Journal of Pain Research

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CLINICAL TRIAL REPORT

Clinical Efficacy and Safety of a Modified Moxibustion Therapy for Low Back Pain in Lumbar Disc Herniation: A Two-Center, Randomized, Controlled, Non-Inferiority Trial

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Objective: Our pilot study shows that a modified moxibustion therapy called Ma's bamboo-based medicinal moxibustion can alleviate the symptoms of low back pain in lumbar disc herniation (LDH), and has the potential to treat LDH. The aim of this study is to evaluate the efficacy and safety of Ma's bamboo-based medicinal moxibustion for low back pain in LDH.

Methods: A total of 312 LDH patients with low back pain were randomized to receive Ma's bamboo-based medicinal moxibustion (MBMM) or acupuncture (AT). The primary efficacy measure was the change of Visual Analogue Scale (VAS) on the 14th day compared with that at baseline. The secondary efficacy measures included VAS score, Oswestry disability index (ODI), modified Japanese Orthopaedic Association (M-JOA) score, and the content of β-endorphin (β-EP) and substance-P (SP). The safety measures included the occurrence of adverse events and the changes in laboratory indicators.

Results: In total, 304 patients were incorporated for the analysis of efficacy, including 96 males and 208 females, aged 21–65 years. There was no statistically significant difference in the change of VAS score between the two groups on the 14th day [mean difference (95% CI) = −2.31 (−2.48, −2.13) and −2.28 (−2.45, −2.11), respectively; $p = 0.819$]. The VAS, ODI, and M-JOA scores changed after the intervention in both groups ($p < 0.001$), with increased β-EP content ($p = 0.014$, $p = 0.032$) and decreased SP content ($p < 0.001$, $p = 0.048$). The ODI score ($p = 0.039$) and M-JOA score ($p = 0.032$) of the MBMM group on the 28th day were lower than those of the AT group.

Conclusion: The efficacy of Ma's bamboo-based medicinal moxibustion therapy in relieving low back pain of LDH patients is comparable to that of acupuncture, and it has post-effect advantages in improving lumbar dysfunction and daily living ability, which can be used as a safe and effective alternative method for LDH treatment.

Keywords: LDH, low back pain, Ma's bamboo-based medicinal moxibustion, acupuncture, randomized controlled trial

Introduction

LDH refers to a clinical syndrome in which the nucleus pulposus migrates through the damaged annulus fibrosus and protrudes around due to external force or intervertebral disc degeneration to compress and stimulate the nerve root or spinal cord, inducing symptoms such as low back pain, sciatica, lower limb sensory disturbance, etc.[1] LDH has a prevalence of about 1% and involves L4/5 and L5/S1 segments commonly.[2] Low back pain is the initial and main symptom of LDH,[3] as well as the leading cause of disability and decreased productivity worldwide,[4] and LDH has been recognized to be the most common disease causing low back pain.[5] Therefore, the occurrence of LDH may induce huge individual, family, and socioeconomic burden. At present, it is believed that the pathogenesis of LDH may be explained

Received: 3 January 2024
Accepted: 8 May 2024
Published: 23 May 2024

by mechanical compression, inflammatory stimulation, and autoimmune reaction.[6] It can be induced and aggravated by genetic factors, trauma, smoking, obesity, pregnancy, long-term unreasonable exercise, etc.[7]

Surgery for LDH is necessary when the symptoms are not significantly improved after continuous conservative treatment. However, there may be postoperative intractable complications such as unstable spinal force line, recurrent protrusion, and pain.[8] Currently, it is believed that only 1–5% of patients need surgical treatment,[9] about 15–25% of which still have symptoms of low back pain after surgery.[10] Therefore, conservative treatment such as exercise, manual therapy, spinal traction, physical therapy, oral medicine (anti-inflammatory and analgesic, neurotrophic treatment), and epidural steroid injection are widely considered as the first therapeutic option for LDH.[11–13]

To some extent, measures that can alleviate low back pain have the potential to treat LDH. Acupuncture,[14] moxibustion,[15] cupping,[16] and other complementary therapies of traditional Chinese medicine have been confirmed to alleviate the low back pain. In recent decades, spontaneous resorption of nucleus pulposus induced by conservative treatment has been widely reported,[17] which provides more possibilities for the treatment of LDH with the complementary therapies of traditional Chinese medicine. However, it remains a challenge for doctors and LDH patients to choose a suitable complementary therapy with better efficacy, higher safety, and lower cost.

Ma's bamboo-based medicinal moxibustion therapy, belonging to the category of "cake-separated moxibustion", is an excellent project protected by the State Administration of Traditional Chinese Medicine.[18] Based on unique drug prescription and moxibustion apparatus, the therapy has accumulated rich experience in treating diseases such as LDH. However, due to the lack of evidence for evidence-based evaluation of clinical efficacy and safety, it is still unable to support clinical decision-making, which limits the inheritance and promotion of this therapy. Our early pilot study supports that Ma's bamboo-based medicinal moxibustion can effectively relieve the low back pain in patients with LDH,[19] suggesting the value of in-depth research, promotion, and application.

