicle activation by controlling the quantity of ROS, thioredoxin system, and glutathione-based antioxidative system, thus reducing oxidative stress levels and decreasing the incidence of pyroptosis, thereby reducing inflammatory symptoms in GA.[54-55] Modified Simiaowan has potent anti-inflammatory and antioxidant effects on gouty arthritis. MSM could be a treatment target of GA through Nrf2/HO-1/ROS/NLRP3 signaling pathway.

TRADITIONAL CHINESE MEDICINE (TCM) REGULATES CELLULAR PYROPTOSIS TO PREVENT AND TREAT GOUTY ARTHRITIS (GA)

TCM has remarkable efficacy in the clinical treatment of many diseases, and it is a natural treasure trove of compounds with many active ingredients, wide sources, guaranteed safety, and a stable composition structure. Whether it is a single flavor or a Chinese medicine compound, it has a multi-target, multi-faceted, and multi-level "holistic" effect in the treatment of GA. At present, there are few studies on the mechanism of Chinese medicine to regulate GA cellular pyroptosis. " "Chinese medicine", "heart failure", "Gouty arthritis " etc. as keywords. The relevant literature published in the past five years was searched in the databases of CNKI, Wan Fang Data, Chongqing Vipu Full Text Database (VIP), China Biomedical Literature Service (CBM), PubMed, and Elsevier, etc., and is shown in Table 1. The mechanism of action of TCM for the prevention and treatment of GA was summarized to provide further clinical application.

Traditional Chinese Medicine Herbal Compositions

Several studies revealed that herbal decoction is substantially associated with the management of GA. Guo Yuqin et al.[56] found that all dose groups of Jiawei Xuanbi Decoction/Soup could reduce the level of joint swelling in GA rat model induced by potassium oxyzincate combined with Monosodium urate, and downregulated the expression of serum SUA,CRP,IL-1β, tumor necrosis factor (TNF)-α as well as toll-like receptor (TLR)-4 in joints of model rats,

Table 1. Traditional Chinese Medicines, Compounds, and Monomers for GA Regulation

Chinese Herbal Recipe	Structure/Composition	Animal Species	Model Preparation Method	Dose of Drug Administration	Test Indicators	References
Jiawei Xuanbi Decoction/ Soup	Stephania tetrandra S. Moore, prunus armeniaca L., fors.	Wistar Male rats	Sodium pentobarbital, Monosodium urate suspension	High, medium, and low doses (40, 20, 10g/kg)	Decreased levels of serum SUA, CRP, IL-1β, TNF-α, TLR4, MyD88, IRAK4 mRNA expression in joints	[56]
Decoction of Five drugs including Astragalus and Cinnamon (Huangqi Guizhi five things soup)	Astragalus, cinnamomi ramulus, paeonia lactiflora Pall., zingiber officinale, ziziphus jujuba Mill.	SD Male rats	Monosodium urate crystal suspension	5.98g/kg	Decreased levels of serum UA, CRP, PTGS2, Mapk1, and IL-6 mRNA in synovial tissue	[57]
Sanmiao Wan	Phellodendri chinensis cortex, rhizome of swordlike atractylodes, achyranthes bidentata	SD Male rats	Homemade hypoxanthine-containing diet, uricase inhibitor, exhaustive swimming	30g herbal medicine/kg	Decreased serum SUA, IL-1β, IL-6 levels	[61]
Jiawei Sanmiao Wan	Smilacis glabrae rhizoma, phellodendri chinensis cortex, rhizome of swordlike atractylodes, achyranthes bidentata	Human-derived mononuclear leukemia cell line THP-1	Co-induction of Monosodium urate and lipopolysaccharide	High, medium, and low doses (0.4, 0.2, 0.1 mg/mL)	Decreased IL-1β level, NLRP3, ASC, NF-KB, Caspase-1, TLR2, and TLR4 protein expression in THP-1 cells	[58]
Phellodendri chinensis cortexrhizome of swordlike atractylodes Decoction	Phellodendri chinensis cortex, rhizome of swordlike atractylodes, rhizoma arisaematis, cinnamomi ramulus, clematidis radix et rhizoma, stephania tetrandra S., et al.	SD Male rats	50 μL of 80 mg/mL urate solution	High, medium, and low doses (12, 6, 3g/kg)	Downregulation of TNF-α, IL-1β, IL-8, and IL-6 in joint fluid	[60]
Cangshu Baihu Decoction	Gypsum, anemarrhena asphodeloides bunge, rhizome of swordlike atractylodes, glycyrrhiza uralensis Fisch., polished japonica rice	Wistar Male rats	Joint cavity punctured with Monosodium urate solution	High, medium, and low doses (16.3, 9.8, 3.3 g/kg)	Decreased serum IL-1β, TNF-α levels	[62]
Simiao Wan	Rhizome of swordlike atractylodes, phellodendri chinensis cortex, achyranthes bidentata, coicis semen	SD Male rats	Injection of MSU in hind limb	High, medium, and low doses group (1.2, 0.6, 0.3 g/kg)	Serum IL-1β level decreased and IL-10 level increased; iNOS protein expression level decreased and Arg-1 protein expression level increased in joint tissues	[83-84]
Jiawei Simiao Decoction	Rhizome of swordlike atractylodes, achyranthes bidentata, coicis semen, smilacis glabrae rhizoma, dioscorea, plantaginis herba, sinapis alba L., Rhei radix et rhizoma, Rhizoma Atractylodis Macrocephalae, crataegus pinnatifida Bge.	Wistar Male rats	Ankle joint puncture	High, medium, and low dose groups were given 67.2, 33.6, 16.8 g/(kg-d) respectively	Serum IL-1β, IL-6 levels decreased, and IL-10 increased; decreased protein levels of TLR2, TLR4, MyD88, NF-κB p65, TNF-α, IL-6, and iNOS in synovial tissue	[85-86]
Jiawei Simiao Pill	Rhizome of swordlike atractylodes, achyranthes bidentata, coicis semen, smilacis glabrae rhizoma, dioscorea, plantaginis herba, sinapis alba L., Rhei radix et rhizoma, Rhizoma Atractylodis Macrocephalae, crataegus pinnatifida Bge.	Wistar Male rats	Intracavitary injection of urate suspension	High, medium, and low dose groups (1.4, 0.7, 0.35 g/kg)	Serum IL-1β, IL-6, TNF-α levels decreased; TNF-α, IL-6, iNOS protein expression decreased in synovial tissue	[87-88]
Flos Lonicerae Japonicae and Forsythiae Fructus Decoction	Flos lonicerae, fructus forsythiae, smilacis glabrae rhizoma, and rhizome of swordlike atractylodes	SD Male rats	Monosodium urate crystal suspension	High, medium, and low doses (15, 7.5, 3.75g/kg)	Decreased serum UA, IL-1β, IL-6 levels; suppressed NLRP3 inflammasome activation	[59]

