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Safety and efficacy of Yaobitong capsules for lumbar disc herniation: A multicenter, randomized, double-blinded, parallel, positive-controlled clinical trial

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Abstract

Background. Lumbar disc herniation (LDH) is one of the most common diseases and is a global medical and socioeconomic problem characterized by leg or back pain, weakness in the lower extremities and paresthesia.

Objectives. A multicenter, randomized, double-blinded, parallel, positive-controlled clinical trial was conducted to evaluate the efficacy and safety of Yaobitong capsules (YBT) for LDH.

Materials and methods. Patients (n = 479) were recruited and randomized into YBT and Jingyaokang capsule (JYK) groups (the positive control), and received YBT or JYK at a dose of 3 capsules 3 times per day after a meal for 30 days. The primary efficacy outcome was the Oswestry Disability Index (ODI), with the visual analogue scale (VAS) used as the secondary efficacy outcome. The adverse events and adverse reactions were also evaluated.

Results. There was no significant difference in baseline characteristics between YBT (n = 358) and JYK groups (n = 120), and no difference was observed between groups for mean ODI score at day 0 ($p = 0.064$) or day 7 ($p = 0.196$), but there were differences at days 14, 21 and 30 ($p < 0.001$). The YBT showed more decline from baseline, and the decreased ODI score was substantially different from JYK ($p < 0.001$). The differences in decreased VAS scores between YBT and JYK were also significant at each time point (days 7, 14, 21, and 30), with better scores in the YBT group than in the JYK group ($p < 0.001$). In terms of safety, there was no obvious disparity in adverse events or adverse reactions between the 2 groups ($p > 0.05$).

Conclusions. Yaobitong was better than JYK for LDH treatment, with no significant difference in safety. The study suggests that YBT is a promising and effective treatment for LDH.

Key words: lumbar disc herniation (LDH), clinical trial, Jingyaokang, Yaobitong

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Background

Lumbar disc herniation (LDH) is one of the most common diseases and is a global medical and socioeconomic problem characterized by leg or back pain, weakness in the lower extremities and paresthesia.[1,2] One epidemiological investigation showed LDH incidence at approx. 5 per 1000 adults each year worldwide.[3] In addition, lower back pain is the primary cause of worldwide productivity loss per year in 195 countries and the top cause of disability in 126.[4] In China, relevant epidemiological investigations show that LDH incidence is as high as 14.3%, and with changes in lifestyle and the aging population, LDH incidence has increased significantly, particularly in younger persons.[5] The most common LDH treatment options are surgical options and conservative treatments.[6] Only 10% of LDH cases are candidates for immediate surgery, and 8–40% of patients still feel pain after surgery.[7,8] Physical therapy, complementary treatments, alternative medicine (acupotomy, acupuncture, Chinese herbal medicine, and Chinese massage), pharmacotherapy (including non-steroidal anti-inflammatory drugs (NSAIDs), systemic steroids, steroid injections, and muscle relaxants), and an active lifestyle are routinely used as effective conservative treatments for LDH.[9] Most LDH patients gradually prefer continued conservative management due to its unique advantages in mid-term and long-term follow-up.[10]

At present, conservative LDH treatments are numerous, though a single satisfactory treatment method is still lacking. Traditional Chinese medicine (TCM), as an important component of complementary and alternative medicine, has developed for over 1000 years and has shown to be effective for the treatment of a variety of disorders, particularly musculoskeletal diseases, in Asian countries, especially China.[11,12] For instance, Yaobitong capsules (YBT) are a new Chinese patented medicine for LDH treatment, originating from the clinical experience in Chinese herbal compounds by Shuchun Sun, a famous TCM physician.[13] Our preclinical animal experiments have indicated that YBT has significant therapeutic effects on rat lumbar radiculopathy, with a positive analgesic effect on physical and chemical pain stimulation. However, the lack of a large sample and the need for high-quality clinical trials call for more evidence on the efficacy of YBT in treating LDH. The Jingyaokang capsule (JYK) is considered an effective drug for LDH in China and is approved by the China Food and Drug Administration.

Objectives

The objective of this trial was to compare the efficacy of YBT with JYK in the treatment of LDH patients, to understand the performance of YBT in relieving patient symptoms and improving quality of life, and to evaluate its safety.

Materials and methods

Study design

This multicenter, randomized, double-blinded, parallel positive-controlled clinical trial used a computer-generated list of random numbers in Microsoft Excel 2013 (Microsoft Corp. Armonk, USA), with patients randomly allocated into YBT and JYK groups in a 3:1 ratio. The randomized assignments sealed in opaque envelopes were prepared by a nurse who was blinded to the study design. The nurse opened the envelopes for each participating patient and then submitted them to the clinical trial unit and sponsor for safekeeping. The researchers were blinded to the medication management throughout the whole process, and the participants were given similar vials with YBT or JYK by the pharmacy.

