Journal of Orthopaedic Translation 27 (2021) 44–56

Contents lists available at ScienceDirect

Journal of Orthopaedic Translation

journal homepage: www.journals.elsevier.com/journal-of-orthopaedic-translation

ORIGINAL ARTICLE

Jingshu Keli for treating cervical spondylotic radiculopathy: The first multicenter, randomized, controlled clinical trial

Jianhua Hu [a,1], Feng Chen [a,1], Guixing Qiu [a,*], Tiansheng Sun [b], Huilin Yang [c], Huiyong Shen [d], Peijian Tong [e], Yimin Chai [f], Xueli Zhang [g], Weibin Zhang [h], Zhidong Yang [i], Hong Jiang [j], Yalin Pan [k], Tianliang Zhu [l], Chengjian He [m], Weiping Xiao [n]

[a] Department of Orthopedics, Peking Union Medical College Hospital (PUMCH), Peking, China
[b] Department of Orthopedics, People's Liberation Army General Hospital, Peking, China
[c] Department of Orthopedics, The First Affiliated Hospital of Soochow University, Soochow, Jiangsu, China
[d] Department of Orthopedics, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, Guangdong, China
[e] Department of Orthopedics, Zhejiang Provincial Hospital of TCM, Hangzhou, Zhejiang, China
[f] Department of Orthopedics, Shanghai Sixth People's Hospital, Shanghai, China
[g] Department of Spine Surgery, Tianjin People's Hospital, Tianjin, China
[h] Department of Orthopedics, Ruijin Hospital, Shanghai Jiaotong University, Shanghai, China
[i] Department of Orthopedics, First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, China
[j] Department of Orthopedics, Suzhou Hospital of Traditional Chinese Medicine, Soochow, Jiangsu, China
[k] Department of Orthopedics, People's Hospital of Anyang City, Anyang, Henan, China
[l] Department of Orthopedics, Chongqing General Hospital, Chongqing, China
[m] Department of Orthopedics, Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan, Hubei, China
[n] Department of Orthopedics, Affiliated Hospital of Jiangxi University of Traditional Chinese Medicine, Nanchang, Jiangxi China

ARTICLE INFO

Keywords:
Cervical spondylotic radiculopathy
Herbal medicine
Jingshu keli
Randomized controlled trial
Traditional Chinese medicine

ABSTRACT

Background: Jingshu Keli (or Jingshu granules), a traditional Chinese medicine, are widely used for treating cervical spondylotic radiculopathy in China; however, no randomized, double-blind, controlled study has verified their effectiveness.
Purpose: To evaluate the efficacy and safety of Jingshu Keli for the treatment of cervical spondylotic radiculopathy in a randomized controlled trial.
Design: From August 2015 to July 2017, a multicenter, randomized, double-blind, placebo-controlled trial was conducted at 13 large- and medium-sized hospitals in China.
Patient sample: A total of 360 and 120 patients were initially enrolled in the Jingshu and control groups, respectively; 386 patients completed the study, with 299 in the Jingshu group and 87 in the control group.
Outcome measures: The main index for evaluating the curative effect was the pain score on a visual analogue scale (VAS; 0–100 points).
Methods: All patients were administered a bag of Jingshu Keli or placebo 3 times a day for 4 weeks, and were interviewed at the second and fourth weeks. The decrease in pain scores and rate of change in pain scores after treatment were calculated, related laboratory indices were reviewed, and adverse reactions were recorded.
Results: In the Per Protocol Set (PPS) analysis, the baseline pain VAS scores in the control and Jingshu groups were 49.31 ± 6.97 and 50.06 ± 7.33, respectively, with no significant difference between the groups ($P > 0.05$). While

Abbreviations: RCT, randomized controlled trial; VAS, visual analogue scale; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; TBIL, total bilirubin; γ-GT, γ-glutamyl transpeptidase; Cr, creatine; BUN, blood urea nitrogen; NAG, urine N-acetyl-beta-D-glucosaminidase; FAS, full analysis set; ITT, intention-to-treat; LOCF, last observation carried forward; PPS, per-protocol set; SAS, safety analysis set; SNL, spinal nerve ligation; PT, preferred term; SOC, system organ class; ANCOVA, analysis of covariance.

* Corresponding author. Department of Orthopedics, Peking Union Medical College Hospital, Beijing, 100730, China.
E-mail addresses: pumch_hujianhua@163.com (J. Hu), pumc98chenfeng@hotmail.com (F. Chen), qguixing@126.com, qgxpumc@126.com (G. Qiu), stssuntiansheng@163.com (T. Sun), yanghuilinsz@163.com (H. Yang), shyshenhuiyong@sina.com (H. Shen), shanghaitong123@sina.com (P. Tong), chaiyim@126.com (Y. Chai), xuelizhang134@163.com (X. Zhang), zhangwb198@163.com (W. Zhang), yangzhidong806@163.com (Z. Yang), jianghong362@163.com (H. Jiang), yalinpanay@sohu.com (Y. Pan), zhutliang@sohu.com (T. Zhu), hechengj143@sina.com (C. He), xiaowpjx@sina.com (W. Xiao).
[1] Co-first author

https://doi.org/10.1016/j.jot.2020.10.010
Received 24 May 2020; Received in revised form 22 October 2020; Accepted 28 October 2020

there were no differences at 2 weeks between groups, at four weeks the pain VAS scores in the control and Jingshu groups decreased by 12.86 ± 13.45 and 22.72 ± 15.08, respectively relative to the values at baseline, with significant group differences ($P < 0.0001$). While there were similar significant differences between the groups ($P < 0.0001$) in the Full Analysis Set (FAS) analyses neither group achieved the minimal clinically important difference at any time point.

Conclusions: Jingshu Keli are effective for the treatment of cervical spondylotic radiculopathy.

Translational potential statement: This is the first prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial that confirmed the clinical efficacy and safety of Jingshu Keli for treating cervical spondylotic radiculopathy, which can provide evidence for clinical treatment.

Introduction

Cervical spondylotic radiculopathy is one of the most common diseases seen in clinical practice [1], and is mainly caused by intervertebral disc degeneration, herniation, segmental instability, bone hyperplasia, osteophyte formation, or other conditions that result in the stimulation of the spinal canal or intervertebral foramen, eventually compressing the cervical nerve root. Cervical spondylotic radiculopathy has the highest incidence among patients with cervical spondylosis (around 60%–70%), can severely affect the quality of life and work capabilities of the patient, and results in a significant financial burden.

Currently, most patients with cervical spondylotic radiculopathy are treated by non-surgical modalities [2], mainly including traction, cervical collar immobilization, physiotherapy, massage, symptomatic treatment, and changes in bad working and sleeping postures. After a period of treatment, the symptoms of most patients improve or disappear. Only a few patients, for whom non-surgical treatment is ineffective or the condition is serious, require surgery.

Jingshu Keli (or Jingshu granules) combine traditional Chinese medicinal theories with herbal medicine and are a type of traditional Chinese patent medicine manufactured using modern pharmaceutical techniques by China TCM Co., Ltd. The granules are concentrated traditional Chinese medicine granules that contain extracts of *Panax notoginseng, Angelica sinensis*, *Ligusticum striatum, Carthamus tinctorius* L., *Gastrodia elata, Cinnamomum cassia*, and *Calculus bovis*. Jingshu Keli are widely used in many Chinese hospitals for treating cervical spondylosis, particularly cervical spondylotic radiculopathy in the past few decades. However, no research validation has, thus far, been conducted utilizing the standards of a randomized controlled trial (RCT). Therefore, we aimed to evaluate the efficacy and safety of Jingshu Keli for the treatment of cervical spondylotic radiculopathy. This RCT was prototered in the *Chinese Clinical Trial Registry* official system (registration number, ChiCTR1900021012).