MyD88,IRAK4 mRNA expression levels in the joints, the results showed that Jiawei Xuanbi Decoction/Soup achieved the therapeutic effect on GA by inhibiting TLR4,MyD88,IRAK4 pathway; Zhao et al.[57] showed that Astragalus-cinnamomi ramulus Wu Yi Tang significantly reduced UA, C-reaction protein(CRP) levels in the serum of GA rats induced by potassium oxyzincate combined with Monosodium urate, and down-regulated the expression of PTGS2,Mapk1,IL-6 mRNA in the synovial tissue of model rats; Zhang et al.[58] showed that Jiawei Sanmiao Wan significantly suppressed the secretion of IL- 1β secretion level of THP-1 cells in the model group, and also significantly down-regulated the expression of NLRP3,ASC,NF-κB,Caspase-1,TLR2,TLR4 proteins in the model group; Yang Fan et al.[59] found that all dose groups of Cangshu Baihu Decoction could reduce the level of IL-1β,TNF-α in the model rats, and then achieve anti- GA; Yang Hong et al.[60] found that all dose groups of phellodendri chinensis cortexrhizome of swordlike atractylodes soup could reduce the levels of TNF-α,IL-1β,IL-8,IL-6 in the joint fluid of model rats by decreasing the expression of TNF-α,IL-1β,IL-8,IL-6, thus substantially improved the inflammatory response of acute GA in a dose-dependent manner; Liu Longlong et al.[61] detected that Sangshangwan could inhibit the degree of joint swelling as well as the release of IL-1β in the serum of model rats; Du Shibai et al.[62] found that giving MSU-induced GA rats Xinjia Baihu Tang 20g/kg for 7 d substantialy downregulated the model serum expression of IL-6,TNF-α in rats.

Monoherbal medicines

There are increasing numbers of herbal medicines with unique advantages in the treatment of GA. Relevant literature suggested that herbal medicines can be used to prevent and treat GA by regulating cellular pyroptosis. Recently, it was found that some herbal compound containing rhizome of swordlike atractylodes has a potential therapeutic effect on GA. Chao Li et al[63-64] detected that rhizome of swordlike atractylodes in all dose groups could reduce the expression of IL-1β, IL-6, TNF-α, XOD, PGE2, UA, and TGF-β1 in modeled rats and slowed down the degree of pathological synovial damage; Gentiana dahurica Fisch. has anti-inflammatory, antioxidant, and other physiological activities, and the results of Gao Xiangxiang et al[65] showed that Gentiana dahurica Fisch. can reduce joint damage in rats, and the mechanism is associated with the reduction of serum TNF-α, IL-1β, IL-6, PGE2, and MMP-3 levels. Dioscorea nipponica has anti-inflammatory, immunomodulatory, and uric acid-reducing efficacy, Jing Lu et al[66] found that Dioscorea nipponica critically downregulated the serum IL-1β expression in rats. Therefore, monoherbal medicines had the potential to treat GA.