Therefore, this two-center, single-blind, randomized, controlled, non-inferiority trial was performed by adopting a parallel design, with the purpose to verify that the therapeutic effect of Ma's bamboo-based medicinal moxibustion therapy on low back pain in LDH patients is not inferior to acupuncture. This study was expected to provide high-quality evidence-based evidence for the effectiveness and safety of Ma's bamboo-based medicinal moxibustion therapy in the treatment of low back pain in LDH patients, and offer a feasible alternative for LDH patients, so as to improve the service level of traditional Chinese medicine. This trial was carried out following the Consolidated Standards of Reporting Trials statement (CONSORT 2010)[20] and the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA 2010),[21] with the corresponding protocol[19] released in advance.

Methods

Study Design and Setting

The present study was designed as a two-center, single-blind, randomized, controlled, non-inferiority clinical trial to evaluate the therapeutic effect and safety of Ma's bamboo-based medicinal moxibustion and acupuncture on low back pain in LDH patients. This trial was conducted in the First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine and the Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine. Patients were recruited from the Outpatient and Inpatient Departments of Acupuncture and Moxibustion of the two hospitals. Before the start of the trial, the enrolled patients were fully informed of the possible inconvenience of participating in the trial by the researchers. All patients agreed to participate in the trial and provided written informed consent. The eligible patients were randomly assigned to the MBMM group and the AT group in a ratio of 1:1. This trial was approved by the Ethics Review Committee of the First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine (Approval number: K2020-039) and registered in the Chinese Clinical Trial Registry on September 29, 2020 (Study identifier: ChiCTR2000038725).

Diagnostic Criteria

All patients were diagnosed by acupuncturists with >5 years of clinical experience. The diagnostic criteria of LDH (ICD-10: M51.202) were based on previously published protocols:[19] 1) Lower limb radiative pain, of which the

pain location was consistent with the corresponding affected innervation area; 2) Lower limb sensory abnormalities, with decreased superficial sensation of the skin in the corresponding affected innervated area; 3) Positive result of Lasegue test, Bragard test, Lasegue test of the unaffected side, or femoral nerve stretching test; 4) Weaker tendon reflex than that of the unaffected side; 5) Muscle weakness; 6) Intervertebral disc herniation indicated by lumbar MRI or CT, of which the nerve compression was consistent with the symptoms and signs of affected nerves; and 7) In the first five criteria, patients could be diagnosed as LDH when meeting three of them combined with item 6.

Inclusion Criteria

1) Patients who met the above diagnostic criteria, with the lesion located in L3-S1; 2) males or females aged 18–65 years; 3) patients with the course of disease ≥6 months; 4) drug users with drug withdrawal for 4 weeks, and non-drug users with discontinued treatment for 2 weeks; 5) patients with 3≤VAS scores≤6; and 6) willingness to sign written informed consent.

Exclusion Criteria

1) Acute onset of low back pain in LDH; 2) low back pain caused by other causes; 3) patients with other diseases requiring treatment with anti-inflammatory and analgesic drugs; 4) pregnancy, breastfeeding, or preparing for pregnancy; 5) rashes, broken skin, ulcers, or other infectious diseases at the waist; 6) patients with serious diseases of heart, liver, kidney, or blood system; 7) patients with mental disorders or communication disorders; and 8) patients with high fever or Yin deficiency.

Sample Size

The PASS software version 15.0 (NCSS, LLC. Kaysville, UT) was used to calculate the sample size. This study was designed as a non-inferiority trial. According to the previous literature[22] and the joint consideration of clinicians and statisticians, it is assumed that the standard deviation of VAS score reduction of patients using bamboo-based medicinal moxibustion is 2.0, the non-inferiority margin was set at 0.78, the significance level of the test is unilateral 0.05 and power of the test is 90%. According to the 1:1 grouping, the sample size required by each group was 140 cases. Assuming a 10% dropout rate, the final sample size of the MBMM group and the AT group was 156 cases, respectively, and the total sample size was 312 cases.

Randomization and Blinding

Stratified block randomization was carried out by an independent statistician who did not participate in any other part of the trial. Central randomization was conducted by INTELLIGENCE FUTURE Soft Co., Ltd. (Tianjin, China). A random sequence was generated using SAS 9.2 (SAS Institute, Inc., Cary, NC) by a third party statistician, and the sequence was stored in a central randomization system (interactive web response (IWR) system). According to the central factor, the patients were stratified based on different centers and randomly divided into two groups of the MBMM group and the AT group at the ratio of 1:1.

In this trial, it was impossible to blind patients and therapists due to the particularity of intervention measures. Therefore, the method of blinding was employed for data collectors and statistical analysts. Patients were informed of the specific grouping only when they withdraw from the trial due to adverse events or at the end of the trial.

Interventions

All treatments for the enrolled patients were performed by acupuncturists with >5 years of clinical experience in the Outpatient Treatment Room of the two centers. All these therapists had received standardized training of the corresponding operation plan before the trial. Patients in each group were treated once a day, 6 times a week, 12 times in total. All treatments were completed within 13 days, and the follow-up was conducted 14 days after the end of treatment.