All researchers received protocol training before the beginning of this trial, with the full-time Clinical Research Coordinator (CRC) staffed to schedule the treatment procedure in each center. A supervisor sent to all centers monitored the study to ensure data integrity and quality. The entire trial complied with Good Clinical Practice (GCP), which was ensured by 2 independent quality audits.

The Institutional Review Board of Shuguang Hospital affiliated with the Shanghai University of Traditional Chinese Medicine (batch No. 2014-352-48-01), approved the trial (approval No. 2014-352-48-01), and it was registered at the Chinese Clinical Trial Registry (No. ChiCTR2200057819). All patients gave written informed consent.

Participants

From June 2015 to February 2016, 479 LDH patients were recruited from 10 Chinese centers. The inclusion criteria were: 1) LDH patients meeting the standard of Western and TCM diagnostic criteria (patients have local pain and tenderness in the lower back and legs,

flexion or extension negative, purple tongue with ecchymosis, thin and white coating, as well as Wiry and tense pulse or uneven pulse)[14,15]; 2) aged 18–60 years (including 18 and 60 years), male or female; 3) Oswestry Disability Index between 30% and 80%; 4) visual analogue scale (VAS) between 30 mm and 80 mm; 5) not taking NSAIDs or other medications for LDH within 1 week before visit; and 6) who gave informed consent. The exclusion criteria included: 1) pregnant or breastfeeding women; 2) allergic constitution or an allergy to YBT or JYK; 3) recurrent LDH after surgery; 4) asymptomatic LDH or non-discogenic low back and leg pain; 5) LDH complicated with cauda equina syndrome or conus medullaris syndrome; 6) LDH complicated with lumbar tumor or tuberculosis, lumbar spondylolisthesis above 0, lumbar spinal stenosis, ankylosing spondylitis, or severe osteoporosis; 7) LDH complicated with severe hypertension, heart disease, or other serious primary organ system or psychiatric diseases; 8) other acute and chronic pain, such as migraines and joint pain affecting how patients describe pain; 9) recently receiving epidural steroid injection or various interventional and surgery treatments; 10) allergy to meloxicam; 11) serious primary diseases of the heart, liver and kidney, including alanine transaminase (ALT), aspartate aminotransferase (AST) ≥normal upper limit, creatinine (Cr) >normal upper limit, hematopoietic system and endocrine system, psychosis, and epilepsy; 12) taking part in another study within 3 months; and 13) those judged inappropriate for the study by the researchers.

Intervention

The drugs used in the YBT group were YBT and JYK simulation agents, whose main ingredient was placebo starch. The main ingredients of YBT are San Qi (Notoginseng Radix), Du Huo (Angelicae Pubescentis Radix), Chuan Xiong (Chuanxiong Rhizoma), Bai Shao (Paeoniae Radix Alba), Niu Xi (Cyathulae Radix), Gou Ji (Cibotii Rhizoma), Shu Da Huang (Rhei Radix et Rhizoma), and Yan Hu Suo (Corydalis Rhizoma). The drugs used in the JYK group were JYK and YBT simulation agents whose main ingredient was placebo starch. The main ingredients of JYK are Ma Qian Zi (Strychni Semen), Shen Jin Cao (Lycopodii Herba), Hong Hua (Carthami Flos), Xiang Jia Pi (Periplocae Cortex), Ru Xiang (Olibanum), Di Long (Pheretima), Gu Cui Bu (Drynariae Rhizoma), Fang Ji (Stephaniae Tetrandrae Radix), Niu Xi (Cyathulae Radix), and Mo Yao (Myrrha). Jiangsu Kangyuan Pharmaceutical Co. Ltd. (Lianyungang, China) provided JYK (specification: 0.33 g/capsule, batch No. 140438), YBT (specification: 0.42 g/capsule, batch No. 140438) and simulation agent (batch No. 140701 and No. 140702) for this study. All drugs were stored at room temperature. Patients in both groups were given 3 drug capsules 3 times per day after meals for 30 days.

Outcome measurements

Symptom burden and quality of life, including pain intensity, personal care, lifting, walking, sitting, standing, sleeping, social life, and travelling, were assessed as primary outcomes using the ODI (ranging from 0 to 45 points), which has been validated in the LDH population.[16] Patients answered the questions to evaluate the severity of their symptoms through a numerical rating scale of 0–5 over the previous 24 h, with 0 meaning the absence of symptom and 5 meaning the worst symptom. The ODI dysfunction index is the percentage of the sum score of 9 items to the highest score (45 points), with a higher percentage equating to more severe dysfunction.[17]

The VAS (ranging from 0 to 100 points) score was included as the secondary efficacy outcome of LDH. Visual analogue scale was a 10 cm horizontal line drawn on paper, with 0 marked at one end and 10 at the other. The line was equally divided into 10 segments. A 0 VAS score indicated no pain and a 10 score signified the most severe pain.[18] Patients were asked to mark on the line to express their degree of self-reported pain within 48 h. The ODI and the VAS were evaluated at baseline (0 days) and at 7, 14, 21, and 30 days. Before using the scale, all patients received an illustration and practice on using the scale by professionals. Professional statisticians collected and analyzed the data.