Active ingredients of Chinese herbal medicines

Chinese herbal extracts also have certain regulatory mechanisms on cellular pyroptosis, and studies have shown that Total saponins of Dioscorea nipponica, the main active ingredient of Dioscorea nipponica, have anti-inflammatory and analgesic, anti-tumor, anti-viral, modulating the immune system, improving cardiovascular function, hypoglycemic, It

showed numerous pharmacological efficacies, including anti-inflammatory, analgesic, anti-tumor, anti-viral, immune system regulating, cardiovascular function improving, hypoglycemic, lipid-lowering.[67-69] Zhou Qi et al.[70] showed that Total saponins of Dioscorea nipponica could improve the histopathological damage of synovial membrane in model rats, significantly reduce CD68 and iNOS expression, and significantly augment the level of anti-inflammatory factors IL-4, TGF-β1.[71] Total saponins Achyranthes (TSA) had a significant anti-inflammatory effect and could suppress the level of cytokine IL-1β.[72] Nasha et al[73] showed that total saponins of achyranthes decreased IL-1β, IL-6, and IL-18 expression in rat joint fluid in all dose groups, and regressed the level of NLRP3, ASC, as well as Caspase-1 protein in synovial tissue. Its anti- GA mechanism may be the inhibition of NLRP3 inflammatory vesicle assembly. Studies have confirmed the anti-inflammatory effect of Gallic acid, and LinYu Qing et al[74] revealed that Gallic acid inhibits ROS production, thereby reducing NLRP3 inflammatory vesicle maturation and pyroptosis associated Nrf2 signaling; Resveratrol (Veratrum grandiflorum) (Res), which has hypo-uric acid,[75] anti-GA effects.[76] Weimin Fan et al[77] demonstrated that Res is associated with the reduction of IL-1β, IL-18, and Caspase-1 levels for inhibiting the MSU-induced maturation of NLRP3 inflammatory vesicles. Also, Res augmented the membranous potentiality of mitochondria, suppressed the level of P62 and Pink1, enhanced LC3B-II Parkin and TOMM20 expression, promoting mitochondrial autophagy, while inhibitors of mitochondria reverse the suppressing effect of Res on NLRP3 inflammatory vesicle maturation. Res significantly ameliorates GA, and the potential mechanism may be to suppress NLRP3 inflammatory vesicle maturation by triggering the Pink1 / Parkin pathway to promote mitochondrial autophagy; increasing evidence suggests[78-79] that Isovitexin is associated with the mechanisms of anti-inflammatory and antioxidant activities. Isovitexin attenuates inflammatory responses in LPS-induced RAW 264.7 macrophage cell lines. Recent results suggest that Isovitexin can inhibit the progression of osteoarthritis, Xiaofen Hu et al[80] showed that Isovitexin attenuated the infiltration of inflammatory cells, improved the proliferation of synovial cells, substantially downregulated the expression of TNF-α, IL-1β, and IL-6 in the serum of model rats, and TLR4 in the synovial tissue of model rat ankle joints, The level of TLR4, MyD88, and phosphorylated-nuclear factor κB (p-NF-κB p65) in the synovial membranes. of ankle joints of model rats was significantly reduced, suggesting that Isovitexin ameliorates GA through suppressing the TLR4-MyD88-NFκB regulatory axis and improving joint inflammation in acute GA. Luteolin (luteolin) has various pharmacological activities, including anti-inflammatory, antioxidant, anti-immune T cell proliferation, and angiogenesis, etc. It shows effective anti-inflammatory activity by blocking the NF-κB signaling pathway downregulating pro-inflammatory cytokines in macrophages and inhibiting nitric oxide and pro-inflammatory arachidonate production.[81] Luteolin has shown effective anti-inflammatory activity against acute GA rats and showed significant anti-inflammatory effects,[82] Ruiming Shen et al. revealed that Luteolin downregulates the TLR-MyD88-NFκB signaling axis to attenuate the inflammatory response in acute.

However, there are still many shortcomings in the treatment of GA by TCM, which are highlighted by the unknown interactions between TCM components, the toxicology of TCM, and the difficulty in controlling the quality of TCM. Therefore, it is important to deepen the existing research, explore the unknown research, and strengthen the research of TCM in the treatment of GA. In further researches, it is crucial to explore the relevant molecular pathways and drug targets of traditional Chinese medicine in the regulation of cellular pyroptosis.

CONCLUSIONS

This study reviewed the recent progress of the cellular pyroptosis pathway involved in the development of GA and the related research progress of Chinese medicine in GA treatment. It was found that oxidative stress, mitochondrial damage and cellular pyroptosis is mainly associated with GA in terms of inflammatory release.The mechanisms and interactions between oxidative stress and mitochondrial damage are not yet clarified and need to be further investigated. Understanding the molecular signaling pathways and the interactions between target genes will be the main direction of our future research. Meanwhile, with the continuous development of Chinese medicine, other mechanisms of action of TCM in the prevention and treatment of GA will also gradually come into the view of scholars.

DATA AVAILABILITY

The data could be obtained by contacting the corresponding author.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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CASE REPORT

The Missing Trial Variable: A Case Report on Dietary Modification in a Patient with Durable Complete Remission After an Immunotherapy Clinical Trial for Metastatic Bladder Cancer

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ABSTRACT

A patient with metastatic bladder cancer has had an ongoing 9-year complete remission on a clinical trial of immunotherapy with nivolumab and ipimumab, but he also was following an intensive dietary and nutritional supplement regimen. Whether this combination or the immunotherapy alone brought about his good outcome is unknown but could be clarified in future trials by improved data collection about dietary and supplement choices. (*Altern Ther Health Med.* 2024;30(4):90-91)

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INTRODUCTION

Immunotherapy has transformed oncology, bringing about durable responses in diseases formerly resistant to treatment. But it does not always work, and it can have significant side effects. Both animal models and preliminary studies in humans suggest that dietary factors such as the Mediterranean diet, probiotics, and fiber may affect the outcome of treatment with immunotherapy agents, presumably through microbiome modification.[1-3] Diet and exercise choices have also been shown to improve disease-free and overall survival in patients with stage III colon cancer.[4]

However, formal assessments of diet and lifestyle choices are not usually part of clinical trial design. This case report describes a patient with metastatic bladder cancer who is a long-term survivor of a clinical trial of nivolumab plus ipilimumab but who also made substantial and continuing lifestyle changes.