MBMM Group

1. Preparation of tool for moxibustion: A bamboo tube with an inner diameter of 5 cm was taken with the stem nodes removed, and the bamboo tube was cut according to the specification of 5×4 cm (inner diameter × height) with a hacksaw;
2. Preparation of Ma's medicinal powder for low back pain: Each 250 g of Wei Ling Xian (Clematidis Radix Et Rhizoma), Du Huo (Angelicae Pubescentis Radix), Rou Gui (Cinnamomi Cortex), Xi Xin (Asari Radix Et Rhizoma), Chuan Xiong (Chuanxiong Rhizoma), and Sang Ji Sheng (Taxilli Herba) were mixed and powdered through a 300-mesh sieve, and stored in the dark at room temperature for later use;
3. Preparation of Ma's medicinal liquor: Each 200 g of Wei Ling Xian (Clematidis Radix Et Rhizoma), Ji Xue Teng (Spatholobi Caulis), Chuan Niu Xi (Cyathulae Radix), Xi Xin (Asari Radix Et Rhizoma), Du Huo (Angelicae Pubescentis Radix), Chuan Xiong (Chuanxiong Rhizoma), Sang Ji Sheng (Taxilli Herba), and Rou Gui (Cinnamomi Cortex) were placed in 21,000 mL Baijiu (50°) for 7 days for later use;
4. Preparation of medicinal cake: 15 g of the prepared medicinal powder and 20 mL of the prepared medicinal liquor were taken and mixed well, and the mixture was placed into the tool for moxibustion to medicinal cakes with a thickness of about 1.5 cm;
5. Preparation of moxa cone: 3 g moxa were made into several conical moxa cones of 2.5×2 cm (bottom diameter × height) in size for later use; and
6. Operation: After the medicinal cake preheated, patients were instructed to take a prone position, followed by the moxibustion of L1–L5 Jia ji (EX-B2), Shenshu (BL23), Mingmen (GV4), and Yaoyangguan (GV3) according to the Nomenclature and Location of Acupuncture Point (GB/T 12346–2006),[23] with three moxa cones used for moxibustion each time. The operation process and selected acupoints of Ma's bamboo-based medicinal moxibustion are displayed in Figures 1 and 2.

The above plant materials were identified by Professor Sun Qingwen from the School of Pharmacy of Guizhou University of Traditional Chinese Medicine to ensure the accuracy and effectiveness of the materials. The reference materials for the relevant plant material certificate specimens can be found in Guizhou Ethnic Commonly Used Natural

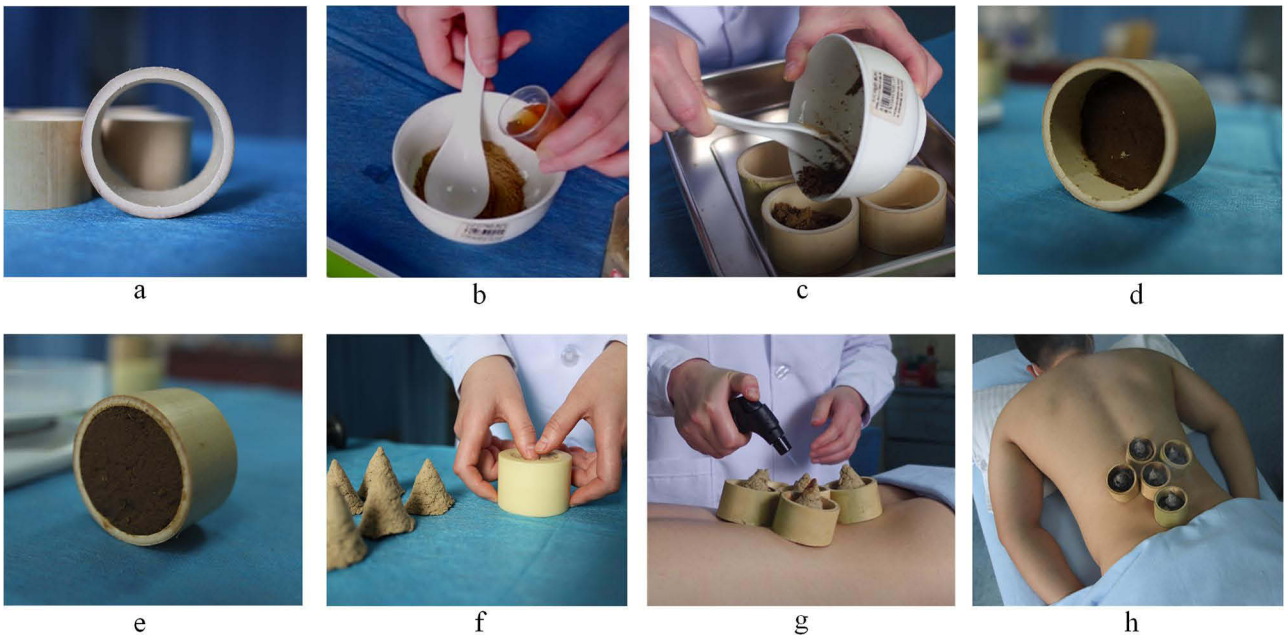

Figure 1 The operation process of MBMM therapy. (**a**) The empty bamboo tube. (**b**) 15g of medicinal powder and 20 mL of medicinal liquor are mixed evenly. (**c**) Medicinal cake making. (**d**) The front of the filled bamboo tube. (**e**) The bottom of the filled bamboo tube. (**f**) Moxa-cone making. (**g**) Preheating. (**h**) Moxibustion at the acupoints.

