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Original Article

Effect of traditional Chinese manual therapy on alleviating pain and dysfunction of lumbar disc herniation: a randomized controlled pilot study

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Abstract: Objective: To investigate the effect of traditional Chinese manual therapy (TCMT) in alleviating pain and dysfunction in patients with lumbar disc herniation (LDH). Methods: Sixty-six patients with LDH were recruited as the study cohort and randomly assigned to an observation group and a control group. The patients in the observation group underwent TCMT, whereas those in the control group underwent conventional lumbar traction (LT). The observed indexes comprised primary index, which referred to clinical efficacy, and secondary indexes, which include Simplified McGill Pain Questionnaire, Oswestry Disability Index (ODI), range of motion (ROM) of the lumbar spine, difference in muscle tone (MT) and pressure pain threshold (PPT) of the bilateral erector spinae, and serum inflammatory factor levels. Results: The total effective rate was significantly higher in the observation group than in the control group (96.67% vs. 66.67%, $P < 0.001$). Compared with the control group after treatment, patients in the observation group had significantly lower ODI, pain rating index, visual analog scale and present pain intensity scores (all $P < 0.05$), and had significantly smaller differences in MT and PPT of the bilateral erector spinae (both $P < 0.001$), but had remarkably greater ROM of the lumbar spine ($P < 0.001$). In addition, interleukin (IL)-6, IL-8, and interferon-γ concentrations in the observation group were significantly lower than those in the control group after treatment (all $P < 0.05$). Conclusion: TCMT has positive effects on alleviating pain and improving dysfunction of patients with LDH and helps in reducing serum inflammatory factor levels.

Keywords: Traditional Chinese manual therapy, lumbar disc herniation, pain, dysfunction, lumbar traction

Introduction

Most people experience acute low back pain (LBP) at least once in their lives [1], and LBP often becomes chronic. This is accompanied by tremendous social and economic pressure. A study conducted in 195 countries and territories found that LBP is the leading cause of global productivity loss and the primary cause of disability in 126 countries [2]. In the United States, the annual cost of treating patients with LBP is estimated to exceed $100 billion [3]. Lumbar disc herniation (LDH) is a common cause of LBP. It affects approximately 9% of the global population [4]. Pain and dysfunction caused by mechanical nerve root compression and chemical irritation from all types of inflammatory mediators are the most prominent symptoms of LDH [5]. Surgery and conservative treatment can resolve these symptoms [6], but the vast majority of patients can improve their symptoms with conservative treatment [7]. Therefore, conservative treatment is the primary choice for most patients with LDH [8].

As a type of conservative therapy for LDH, traditional Chinese manual therapy (TCMT), also called Tuina in China, has a long history of more than 2000 years [9], is widely used in East Asia, and has been recommended by clinical practice guidelines in many countries [10, 11]. It refers to the skillful operation of the human body with the practitioner's hands, fingers, elbows, or other parts, according to a certain frequency and method. Manipulation can take various forms, including kneading, pressing, pushing

etc. All of them are required to be manipulated in a powerful but lasting, soft, and uniform manner to allow the force of the manipulation to penetrate deep into the muscles of the human body. Consequently, this therapy has positive effect on various musculoskeletal disorders [12-14]. Patients with LDH have significant imbalances in spine and muscle mechanics [15], often manifesting as increased muscle tone (MT) [16] and restricted movement [17]. Furthermore, chemical stimulation by inflammatory factors plays an important role in the pathogenesis of LDH [18, 19]. Through the literature review and the team's previous study, we found that three inflammatory factors, interleukin (IL)-6, IL-8, and interferon (IFN)-γ, are closely related to radicular pain of LDH [20, 21]. Currently, the clinical application of TCMT for LDH is already been commonly used, and its clinical efficacy is remarkable. However, few randomized controlled trials have evaluated it, and most of these trials lack objective evaluation indexes. Therefore, in this study, we performed lumbar traction (LT), a classical conservative treatment for LDH [22], as a control treatment and observed the effects of the two treatments (LT and TCMT) on subjective scales, muscle and joint status, and serum IL-6, IL-8, and IFN-γ levels to provide clinical evidence for the effectiveness of TCMT in improving pain and dysfunction of LDH.

Methods/design

Study design

This was a single-center, assessor- and analyst-blinded randomized controlled trial conducted at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with Shanghai University of Traditional Chinese Medicine, Shanghai, China. This trial protocol was reviewed and approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine (project number 2021-68) and registered with the Chinese Clinical Trials Registry (ChiCTR2100053542).