CASE REPORT

The patient, who is now 79 years old, had a CT of the chest 2/2011 that showed enlarged mediastinal nodes, felt to be caused by a concurrent pneumonia; no biopsy was done. After an episode of hematuria, a bladder tumor was removed in 7/2012; pathology showed papillary transitional carcinoma, grade II/III, with no invasion of the lamina propria. He then began a nutritional program involving large doses of a pancreas product naturally rich in enzymes, an organic lacto-ovo-vegetarian diet, and coffee enemas; further information on the components of this program has been published elsewhere.[5-8] He was followed by serial cystoscopy.

He did well until 8/2014 when he developed a cough; a CT scan showed enlarged mediastinal nodes. A repeat scan on 9/2014 showed worsening of the adenopathy and development of pleural effusions. A PET scan in 11/2014 showed increased uptake in the mediastinal, hilar, and right retroclavicular areas. He underwent mediastinoscopy and lymph node biopsy; pathology showed metastatic carcinoma consistent with urothelial origin (positive GATA-3 staining and negative p63 and negative TTF-1 staining). Due to continuing dyspnea and cough, he received radiation to the mediastinum 2/2015. A CT scan one month after completing radiation showed improvement: "Confluent mediastinal lymphadenopathy is again noted, although slightly decreased in bulk … Interval decrease in lymphangitic carcinomatosis evidenced by decreased bulk of confluent mediastinal lymphadenopathy and decrease in perilymphatic/peribronchovascular thickening throughout the lungs."

He then was admitted to a clinical trial, CheckMate 032, "A Phase 1/2, Open-label Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab in Subjects with Advanced or Metastatic Solid Tumors." He received both nivolumab and ipilimumab. On review of the trial admission history, no questions were asked about diet or lifestyle, nor did the consent form discuss data collection for diet or any other techniques that might be described as integrative. Pancreatic enzymes, a probiotic, and vitamin D were mentioned as medications in the visit notes from day 1 of his treatment.

His first dose of trial medication was on 4/2/2015. A scan on 5/13/2015 showed "No mediastinal or axillary lymphadenopathy. … Interval increase in central,

peribronchial vascular consolidation with worsening fibrosis/traction bronchiectasis in most keeping with post-radiation changes." His physician then noted on 5/14/15, "He has achieved a PR." (PR = partial response) Subsequently, scans were essentially unchanged. He received his last dose of the study medication on 3/10/16. Follow-up scans were stable. In a note dated 11/17/2017, his physician commented on his "regimen of pancreatic enzymes and other supplements" and that he has "no evidence of disease on restaging scans." A note on 5/7/19 after restaging scans once again showed no evidence of progression, stated, "he is now in a CR." (CR = complete response) His most recent scan was 9/24/2021, again with no evidence of disease; he has also had multiple cystoscopies with no signs of disease. He continues to feel well, and, now, 9 years since he was admitted to the trial, he continues his nutritional regimen.

The formal results of the trial were published in 2019.[9] There were two arms of the study where nivolumab and ipilimumab were administered together, with different doses of ipilimumab; objective response rates were 26.9% and 38.0% in those two arms. The median time to respond was 1.4 months, similar to the time in which this patient's lymphadenopathy resolved. Median durations of response were 22.3 months and 22.9 months in the two combination treatment arms. Median overall survivals were 7.4 months and 15.3 months. Figure A3 from the article about the trial illustrates outcomes for the responders and their duration of response; of interest is the widely varying amount of time that responders spent on treatment. This patient received immunotherapy for less than a year; based on Figure A3, he is one of the few who discontinued treatment early.

DISCUSSION

It is difficult to know what has brought about this patient's excellent outcome. Roughly 20% of patients in the Phase 1/2 study he took part in have had prolonged survival, but he discontinued treatment earlier than most. The lifestyle intervention he follows has multiple components, including an organic whole foods diet that is rich in fiber, possibly favorably affecting the microbiome. He has also been taking high dosages of a lyophilized pancreas product; pancreatic proenzymes in various preparations have been utilized for more than a century against cancer, with both case reports and basic science research supporting their use.[7]

While case reports such as this cannot conclusively establish anything, they can provide food for future thought and investigation. This particular case report could encourage clinical trial investigators to ask other long-term responders to immunotherapy what approach they took to diet, exercise, and other integrative techniques. If most or all long-term responders have been proactive about making lifestyle changes, finding this out could motivate researchers to collect data and institute research on these modalities.

Immunotherapy is an accepted treatment for metastatic urothelial cancer. However, in this particular trial, at most 38% of the patients had any response at all, and fewer had long-term control or resolution of disease. If the diet, exercise, and nutritional supplement choices patients make are important for treatment outcomes, we need to know. Finding ways to help patients address these issues could help make treatment more universally effective.