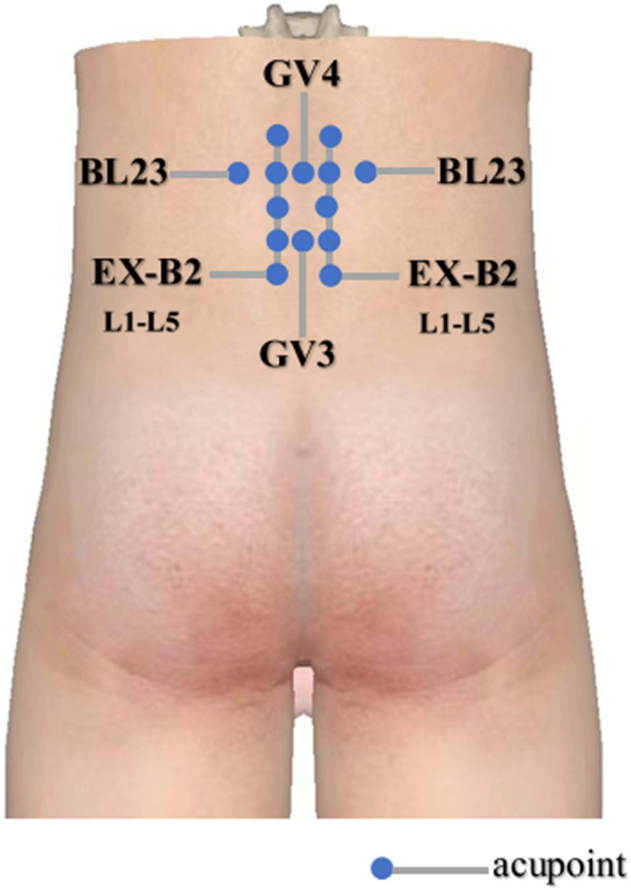

Figure 2 All acupoints selected and their locations in the MBMM group.

Medicines.[24] In addition, the plant material research involved in this research project does not require additional approval.

AT Group

The selection of acupoints in the AT group was formulated according to the prescription of the Evidence-Based Guidelines of Clinical Practice with Acupuncture and Moxibustion for Low Back Pain.[25] L1–L5 Jia ji (EX-B2), Shenshu (BL23), Dachangshu (BL25), Weizhong (BL40), and Ashi acupoints were selected following the Nomenclature and Location of Acupuncture Points (GB/T 12346–2006).[23] Patients were instructed to take a prone position to fully expose the waist and back. Acupuncture was performed with a disposable sterile needle of 0.30×40 mm and 0.30×50 mm (Suzhou Medical Appliance Co., Ltd., Suzhou, Jiangsu, China) after the targeted skin for acupoint was routinely disinfected. Practitioners performed the treatment according to the national standard of acupuncture manipulation (GB/T 21709.20–2009,[26] GB/T 21709.21–2013).[27] After needling, the basic manipulations of lifting, thrusting and twirling were used until "deqi", which literally means "the arrival of vital energy", was achieved.

Efficacy Outcomes

The primary efficacy outcome was the change of Visual Analogue Scale (VAS) score on the 14th day compared with that at baseline. VAS score is one of the methods with relatively higher sensitivity and reliability to assess pain.[28] The change of VAS score was calculated by subtracting the score at the baseline from that on the 14th day, and the negative value showed a relieved symptom of low back pain in patients. The secondary efficacy outcomes included:

1) VAS, ODI, and M-JOA scores at baseline, and on the 7th, 14th, and 28th day. The Oswestry Disability Index (ODI)[29] is one of the most widely used scales for evaluating the functional results of patients with low back pain. The ODI consists of 10 questions involving the intensity of pain, self-care, lifting, walking, sitting, standing,

interference with sleep, sexual life, social life, and tourism. The higher the score, the more severe the dysfunction. The Modified Japanese Orthopaedic Association (M-JOA) score for low back pain[30] includes subjective symptoms (low back pain, lower limb radiating pain, and numbness), objective symptoms (paravertebral tenderness, muscular tension, straight-leg raising test, and femoral nerve stretching test), and activity of daily living (work ability, sleep, bending, and lifting). A lower score suggests a milder condition of illness and a better ability for daily living.

2) The serum content of β-endorphin (β-EP) and substance-P (SP) at baseline and on the 14th day. It has been documented that the degree of low back pain in LDH patients is associated with the expression levels of serum β-EP and SP,[31,32] both of which can be regarded as biomarkers of low back pain. Fasting enous whole blood specimens of 2–3 mL were collected in disposable BD vacuum serum separator tubes, kept static at room temperature for 2 hours, centrifuged at 1,000 × g for 20 minutes, then the supernatant was moved to the freezing tube and placed in a −80°C refrigerator to be preserved for measurement. The serum β-EP and SP levels of patients were detected by ELISA.

Safety Outcome

All adverse reactions related to the intervention measures during this trial were determined as adverse events, all of which were filled into the Adverse Reaction Report form by the researcher truthfully. Routine blood test, liver and kidney function test, and electrocardiogram of each patient were performed at baseline and on the 14th day of the trial. The safety of intervention measures was evaluated according to the Adverse Reaction Report form and the results of laboratory tests before and after treatment.

Statistical Analysis

SAS 9.2 (SAS Institute, Inc., Cary, NC) was used for data analysis. The efficacy analysis was carried out according to the Per-Protocol (PP), including all patients who completed the 14th day's evaluation. The missing follow-up data were filled in by the carry-over of the post-treatment measurement data. The safety analysis was made according to the intention-to-treat (ITT) for all patients who had received ≥1 times of treatment. Data with normal distribution were represented by "mean ± standard deviation", and the paired *t*-test was used for intra-group comparisons and independent *t*-test for intergroup comparisons. Data with non-normal distribution were expressed by "median (Q1, Q3)", and the Wilcoxon signed-rank test was used for intra-group comparisons and the Mann–Whitney *U*-test for intergroup comparisons. To avoid errors that might be related to the initial value, the difference between the baseline VAS score and the primary outcome after treatment was corrected by analysis of covariance (ANCOVA). Friedman test was performed on VAS, ODI, and M-JOA scores which were measured many times. Chi-square test or Fisher's exact test was employed for categorical variables. Meta-analysis was used for heterogeneity among different centers. $P < 0.05$ meant that the difference was statistically significant.