This study was conducted in accordance with the Consolidated Standards of Reporting Trials reporting guidelines. A total of 66 patients were recruited and randomly assigned in a 1:1 ratio to the TCMT or LT arm. Randomization was performed using a computer-generated table of random numbers maintained by the study coordinator. Written informed consent was obtained from all patients before screening and enrollment. TCMT and LT were performed three times per week for 4 consecutive weeks. The investigators blinded to treatment allocation and independent of each other were instructed to record results and analyze statistics. A trial flowchart is shown in **Figure 1**.

Sample size calculation

We calculated the required sample size for this trial using two independent sample rates. According to our previous study, the expected effective rates of TCMT and LT were 95% and 60%, respectively, with an alpha of 0.05 and a power of 0.80. According to the formula $nA = nB = [pA(1 - pA) + pB(1 - pB)]\left(\frac{z1 - \frac{\alpha}{2} + z1 - \beta}{pA - pB}\right)^2$ [23], it was estimated that 29 cases were needed in each of the two groups, and then considering a 10% dropout, 33 participants were required to be included in each of the two groups, for a total of 66 cases.

Study participants

Patients with LDH (n = 66) were randomly assigned to the two following treatment groups (33 patients per group): (1) TCMT and (2) LT. The Box below lists the detailed inclusion and exclusion criteria of this study. To screen qualified participants and rule out LBP caused by other diseases, all potential participants were instructed to complete an online survey; if they met the inclusion and exclusion criteria preliminarily, then a physical examination was completed. Moreover, we reviewed the patients' medical history, including computed tomography (CT) or magnetic resonance imaging (MRI), at the first meeting. To exclude the influence of other factors, all treatments, except TCMT or LT, were prohibited during this trial.

Inclusion and exclusion criteria for study participation

Inclusion:

- Those with a lumbar spine CT or MRI revealing disc herniation.
- Those aged 18-55 years, regardless of sex.