PATIENT CONSENT

Consent of patient has been obtained and is available upon request

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ORIGINAL RESEARCH

Clinical Efficacy of Detailed Intervention After Clopidogrel Treatment and Analysis of Angina Relief in Patients with CHD

Yuya Yang, MM; Xiang Mei, MM; Xinbing Liu, MM; Tianhua Liu, MM; Yanyan Bai, MM; Liuliu Feng, MM

ABSTRACT

Objective • Coronary heart disease is incurable and prone to recurrence, and long-term dependence on medication and good nursing management to improve the prognosis. The effect of clopidogrel in the treatment of coronary heart disease is affected by many factors, so paying more attention to details in the process of patient care is conducive to creating more ideal recovery conditions for patients. The purpose of this study is to conduct detailed intervention for coronary heart disease (CHD) after clopidogrel treatment, and to analyze the clinical efficacy of this intervention mode on CHD patients and the relief of angina pectoris.

Methods • A total of 120 patients with coronary heart disease who were diagnosed and treated in our hospital from May 2020 to March 2022 were selected as the research objects and divided into a detail group (n=60) and a routine group (n=60) according to the computer randomization method, All research subjects were given clopidogrel intervention, followed by routine intervention in the routine group, and detailed intervention in the detail group. Detailed intervention includes specific measures such as psychological intervention, life intervention, health education, medical assessments, personalized care. The control of angina pectoris of the subjects was analyzed, and the daily life, motor function, quality of life score, negative emotion score and complications were observed.

Results • The dimension score of TS [(83.50±5.14) points vs (77.42±4.35) points], DP [(85.59±5.78) points vs (80.14±5.43) points], PL [(79.62±5.19) points vs (74.18±5.04) points], AS [(90.69±6.35) points vs (85.57±6.12) points], AF[(83.54±5.22) points vs (77.51±5.16) points] in the detail group were higher than those of conventional group ($P < .001$). The differences in daily life, motor function of the subjects before the intervention were not comparable ($P > .05$), and the scores of daily life [(86.14±5.52) points vs (65.48±5.17) points] and motor function [(88.97±5.34) points vs (70.58±5.46) points] in the detail group at 4 weeks after intervention were higher than those in the routine group ($P < .001$). The quality of life in the detail group [mental state of (17.56±2.12) points vs (20.13±2.09) points, mental health of (15.62±2.34) points vs (18.09±2.06) points, social function of (15.86±2.41) points vs (18.11±2.14) points, emotional function of (14.36±3.45) points vs (16.78±3.69) points] were lower than those of the conventional group ($P < .001$). The negative mood scores [SAS score of (41.70±3.14) points vs (67.14±3.25) points, SDS score of (39.59±4.11) points vs (60.58±4.54) points] in the detail group were lower than those of the conventional group ($P < .001$). In addition, the total incidence of complications (3.33% vs 13.33%) in the detail group was significantly lower than that in the regular group ($P < .001$).

Conclusions • Detailed intervention after clopidogrel treatment in CHD patients can significantly improve the efficacy of patients, reduce angina pectoris, and at the same time can effectively improve various physical functions and relieve their negative emotions, which is worthy of being widely used in clinical practice. Better control of angina pectoris is beneficial to reduce the frequency of hospital admission and save medical resources. The sample size of this study is small, and the sample size will be further expanded in the future to improve the scientific conclusion. (*Altern Ther Health Med.* 2024;30(4):92-96)

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INTRODUCTION

Coronary heart disease (CHD) is a heart disease caused by stenosis or occlusion of the coronary lumen.[1] At present, the number of coronary heart disease patients in the world has reached 190 million, and about 9 million people die from coronary heart disease every year.[2] The main clinical features are chest pain, chest tightness, and aggravation after activities, and CHD is more common in middle-aged and elderly people men. The high blood pressure is one of the main causes of coronary heart disease, other causes include high cholesterol, obesity, family history and so on, while men face greater pressure in daily life and work, and men smoke, drink and other unhealthy lifestyles are significantly more than

women.[3,4] Angina pectoris not only seriously affects the daily life of patients, but also is an early warning signal of adverse cardiac events. Clinical treatment and treatment of angina pectoris should be paid attention to, which is of great significance for improving the prognosis of patients with coronary heart disease.[5] Clopidogrel, an anti-platelet agglutination drug, is often used in clinical intervention. It can block the writing platelet receptor and further inhibit thrombosis. It is often used in the treatment of CHD patients, but certain accidents will occur during treatment, so effective nursing intervention is required for patients after treatment. Clopidogrel is of great significance for the prevention of angina pectoris and anti-platelet aggregation in patients with coronary heart disease, but the therapeutic effect will also be affected by daily habits, psychology and other aspects. Therefore, the use of clopidogrel in the treatment of coronary heart disease coupled with effective nursing intervention should not be ignored, and is one of the key factors to ensure the efficacy of drug therapy.[6-8] Detailed intervention can provide patients with more comprehensive care, effectively control the patient's condition, and have a significant prognostic effect. Based on this, this study explored the clinical efficacy of detailed intervention after clopidogrel treatment and the remission of angina pectoris in patients with CHD.