Results

Study Participants and Baseline Characteristics

From November 3, 2020 to March 27, 2021, a total of 330 patients were screened from the two centers; 18 ineligible patients were excluded, and 312 patients were enrolled. During the whole process of the trial, 10 patients (3.21%) were lost in the two groups. Among them, seven patients (4.49%) were lost in the MBMM group, with a compliance rate of 95.51%, and three patients (1.92%) were lost in the AT group, with a compliance rate of 98.08%. Five patients from the MBMM group and three patients from the AT group were not included in the efficacy analysis with missing the post-treatment data. The details of registration, enrollment, and distribution of patients are shown in Figure 3. Finally, this study analyzed the clinical efficacy of 304 patients (MBMM group, n = 151; AT group, n = 153). All patients were included in the safety analysis. There was no statistical difference between the two groups following randomization in the demographic variables or efficacy outcomes (Table 1).

The Primary Efficacy Outcome

In the ANCOVA after the adjustment of baseline VAS score, the mean difference (95% CI) of the VAS score was −2.31 (−2.48, −2.13) and −2.28 (−2.45, −2.11) in the MBMM group and AT group on the 14th day of the trial, respectively. There was no statistically significant difference in the mean difference (95% CI) between the two groups ($P = 0.819$).

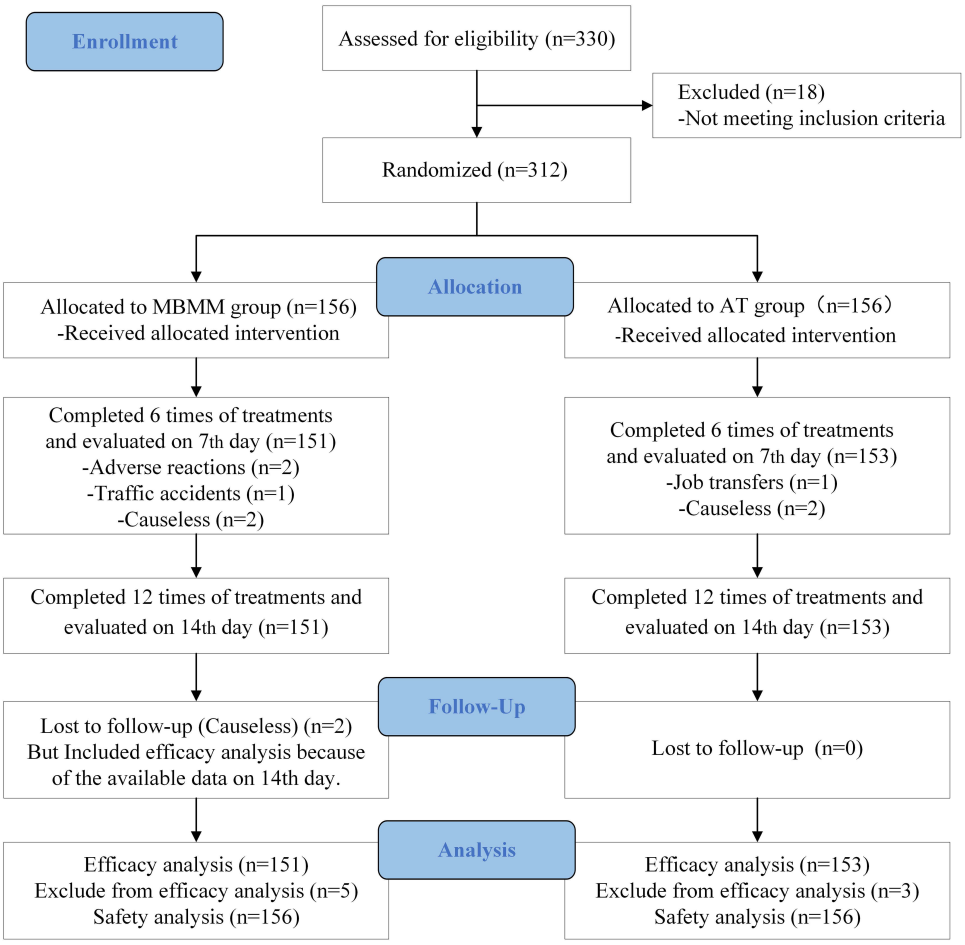

Figure 3 Participant flowchart.

Meta-analysis was used to test the center effect, and the heterogeneity among the two centers was low and the research conclusions were consistent (I^2 = 20.7%, P = 0.436).

The Secondary Efficacy Outcome

Changes in the Scale Scores Over Time

Friedman test showed that, with the advancement of treatment, the VAS, ODI, and M-JOA scores changed significantly in both groups (P <0.001, Table 2). According to paired comparison, there was no significant change in M-JOA scores of the MBMM group between the 28th day and the 14th day, or VAS, ODI, and M-JOA scores of the AT group between the 28th day and the 14th day; while significant differences were observed in any other pairwise comparisons (Table 2). No statistical difference was detected in VAS score between the two groups at each time point. The ODI score (P = 0.039) and M-JOA score (P = 0.032) of the MBMM group on the 28th day were lower than those of the AT group, with statistically significant differences (Table 2).