Treatment safety was evaluated using 1) serum biochemicals, including ALT, AST, total bilirubin (TBIL), gamma-glutamyl transpeptidase (γ-GT), alkaline phosphatase (AKP), blood urea nitrogen (BUN), and Cr; 2) routine blood and urine examinations (e.g., urine protein, red blood cell and white blood cell count); 3) routine stool and occult blood; 4) electrocardiogram; and 5) adverse events and adverse reactions.

Sample size

The sample size was calculated using the superiority test and estimated on account of the rate of decline from the baseline ODI score, the primary efficacy measure of this study. It was assumed that the therapeutic effect of YBT on LDH was better than JYK. We assumed an $\alpha = 0.05$ and a power = 80% for YBT:JYK, according to a 3:1 design. The difference in the reduction rate of ODI score from baseline between the YBT group and the JYK group was estimated to be 15%, and the combined variance was 40%, with an estimated number of 228 patients in the YBT group and of 76 in the JYK group. Considering the possible loss of follow-up (20%), the number of cases in the clinical trial was 360 in the YBT group and 120 in the JYK group, according to the requirements of national regulations in China.

Statistical analyses

All data were analyzed using Statistical Analysis System (SAS) v. 9.2 (SAS Institute, Cary, USA) and R v. 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Data management adopted epidata v. 3.0 using double independent input, and statistical analysis was carried out after assessment. Kolmogorov–Smirnov tests and Q–Q plots evaluated data distribution, while Bartlett's or Levene's test checked for homogeneity of variances. The results of these tests can be found in the Supplementary materials.

The equilibrium analysis of basic values adopted t-tests, Wilcoxon tests or χ^2 test/Fisher exact tests to compare demographic data and other indicators of balance between the 2 groups. Effectiveness analysis employed repeated-measures linear mixed models (R package: lmerTest) to assess the effect of treatment on LDH. The models included outcome data collected at every follow-up visit, with fixed effects for the treatment, time point as a categorical variable, baseline of ODI, sex, age, center, with and without the interaction between treatment and time point, and random intercepts for participants accounted for the dependence of repeated measures, with the same models used to estimate VAS score. The last observation carried forward (LOCF) was used to fill missing primary outcome data. Robust mixed analysis of variance (ANOVA) (R package: WRS2) was used for sensitivity analysis of primary endpoint and different terms of ODI score;[19] 20% trimmed means were used to fit between-within-subjects ANOVA, with post hoc comparisons on single effects performed with modified one-step estimators (MOM). Safety analysis mainly used descriptive statistical analysis, with adverse events described on a list. If necessary, Fisher's exact probability method was used to compare the incidence of adverse events between the 2 groups. The laboratory test results described the normal conditions before the test but abnormal conditions after treatment, as well as the relationship between abnormal changes and the test drug. A 2-sided test was used for all hypotheses testing, and $p \leq 0.05$ was considered statistically significant. The reliability of all confidence intervals was assumed as 95% (95% CI).