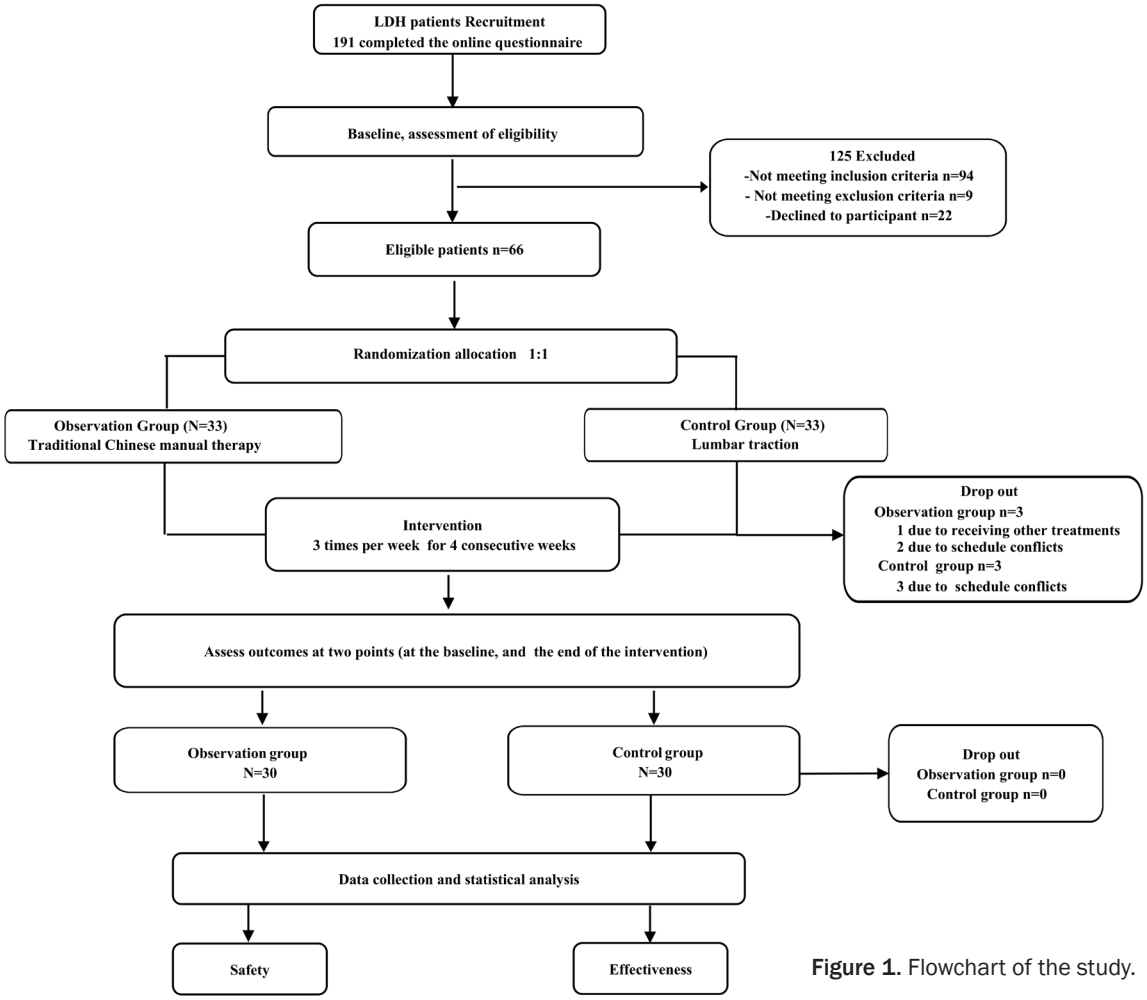

Figure 1. Flowchart of the study.

● Those with a recurrent low back pain more than 3 months and with visual analog score > 3.

● Those receiving no other treatments at present.

● Those who volunteered to participate in this study and signed the informed consent form.

Exclusion:

● Those complicated with other major lumbar diseases, such as tumor and tuberculosis.

● Those with acute lumbar injury pain caused by trauma and operation.

● Those accompanied by cardiovascular, lung, kidney, hematopoietic system, and other major diseases.

● Those diagnosed with psychiatric disorders.

● Those who were pregnant or lactating.

● Those with a history of spinal surgery.

Participant recruitment

Patients with LDH were diagnosed using MRI or CT, with the presence of ruptured annulus fibrosus and nerve root compression, inducing low back or leg pain. The participants of this study were outpatients in Tuina departments (a department specializing in TCMT) of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with the Shanghai University of Traditional Chinese Medicine. Potential participants were recruited through posters in the outpatient building and WeChat (the most popular social media platform in China). This recruitment resulted in 191 participants completing the online survey to determine their initial eligibility. Those who met the initial eligibility criteria (n = 74) were arranged

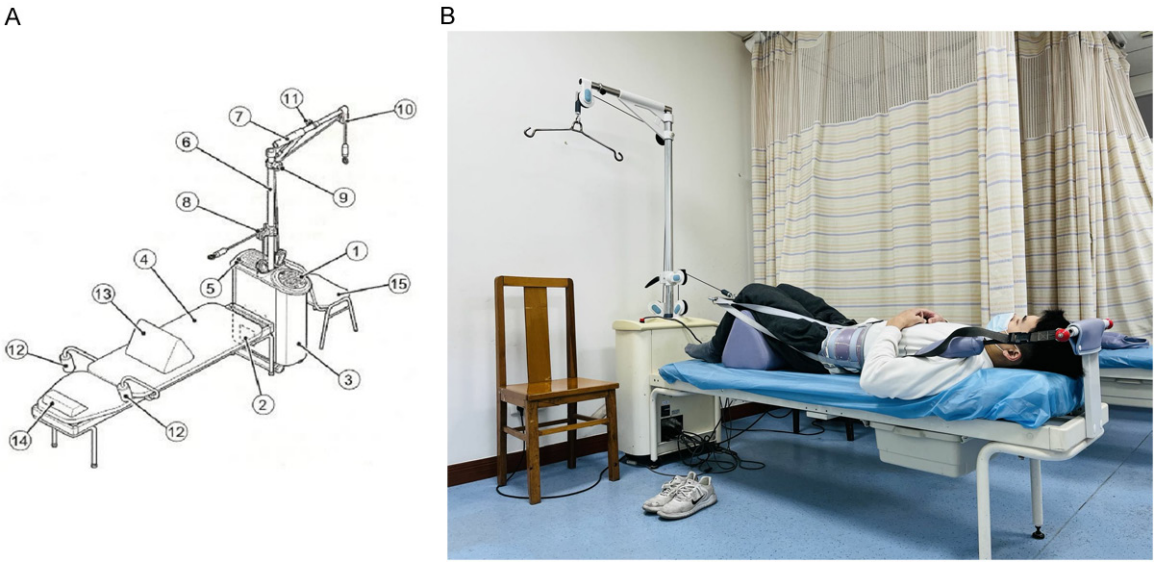

Figure 2. ELKEINE V5021 intelligent thermal traction system. A. Lumbar traction system; B. A patient in lumbar traction.

to have a face-to-face conversation and physical examination before being assigned to the treatment group. Finally, 66 participants were recruited for this study. Some potential participants were excluded owing to the following reasons: (1) they did not meet the age requirements, (2) they had insufficient pain level, (3) they received other treatments in the past month, (4) their location was significantly far for follow-up to be performed regularly, (5) there were conflicts with their schedule.