Materials and methods

Design overview

This multicenter, randomized, double-blinded, placebo-controlled study was conducted between August 2015 and July 2017. As there was

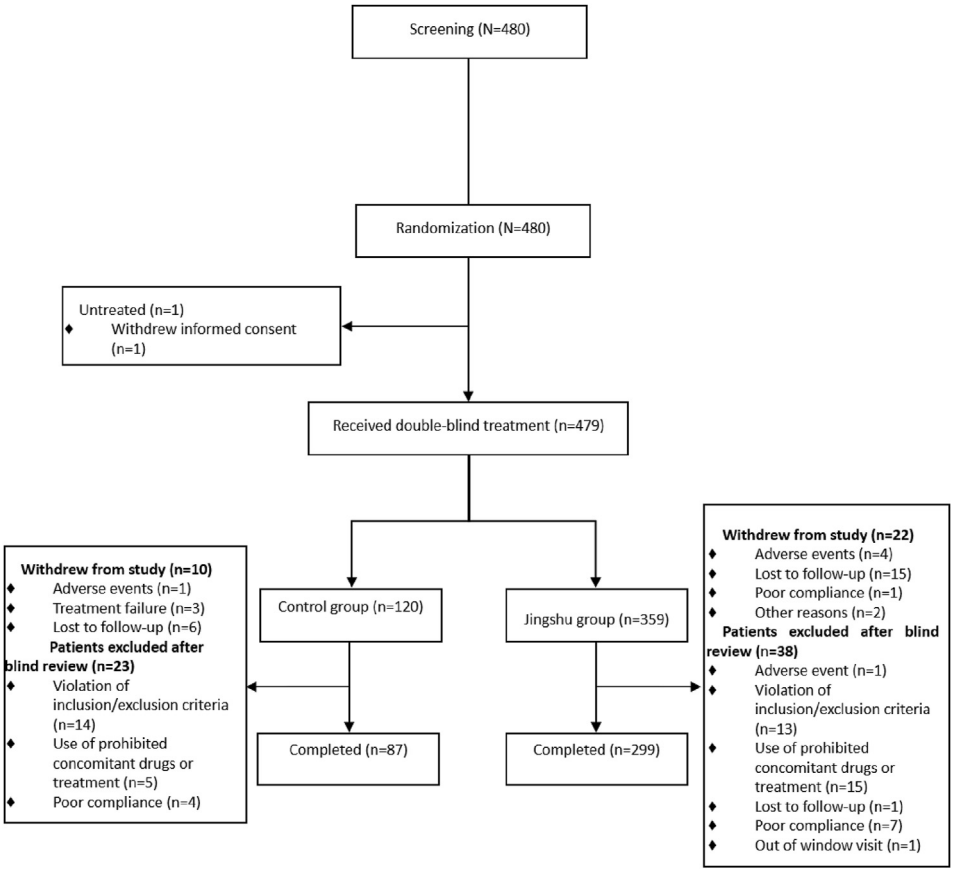

Figure 1. Distribution diagram of subjects.

Table 1
Baseline demographic and clinical characteristics.

Marker	Control group (N = 120)	Jingshu group (N = 359)	P-value
Age (years)			
Mean (standard deviation)	48.13 (10.83)	47.98 (10.63)	0.8023
Median (maximum, minimum)	48.50 (23.00,68.00)	50.00 (18.00,68.00)	
Sex			
Male	42 (35.00%)	132 (36.77%)	0.7272
Female	78 (65.00%)	227 (63.23%)	
Body mass Index (kg/m^2)			
Mean (standard deviation)	23.50 (3.43)	23.75 (3.02)	0.5119
Median (maximum, minimum)	23.44 (17.47,40.12)	23.59 (14.77,34.60)	
History of comorbidities and concomitant medications			
No	75 (62.50%)	242 (67.41%)	0.3768
Yes	43 (35.83%)	114 (31.75%)	

Table 2
Pain VAS scores in the two groups before and after drug administration using the FAS.

Item Mean (standard deviation)	Control group (n = 120)	Jingshu group (n = 359)	P-value for inter-group comparison
Baseline	48.60 (8.36)	50.00 (7.52)	0.1896
Week 2 after treatment	37.19 (15.67)	37.92 (14.72)	—
Week 4 after treatment	32.70 (17.34)	30.16 (16.88)	—
Comparison of the differences in before and after drug administration values			
Week 2 after treatment minus baseline	11.41 (14.24)	12.07 (13.67)	0.2611
P-value for within-group comparison	**P < 0.0001**	**P < 0.0001**	
Week 4 after treatment minus baseline	15.90 (16.05)	19.84 (16.49)	**0.01**
P-value for within-group comparison	**P < 0.0001**	**P < 0.0001**	
Comparison of the rate of change			
Week 2 after treatment minus baseline, %	23.66 (28.71)	24.12 (28.07)	0.4045
P-value for within-group comparison	**P < 0.0001**	**P < 0.0001**	
Week 4 after treatment minus baseline, %	33.12 (33.06)	39.65 (33.21)	**0.0272**
P-value for within-group comparison	**P < 0.0001**	**P < 0.0001**	

FAS, Full Analysis Set

no clinically accepted drug of choice for cervical spondylotic radiculopathy treatment, we used a placebo as a control to evaluate the absolute efficacy and safety of Jingshu Keli for the treatment of cervical spondylotic radiculopathy. The main components of placebo were dextrin and stirring agent, which were the excipients in Jingshu keli but without drug effect. A total of 360 and 120 patients were initially enrolled in the Jingshu and control groups (ratio, 3:1), respectively. All patients were administered the investigational drug or placebo orally, thrice daily for 4 continuous weeks, and were interviewed in follow-up visits at Weeks 2 and 4 after the initiation of drug administration to complete efficacy and safety assessments. The study design was approved by our ethics committee. All patients were informed of the possible benefits and risks of the study; all patients provided signed informed consent. This study was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki and with relevant regulations of the US Health Insurance Portability and Accountability Act (HIPAA).

Setting and participants

Patients were recruited from 13 large- and medium-sized hospitals in China (PUMCH, People's Liberation Army General Hospital, The First Affiliated Hospital of Soochow University, Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University, Zhejiang Provincial Hospital of TCM, Shanghai Sixth People's Hospital, Tianjin People's Hospital, Ruijin Hospital of Shanghai Jiaotong University, First Affiliated Hospital of Guangzhou University of Chinese Medicine, Suzhou Hospital of Traditional Chinese Medicine, People's Hospital of Anyang City, Chongqing General Hospital, and Hubei Provincial Hospital of Traditional Chinese Medicine).

The inclusion criteria were as follows: (1) pure cervical spondylotic radiculopathy or mixed cervical spondylosis that was mainly cervical spondylotic radiculopathy, diagnosed by clinical symptoms, physical examination and imaging; (2) a visual analogue scale (VAS) score for pain $\geq$40 and $<$ 80 points (range, 0–100 points); (3) age 18–65 years; and (4) patient consent. The exclusion criteria were as follows: (1) pure cervical spondylotic myelopathy without radiculopathy symptoms; (2) pain caused by cervical extracervical lesions, such as thoracic outlet syndrome, lateral epicondylitis, carpal tunnel syndrome, cubital tunnel syndrome, periarthritis of the shoulder, and biceps tendinitis; (3) cervical spondylotic radiculopathy for which surgery was indicated (a. Ineffective conventional and systematic non-surgical treatment for 3–6 months or a relapse with severe symptoms after effective non-surgical treatment that affected daily life or work; b. Progressive atrophy of innervated muscles caused by radiculopathy; and c. Apparent nerve root stimulation symptoms, with acute and intense pain (VAS score $\geq$80 points) that severely affected sleep and normal life); (4) comorbid severe primary disease, such as cardiovascular disease, cerebrovascular disease, and diseases of the liver, kidneys, or hematopoietic system; (5) liver or renal impairment (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values more than 3 times higher than the upper limit of the normal range and a creatinine value above normal levels); (6) mental illness or a history of alcohol or drug abuse; (7) atopic constitution and allergy to multiple drugs or known allergy to components of the Jingshu capsules; (8) pregnant, currently lactating, or planning to conceive (except for cases in which the termination of pregnancy was requested); (9) administration of drugs with therapeutic effects toward cervical spondylotic radiculopathy within 1 week before treatment with the study drug (11) participation in other drug clinical trials within the last 3 months; and (12) other conditions considered as unsuitable for participation after a discussion among the study investigators.

Randomization and interventions

Stratified randomization was employed; random numbers were generated by statisticians using SAS version 9.3 software (SAS Institute Inc., Cary, NC, USA), which denoted the drug number as a running serial number for the sample size. The investigator administered the corresponding drug to the participant according to the sequence in which they were enrolled, and numbers could not be skipped. The drug number remained unchanged during the entire study.

Unified manufacturing of the study drugs (Jingshu granules and placebo) was conducted by Sinopharm Group Jingfang (Anhui) Pharmaceutical Co., Ltd. Patients in the Jingshu group were orally administered Jingshu Keli, one bag each time, thrice a day (strength, 6 g/bag; batch number, 150,801) and patients in the placebo group were orally administered a placebo (for which the packaging, administration method, and taste were identical to that in the Jingshu group), one bag each time, thrice a day (strength, 6 g/bag; batch number, S150801). The treatment duration was 4 weeks.