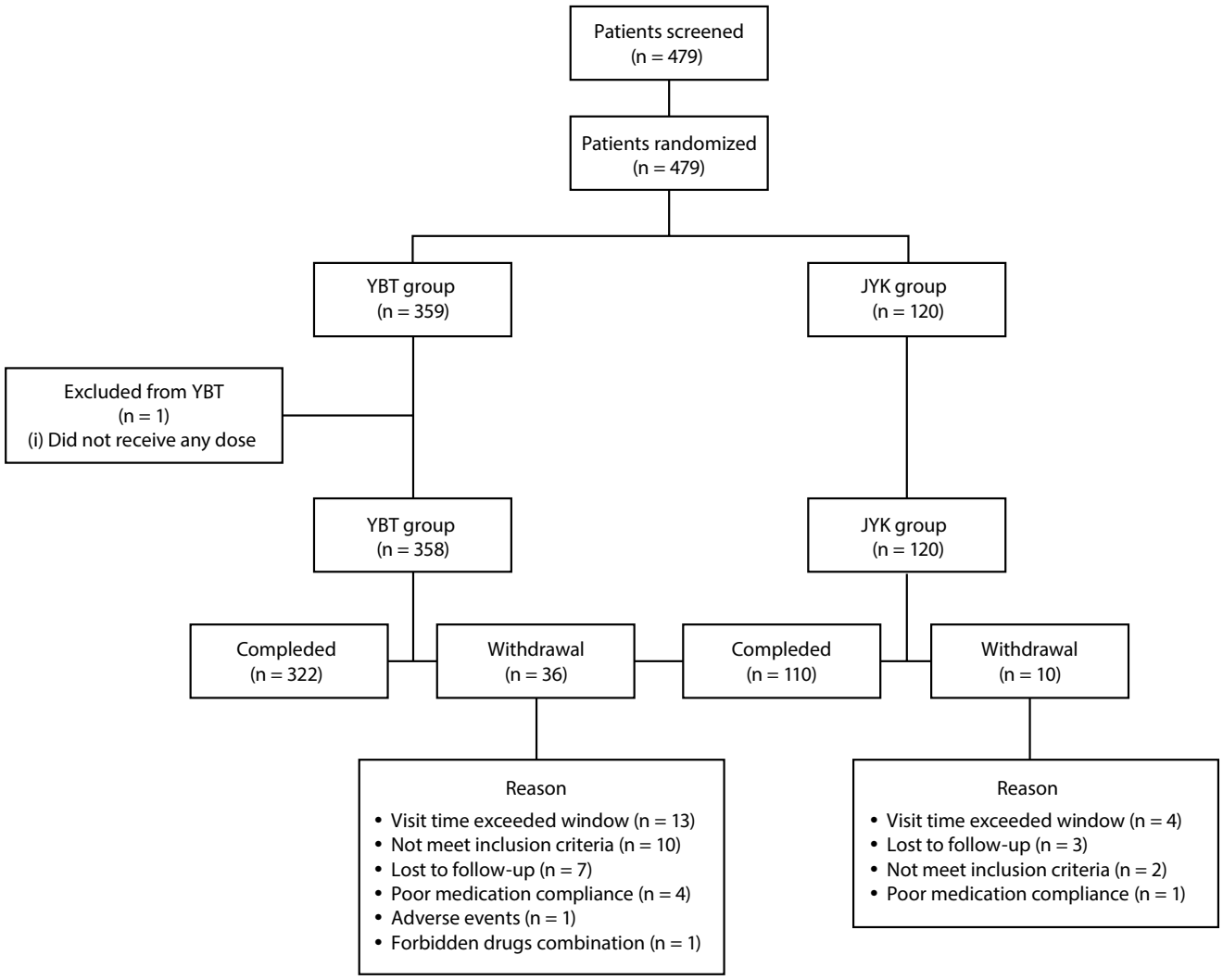

Fig. 1. Screening flowchart

YBT – Yaobitong capsules, JYK – Jingyaokang capsule.

Table 1. Comparison of baseline characteristics

Variable	Variable	YBT (n = 358)	JYK (n = 120)	Test value	p-value
Gender, n (%)	male	125 (34.92)	44 (36.67)	–	0.742*
	female	233 (65.08)	76 (63.33)		
Age [years], mean +SD		47.36 ±10.34	48.13 ±10.30	t = 0.72	0.472
Ethnicity, n (%)	Han nationality	353 (98.60)	118 (98.33)	–	1.000*
	other	5 (1.40)	2 (1.67)		
Weight [kg], mean +SD		63.36 ±10.21	63.46 ±9.59	t = 0.10	0.923
Height [cm], mean +SD		164.17 ±7.35	164.66 ±7.62	t = 0.62	0.533
Heart rate [bpm], mean +SD		69.72 ±8.13	70.55 ±8.91	t = 0.94	0.347
Respiratory rate [bpm], mean +SD		18.61 ±1.96	18.68 ±1.89	t = 0.35	0.727
SBP [mm Hg], mean +SD		123.66 ±9.79	125.18 ±11.49	t = 1.30	0.196
DBP [mm Hg], mean +SD		73.89 ±7.17	74.58 ±8.79	t = 0.77	0.442
Duration of LBP [months], mean +SD		12.00 ±23.00	12.00 ±40.00	t = 0.77	0.141
Baseline of ODI, mean ±SD	total index	43.53 ±8.00	41.94 ±8.30	t = 1.86	0.064
	pain intensity	2.55 ±0.65	2.46 ±0.59	Z = 1.35	0.176#
	personal care	2.13 ±0.58	2.08 ±0.60	Z = 1.13	0.257#
	lifting	2.23 ±0.72	2.18 ±0.66	Z = 0.84	0.399#
	walking	1.21 ±0.68	1.31 ±0.73	Z = 1.39	0.164#
	sitting	2.40 ±0.68	2.19 ±0.74	Z = 3.11	0.002#
	standing	2.30 ±0.67	2.17 ±0.74	Z = 2.00	0.045#
	sleeping	1.70 ±0.76	1.68 ±0.76	Z = 0.30	0.766#
	social life	2.51 ±0.71	2.41 ±0.68	Z = 1.38	0.168#
	travelling	2.56 ±0.85	2.42 ±0.88	Z = 1.73	0.084#
Baseline of VAS, mean ±SD		61.82 ±10.61	61.29 ±11.77	t = 0.46	0.647
History of treatment, n (%)					
TCM treatment	no	301 (84.08)	99 (82.50)	–	0.671*
	yes	57 (15.92)	21 (17.50)		
Drug treatment	no	317 (88.55)	103 (85.83)	–	0.423*
	yes	41 (11.45)	17 (14.17)		
History of allergy, n (%)	no	351 (98.04)	119 (99.17)	–	0.686*
	yes	7 (1.96)	1 (0.83)		
Other diseases combined, n (%)	no	313 (87.43)	104 (86.67)	–	0.875*
	yes	45 (12.57)	16 (13.33)		

*Fisher's exact probability method was used to compare gender, ethnicity, history of treatment, and other diseases combined between the 2 groups. #Wilcoxon test was used to compare each term of ODI at baseline, and t-test was used to compare other items between the 2 groups. YBT – Yaobitong capsule; JYK – Jingyaokang capsule; ODI – Oswestry Disability Index; VAS – visual analogue scale; SD – standard deviation; SBP – systolic blood pressure; DBP – diastolic blood pressure; TCM – traditional Chinese medicine; LBP – low back pain.