Study intervention

Eligible patients were randomly assigned to the observation (n = 33) or control (n = 33) group. The patients in the control group were treated with routine LT using the ELKEINE V5021 intelligent thermal traction system from Japan (**Figure 2**). The initial amount of traction was 25%-30% of the patient's body weight, which was increased by 2 kg/time to 40%-50% of the patient's body weight [22]. Each treatment lasted for 20 min, three times a week for 4 weeks.

The patients in the observation group were treated with TCMT; specific operation methods were referred to national planned teaching material and were as follows: First, rolling manipulation was used on both sides of the spine and on the hip and posterolateral sides of the lower limb for 3-5 min. Second, kneading manipulation was applied to the above parts for 5-7 min. Finally, we used point-pressing manipulation on acupoints, such as Shenshu (BL23), Juliao (GB29), Huantiao (GB30), Weizhong (BL40), and Ashi (pain point) point, with the thumb or olecranon and scrubbed the participants' lumbosacral area to make them feel warm. After completing the above relaxation manipulation, oblique-pulling manipulation (a joint adjustment technique similar to spinal manipulation [24]) was used to adjust the lumbar facet joint disorder. First, the participant was placed in a side-lying position facing the doctor; then, the doctor placed one hand on the participant's waist, and the other hand pulled the participant's lower limbs to bend their knees and hips until the doctor felt that the spinous process of the disordered lumbar vertebrae begin to move. Similarly, the doctor gently pulled the participant's upper limbs to bend his or her torso until the doctor felt the vertebra above the suspected lesion. The shoulder was pushed forward and the pelvis backward to rotate the participant's torso to the restricted position, and the disordered segment was placed at the pivot point. In this position, the doctor applied a dexterous trigger force to generate a rapid but amplitude-controlled thrust on the shoulder (anterior to posterior force) and pelvis (posterior to anterior force). Generally, a click sound is heard, which means the treatment is completed, but the click sound must never be recklessly pursued.

Figure 3. A patient is being tested.

Observed indexes

Primary indexes: The therapeutic effects between the two groups were compared. Clinical efficacy was evaluated according to the diagnostic and curative effect criteria published by the Chinese Traditional Chinese Medicine (TCM) Authority, combined with the patient's symptoms and Oswestry Disability Index (ODI) score. The following four grades were used to assess the treatments' efficacy: Cured (the patient's low back and leg pain were relieved completely, the angle in the straight leg raising test was more than 70°, and the ODI improvement rate was ≥ 95%), markedly effective (the patient's low back and leg pain were relieved, and lumbar movement was greatly improved; meanwhile, the ODI improvement rate was between 70% and 95%), effective (the low back and leg pain were partially relieved, lumbar movement was improved, and the ODI improvement rate was between 30% and 70%), and invalid (there was no improvement in the clinical symptoms and signs). The total effective rate was calculated as follows: (number of cured and effective)/total number × 100%.

Secondary indexes: The Simplified McGill Pain Questionnaire (SF-MPQ) was used to evaluate pain intensity, which includes three parts: pain

Figure 4. OE-220 muscle condition rapid measurement system.

rating index (PRI), visual analog scale (VAS), and present pain intensity (PPI) [25]. The PRI assesses the patients' pain intensity from emotional and sensory perspectives. The VAS reflects patients' pain intensity briefly and clearly with a score of 0-10; as the score increases, the pain gradually becomes severe to a degree that is unbearable and seriously affects patients' appetite and sleep [26]. The PPI describes patients' current pain intensity from six levels (0-5 points): no pain, mild pain, discomfort, distressing pain, horrible pain and excruciating pain.

The ODI was used to assess lumbar spine and lower extremity dysfunction before and after the treatment. The ODI scale specifically includes 10 items for pain, single function, and individual composite function, such as travel and social activities. Each item scores 0-5 points. The final score was calculated as the sum of the actual scores/50 × 100%. A higher score indicates a more severe degree of dysfunction [27].