There were two levels of blinding: first, the blinding of each drug number to its corresponding group and second, the blinding of the drug that corresponded to each treatment group. Thus, two rounds of unblinding were used to unblind the data. The first round of unblinding

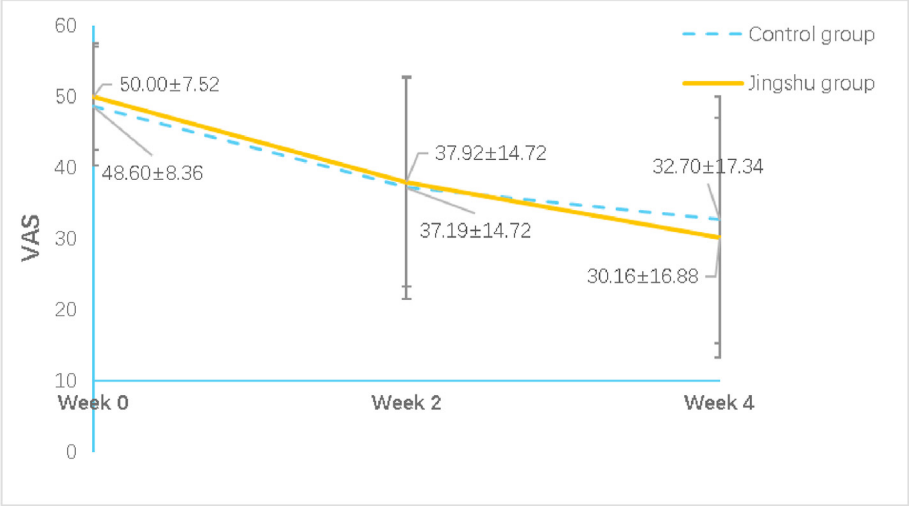

Figure 2. Change in pain VAS scores before and after drug administration using the full analysis set (FAS).

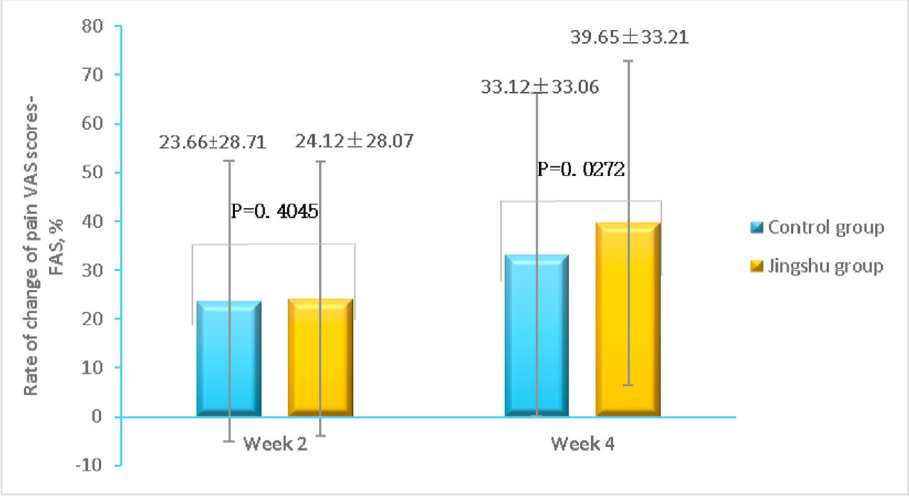

Figure 3. Rate of change in pain VAS scores before and after drug administration using the full analysis set (FAS).

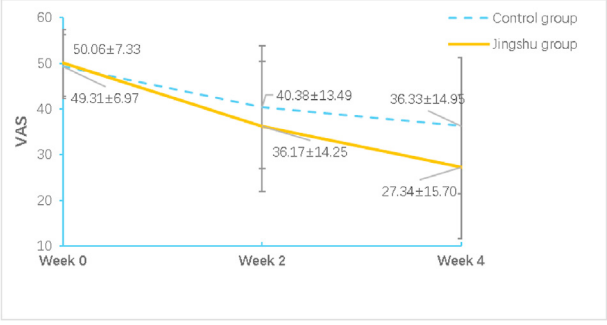

Figure 4. Change in pain VAS scores before and after drug administration using the per protocol set (PPS).

was conducted by the blinding staff after data management (blinding status examination and data locking) was completed, and only the respective group for each drug number was revealed (expressed as the control or Jingshu group). The second round of unblinding was performed after the completion of the statistical analysis report, and revealed that the control and Jingshu groups corresponded to the placebo and experimental groups, respectively. The participants, investigators, and analysis staff were all blinded. All data monitoring, entry, and analysis were performed by a third-party research company (Shanghai Clinical Research Organization for Medicines (InCROM CHINA) with no conflict of interest.

Outcomes and measurements

The evaluated primary efficacy markers were the changes in pain VAS scores (overall pain, shoulder pain, neck pain, and scapular pain) after 4 weeks of therapy relative to those at baseline. For improved data accuracy, VAS scores were evaluated and reported from 0 to 100 points. The secondary efficacy markers were as follows: (1) the change in the neck disability index (NDI) score; (2) change in the numbness VAS score; (3) pain disappearance rate; (4) numbness disappearance rate (all relative to baseline values); and (5) SF-36 health questionnaire.

Safety markers were as follows: (1) physical examination data; (2) vital sign data, including blood pressure (systolic and diastolic) after resting for 10 min, body temperature, resting heart rate, and respiration; (3) laboratory test data, including routine blood data (RBC, WBC, PLT, and Hb), routine urine data (urine protein, urine leukocytes, and urine

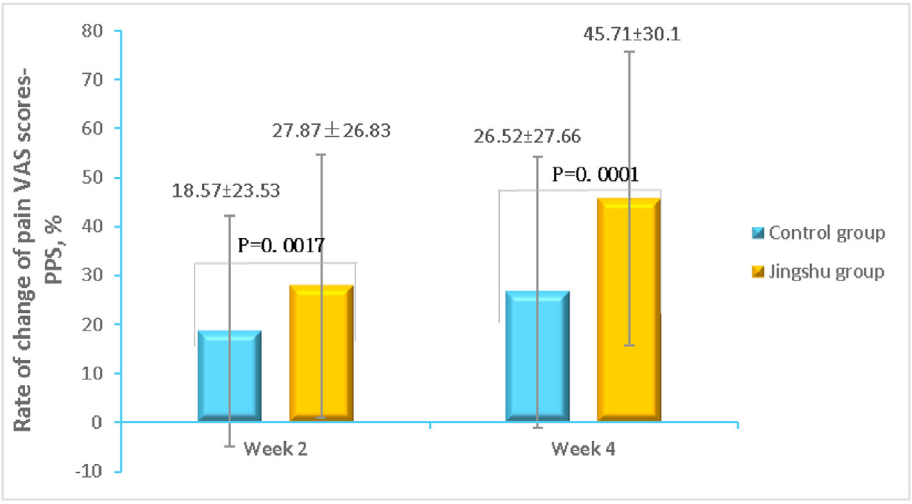

Figure 5. Rate of change in pain VAS scores before and after drug administration using the per protocol set (PPS).

erythrocytes), liver and kidney function (ALT, AST, ALP, TBIL, γ-GT, Cr, and BUN) and urine N-acetyl-beta-D-glucosaminidase (NAG); (4) 12-lead electrocardiography; and (5) adverse events during the study.

Statistical analysis

Datasets

The full analysis set (FAS) comprised all patients who underwent randomization and took at least one dose of the drug, according to the intent-to-treat (ITT) principles; the last observation carried forward (LOCF) was used for patients whose data were not observed for the entire study. The per-protocol set (PPS) comprised all patients who conformed to the study protocol, had good compliance, did not take prohibited drugs during the study, and whose case report forms were complete; no imputation was carried out for missing data. The FAS and PPS were both used in the drug efficacy analyses.

Safety analysis set (SAS) comprised all enrolled patients who took at least one dose of the study drug, for whom drug safety assessments were recorded. This dataset was used for safety analyses.

Table 3
Pain VAS scores in the two groups before and after drug administration using the PPS.