Results

Baseline characteristics of patients

Between June 2015 and February 2016, 479 patients fulfilled the screening process and were recruited for the trial (Fig. 1). One patient withdrew from the YBT group. A total of 478 patients entered the full analysis set and safety analysis set (YBT group n = 358; JYK group n = 120). An intention-to-treat analysis was used in this trial. As shown in Table 1, there was no significant difference in demographic data or vital signs between the 2 groups ($p > 0.05$). Among disease conditions, there was no obvious correlation between groups ($p = 0.875$). In addition, each baseline ODI and VAS score had no statistical difference between the groups, indicating comparability ($p > 0.05$).

Efficacy results

After adjusting for baseline ODI, center, age, and sex, the linear mixed models showed that the YBT provided a significant benefit over JYK. As shown in Table 2 (model 1), the mean ODI in the YBT group decreased by 5.25 points more than in the JYK group (95%

Table 2. Linear mixed model results for ODI and VAS. Linear mixed model adjust center, age, sex and baseline of ODI or VAS, model 2 and model 4 also add interaction term in the model

Variable	ODI			VAS		
	estimate (95% CI)	t-value	p-value	estimate (95% CI)	t-value	p-value
	Model 1			Model 3		
group	−5.25 (−6.09, −4.41)	−12.10	<0.001	−5.06 (−6.10, −4.01)	−9.35	<0.001
time_7D	−5.98 (−6.59,−5.36)	−19.02	<0.001	−9.65 (−10.49, −8.82)	−22.60	<0.001
time_14D	−14.83 (−15.45,−14.21)	−47.19	<0.001	−21.47 (−22.31, −20.63)	−50.26	<0.001
time_21D	−23.15 (−23.77, −22.54)	−73.67	<0.001	−32.89 (−33.72, −32.05)	−76.99	<0.001
time_30D	−29.09 (−29.71, −28.48)	−92.58	<0.001	−43.38 (−44.22, −42.54)	−101.48	<0.001
	Model 2			Model 4		
group	0.37 (−0.80, 1.55)	0.62	0.535	0.10 (−1.45, 1.66)	0.13	0.900
time_7D	−3.96 (−5.08, −2.84)	−6.91	<0.001	−8.00 (−9.60, −6.41)	−9.81	<0.001
time_14D	−10.78 (−11.9, −9.66)	−18.80	<0.001	−17.85 (−19.45, −16.25)	−21.88	<0.001
time_21D	−16.81 (−17.94, −15.69)	−29.33	<0.001	−27.10 (−28.69, −25.50)	−33.22	<0.001
time_30D	−20.44 (−21.57, −19.32)	−35.66	<0.001	−34.90 (−36.50, −33.31)	−42.78	<0.001
time_7D:YBT	−2.69 (−3.99,−1.4)	−4.06	<0.001	−2.20 (−4.05, −0.36)	−2.34	0.020
time_14D:YBT	−5.41 (−6.71, −4.11)	−8.17	<0.001	−4.83 (−6.68, −2.99)	−5.13	<0.001
time_21D:YBT	−8.46 (−9.76, −7.17)	−12.77	<0.001	−7.73 (−9.57, −5.88)	−8.20	<0.001
time_30D:YBT	−11.55 (−12.84, −10.25)	−17.43	<0.001	−11.32 (−13.16, −9.47)	−12.01	<0.001

ODI – Oswestry Disability Index; VAS – visual analogue scale; 95% CI – 95% confidence interval.

Table 3. Comparison of ODI total index and VAS score between 2 groups before and after intervention

Variable	Time	Decreased value from baseline in the group, mean ±SD		M-estimators (YBT-JYK)	Average M-estimators	p-value
		YBT (n = 358)	JYK (n = 120)			
ODI total score	7 D	−6.65 ±4.91	−3.96 ±4.87	−2.54	−7.76#	<0.001
	14 D	−16.19 ±6.62	−10.78 ±5.91	−5.12		
	21 D	−25.28 ±7.56	−16.82 ±6.30	−9.59		
	30 D	−32.00 ±8.13	−20.45 ±7.13	−13.80		
VAS score	7 D	−10.22 ±6.68	−7.93 ±6.71	−2.58	−7.62#	<0.001
	14 D	−22.70 ±8.61	−17.78 ±9.64	−6.93		
	21 D	−34.84 ±10.12	−27.03 ±11.31	−8.90		
	30 D	−46.23 ±10.99	−34.83 ±13.12	−12.06		

Comparison between YBT group and JYK group was done using robust mixed ANOVA. # average across measurement; YBT – Yaobitong capsule; JYK – Jingyaokang capsule; ODI – Oswestry Disability Index; VAS – visual analogue scale; ANOVA – analysis of variance.