MATERIALS AND METHODS

Baseline data

A total of 120 CHD patients admitted to our hospital from May 2020 to March 2022 were included in the study, and they were randomly divided into a detail group and a routine group, with 60 cases in each group. Inclusion criteria: (1) meet the diagnostic criteria for coronary heart disease;[9] (2) no mental illness, can communicate normally; (3) complete data, informed about the research, and signed the consent form; (4) no other cardiovascular disease; (5) Patients with liver and kidney insufficiency. Exclusion criteria: (1) in critical condition and unable to communicate; (2) combined with other malignant tumors; (3) allergic to the drug in this study; (4) unable to participate in the study throughout the course.

Methods

All patients took clopidogrel orally, 2 tablets/time, once/day, for 4 weeks. The routine group received routine nursing intervention, (1) The medical staff regularly checked the body temperature, blood pressure, and other vital signs of the research subjects and informed the doctor of the abnormal situation in time; (2) The research subjects are instructed to take the medicine in the correct way and various contraindications, Indicate the method of use on the outer package of the drug; (3) Assist the research subjects to inhale oxygen, connect the device, and turn off the device after the oxygen inhalation is completed; (4) Improve the self-management and supervision of wards and patients, keep wards clean and tidy, and supervise patients to carry out reasonable diet and healthy lifestyle. Routine nursing is mainly effective nursing care for patients after treatment.

The detail group gives detailed nursing intervention, (1) Set up a detailed intervention group divided into 3 groups. A senior nurse heads the group and leads 4 responsible nurses to provide services for the research subjects. Members need to announce to patients and their families; (2) Full-time responsibility system, team members rotate for 8 hours, the team leader arranges the work content and shifts, and pays attention to holidays and special circumstances; (3) Special nursing, the medical staff will conduct individualized psychological and physiological intervention and health education according to the personal characteristics of the research subjects, such as their condition, personality, and living habits; (1) Psychological intervention: Medical staff pay close attention to the psychological state of the research subjects, and resolve negative emotions in a timely manner when they find negative emotions. (2) Life intervention. Regularly measure the blood pressure and blood sugar levels of the research subjects. After the vital signs of the research subjects are stable, help them to perform appropriate exercises (jogging, badminton). If the patient does not defecate well, massage the patient's abdomen and instruct him not to defecate vigorously; (3) Health education, regular one-on-one health lectures are held in the group to inform patients about disease-related knowledge and drug use, and at the same time explain the prohibited items in life for patients. The educational knowledge can be made into a book for easy viewing. Detailed intervention after treatment can provide special nursing care for patients with a whole-day responsibility system and effectively control patients' condition. (4) Medical assessments. Pay attention to the patient's heart rate and pain relief after medication, and strengthen night rounds to prevent early morning or night angina. To evaluate the severity and duration of angina pain, ECG should be performed and reported to the doctor when angina is aggravated. (5) Personalized care. Help patients adjust reasonable dietary structure according to patient preferences, avoid tobacco, alcohol, spicy food. At any time can not be too hungry too full, especially before going to bed should not be too full, at the same time should guide the patient to do appropriate exercise, gradually exercise the body's ability to adapt, should rest early at night, maintain adequate sleep.

Observation indicators

(1) The Seattle Angina Questionnaire (SAQ) was used to assess patients' control of angina symptoms, which includes treatment satisfaction (Treatment Satisfaction, TS), disease awareness (Disease Awareness, DP), and physical activity satisfaction. Physical activity Limitation (PL), angina pectoris Stable state (AS) and angina attack (Angina Attack, AF) 5 items, the full score is 100 points; the higher the score, the better the control of angina pectoris.[10]

(2) The modified Barthel Index (MBI) was used to assess the subjects' ability to perform daily living, and the Fugel-

Meyer (FMA) was used to assess the subjects' ability to perform physical movements, both with an overall score of 100 points, with the higher the score, the better the daily activity ability and motor function.[11,12]

(3) Since angina pectoris symptoms can significantly affect patients' quality of life, simple Quality of life Rating Scale (QOL) was used to evaluate patients' quality of life after intervention, mainly including mental health, mental state, social function and emotional function, with a full score of 100 for each. The lower the score, the better the quality of life.[13]

(4) Patients with coronary heart disease usually have obvious negative emotions. Self-rating Anxiety Scale (SAS) and self-rating Depression Scale (SDS) were used to evaluate the emotional state of patients. The higher the score, the more severe the bad mood.[14,15]

(5) Patients with coronary heart disease are prone to adverse cardiac events, so the complications of the study subjects were observed, including heart failure, myocardial infarction, and angina pectoris.

Statistical analysis

Statistic Package for Social Science (SPSS) 26.0 software (IBM, Armonk, NY, USA) was used for data processing, mean±standard deviation ($\bar{x} \pm s$) represents measurement data, an independent samples t test was used for group comparisons of measurement data, and F test was used for multiple groups; between groups repeated measures analysis of variance was used for comparison of each time period, and spherical test was performed; percentage (%) represented count data, the χ^2 test was used for group comparisons of count data; $P < .05$, the difference was statistically significant.

RESULTS

Baseline data

There were no differences in baseline data such as age, gender, body weight, disease course and cardiac function classification among the study subjects ($P > .05$). Table 1.

Comparison of angina pectoris control

The SAQ scale showed that the detail group's TS, DP, PL, AS and AF indexes were significantly higher than those of the routine group ($t = 6.758, 7.341, 7.692, 6.337, 6.284$, $P < .05$). Table 2.