Item Mean (standard deviation)	Control group (n = 91)	Jingshu group (n = 299)	P-value for inter-group comparison
Baseline	49.31 (6.97)	50.06 (7.33)	0.4507
Week 2 after treatment	40.38 (13.49)	36.17 (14.25)	
Week 4 after treatment	36.33 (14.95)	27.34 (15.70)	
Comparison of the difference in before and after drug administration values			
Week 2 after treatment minus baseline	8.93 (11.35)	13.89 (13.19)	**0.0010**
P-value for within-group comparison	**<0.0001**	**<0.0001**	
Week 4 after treatment minus baseline	12.86 (13.45)	22.72 (15.08)	**<0.0001**
P-value for within-group comparison	**<0.0001**	**<0.0001**	
Comparison of the rate of change			
Week 2 after treatment minus baseline, %	18.57 (23.53)	27.87 (26.83)	**0.0017**
P-value for within-group comparison	**<0.0001**	**<0.0001**	
Week 4 after treatment minus baseline, %	26.52 (27.66)	45.71 (30.10)	**0.0001**
P-value for within-group comparison	**<0.0001**	**<0.0001**	

PPS, Per Protocol Set

General analytical principles

Statistical analyses were performed using SAS 9.3 software. The analysis process was fully programmed. The statistical description of quantitative data includes the number of patients, mean, standard deviation, median, maximum, minimum, test statistic, and P-value. The statistical description of qualitative data includes the frequency distribution, composition ratio, test statistic, and P-value. As appropriate, the suitable statistical analysis methods were used for inter-group and intra-group comparisons. All statistical tests were used to obtain the test statistic and corresponding P-value. Fisher's exact probability was used to directly obtain the P-value. All statistical tests were two-tailed. A $P \leq 0.05$ was considered statistically significant (with the exception of special cases, as noted).

Analysis of dropout patients

The numbers of patients who were enrolled, dropped out, were removed, and completed analysis are listed, along with the number of patients in each analysis set. Fisher's exact probability was used for inter-group comparisons in the overall and adverse event dropout rates.

Homogeneity analysis

The analysis of variance, Kruskal–Wallis H-test, Chi-square test, or Cochran-Mantel-Haenszel (CMH) test was used for inter-group comparisons in demographics and various baseline characteristics of the enrolled patients to examine their homogeneity and comparability.

Efficacy analyses

An analysis of covariance (ANCOVA), controlling for site effects, was used for comparisons in the primary marker (VAS pain scores). The dependent variable was the difference in VAS scores before and after treatment, with pre-treatment values as the baseline. Interactions between sites and groups were analyzed.

For secondary markers, quantitative data were compared between groups in terms of the difference in before and after treatment values and the rate of change. When quantitative data were normally distributed, an independent samples t-test was used. When the quantitative data did not follow a normal distribution or had heterogeneous variance, the Wilcoxon rank-sum test was used. The paired t-test was used for intra-group comparisons in before and after treatment values when the difference followed a normal distribution, otherwise, the signed-rank test was used. Fisher's exact probability test was used for the analysis of the disappearance rate. The product limit estimator was used for the time of

Table 4
Pain VAS scores in the two groups before and after drug administration in the FAS sensitivity analysis.

Item	Control group	Jingshu group	Control vs. Jingshu group
Baseline			
N (Missing)	105 (0)	346 (0)	
Mean (standard deviation)	49.15 (6.95)	50.18 (7.36)	P = 0.2539
Median (maximum, minimum)	48 (40.00,62.00)	50 (40.00,70.00)	
Week 2 after treatment			
N (Missing)	105 (0)	346 (0)	
Mean (standard deviation)	40.24 (13.76)	37.70 (14.46)	—
Median (maximum, minimum)	42 (33.00,50.00)	40 (30.00,49.00)	
Week 4 after treatment			
N (Missing)	105 (0)	346 (0)	
Mean (standard deviation)	36.28 (15.34)	29.74 (16.84)	—
Median (maximum, minimum)	39 (24.00,50.00)	30 (17.00,42.00)	
Comparison of the difference in before and after drug administration values			
Week 2 after treatment minus baseline			
N (Missing)	105 (0)	346 (0)	
Mean Difference (standard deviation)	8.91 (12.35)	12.48 (13.44)	
Median (maximum, minimum)	6 (0.00, 17.00)	10 (3.00, 20.00)	
P-value	**P < 0.0001**	**P < 0.0001**	**P = 0.0044**
Week 4 after treatment minus baseline			
N (Missing)	105 (0)	346 (0)	
Mean Difference (standard deviation)	12.88 (14.04)	20.44 (16.34)	
Median (maximum, minimum)	10 (0.00, 23.00)	20 (8.00, 33.00)	
P-value	**P < 0.0001**	**P < 0.0001**	**P < 0.0001**
Comparison of the rate of change			
Week 2 after treatment minus baseline			
N (Missing)	105 (0)	346 (0)	
Mean rate of change (standard deviation), %	18.29 (25.16)	24.91 (27.35)	
Median (maximum, minimum)	12.5 (0.00, 33.33)	21.16 (5.17, 41.67)	
P-value	**P < 0.0001**	**P < 0.0001**	**P=0.0069**
Week 4 after treatment – baseline			
N (Missing)	105 (0)	346 (0)	
Mean rate of change (standard deviation), %	26.46 (29.02)	40.88 (32.73)	
Median (maximum, minimum)	22.41 (0.00, 50.00)	41.18 (15.22, 66.67)	
P-value	**P < 0.0001**	**P < 0.0001**	**P < 0.0001**

FAS, full analysis set

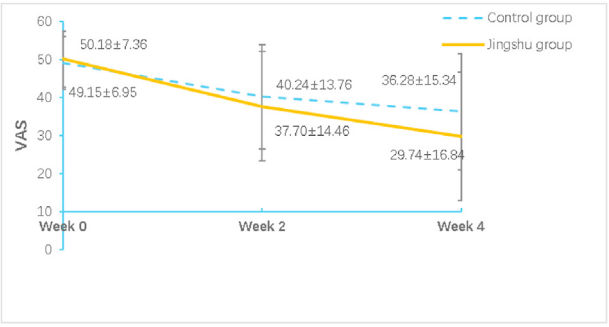

Figure 6. Change in pain VAS scores before and after administration using the sensitivity analysis dataset of the full analysis set (FAS).

disappearance, which was calculated at 25%, 50%, and 75%. The log-rank test was used for comparisons between the two groups.

The LOCF value was carried forward for missing data, i.e., the last observed treatment situation was used as the endpoint for the subsequent estimation of missing values.

Safety analysis

The safety analysis was based on the SAS. The Chi-square test or Fisher's exact probability test was used to compare the incidence of adverse events between the two groups. The number of patients with adverse events, adverse reactions, significant adverse events, serious adverse events, time of adverse events, severity, and relationships with the study drugs are listed and described.

Descriptive statistics were used to analyze the changes in vital signs (such as temperature, respiration, heart rate, and blood pressure) before and after treatment. The t-test or Wilcoxon rank-sum test was used for inter-group comparisons. The paired t-test or signed-rank test were used for intra-group comparisons. The Chi-square test or Fisher's exact probability test was used for comparisons of vital sign outliers in the two groups.

Descriptive statistics were used to determine the number of patients with normal and abnormal laboratory test markers before and after treatment and post-treatment laboratory test abnormalities with clinical significance. The rates of abnormalities in the two groups before and after treatment were compared using the Chi-square test or Fisher's exact probability test.

Compliance analysis

The compliance data and collection records of administered drugs were used to assess the compliance of each patient. The Chi-square test or Fisher's exact probability test was used to compare the incidence of poor compliance between the two groups and descriptive statistics were used to determine the overall compliance of two groups, along with details regarding poor compliance in patients.

Results

Patient characteristics

We planned to enroll 480 patients, with 360 and 120 patients in the Jingshu and control groups, respectively. In reality, 386 patients completed the study, of which 299 and 87 were in the Jingshu and control groups, respectively. The participant distribution flowchart is provided in Fig. 1. The mean onset time of pain symptoms was 46d (18–111d) in Jingshu group and 54d (22–117d) in control group, respectively. The P value was 0.3253. Thirty-three patients dropped out, of which 23 and 10 patients were from the Jingshu and control groups, respectively. Sixty-one patients were excluded, of which 38 and 23 were from the Jingshu and control groups, respectively. Excluding reasons included using drugs that violated the program, or the subjects refused to continue the trail. Overall, 359 and 120 patients from the Jingshu and control groups, respectively, were included in the FAS; 299 and 91, respectively, were included in the PPS; and 358 and 117, respectively, were included in the SAS. There were 4 patients in the control group showed certain intolerance to the drug at very beginning, which may be due to the smell and taste of TCM. However, they were gradually alleviated by intermittent use and insisted on completing the final evaluation. After blinded review, they were finally included in the PPS set.

There were no statistical differences in sex, age, body mass index, comorbidities, and concomitant medications between the Jingshu and control groups (Table 1).