CI: −6.09 to −4.41). Compared to baseline, the ODI on 7, 14, 21, and 30 days all decreased significantly, with scores of −5.98 (−6.59 to −5.36), −14.83 (−15.45 to −14.21), −23.15 (−23.77 to −22.54), and −29.09 (−29.71 to −28.48), respectively. Considering the interaction between treatment and time point, model 2 showed that, compared to JYK, the ODI in YBT group decreased more visibly at days 7, 14, 21, and 30, with significantly lower scores of −2.69 (−3.99 to −1.4), −5.41 (−6.71 to −4.11), −8.46 (−9.76 to −7.17), and −11.55 (−12.84 to −10.25), respectively.

The same models were applied to the total VAS score, with model 3 showing a mean YBT decrease of 5.06 more than in the JYK group (95% CI: −6.10 to 4.01). Compared to baseline, the VAS of 7, 14, 21, and 30 days all decreased significantly, with scores of −9.65 (−10.49 to −8.82), −21.47 (−22.31 to −20.63), −32.89 (−33.72 to −32.05), and −43.38 (−44.22 to −42.54). Considering the interaction between treatment and time point, model 4 showed that, compared to JYK, the VAS in the YBT group decreased more at days 7, 14, 21, and 30, with statistically significant decreased scores of −2.20 (−4.05 to −0.36), −4.83 (−6.68 to −2.99), −7.73 (−9.57 to −5.88), and −11.32 (−13.16 to −9.47), respectively.

As shown in Fig. 2 and Table 2,3, both YBT and JYK groups showed a tendency of a decreased total ODI score, with no statistically significant difference observed between groups on days 0 ($p = 0.064$) and 7 ($p = 0.196$), but with significant differences at 14, 21 and 30 days ($p < 0.001$). The decreased ODI improved gradually over time in both groups ($p < 0.001$), though the YBT group showed more

Table 4. Comparison of decreased ODI score from baseline

Variable	Time	Decreased value from baseline in the group, mean ±SD		M-estimators (YBT-JYK)	Average M-estimators	Average M-estimators p-value	p-value
		YBT (n = 358)	JYK (n = 120)				
Pain intensity	7 D	−0.35 ±0.53	−0.14 ±0.40	0.00	−0.35#	<0.001	<0.001
	14 D	−0.87 ±0.63	−0.60 ±0.63	−0.40			
	21 D	−1.39 ±0.69	−1.04 ±0.61	0.00			
	30 D	−1.78 ±0.78	−1.31 ±0.67	−1.00			
Personal care	7 D	−0.30 ±0.50	−0.20 ±0.46	0.00	−0.25#	<0.001	<0.001
	14 D	−0.83 ±0.59	−0.61 ±0.66	0.00			
	21 D	−1.36 ±0.68	−0.88 ±0.58	0.00			
	30 D	−1.72 ±0.65	−1.11 ±0.67	−1.00			
Lifting	7 D	−0.29 ±0.52	−0.17 ±0.51	0.00	−0.38#	<0.001	0.030
	14 D	−0.76 ±0.68	−0.44 ±0.63	−1.00			
	21 D	−1.18 ±0.74	−0.79 ±0.61	0.00			
	30 D	1.52 ±0.80	−0.99 ±0.60	−0.52			
Walking	7 D	−0.12 ±0.41	−0.13 ±0.48	0.00	−0.11#	0.204	0.416
	14 D	−0.53 ±0.54	−0.35 ±0.54	0.00			
	21 D	−0.91 ±0.51	−0.64 ±0.62	−0.44			
	30 D	−1.09 ±0.53	−0.83 ±0.64	0.00			
Sitting	7 D	−0.36 ±0.51	−0.13 ±0.49	0.00	−0.58#	<0.001	<0.001
	14 D	−0.87 ±0.66	−0.43 ±0.65	−1.00			
	21 D	−1.32 ±0.74	−0.76 ±0.70	−0.30			
	30 D	−1.73 ±0.76	−0.91 ±0.71	−1.00			
Standing	7 D	−0.39 ±0.53	−0.24 ±0.47	0.00	−0.25#	0.026	0.18
	14 D	−0.84 ±0.64	−0.57 ±0.62	0.00			
	21 D	−1.30 ±0.68	−0.84 ±0.71	0.00			
	30 D	−1.72 ±0.78	−0.95 ±0.71	−1.00			
Sleeping	7 D	−0.49 ±0.59	−0.38 ±0.55	0.00	−0.10#	0.088	0.134
	14 D	−0.87 ±0.70	−0.67 ±0.57	0.00			
	21 D	−1.24 ±0.75	−0.93 ±0.60	0.00			
	30 D	−1.45 ±0.76	−1.05 ±0.63	−0.41			
Social life	7 D	−0.37 ±0.61	−0.15 ±0.53	0.00	−0.42#	<0.001	<0.001
	14 D	−0.90 ±0.72	−0.63 ±0.65	−0.38			
	21 D	−1.43 ±0.76	−0.89 ±0.66	−0.42			
	30 D	−1.88 ±0.84	−1.08 ±0.75	−0.88			
Travelling	7 D	−0.38 ±0.57	−0.29 ±0.54	0.00	−0.37#	<0.001	<0.001
	14 D	−0.93 ±0.74	−0.66 ±0.72	−0.36			
	21 D	−1.41 ±0.76	−0.92 ±0.75	−0.40			
	30 D	−1.72 ±0.84	−1.13 ±0.75	−0.71			