As one of the most frequent movements of the lumbar spine in daily life, spinal flexion and extension can reflect the severity of the patients' condition to a certain extent [28]. The more severe the disease, the smaller is the range of motion (ROM) of the lumbar spine. Therefore, we used a motion capture system (Oxford Metrics Limited, UK) to observe patients' ROM of the lumbar spine. This system uses 15 infrared ultra-wide cameras to capture 51 reflective points affixed to the body surface (**Figure 3**), thereby recording the move-

Table 1. Comparison of the basic information between the two groups

Group	Observation group (n = 30)	Control group (n = 30)	t/X^2 value	*P* value
Male/Female (n)	17/13	18/12	0.069	0.793
Age (year)	40.03±12.02	38.67±12.57	0.430	0.668
Height (m)	1.69±0.07	1.71±0.08	-0.864	0.391
Weight (kg)	68.58±11.73	72.80±10.72	-1.454	0.151
BMI (kg/m^2)[a]	23.80±3.10	24.83±2.95	-1.318	0.193
ODI (%)	40.54±10.12	41.15±12.93	-0.203	0.839
PRI	14.30±7.71	15.30±7.64	-0.505	0.616
VAS	5.73±1.26	5.60±0.97	0.460	0.647
PPI	2.37±0.41	2.57±0,37	-0.815	0.418

[a]Calculated as weight in kilograms divided by height in meters squared.

ment trajectory of each joint of the participant [29].

LDH often manifests as asymmetry of the paraspinal muscles [30]. Differences in muscle cross-sectional area and fatty infiltration are often observed [30]. Clinically, this usually appears as a difference in MT and pressure pain threshold (PPT) in the paraspinal muscles. Therefore, we selected the difference in MT and PPT of the bilateral erector spinae as the observation index and completed the measurement using the OE-220 muscle condition rapid measurement system (ITO Co., Ltd, Japan) (**Figure 4**). The location of the MT measurement was approximately 2-3 cm away from the third lumbar vertebra, and the location of the PPT test was selected at the tender point of the patient's low back and the corresponding location on the opposite side of the spine.

The serum IL-6, IL-8, and IFN-γ levels were compared between the two groups. Moreover, 5 mL of venous blood was drawn from every patient who had fasted before and after the treatment. A CTK120 centrifuge (Xiangyi Co., Hunan Province, China) was used to complete the separation of serum, and the centrifugation parameters were set to 3000 r/min for 10 min. Enzyme-linked immunosorbent assays were used to measure the serum IL-6, IL-8, and IFN-γ levels according to the IL-6, IL-8 and IFN-γ kit instructions (Abcam Science, UK).

Statistical analysis

We used the Statistical Package for the Social Sciences version 21.0 for the statistical analyses of the experimental data and GraphPad Prism version 8.0 for the presentation of the figures. Quantitative data are presented as mean ± standard deviation. A paired samples t-test was used to compare the experimental data before and after the treatment, and two independent samples t-tests were used to compare the data between the two groups. Qualitative data are expressed as the number of cases or percentages, and the chi-squared test was used to compare the experimental data between the two groups. $P < 0.05$ was considered statistically significant, and $P < 0.001$ denoted extremely remarkable statistical significance [31].

Quality control

The doctor conducting the intervention must have a medical certificate and at least 3 years of clinical experience. In addition, experts in TCMT and traction equipment manufacturers were hired to provide them with no less than three sessions of centralized training on manipulation and LT before the implementation of this study. All negative changes in health status were recorded as adverse events and were reported to the ethics committee for evaluation. Experimenters who were blinded to the experimental conditions were responsible for data entry and statistical analyses.

Results

Basic information

In total, 33 participants were enrolled in each of the two groups. Because of failure to complete follow-up on time and for other reasons, three and three patients in the TCMT and LT groups withdrew from this study, respectively. Therefore, 30 patients in each of the two

Table 2. Comparison of the clinical efficacy in the two groups [n (%)]

Group	Cured	Markedly effective	Effective	Invalid	Total effective rate (%)
Observation group	5 (16.67)	8 (26.67)	16 (53.33)	1 (3.33)	29 (96.67)
Control group	0 (0)	6 (20.00)	14 (46.67)	10 (33.33)	20 (66.67)
X^2 value					18.468
P value					< 0.001