Clinical efficacy

The primary efficacy marker data are shown in Table 2. In the FAS analysis, baseline pain VAS scores in the control and Jingshu groups were

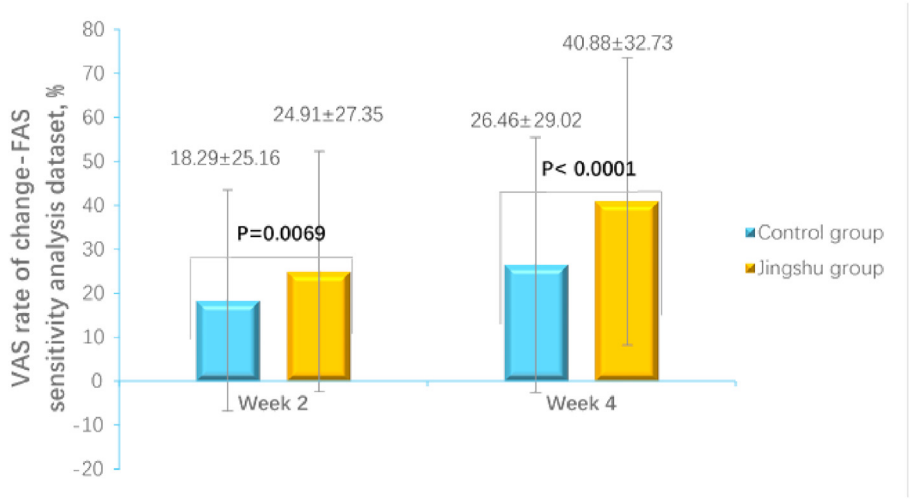

Figure 7. Rate of change in pain VAS scores before and after drug administration using the sensitivity analysis dataset of the full analysis set (FAS).

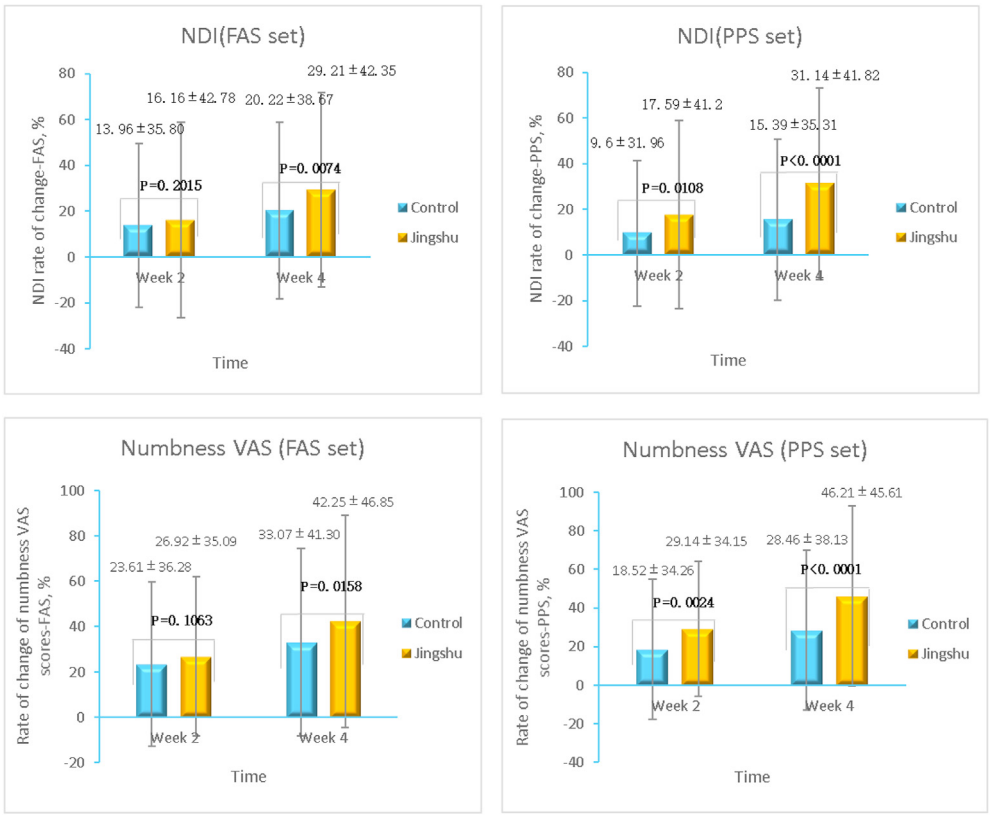

Figure 8. Rate of change in neck disability index (NDI) and numbness VAS scores before and after administration.

48.60 ± 8.36 and 50.00 ± 7.52, respectively, and the difference between the two groups was not statistically significant (P > 0.05). After 4 weeks of treatment, the pain VAS scores in the control and Jingshu groups significantly decreased by 15.90 ± 16.05 (P < 0.0001) and 19.84 ± 16.49 (P < 0.0001), respectively, relative to the baseline scores (Fig. 2). Additionally, the rate of change was significant in the control and Jingshu groups, at 33.12 ± 33.06% and 39.65 ± 33.21%, respectively (P < 0.0001; Fig. 3). Furthermore, the reduction and rate of change in pain VAS scores was significantly greater in the Jingshu group than in the control group (P < 0.05). In the ANCOVA of the reduction of the pain VAS scores after 4 weeks of treatment, there was no significant interaction between site and group (F = 1.11, P = 0.3505).

In the PPS analysis, the baseline pain VAS scores in the control and Jingshu groups were 49.31 ± 6.97 and 50.06 ± 7.33, respectively, without a significant group difference (P > 0.05). After 4 weeks of treatment, pain VAS scores significantly decreased by 12.86 ± 13.45 and 22.72 ± 15.08 relative to the baseline scores in the control and Jingshu groups, respectively (P < 0.0001; Fig. 4) and the rate of change was significant at 26.52 ± 27.66% and 45.71 ± 30.10%, respectively (P < 0.0001; Fig. 5). Furthermore, the inter-group differences in the reduction and rate of change in pain VAS scores were statistically significant (P < 0.0001). In the ANCOVA of the differences in the reduction of the pain

Table 5
Occurrence and comparison of adverse events between the two groups using the SAS.

Category		Control group (n = 117)	Jingshu group (n = 358)	Test method	Test-statistic	P-value
Adverse event	n	35	141	Chi-square test	3.39	0.0655
	Incidence (%)	29.91	39.39			
Adverse reaction	n	9	49	Chi-square test	2.96	0.0855
	Incidence (%)	7.69	13.69			
Serious adverse event	n	0	2	Exact probability method	.	1.0000
	Incidence (%)	0.00	0.56			
Significant adverse event	n	19	68	Chi-square test	0.45	0.5036
	Incidence (%)	16.24	18.99			
Adverse event resulting in dropout	n	1	6	Corrected Chi-square test	0.04	0.8429
	Incidence (%)	0.85	1.68			
Adverse reaction resulting in dropout	n	1	April	Corrected Chi-square test	0.00	1.0000
	Incidence (%)	0.85	1.12			

SAS, Safety analysis set

Table 6
Occurrence of adverse events.