Comparison between YBT group and JYK group was done using robust mixed ANOVA. # average across measurement; YBT – Yaobitong capsule; JYK – Jingyaokang capsule; ODI – Oswestry Disability Index; VAS – visual analogue scale; ANOVA – analysis of variance.

decline compared to baseline, and the ODI decreases were significantly different from the JYK group ($p < 0.001$).

For the between-within-subject ANOVA on the 20% trimmed means, the main effects and interaction of the ODI total score, VAS score and different terms of the ODI score were all significant, with single effects of intervention as the main focus, as shown in Table 3,4. There was no significant difference between YBT and JYK groups after 7 days of treatment in terms of lifting, walking and sleeping, and within the pairwise group comparisons of standing (not average) ($p > 0.05$). However, statistically significant differences were found between the groups in other ODI scores at each time point, as shown in Table 4 ($p < 0.05$).

As shown in Fig. 2, the mean VAS score of both groups decreased gradually, and no comparable difference in VAS score was found between the groups on days 0 and 7

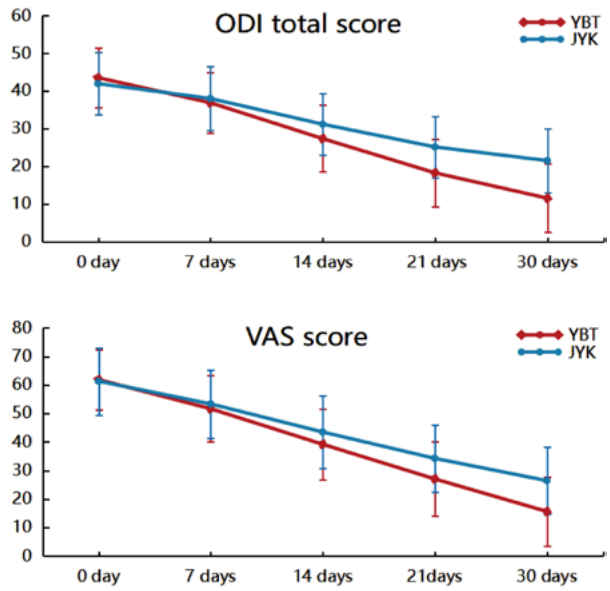

Fig. 2. Mean change of the Oswestry Disability Index (ODI) (A) and visual analogue scale (VAS) score (B). The means of outcomes are shown for the Yaobitong capsule (YBT) group (diamond) and the Jingyaokang capsule (JYK) group (circle). Measurements were observed at baseline and at 7, 14, 21, and 30 days after intervention. ODI total score ranged from 0 to 45 points and VAS scores ranged from 0 to 100 points

($p > 0.05$). As shown in Table 2,3, the differences in decreased VAS score between YBT and JYK were statistically significant at each time point, and YBT group showed more decline than JYK group ($p < 0.001$).

Safety results

As shown in Table 5, 38 adverse events were reported (YBT group, n = 31 (8.66%); JYK group, n = 7 (5.83%)), as were 11 adverse reactions, with 9 (2.51%) in the YBT group and 2 (1.67%) in the JYK group. In the incidence of adverse events and adverse reactions, no significant difference was found between the 2 groups ($p = 0.435$). Meanwhile, no serious adverse event occurred in any group. Among the 11 cases of adverse reactions, 6 cases exhibited ALT and AST elevation, including 5 (1.40%) cases in the YBT group and 1 (0.83%) in the JYK group. Three (0.84%) cases occurred with γ-GT abnormalities in the YBT group. One (0.28%) case each of BUN elevation, dyspepsia, nausea, and stomach discomfort occurred in the YBT group, and 1 (0.83%) case of tongue numbness was found in the JYK group. Overall, there was no significant difference between the YBT and JYK groups for adverse reactions ($p = 0.738$).

During the study, 59 patients, including 44 (12.29%) in the YBT group and 15 (12.50%) in the JYK group, used drug combinations, and there was no clear difference between the 2 groups ($p = 1.000$) in this regard. After treatment, no statistically significant differences in routine blood, blood biochemical values, urine, stool, occult blood, and electrocardiogram were found compared to those at baseline ($p > 0.05$).