Changes in the Serum Indexes Over Time

The serum β-EP content (P = 0.014, P = 0.032, Table 3) of patients in both groups increased and the serum SP content (P <0.001, P = 0.048, Table 3) decreased on the 14th day when compared with those at baseline, showing statistically significant differences. However, inter-group comparison revealed no statistical difference (P = 0.514, P = 0.787, Table 3).

Table 1 Comparison of the Baseline Data Between the Two Groups

Measures	MBMM (n = 151)	AT (n = 153)	*P*
Gender, N (%)			0.568
Male	50 (33.1%)	46 (30.1%)	
Female	101 (66.9%)	107 (69.9%)	
Marital status, N (%)			0.210
Single	43 (28.5%)	34 (22.2%)	
Married	108 (71.5%)	119 (77.8%)	
Family history, N (%)			0.595
Have	24 (15.9%)	21 (13.7%)	
Not have	127 (84.1%)	132 (86.3%)	
Age, median (Q1, Q3), years	48 (28, 57)	50 (33, 57)	0.190
Height, median (Q1, Q3), cm	160 (156, 167)	160 (157, 165)	0.892
Weight, median (Q1, Q3), kg	62 (54, 69)	60 (54, 65)	0.233
Disease course, median (Q1, Q3), months	36 (16, 60)	36 (18, 60)	0.875
Heavy manual labor, median (Q1, Q3), hours	0.5 (0, 2)	0.5 (0, 1)	0.099
VASa, median (Q1, Q3)	5 (4.1, 5.5)	5 (4.1, 5.7)	0.963
ODI a, median (Q1, Q3)	28 (18, 34)	26 (18, 34)	0.803
M-JOAa, median (Q1, Q3)	7 (6, 13)	8 (7, 13)	0.759
β-EPb, median (Q1, Q3), pg/mL	5.89 (4.67, 7.75)	5.5 (4.32, 7.53)	0.461
SPa, median (Q1, Q3), pg/mL	20.69 (13.65, 30.54)	18.76 (12.3, 27.7)	0.096

Notes: *P* >0.05 for all comparisons.
Abbreviations: VAS, Visual Analogue Sscale; ODI, Oswestry Disability Index; M-JOA, modified Japanese Orthopaedic Association; β-EP, β-endorphin; SP, substance P.

Table 2 Comparison of Scale Scores for the Two Groups

	MBMM (n = 151)	AT (n = 153)	*P* value[a]
	Median (Q1, Q3), Mean (95% CI)	Median (Q1, Q3), Mean (95% CI)	
VAS			
Baseline	5 (4.1, 5.5), 4.91 (4.78–5.04)*	5 (4.1, 5.7), 4.91 (4.77–5.05)*	–
7th day	4 (3, 4.1), 3.68 (3.51–3.85)*	4 (3, 4), 3.62 (3.45–3.79)*	0.637
14th day	3 (1.7, 3.2), 2.6 (2.42–2.79)*	3 (2, 3.1), 2.63 (2.46–2.81)	0.794
28th day	2 (1.5, 3.1), 2.42 (2.21–2.62)*	3 (2, 3), 2.58 (2.39–2.77)	0.246
P value[b]	<0.001	<0.001	
ODI			
Baseline	28 (18, 34), 27.01 (25.26–28.77)*	26 (18, 34), 26.69 (24.78–28.59)*	–
7th day	18 (12, 24), 18.41 (16.81–20.01)*	20 (12, 26), 19.96 (18.34–21.58)*	0.180
14th day	14 (6, 20), 13.1 (11.77–14.43)*	14 (8, 20), 14.59 (13.25–15.93)	0.121
28th day	12 (6, 16), 12.17 (10.92–13.41)*	14 (8, 20), 13.99 (12.77–15.21)	0.039
P value[b]	<0.001	<0.001	
M-JOA			
Baseline	7 (6, 13), 8.64 (8.94–10.33)*	8 (7, 13), 9.18 (9.13–10.44)*	–
7th day	6 (4, 10), 6.9 (6.24–7.56)*	6 (4, 10), 7.04 (6.37–7.71)*	0.770
14th day	5 (2, 6), 4.47 (3.99–4.95)	5 (3, 8), 5.11 (4.58–5.64)	0.079
28th day	5 (2, 6), 4.23 (3.77–4.69)	5 (2, 7), 4.97 (4.48–5.47)	0.032
P value[b]	<0.001	<0.001	

Notes: [a]*P*-value for the intergroup comparison using the Mann–Whitney *U*-test, [b]*P*-value for the intra-group comparison using the Friedman test, * Pairwise comparison: Significant differences were observed compared with any data in the group.
Abbreviations: VAS, Visual Analogue Scale; ODI, Oswestry Disability Index; M-JOA, modified Japanese Orthopaedic Association.