Category	Control group			Jingshu group			P-value
	Number of cases	Number of patients	Incidence (%)	Number of cases	Number of patients	Incidence (%)	
Gastrointestinal disorders	**9**	**9**	**7.69**	**84**	**71**	**19.83**	**0.0023**
Diarrhea	1	1	0.85	29	24	6.70	0.0140
Upper abdominal pain	0	0	0.00	10	10	2.79	0.0680
Abdominal discomfort	2	2	1.71	7	7	1.96	0.8656
Dry mouth	2	2	1.71	7	7	1.96	0.8656
Nausea	1	1	0.85	7	7	1.96	0.4224
Abdominal pain	1	1	0.85	4	4	1.12	0.8093
Toothache	1	1	0.85	4	4	1.12	0.8093
Abdominal distension	0	0	0.00	2	2	0.56	0.4183
Gastroenteritis	0	0	0.00	2	2	0.56	0.4183
Constipation	0	0	0.00	1	1	0.28	0.5675
Gingival pain	0	0	0.00	1	1	0.28	0.5675
Dry lips	0	0	0.00	1	1	0.28	0.5675
Non-infectious gingivitis	0	0	0.00	1	1	0.28	0.5675
Stool abnormalities	0	0	0.00	1	1	0.28	0.5675
Oral ulcers	0	0	0.00	1	1	0.28	0.5675
Vomiting	0	0	0.00	1	1	0.28	0.5675
Hypersalivation	1	1	0.85	0	0	0.00	0.0803
Dysgeusia	0	0	0.00	1	1	0.28	0.5675
Gastrointestinal disease	0	0	0.00	1	1	0.28	0.5675
Gastritis	0	0	0.00	1	1	0.28	0.5675
Lower abdominal pain	0	0	0.00	1	1	0.28	0.5675
Indigestion	0	0	0.00	1	1	0.28	0.5675
Respiratory, chest, and mediastinal diseases	**13**	**12**	**10.26**	**51**	**49**	**13.69**	**0.3361**
Upper respiratory tract viral infection	3	3	2.56	21	21	5.87	0.1573
Upper respiratory tract infection	4	4	3.42	12	11	3.07	0.8527
Cough	1	1	0.85	7	7	1.96	0.4224
Rhinorrhea	1	1	0.85	3	2	0.56	0.7259
Oropharyngeal pain	2	2	1.71	1	1	0.28	0.0904
Nasal congestion	0	0	0.00	2	2	0.56	0.4183
Asthma	0	0	0.00	2	2	0.56	0.4183
Chest discomfort	0	0	0.00	2	2	0.56	0.4183
Nasal discomfort	1	1	0.85	0	0	0.00	0.0803
Tonsillitis	1	1	0.85	0	0	0.00	0.0803
Sore throat	0	0	0.00	1	1	0.28	0.5675
Various neurological diseases	**10**	**7**	**5.98**	**38**	**33**	**9.22**	**0.2745**
Headache	6	4	3.42	16	14	3.91	0.8091
Dizziness	2	1	0.85	13	12	3.35	0.1511
Insomnia	0	0	0.00	May	May	1.40	0.1992
Tinnitus	1	1	0.85	2	2	0.56	0.7259
Hypoesthesia	0	0	0.00	1	1	0.28	0.5675
Oral hypoesthesia	1	1	0.85	0	0	0.00	0.0803
Migraine	0	0	0.00	1	1	0.28	0.5675
Various tests	**3**	**3**	**2.56**	**18**	**15**	**4.19**	**0.4244**
Urine leukocyte positivity	0	0	0.00	4	4	1.12	0.2514
Leukocytosis	0	0	0.00	3	3	0.84	0.3211
Abnormal urinalysis	1	1	0.85	2	2	0.56	0.7259
Acid–base imbalance	1	1	0.85	1	1	0.28	0.4045
γ-glutamine transferase elevation	0	0	0.00	1	1	0.28	0.5675
Leukopenia	0	0	0.00	1	1	0.28	0.5675
Alanine transaminase abnormalities	0	0	0.00	1	1	0.28	0.5675

(*continued on next page*)

Table 6 (*continued*)

Category	Control group			Jingshu group			P-value
	Number of cases	Number of patients	Incidence (%)	Number of cases	Number of patients	Incidence (%)	
Abnormal liver function test results	0	0	0.00	1	1	0.28	0.5675
Detection of urine glucose	0	0	0.00	1	1	0.28	0.5675
Elevated aspartate transaminase	1	1	0.85	0	0	0.00	0.0803
Hyperbilirubinemia	0	0	0.00	1	1	0.28	0.5675
Hyperuricemia	0	0	0.00	1	1	0.28	0.5675
Musculoskeletal and connective tissue diseases	**5**	**5**	**4.27**	**9**	**9**	**2.51**	**0.3291**
Back pain	2	2	1.71	3	3	0.84	0.4232
Skeletal muscle pain	1	1	0.85	2	2	0.56	0.7259
Arthralgia	0	0	0.00	1	1	0.28	0.5675
Periarthritis	1	1	0.85	0	0	0.00	0.0803
Ligament sprain	0	0	0.00	1	1	0.28	0.5675
Cartilage pain	1	1	0.85	0	0	0.00	0.0803
Limb pain	0	0	0.00	1	1	0.28	0.5675
Sciatica	0	0	0.00	1	1	0.28	0.5675
Heart diseases	**4**	**4**	**3.42**	**9**	**9**	**2.51**	**0.6029**
Heart palpitations	1	1	0.85	6	6	1.68	0.5226
Premature ventricular contraction	1	1	0.85	0	0	0.00	0.0803
Myocardial ischemia	0	0	0.00	1	1	0.28	0.5675
Cardiac discomfort	1	1	0.85	0	0	0.00	0.0803
First-degree atrioventricular block	0	0	0.00	1	1	0.28	0.5675
Sinus bradycardia	0	0	0.00	1	1	0.28	0.5675
Sinus tachycardia	1	1	0.85	0	0	0.00	0.0803
Skin and subcutaneous disorders	**3**	**3**	**2.56**	**4**	**4**	**1.12**	**0.2600**
Rashes	1	1	0.85	3	3	0.84	0.9863
Eczema	1	1	0.85	1	1	0.28	0.4045
Acne	1	1	0.85	0	0	0.00	0.0803
Systemic diseases and reactions at the site of administration	**0**	**0**	**0.00**	**7**	**7**	**1.96**	**0.1280**
Hyperhidrosis	0	0	0.00	1	1	0.28	0.5675
Fever	0	0	0.00	1	1	0.28	0.5675
Fatigue	0	0	0.00	1	1	0.28	0.5675
Spinal pain	0	0	0.00	1	1	0.28	0.5675
Sleepiness	0	0	0.00	1	1	0.28	0.5675
Pain	0	0	0.00	1	1	0.28	0.5675
Peripheral swelling	0	0	0.00	1	1	0.28	0.5675
Diseases of the kidneys and urinary system	**1**	**1**	**0.85**	**5**	**5**	**1.40**	**0.6490**
Urinary tract infection	1	1	0.85	3	3	0.84	0.9863
Cystitis	0	0	0.00	1	1	0.28	0.5675
Frequent urination	0	0	0.00	1	1	0.28	0.5675
Diseases of the reproductive system and breasts	**1**	**1**	**0.85**	**4**	**4**	**1.12**	**0.8093**
Menorrhagia	1	1	0.85	2	2	0.56	0.7259
Mastalgia	0	0	0.00	1	1	0.28	0.5675
Amenorrhea	0	0	0.00	1	1	0.28	0.5675
Psychiatric disorders	**1**	**1**	**0.85**	**3**	**3**	**0.84**	**0.9863**
Drowsiness	1	1	0.85	3	3	0.84	0.9863
Infections	**0**	**0**	**0.00**	**3**	**3**	**0.84**	**0.3211**
Shingles	0	0	0.00	1	1	0.28	0.5675
Pharyngitis	0	0	0.00	1	1	0.28	0.5675
Bronchitis	0	0	0.00	1	1	0.28	0.5675
Immune disorders	**2**	**2**	**1.71**	**1**	**1**	**0.28**	**0.0904**
Hypersensitivity reaction	1	1	0.85	1	1	0.28	0.4045
Rheumatoid arthritis	1	1	0.85	0	0	0.00	0.0803
Metabolic and nutritional diseases	**0**	**0**	**0.00**	**2**	**2**	**0.56**	**0.4183**
Hypoglycemia	0	0	0.00	1	1	0.28	0.5675
Hyperuricemia	0	0	0.00	1	1	0.28	0.5675
Blood and lymphatic disorders	**0**	**0**	**0.00**	**2**	**2**	**0.56**	**0.4183**
Epistaxis	0	0	0.00	1	1	0.28	0.5675
Hematuria	0	0	0.00	1	1	0.28	0.5675
Hepatobiliary diseases	**0**	**0**	**0.00**	**1**	**1**	**0.28**	**0.5675**
Hepatic dysfunction	0	0	0.00	1	1	0.28	0.5675
Various surgeries and medical procedures	**0**	**0**	**0.00**	**1**	**1**	**0.28**	**0.5675**
Tooth extraction	0	0	0.00	1	1	0.28	0.5675
Early menstruation	**0**	**0**	**0.00**	**1**	**1**	**0.28**	**0.5675**
Early menstruation	0	0	0.00	1	1	0.28	0.5675
Eye diseases	**0**	**0**	**0.00**	**1**	**1**	**0.28**	**0.5675**
Dry eyes	0	0	0.00	1	1	0.28	0.5675

Table 7
Comparison of the incidences of various adverse events between the two groups.