Daily life and motor function

Before the intervention, the MBI and FMA scores of the research subjects were not comparable ($P > .05$); After 2 weeks and 4 weeks of intervention, the scores of the subjects were improved compared with those before the intervention, and the scores of daily life ($F_{\text{time point}} = 125.117$, $F_{\text{time point * group}} = 184.206$, $P < .001$) and motor function in the detail group were higher than those in the conventional group ($F_{\text{time point}} = 154.028$, $F_{\text{time point * group}} = 173.226.206$, $P < .001$). Table 3, Figures 1, 2.

Table 1. Baseline data comparison of research subjects [n, % ($\bar{x} \pm s$)]

Project		Detail group (n = 60)	Regular group (n=60)	t/χ^2	P value
Age		59.49±2.24	58.79±2.17	0.132	.079
Gender	Female	26 (43.33)	28 (46.67)	0.214	.068
	Male	34 (56.67)	32 (53.33)		
Body mass (kg/m²)		22.43±1.68	22.09±1.34	0.117	.085
Disease duration (years)		3.79±0.04	3.24±0.05	0.098	.091
Cardiac function classification	Class II	23 (38.33)	25 (41.67)	0.076	.096
	Class III	18 (30.00)	19 (31.67)		
	Class IV	19 (31.67)	16 (26.66)		

Table 2. Comparison of SAQ scale scores of research subjects ($\bar{x} \pm s$, points)

Project	Detail group (n = 60)	Regular group (n = 60)	t	P value
TS	83.50±5.14	77.42±4.35	6.758	<.001
DP	85.59±5.78	80.14±5.43	7.341	<.001
PL	79.62±5.19	74.18±5.04	7.692	<.001
AS	90.69±6.35	85.57±6.12	6.337	<.001
AF	83.54±5.22	77.51±5.16	6.284	<.001

Table 3. Comparison of MBI and FMA scores before intervention, 2 weeks and 4 weeks after intervention ($\bar{x} \pm s$)

Group	Time point	MBI (Score)	FMA (Score)
Detail group (n = 60)	before intervention	55.72±4.17	60.11±4.24
	2 weeks after intervention	68.43±5.34	74.32±5.16
	4 weeks after intervention	86.14±5.52	88.97±5.34
Regular group (n = 60)	before intervention	55.58±4.13	60.35±4.48
	2 weeks after intervention	60.72±5.07	64.33±5.11
	4 weeks after intervention	65.48±5.17	70.58±5.46
$F_{\text{time point}}$		125.117	154.028
$P_{\text{time point}}$		<.001	<.001
$F_{\text{time point * group}}$		184.206	173.226
$P_{\text{time point * group}}$		<.001	<.001

Figure 1. MBI scores of the subjects before the intervention, 2 weeks and 4 weeks after the intervention

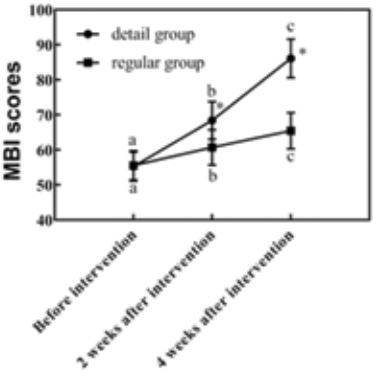

Figure 2. FMA scores of the subjects before the intervention, 2 weeks and 4 weeks after the intervention

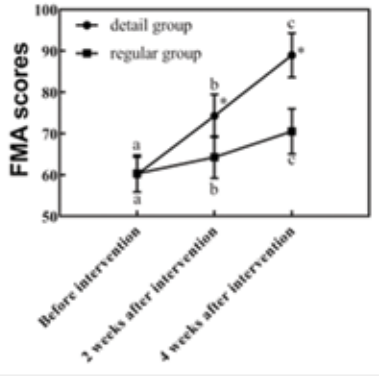

Table 4. QOL scores of study subjects after intervention ($\bar{x} \pm s$)

Project	Detail group	Regular group	*t*	*P* value
Number of cases	60	60		
Mental state	17.56±2.12	20.13±2.09	7.814	<.001
Mental health	15.62±2.34	18.09±2.06	8.772	<.001
Social function	15.86±2.41	18.11±2.14	8.013	<.001
Emotional function	14.36±3.45	16.78±3.69	7.647	<.001

Table 5. Comparison of SAS and SDS of research objects ($\bar{x} \pm s$)

Group	Number of cases	SAS (score)	SDS (score)
Detail group	60	41.70±3.14	39.59±4.11
Regular group	60	67.14±3.25	60.58±4.54
t		8.742	8.694
P value		<.001	<.001

Table 6. Comparison of complication rates among study subjects (n, %)

Group	Number of cases	Heart failure	Angina pectoris	Myocardial infarction	Total incidence
Detail group	60	1 (1.67)	0 (0.00)	1 (1.67)	2 (3.33)
Regular group	60	3 (5.00)	2 (3.33)	3 (5.00)	8 (13.33)
χ^2		6.547	6.382	7.118	6.324
P value		<.001	<.001	<.001	<.001

Quality of life

The scores of mental state, mental health, social function and emotional function in the detail group were lower than those in the routine group (t = 7.814, 8.772, 8.013, 7.647, P < .001). Table 4.