Table 3 Comparison of Serum Indexes for the Two Groups

	MBMM (n = 151)	AT (n = 153)	*P* value[a]
	Median(Q1,Q3), mean (95% CI)	Median(Q1,Q3), mean (95% CI)	
β-EP,pg/mL			
Baseline	5.89 (4.67, 7.75), 8.24 (7.05–9.43)	5.5 (4.32, 7.53), 7.63 (6.49–8.77)	–
14th day	8.32 (5.06, 9.52), 10.8 (7.76–9.83)	6.72 (5.46, 10.26), 9.47 (7.73–11.21)	0.514
P value[c]	0.014	0.032	
SP, pg/mL			
Baseline	20.69 (13.65, 30.54), 26.88 (23.44–30.31)	18.76 (12.3, 27.7), 23.32 (20.86–25.77)	-
14th day	16.21 (12.2, 22.29), 21.75 (18.44–25.05)	14.72(10.02, 24.29), 20.79 (18.2–25.38)	0.787
P value[c]	<0.001	0.048	

Notes: [a]*P*-value for the intergroup comparison using the Mann–Whitney *U*-test, [c]*P*-value for the intra-group comparison using the Wilcoxon signed-rank test.
Abbreviations: β-EP, β-endorphin; SP, substance P.

Safety Assessments

A total of 11 cases (3.5%) of adverse events were reported in two groups during the trial period. There were six cases (3.8%) in the MBMM group and five cases (3.2%) in the AT group, without statistically significant differences between the two groups ($P = 0.759$). In the MBMM group, one patient developed blisters and five patients developed skin rash and itching (two of them dropped out). While in the AT group, three patients developed needle stagnation and two patients developed subcutaneous hematoma after needle removal. All patients with adverse reactions were carefully treated by doctors until the disappearance of corresponding symptoms. After treatment, there were no abnormalities related to routine blood tests, liver and kidney function tests, and electrocardiograms of any patients.

Discussion

In our study, both Ma's bamboo-based medicinal moxibustion therapy and acupuncture can significantly relieve the symptoms of low back pain, and improve the lumbar dysfunction and daily living ability of LDH patients. Compared with the AT group, there was no statistically significant difference in the improvement of the primary efficacy index (change of VAS score from baseline to the 14th day) in the MBMM group, but the statistically significant difference was observed in the improvement of ODI and M-JOA scores on the 28th day. The data suggest that the therapeutic effect of Ma's bamboo-based medicinal moxibustion therapy on relieving low back pain is not inferior to that of acupuncture, and it has post-effect advantages in improving lumbar dysfunction and daily living ability. Simultaneously, according to the occurrence of adverse events and the results of laboratory tests before and after treatment, both Ma's bamboo-based medicinal moxibustion therapy and acupuncture are safe to apply in clinical practice.

The symptoms of pain in some LDH patients may not be significantly relieved after surgical reduction in nerve root compression by the nucleus pulposus.[10] Therefore, the mechanism of pain in LDH patients cannot be explained completely by the traditional theory of mechanical compression. The rupture of annulus fibrosus will cause immune reaction, inflammatory stimulation, and other knock-on effects, resulting in low back pain. Meanwhile, the deposition of immune complex and inflammatory stimulation can further aggravate the microenvironment of the intervertebral disc, thus exacerbating the degeneration of the intervertebral disc.[33] The occurrence of low back pain may be associated with the increase of β-EP content and the decrease of SP content, which are involved in inflammatory reaction and immune regulation, respectively. Specifically, SP is a nociceptive neuropeptide released from nerve endings, which can stimulate the release of macrophages to produce inflammatory stimuli. Its serum level has been reported to be positively correlated with the degree of low back pain.[32] β-EP is an endogenous opioid peptide, which can be regarded as a regulatory factor of immune response and exert an analgesic effect by inhibiting the release of SP in vivo. Its serum level reveals a negative correlation with the degree of low back pain.[31] In our study, both Ma's bamboo-based medicinal moxibustion therapy and acupuncture can increase the content of serum β-EP and reduce the content of serum SP, thus exerting the analgesic effect. Moreover, the two intervention measures showed the same regulatory effect.

Acupuncture was selected as a control therapy in our study. The definite efficacy of acupuncture in treating low back pain has been demonstrated by the existing systematic review,[34] meta-analysis,[35] and randomized controlled trial.[22] Moreover, acupuncture is also recommended as a therapeutic approach for low back pain by the American College of Physicians.[36] Therefore, acupuncture was taken as a control measure in our study, which may strengthen the persuasiveness of the results of this controlled trial.

As evidenced by previous research,[37] cake-separated moxibustion can relieve the symptoms of low back pain in patients with LDH. However, traditional cake-separated moxibustion has some disadvantages, such as the limited area of applying moxibustion, the difficulty of temperature control, and the high risk of burns and scalds, which directly affect the efficacy and safety of moxibustion. Significantly, in terms of Ma's bamboo-based medicinal moxibustion therapy, the bamboo tube was used, which was convenient for controlling the dose of drugs and moxa, and can also polymerize the heating power and drug properties, while avoiding the occurrence of adverse events such as burns and scalds. In addition, the bamboo tube is cheap and reusable, which reduces the medical cost.