	Control group (n = 117)			Jingshu Group (n = 358)			
Classification	Onsets	Cases	Incidence (%)	Onsets	Cases	Incidence	P-value
Gastrointestinal disorders	**9**	**9**	**7.69**	**84**	**71**	**19.83**	**0.0023**
Diarrhea	1	1	0.85	29	24	6.70	0.0140
Upper abdominal pain	0	0	0.00	10	10	2.79	0.0680
Abdominal discomfort	2	2	1.71	7	7	1.96	0.8656
Dry mouth	2	2	1.71	7	7	1.96	0.8656
Nausea	1	1	0.85	7	7	1.96	0.4224
Abdominal pain	1	1	0.85	4	4	1.12	0.8093
Toothache	1	1	0.85	4	4	1.12	0.8093
Abdominal distension	0	0	0.00	2	2	0.56	0.4183
Gastroenteritis	0	0	0.00	2	2	0.56	0.4183
Constipation	0	0	0.00	1	1	0.28	0.5675
Gingival pain	0	0	0.00	1	1	0.28	0.5675
Dry lips	0	0	0.00	1	1	0.28	0.5675
Non-infectious gingivitis	0	0	0.00	1	1	0.28	0.5675
Abnormal stools	0	0	0.00	1	1	0.28	0.5675
Oral ulcer	0	0	0.00	1	1	0.28	0.5675
Vomiting	0	0	0.00	1	1	0.28	0.5675
Excessive saliva secretion	1	1	0.85	0	0	0.00	0.0803
Dysgeusia	0	0	0.00	1	1	0.28	0.5675
Gastrointestinal diseases	0	0	0.00	1	1	0.28	0.5675
Gastritis	0	0	0.00	1	1	0.28	0.5675
Lower abdominal pain	0	0	0.00	1	1	0.28	0.5675
Indigestion	0	0	0.00	1	1	0.28	0.5675
Respiratory, thoracic, and mediastinal disorders	**13**	**12**	**10.26**	**51**	**49**	**13.69**	**0.3361**
Upper respiratory tract viral infection	3	3	2.56	21	21	5.87	0.1573
Upper respiratory tract infection	4	4	3.42	12	11	3.07	0.8527
Cough	1	1	0.85	7	7	1.96	0.4224
Rhinorrhea	1	1	0.85	3	2	0.56	0.7259
Oropharyngeal pain	2	2	1.71	1	1	0.28	0.0904
Nasal congestion	0	0	0.00	2	2	0.56	0.4183
Asthma	0	0	0.00	2	2	0.56	0.4183
Chest discomfort	0	0	0.00	2	2	0.56	0.4183
Nose discomfort	1	1	0.85	0	0	0.00	0.0803
Tonsillitis	1	1	0.85	0	0	0.00	0.0803
Laryngeal pain	0	0	0.00	1	1	0.28	0.5675
Neurological disorders	**10**	**7**	**5.98**	**38**	**33**	**9.22**	**0.2745**
Headache	6	4	3.42	16	14	3.91	0.8091
Dizziness	2	1	0.85	13	12	3.35	0.1511
Insomnia	0	0	0.00	5	5	1.40	0.1992
Tinnitus	1	1	0.85	2	2	0.56	0.7259
Hypoesthesia	0	0	0.00	1	1	0.28	0.5675
Oral hypoesthesia	1	1	0.85	0	0	0.00	0.0803
Migraine	0	0	0.00	1	1	0.28	0.5675
Investigations	**3**	**3**	**2.56**	**18**	**15**	**4.19**	**0.4244**
Urine white blood cell positive	0	0	0.00	4	4	1.12	0.2514
Increased white blood cell count	0	0	0.00	3	3	0.84	0.3211
Abnormal urinalysis	1	1	0.85	2	2	0.56	0.7259
Acid-base balance abnormalities	1	1	0.85	1	1	0.28	0.4045
Increased gamma-glutamyltransferase levels	0	0	0.00	1	1	0.28	0.5675
Decreased white blood cell count	0	0	0.00	1	1	0.28	0.5675
Abnormal alanine aminotransferase levels	0	0	0.00	1	1	0.28	0.5675
Abnormal liver function tests	0	0	0.00	1	1	0.28	0.5675
Abnormal investigations	0	0	0.00	1	1	0.28	0.5675
Urine glucose detected	0	0	0.00	1	1	0.28	0.5675
Increased aspartate aminotransferase levels	1	1	0.85	0	0	0.00	0.0803
Increased blood bilirubin levels	0	0	0.00	1	1	0.28	0.5675
Hyperuricemia	0	0	0.00	1	1	0.28	0.5675
Musculoskeletal and connective tissue disorders	**5**	**5**	**4.27**	**9**	**9**	**2.51**	**0.3291**
Back pain	2	2	1.71	3	3	0.84	0.4232
Musculoskeletal pain	1	1	0.85	2	2	0.56	0.7259
Arthralgia	0	0	0.00	1	1	0.28	0.5675
Periarthritis	1	1	0.85	0	0	0.00	0.0803
Ligament sprain	0	0	0.00	1	1	0.28	0.5675
Chondralgia	1	1	0.85	0	0	0.00	0.0803
Limb pain	0	0	0.00	1	1	0.28	0.5675
Sciatica	0	0	0.00	1	1	0.28	0.5675
Cardiac disorders	**4**	**4**	**3.42**	**9**	**9**	**2.51**	**0.6029**
Palpitation	1	1	0.85	6	6	1.68	0.5226
Ventricular extrasystole	1	1	0.85	0	0	0.00	0.0803
Myocardial ischemia	0	0	0.00	1	1	0.28	0.5675
Heart discomfort	1	1	0.85	0	0	0.00	0.0803
First-degree atrioventricular block	0	0	0.00	1	1	0.28	0.5675
Sinus bradycardia	0	0	0.00	1	1	0.28	0.5675

(*continued on next page*)

Table 7 (*continued*)

	Control group (n = 117)			Jingshu Group (n = 358)			
Classification	Onsets	Cases	Incidence (%)	Onsets	Cases	Incidence	P-value
Sinus tachycardia	1	1	0.85	0	0	0.00	0.0803
Skin and subcutaneous tissue disorders	**3**	**3**	**2.56**	**4**	**4**	**1.12**	**0.2600**
Rash	1	1	0.85	3	3	0.84	0.9863
Eczema	1	1	0.85	1	1	0.28	0.4045
Acne	1	1	0.85	0	0	0.00	0.0803
General disorders and administration site conditions	**0**	**0**	**0.00**	**7**	**7**	**1.96**	**0.1280**
Hyperhidrosis	0	0	0.00	1	1	0.28	0.5675
Fever	0	0	0.00	1	1	0.28	0.5675
Asthenia	0	0	0.00	1	1	0.28	0.5675
Spinal pain	0	0	0.00	1	1	0.28	0.5675
Drowsiness	0	0	0.00	1	1	0.28	0.5675
Pain	0	0	0.00	1	1	0.28	0.5675
Peripheral swelling	0	0	0.00	1	1	0.28	0.5675
Renal and urinary disorders	**1**	**1**	**0.85**	**5**	**5**	**1.40**	**0.6490**
Urinary tract infection	1	1	0.85	3	3	0.84	0.9863
Cystitis	0	0	0.00	1	1	0.28	0.5675
Frequent urination	0	0	0.00	1	1	0.28	0.5675
Reproductive system and breast disorders	**1**	**1**	**0.85**	**4**	**4**	**1.12**	**0.8093**
Menorrhagia	1	1	0.85	2	2	0.56	0.7259
Breast pain	0	0	0.00	1	1	0.28	0.5675
Irregular menstruation	0	0	0.00	1	1	0.28	0.5675
Psychiatric disorders	**1**	**1**	**0.85**	**3**	**3**	**0.84**	**0.9863**
Somnolence	1	1	0.85	3	3	0.84	0.9863
Infections and infestations	**0**	**0**	**0.00**	**3**	**3**	**0.84**	**0.3211**
Shingles	0	0	0.00	1	1	0.28	0.5675
Pharyngitis	0	0	0.00	1	1	0.28	0.5675
Bronchitis	0	0	0.00	1	1	0.28	0.5675
Immune system disorders	**2**	**2**	**1.71**	**1**	**1**	**0.28**	**0.0904**
Hypersensitivity	1	1	0.85	1	1	0.28	0.4045
Rheumatoid arthritis	1	1	0.85	0	0	0.00	0.0803
Metabolic and nutritional disorders	**0**	**0**	**0.00**	**2**	**2**	**0.56**	**0.4183**
Hypoglycemia	0	0	0.00	1	1	0.28	0.5675
Hyperuricemia	0	0	0.00	1	1	0.28	0.5675
Blood and lymphatic system disorders	**0**	**0**	**0.00**	**2**	**2**	**0.56**	**0.4183**
Epistaxis	0	0	0.00	1	1	0.28	0.5675
Hematuria	0	0	0.00	1	1	0.28	0.5675
Hepatobiliary disorders	**0**	**0**	**0.00**	**1**	**1**	**0.28**	**0.5675**
Abnormal liver function	0	0	0.00	1	1	0.28	0.5675
Surgical and medical procedures	**0**	**0**	**0.00**	**1**	**1**	**0.28**	**0.5675**
Tooth extraction	0	0	0.00	1	1	0.28	0.5675
Early menstruation	**0**	**0**	**0.00**	**1**	**1**	**0.28**	**0.5675**
Early menstruation	0	0	0.00	1	1	0.28	0.5675
Eye disorders	**0**	**0**	**0.00**	**1**	**1**	**0.28**	**0.5675**
Dry eyes	0	0	0.00	1	1	0.28	0.5675

Table 8
Response rates and cost-effectiveness analysis results for various markers.