Discussion

Lumbar disc herniation is a major contributor to low back pain and physical dysfunction.[20] Based on TCM theory, LDH is mainly induced by blood stasis and qi (the normal flow of vital energy) stagnation, blocked veins caused by strain, wind-cold dampness, and trauma.[21] In clinical practice, blood stasis, qi stagnation and blocked vein syndrome are the most common syndromes in LDH patients.[22] It is crucial to treat inflammation, improve blood circulation and remove stasis.[23] Yaobitong is a new Chinese patented medicine with the effects of promoting circulation, removing stasis, dispelling wind, clearing collaterals, promoting qi, and relieving pain.

Many studies have developed experimental animal models to verify the efficacy and mechanisms of YBT on LDH. In addition, YBT alleviates LDH symptoms and radiculopathy and increases inflammatory factor serum levels in rats.[24] The LDH mechanism relates to endocrine and immune state regulation and the release of inflammatory factors. A network analysis identified 56 components as active YBT capsule ingredients, including ginsenoside Rg1, ginsenoside Rb1, senkyunolide H, and tetrahydropalmatine. These active ingredients regulate 29 pathways via 87 direct target genes, including MAPK, Ras, PI3K-Akt, and NF-kappa B. These active compounds have been demonstrated to inhibit excessive inflammatory reactions, thereby reducing nerve sensitivity and pain. This, in turn, has been shown to relieve LDH.[25] All theoretical and preliminary experiments provide objective evidence for the effectiveness of YBT in treating LDH.

Our main findings indicate that YBT shows more efficacy in LDH patients than the JYK control drug. In this study, JYK was used as a positive control drug because it is a Chinese patented medicine widely used for cervical spondylosis and LDH, and its significant analgesic, anti-inflammatory and detumescence pharmacological effects are similar to YBT.[26,27] Yaobitong significantly decreased the ODI and

Table 5. Comparison of adverse events and adverse reactions

Item	YBT (n = 358)		JYK (n = 120)		p-value
	frequency	case [%]	frequency	case [%]	
Adverse events	31	8.66	7	5.83	0.435
Adverse reactions	9	2.51	2	1.67	0.738

Comparison between YBT group and JYK group done using the Fisher's exact probability method. YBT – Yaobitong capsule; JYK – Jingyaokang capsule.

VAS scores, which may demonstrate that it could improve low back and leg dysfunction and pain. In addition, the curative effect of YBT was better than that of JYK, particularly in the degree of pain, as well as in enhancing daily self-care ability, sitting, standing, and social life in general.

Safety analysis showed that YBT was as safe as JYK. The adverse reactions of YBT manifested as elevated ALT/AST, abnormal γ-GT, elevated BUN, dyspepsia, nausea, and stomach discomfort, indicating YBT may cause liver and kidney dysfunction and gastrointestinal reactions in clinical use. Thus, although few cases were observed, close attention should be given when using YBT in the clinic.

Although NSAIDs are still widely used for pain relief in LDH, taking them regularly should be reduced due to adverse gastrointestinal reactions and the risk of drug dependence.[28] Yaobitong was used in combination with the NSAID celecoxib as routine drugs in some clinical trials.[29] Clinical evidence also shows that YBT, combined with other therapies such as acupuncture, massage and functional exercise is more effective for LDH patients and can be generally used as a reliable and safe option.[30,31]

Limitations

The current study had several limitations, with the 30-day follow-up intervention period being insufficient to confirm the long-term effects of YBT. Second, a dose-dependent YBT design, which could enhance clinical evidence, was not included in this study. Third, manually measuring the VAS score may result in systematic error; an electronic scale is the currently preferred option. Fourth, the study lacked a comparison of YBT and JYK with traditional painkillers and NSAIDs. However, despite these limitations, this trial provides objective and clinically beneficial outcomes for comparing the effects of YBT and JYK.

Conclusions

This multicenter, randomized, double-blinded, parallel, positive-controlled clinical trial conducted in China to assess the efficacy and safety of YBT for LDH patients showed that the curative effect of YBT was significantly better than the JYK control drug, which has been widely used in the market, particularly for alleviating pain and enhancing physical function, which are the most affected aspects in LDH patients. Taken together, YBT appears to be a safe and effective treatment option for LDH patients who do not wish or cannot receive surgical treatment.

Supplementary data

The Supplementary materials are available at https://doi.org/10.5281/zenodo.10671690. The package includes the following files:

Supplementary Table 1. Kolmogorov–Smirnov test of ODI and VAS score relative to baseline.

Supplementary Table 2. Bartlett's test of ODI and VAS score relative to baseline.

Supplementary Table 3. Levene's test of ODI and VAS score relative to baseline.

Supplementary Fig. 1. QQ plot of rate of decline from baseline in ODI score (ODI1_0: 7D-0D, ODI2_0: 14D-0D, ODI3_1: 21D_0D, ODI4_1: 30D_0D).

Supplementary Fig. 2. QQ plot of decline from baseline in VAS score (VAS1_0: 7D-0D, VAS2_0: 14D-0D, VAS3_0: 21D-0D, VAS4_0: 30D-0D).

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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