The efficacy of Ma's bamboo-based medicinal moxibustion may be related to the synergistic effect of drugs, moxibustion, and acupoints. In view of the pathogenesis characteristics of LDH patients with low back pain, such as "cold", "blood stasis", and "deficiency", the prescription of Ma's bamboo-based medicinal moxibustion adopts the methods of "warming", "dredging", and "tonifying". Wei Ling Xian (Clematidis Radix Et Rhizoma),[38] Du Huo (Angelicae Pubescentis Radix),[39] Xi Xin (Asari Radix Et Rhizoma),[40] and other drugs contain saponins, coumarins, and volatile oils, which are important chemical components that exhibit anti-inflammatory and analgesic activities. The volatile oils contained in drugs such as Xi Xin (Asari Radix Et Rhizoma), Rou Gui (Cinnamomi Cortex), and Chuan Xiong (Chuanxiong Rhizoma) can change the fluidity of lipids and proteins in the cuticle of the skin and promote the transdermal penetration of drugs.[39] Importantly, the absorption and distribution of active pharmaceutical ingredients in the human body is a gradual accumulation process, which, to some extent, explained further relief of low back pain in patients from the MBMM group during the follow-up period.

Owing to the comprehensive effect of heat, light, and smoke, the efficacy of moxibustion has been documented to have exact anti-inflammatory and immune regulation functions,[41] which is consistent with the mechanism of low back pain in patients with LDH. According to relevant research,[42] with the increase of moxibustion quantity, there was a more significant long-term effect of moxibustion on low back pain in patients with LDH. As for Ma's bamboo-based medicinal moxibustion therapy, 3 g of moxa were used to make a larger than conventional moxa cone, resulting in a longer duration of moxibustion. Moreover, the bamboo tube can polymerize the heating power to enhance the quantity of moxibustion significantly. Consequently, it may explain that Ma's bamboo-based medicinal moxibustion therapy had post-effect advantages in improving lumbar dysfunction and daily living ability.

Local acupoints were selected for moxibustion in this study, showing the effects of activating meridians, warming the kidney, and strengthening the waist. The acupoint area shows specificity in biological structure.[43] There is a dense distribution of subcutaneous nerve endings, mucopolysaccharide and mast cells, with thinner cuticle than that of the non-acupoint area, and thus relatively weaker skin barrier function. Good permeability can be created combined with the heating of moxibustion, which is also beneficial to the penetration of the prescription.

Clinical Implications

Ma's bamboo-based medicinal moxibustion therapy is a painless, non-invasive technology with low cost and simple operation, which can not only be used in primary medical institutions, but is also suitable for patients' own health care. This study provides scientific evidence for the effectiveness and safety of Ma's bamboo-based medicinal moxibustion therapy on low back pain in lumbar disc herniation by means of evidence-based medicine evaluation method, which is helpful to further guide clinical applications and better serve public health.

Limitations

This study is subject to several limitations. First, this study only included LDH patients with moderate low back pain (VAS score of 3–6 points). It remains to be further explored concerning the therapeutic effect of Ma's bamboo-based medicinal moxibustion therapy in the treatment of LDH patients with mild and severe low back pain. Additionally, the duration of

follow-up was relatively short in this study. Further validation is required to identify the superiority of long-term efficacy of Ma's bamboo-based medicinal moxibustion therapy. Furthermore, there was a poor understanding of the potential mechanism of Ma's bamboo-based medicinal moxibustion, which should be clarified by additional animal experiments.

Conclusion

By evaluating the subjective scale of VAS, ODI, M-JOA, and objective indicators of serum SP and β-EP, we found that the efficacy of Ma's bamboo-based medicinal moxibustion therapy in relieving low back pain of LDH patients is comparable to that of acupuncture, and it has post-effect advantages in improving lumbar dysfunction and daily living ability, which can be used as a safe and effective alternative method for LDH treatment.

Abbreviations

ANCOVA, Analysis of Covariance; ELISA, Enzyme-linked Immunosorbent Assay; AT, acupuncture; ITT, intention-to-treat; IWR, interactive web response; LDH, lumbar disc herniation; MBMM, Ma's bamboo-based medicinal moxibustion; M-JOA, modified Japanese Orthopaedic Association; ODI, Oswestry Disability Index; PP, per-protocol; SP, substance-P; VAS, visual analog scale; β-EP, β-endorphin.

Data Sharing Statement

The research team will preserve the original paper-version CRFs in a locked cabinet at the First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine for at least 5 years after publication of the study results. The datasets are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The protocol (protocol version 2.0, 29 September 2020) was approved by the ethics committee of No.1 Affiliated Hospital of Guizhou University of Traditional Chinese Medicine (Approval number: K2020-039). The study was conducted in accordance with the principles of the Declaration of Helsinki. All study patients signed written informed consent on the sent form prior to participation. Participation in the study was completely voluntary. Patients were able to withdraw at any time. The decision to participate or withdraw did not affect their existing treatment or service received. Caregivers who were found to have significant depressive symptoms or other mental health problems wwere referred to appropriate health services for follow-up. All personal information collected was kept strictly confidential and used for research purposes only. Research team members are responsible for safe-keeping the confidential data.

Acknowledgments

We sincerely thank the Institute of Chinese Medical History and Literature, China Academy of Chinese Medical Sciences for its supervision and support on protocol implementation and safety control of the trial. We are grateful to INTELLIGENCE FUTURE Soft Co., Ltd. for their statistical management. We also acknowledge No.1 Affiliated Hospital of Guizhou University of Traditional Chinese Medicine and No.2 Affiliated Hospital of Guizhou University of Traditional Chinese Medicine for their kind assistance and collaboration. In addition, we are grateful to professor Sun Qingwen for his identification of the medicinal materials in this study.

Funding

The study was financially supported by the National Key Research and Development Project of the Ministry of Science and Technology of China (2019YFC1708403).

Disclosure

The authors have no conflicts of interest to declare in this work.

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