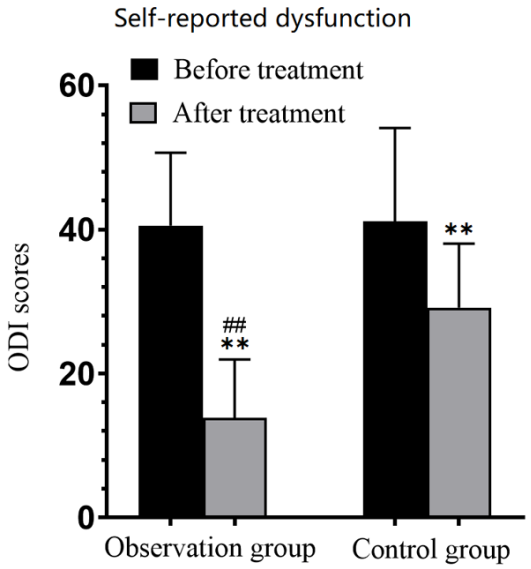

Figure 5. Comparison of the ODI scores between the two groups. Compared with scores before the treatment, ** meant *P* < 0.001; compared with the control group after the treatment, ## indicated *P* < 0.001. ODI: Oswestry disability index.

groups, for a total of 60 patients, were included in the statistical analyses. As shown in **Table 1**, no statistically significant differences were found between the two groups in terms of sex, age, body mass index, and subjective scale scores (*P* > 0.05).

Comparison of the clinical efficacy

As shown in **Table 2**, the total effective rates in the observation and control groups were 96.67% (29/30) and 66.67% (20/30), respectively. The clinical efficacy of the observation group was significantly higher than that of the control group (*P* < 0.001).

Comparison of the Oswestry disability index scores

The ODI scale was used to assess the severity of the patients' dysfunction. As shown in **Figure 5**, there was no significant difference in the ODI scores between the two groups before treatment (*P* > 0.05). After treatment, both groups showed a marked decrease, but the observation group had significantly lower scores than the control group (*P* < 0.001). These results indicate that the observation group has better improvement in dysfunction than the control group.

Comparison of the pain rating index, visual analog scale, and present pain intensity scores

We adopted the SF-MPQ, which includes three items to assess the patients' pain level, and there was little difference in the score of each item between the two groups before treatment (*P* > 0.05). After treatment, both groups had reduced scores in the three items, but compared with the control group, the observation group had notably lower scores for each item, indicating that the observation group had better efficacy in reducing patients' pain level than the control group (*P* < 0.05), as shown in **Figure 6**.

Comparison of range of motion

As shown in **Figure 7**, there was no significant difference in ROM between the two groups before treatment (*P* > 0.05). After treatment, both groups showed remarkably increased ROM, but the ROM of the observation group was significantly higher than that of the control group (*P* < 0.001). These results suggest that the observation group can improve the ROM of the lumbar spine more effectively than the control group.

Comparison of the difference in muscle tone and pressure pain threshold of the bilateral erector spinae

Differences in MT and PPT of the bilateral erector spinae were measured to assess muscle imbalance due to LDH. As shown in **Figure 8**, there was no significant distinction in difference in the MT and PPT before treatment

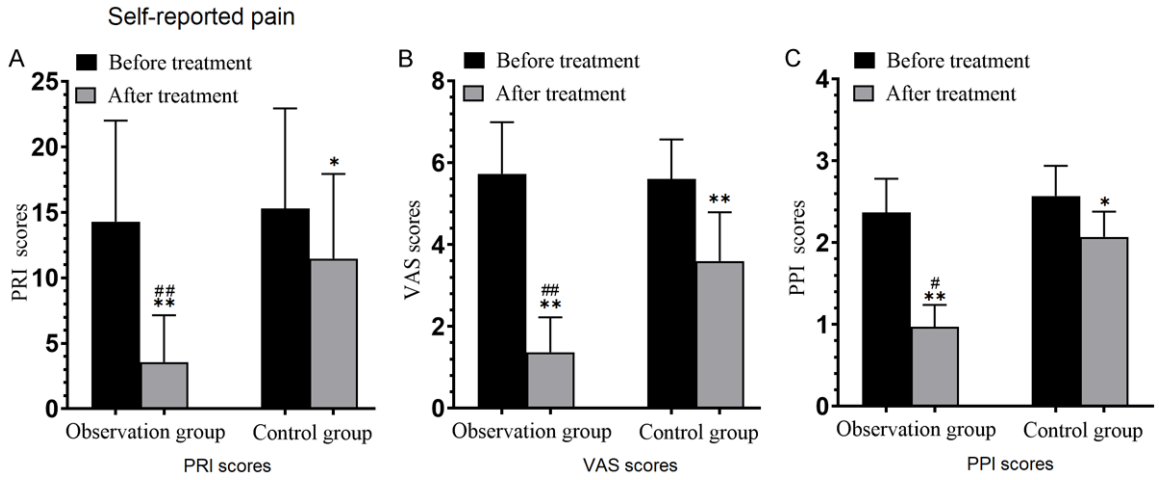

Figure 6. Comparison of the PRI, VAS and PPI scores between the two groups. Compared with scores before the treatment, * meant $P < 0.05$, ** meant $P < 0.001$; compared with the control group after the treatment, # indicated $P < 0.05$, ## indicated $P < 0.001$. PRI: pain rating index, VAS: visual analogue scale, PPI: present pain intensity.