Bad mood

The bad mood in the study group was significantly lower than that in the conventional group (t = 8.742, 8.694, P < .001). Table 5.

Complications

The incidences of heart failure, angina pectoris and myocardial infarction in the detail group were lower than those in the routine group (χ^2=6.547, 6.382, 7.118, 6.324, P < .001). Table 6.

DISCUSSION

Clinical use of antithrombotic drugs (clopidogrel) can inhibit platelet aggregation, avoid thrombosis, reduce the occurrence and progression of coronary heart disease, combined with effective nursing intervention can strengthen the effect.[16,17] Previous studies have shown that paying attention to detail nursing can benefit patients with coronary heart disease from both physical and mental aspects.[18] The results of this study also show that compared with conventional nursing, detailed nursing has more advantages in improving patients' negative emotions, enhancing daily living ability and motor function, and can effectively improve patients' quality of life and control effect of angina pectoris, which is consistent with the results of previous studies.

The Shi G team[19] study found that humanized nursing intervention can effectively control angina pectoris in CHD. The results of this study are similar. The author's experiment found that the control of angina pectoris in the detailed nursing intervention was significantly higher than that in the conventional group. The reason is that detailed nursing intervenes the research objects in the whole process from the aspects of psychophysiology and education, and each research object can receive targeted intervention to effectively control the disease. The on-the-job system ensures that study subjects receive round-the-clock care, further accelerating angina control. In addition, through comparison, the author found that the daily living ability, motor function and quality of life of the detailed group were better than those of the routine group, which was similar to the conclusion of the scholars in Wang C Y[20], indicating that the detailed intervention during the treatment of CHD patients can effectively improve their daily living ability and motor function, thereby improving the quality of life. The reasons may be as follows: the detailed intervention emphasizes life care, pays attention to the reasonable combination of diet and exercise of the research subjects, develops good living habits and diet structure, and ensures a balanced diet and exercise, thereby improving daily living ability and motor function, and regularly. Health education can improve the overall literacy of the research subjects, increase the awareness of disease-related knowledge, promote treatment compliance, speed up recovery, and further improve the quality of life. Compared with conventional nursing, detailed nursing can extend the details of life, which is conducive to helping patients achieve good disease management through the adjustment of diet and activities in their daily life, and has positive significance for improving prognosis.

Zhou X[21] Scholars' studies have shown that predictive intervention can effectively reduce the negative emotions of CHD patients. The author also confirmed this conclusion during the experiment. The results show that detailed intervention can effectively regulate the negative emotions of the research subjects. The reason is that detailed intervention can provide high-quality psychological intervention for patients. Active communication between doctors and patients can reduce the psychological pressure of patients so that they can maintain a relatively stable attitude in the face of diseases, actively preach disease-cure pathology, and increase research subjects' confidence in treatment. The author also found that detailed intervention can effectively reduce the occurrence of adverse reactions, It mainly relies on detailed nursing to provide comprehensive and professional help to the research subjects, reasonably speed up the recovery of the disease, and instruct the patients to live a healthy life to avoid a series of adverse reactions. The results of this study confirm that detailed nursing can improve the quality of life of patients by improving negative emotions and enhancing the life ability and motor function of patients, strengthen the control effect of angina pectoris in patients with coronary heart disease, and bring significant benefits to patients.

The sample size of this study is small, and there is no specific intervention items in psychological intervention and life details, which is the shortcoming and needs to be improved in the future. In addition, considering that the quality of life of patients has been greatly improved after the improvement of negative emotions, psychological

intervention can be strengthened for patients with coronary heart disease, supplemented by appropriate psychological treatment, and the physical and mental state of patients can be improved to the maximum extent.

CONCLUSION

In conclusion, the detailed intervention of patients with coronary heart disease after clopidogrel treatment can improve negative emotions, enhance daily living ability and motor function, improve quality of life, strengthen the control effect of angina pectoris, and reduce adverse cardiac events compared with conventional care. This result also shows that the application of detailed care in the prevention of angina pectoris attack has more advantages, can reduce the readmission of patients, and thus save medical resources. Detailed nursing creates better rehabilitation conditions for patients through psychological intervention, health education, life intervention, medical evaluation and personalized intervention, benefits patients from both physical and psychological aspects, and is conducive to reducing the attack of angina pectoris, with high safety and clinical feasibility, and has a high application prospect. The study also had some limitations, such as a small sample size and no classification of coronary heart disease severity. In the future, the sample size should be expanded and stratified analysis should be carried out to highlight the application effect of detailed nursing in patients with different degrees of coronary heart disease.

There are still some limitations in this study. The results may be biased due to the small selection of subjects or uncertain factors. Further studies can be conducted to avoid the above situations to provide a more accurate basis for treatment and intervention of CHD patients.

ETHICAL COMPLIANCE

This study was approved by the ethics committee of Shidong Hospital affiliated to University of Shanghai for Science and Technology. Signed written informed consents were obtained from the patients and/or guardians.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

YY, XM, YB and LF designed the study and performed the experiments, YY, XM and XL collected the data, YB, LF and TL analyzed the data, YY, XM, YB and LF prepared the manuscript. All authors read and approved the final manuscript. YY and XM contributed equally to this work

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