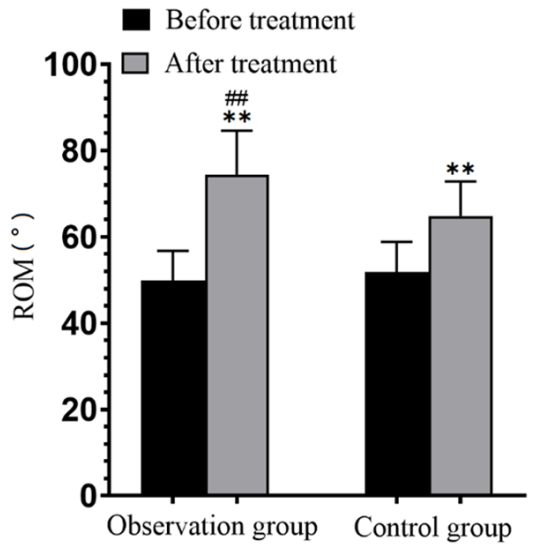

Figure 7. Comparison of ROM between the two groups. Compared with the ROM before the treatment, ** meant $P < 0.001$; compared with the control group after the treatment, ## indicated $P < 0.001$. ROM: range of motion.

between the two groups ($P > 0.05$). After treatment, the difference in the MT of the bilateral erector spinae in the observation group decreased remarkably ($P < 0.001$), but there was no significant change in the control group. Compared to before treatment, the difference in PPT of the bilateral erector spinae in both groups decreased significantly, but the observation group had markedly lower difference than the control group ($P < 0.001$). The results indicate that muscle balance can be restored more effectively in patients with LDH in the observation group than those in the control group.

Comparison of the serum interleukin (IL)-6, IL-8, and interferon-γ levels

As shown in **Table 3**, no significant difference was detected in the serum IL-6, IL-8 and IFN-γ concentrations between the two groups before treatment ($P > 0.05$). After treatment, the concentrations of IL-6, IL-8, and IFN-γ decreased in both groups ($P < 0.001$) and were significantly lower in the observation group than in the control group ($P < 0.05$), suggesting that the observation group is able to improve the level of inflammatory infiltration in patients with LDH more effectively than the control group.

Discussion

LDH is prevalent all over the world, and chronic pain and dysfunction, which are recurrent and persistent [32], are its distinctive features and the main complaints of patients. Therefore, the primary goal of treatment for LDH is to improve pain and movement disorders. TCMT therapy is an ancient technique with a history of more than 2000 years. It is widely accepted owing to its low cost, safety, and effectiveness.

LT is one of the most classical conservative therapies for LDH [33], so we chose it as a control group treatment. The total effective rate

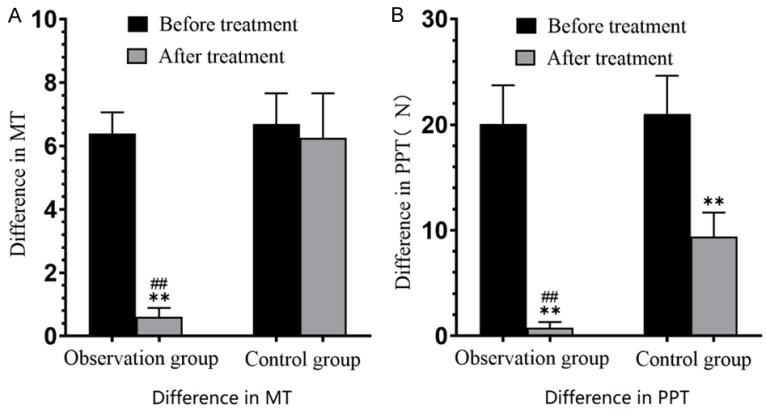

Figure 8. Comparison of the difference in MT and PPT of bilateral erector spinae between the two groups. Compared with the difference before the treatment, **meant $P < 0.001$; compared with the control group after the treatment, ## indicated $P < 0.001$. MT: muscle tone, PPT: pressure pain thresholds.

was selected to represent the efficacy of TCMT visually, and the ODI scale and ROM of lumbar spine were applied to assess the effect of TCMT on improving physical dysfunction. Moreover, we applied the SF-MPQ to assess the effect of TCMT on pain levels and focused on muscle imbalance and proinflammatory factor elevations, which are prevalent in patients with LDH. Through a comprehensive analysis of subjective scales and objective indicators, we provide an evidence-based medical basis for the clinical efficacy of TCMT in the treatment of LDH.

Scale evaluation is often an important reference for therapeutic effects because it directly reflects patients' subjective feelings and has excellent test-retest reliability [34]. In our study, we selected the ODI and SF-MPQ, which are widely used in LDH clinical trials [31, 35]. The ODI is mainly used to assess the functional activity of the patients' lumbar spine and lower extremities, and the SF-MPQ can evaluate pain levels from subjective sensation and emotional perspectives. The results of this study showed that the ODI and each item of the SF-MPQ were significantly lower in the observation group than in the control group, further demonstrating the remarkable advantage of TCMT in improving pain and dysfunction in patients with LDH. There have been many studies on manual therapy for LDH [36, 37], and our study further demonstrated that TCMT, similar with many internationally popular manipulations, is effective in improving the level of pain and dysfunction in patients with LDH.

Mechanical imbalance of joints and muscles is an important cause and a major symptom of LDH, often manifested as a reduction in the ROM of the lumbar spine and an imbalance in MT and PPT [38-40]. The endogenous balance system composed of vertebrae and joints and the exogenous balance system composed of muscles and ligaments together maintain the stability of the spine [41], and an imbalance on either side can lead to spinal instability and induce diseases, such as disc herniation. The relaxing techniques used in TCMT (e.g., rolling manipulation) can have a positive effect on the exogenous balance system [39], whereas adjustment techniques can improve facet joint disorders and maintain the endogenous balance system. Eventually, the mechanical balance of the spine is restored, which may be one of the mechanisms that allow TCMT to be clinically effective.

Studies have shown that inflammatory microenvironment plays a key role in the pathogenesis of LDH [42, 43]. There are various types of inflammatory cytokines, the levels of which are associated with disc herniation severity in patients with LDH [19]. Our study used IL-6, IL-8, and IFN-γ levels as reference indicators to evaluate the efficacy of TCMT. Previous studies have found long-term abnormal increases in serum IL-6 and IL-8 levels in patients with LDH, and these levels were positively correlated with pain intensity [20]. IFN-γ can induce tactile nociceptive hypersensitivity in rats and is strongly correlated with the degree of lumbar dysfunction in patients [44, 45]. Consequently, serum IL-6, IL-8, and IFN-γ levels can significantly reflect the degree of pain and dysfunction. In this study, the concentrations of these inflammatory factors were significantly lower in the observation group than in the control group, indicating that TCMT can effectively reduce the inflammatory response in patients with LDH. Manual therapy regulates local blood circulation [46], which may be one of the mechanisms

Table 3. Comparison of the IL-6, IL-8 and IFN-γ concentrations in the two groups

Group	IL-6 (pg/mL)		IL-8 (pg/mL)		IFN-γ (pg/mL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	17.65±3.37	9.58±2.82	166.06±41.72	74.03±11.22	39.01±7.07	23.48±3.81
Control group	17.63±3.66	11.93±3.31	160.48±45.65	91.84±14.29	38.64±7.91	28.47±3.40
t value	0.030	-2.930	0.488	-5.359	0.182	-5.126
P value	0.976	0.005	0.628	< 0.001	0.856	< 0.001

by which TCMT reduces serum IL-6, IL-8, and IFN-γ levels, and improves inflammatory infiltration.

In conclusion, TCMT has excellent efficacy in the treatment of LDH, which can significantly improve pain and dysfunction in patients with LDH, effectively restore the original balance of the lumbar spine, and improve the inflammatory infiltration status. Therefore, it is worth of clinical promotion and application. This study also has some limitations. As a preliminary exploration of a long-term, large-scale study, the sample size of this part of the experiment was small, and future studies with larger sample sizes are required to further validate the findings. Due to the visual nature of manual therapy intervention, participants and doctors could not be blinded in this study, which may increase the risk of bias during study implementation, although outcome assessors were blinded to the intervention assignment. In addition, the lack of follow-up to assess the long-term efficacy of TCMT may be another limitation; it can be adopted as one of the main observational indicators in future studies with large samples.

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Disclosure of conflict of interest

None.

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