Marker	Group	Treatment cost/RMB (C)	Response rate/% (E)	CER (C/E)	ICER (ΔC/ΔE)
NDI response rate	Jingshu group	1203.12	57.59	2089.11	1608.08
	Control group	813.00	33.33	2439.24	—
Pain VAS response rate	Jingshu group	1203.12	72.91	1650.14	1834.99
	Control group	813.00	51.65	1574.06	—
Health improvement rate	Jingshu group	1203.12	59.20	2032.30	3103.58
	Control group	813.00	46.63	1743.51	—
Pain improvement rate	Jingshu group	1203.12	75.75	1588.28	2587.00
	Control group	813.00	60.67	1340.04	—
Numbness improvement rate	Jingshu group	1203.12	62.86	1913.97	2845.51
	Control group	813.00	49.15	1654.12	—

NDI, neck disability index; VAS, visual analogue scale

VAS scores after 4 weeks of treatment, there was no interaction between site and group (F = 0.99, P = 0.4603) (Table 3).

FAS sensitivity analysis results for pain VAS scores

The baseline pain VAS scores in the control and Jingshu groups were comparable. After treatment, the pain VAS scores in the two groups decreased, with the Jingshu group showing a slightly higher overall reduction in pain VAS scores than that in the control group. During the 4 weeks of treatment, the reduction in pain VAS scores was greater in the first 2 weeks than in the next 2 weeks. After 4 weeks of treatment, the pain VAS scores in the Jingshu group were slightly lower than those in the control group. FAS sensitivity analysis results are shown in Table 4, and in Figs. 6 and 7.

The analyses of the secondary efficacy markers using the FAS and PPS showed that the NDI scores and numbness VAS scores were significantly reduced at week 4 compared to baseline scores for both the Jingshu and control groups (P < 0.0001). However, the reduction in NDI scores and numbness VAS scores were significantly greater in the Jingshu group

than in the control group ($P < 0.0001$) (Fig. 8). The groups did not significantly differ in the change in various items on the SF-36 questionnaire, pain disappearance rate, and numbness disappearance rate ($P > 0.05$).

Safety and tolerability

In the control group, 35 (29.91%) patients had adverse events, which caused 1 (0.85%) patient to drop out. In addition, there were 19 (16.24%) significant adverse events, no serious adverse events, and 9 (7.69%) adverse reactions, with 1 patient (0.85%) dropping out due to adverse reactions. In the Jingshu group, 141 (39.39%) patients had adverse events, which caused 6 (1.68%) patients to drop out. Moreover, there were 68 (18.99%) significant adverse events, 2 serious adverse events, and 49 (13.69%) adverse reactions, with 4 patients (1.12%) dropping out. The inter-group differences in the incidences of adverse events, significant adverse events, serious adverse events, adverse reactions, adverse events causing dropout, and adverse reactions causing dropouts were not statistically significant ($P > 0.05$) (Tables 5 and 6).

Adverse events were defined by the SOC classification. The incidence of adverse events of the respiratory system, chest, and mediastinal diseases was highest (10.26%) in the control group, whereas that of the gastrointestinal system was the highest in the Jingshu group (19.83%). In addition, the incidence of gastrointestinal disorders in the Jingshu group was significantly higher than that of the control group ($P = 0.0023$). When the PT classification system was used, adverse reactions with the highest incidence in the control group were headaches (3.42%), upper respiratory tract infection (3.42%), and upper respiratory tract viral infection (2.56%); whereas those with the highest incidence in the Jingshu group were diarrhea (6.7%), upper respiratory tract viral infection (5.87%), headaches (3.91%), dizziness (3.35%), upper respiratory tract infection (3.07%), and upper abdominal pain (2.79%).

When adverse reactions were grouped according to the SOC classification, the incidence of gastrointestinal disorders and neurological diseases was the highest (2.56%) in the control group, whereas the incidence of gastrointestinal disorders was the highest in the Jingshu group (9.50%). When adverse reactions were grouped according to the PT classification, adverse reactions with the highest incidence in the control group were dry mouth (1.71%) and headaches (1.71%), whereas those in the Jingshu group were diarrhea (3.35%), nausea (1.40%), and abdominal discomfort (1.40%).

When significant adverse events were grouped by the SOC classification, the incidence of significant adverse events in the respiratory system, chest, and mediastinum were the highest in both groups, i.e., 7.69% and 8.66%, respectively.

Two serious adverse events occurred in the Jingshu group. One patient had a past history of comorbid asthma. During enrollment, the patient did not develop asthma or other special symptoms. After enrollment and 2 weeks of treatment, the patient suffered an asthmatic attack, which was relieved after treatment. Another patient developed shingles, which was alleviated after antiviral and symptomatic treatment by the department of dermatology.

Among the evaluated vital signs, the highest incidence of abnormalities after treatment (but were normal before treatment) occurred for the heart rate and respiration in the control group (4.27%) and heart rate in the Jingshu group (3.07%).

There were no special changes in laboratory and electrocardiography tests, blood routine tests, and liver and kidney function tests. The incidence of abnormal urinary erythrocytes after treatment was the highest in the control group (7.69%), whereas that of abnormal urinary leukocytes after treatment was the highest in the Jingshu group (6.70%). The incidences of electrocardiography abnormalities after treatment in the two groups were 10.26% and 12.85%, respectively.

The overall adverse reactions were listed and compared in detail which listed in Table 7.

Discussion

The present study showed that Jingshu Keli are efficacious in the treatment of cervical spondylotic radiculopathy (Table 8). Cervical spondylotic radiculopathy is a common form of cervical spondylosis. Its annual incidence is reported as approximately 1.79/1000 [3]. Cervical spondylotic radiculopathy is mainly an apparent discomfort caused by mechanical compression/local inflammatory responses due to cervical degeneration. Usually, when there is no myelopathy or apparent functional impairment, 75%–90% of patients can show improvements in symptoms after treatment with non-surgical methods [2,3]. Anti-inflammatory drugs and other supportive treatments are mainstay measures for treating this disease. In clinical practice, non-steroidal anti-inflammatory drugs, opioids, and even oral hormonal drugs are used for treatment. However, these drugs often result in poor control and strong side effects [2–4]. Therefore, there is no currently acknowledged drug of first choice for the treatment of cervical spondylotic radiculopathy. Recently, many traditional Chinese herbal medicines have been scientifically proven to be effective in the treatment of various diseases, particularly musculoskeletal diseases [5–7]. In addition, in-depth studies on the efficacy and potential mechanisms of these drugs are gradually being carried out [8,9]. Jingshu Keli is also a Chinese traditional patent preparation, and is a prescription herbal medicine that has been officially approved for the treatment of cervical spondylotic radiculopathy in China for several decades, with demonstrated good clinical efficacy and safety [10–13].

Efficacy and potential effector mechanisms

The PPS analysis revealed a significant reduction in pain VAS scores after 4 weeks of treatment compared to the scores at baseline in the Jingshu group. Results of the FAS analysis were similar. Furthermore, the observed significant improvements after treatment in the Jingshu group were significantly better than those in the control group. Additionally, we found that the NDI scores and numbness VAS scores at week 4 were significantly reduced compared to those at baseline and that these reductions were significantly greater in the Jingshu group than in the control group. Therefore, we believe that Jingshu Keli are effective in alleviating nerve root pain and sensory disturbances and can, to some extent, improve cervical spine function and the quality of life in patients. Although these responses were fairly small and failed to reach the minimal clinical important difference.

Jingshu Keli are concentrated traditional Chinese medicine granules that contain the extracts of *P. notoginseng, A. sinensis*, *L. striatum, C. tinctorius* L., *G. elata, C. cassia,* and *C. bovis*. The active components are ferulic acid from *Angelicae Sinensis* radix and *Chuanxiong Rhizoma* and cinnamaldehyde from Cinnamomi Cortex, which are two major biologically active components reported to partially downregulate inflammatory mediators by preventing the activation of signal transducers and activators of transcription 3 (Stat3) *in vitro* [8,14,15]. Pain in cervical spondylotic radiculopathy is believed to be due to the mixing of mechanical traumatic pain and neuropathic pain. Previous studies have found that the JAK/STAT3 pathway plays an important role in neuropathic pain [16–19]. Therefore, Zheng et al. [12] carried out a study on the application and potential mechanisms of Jingshu Keli in a mouse model of nerve root damage. They found that Jingshu Keli significantly inhibited SNL-induced allodynia as well as microglia activation in the spinal cord on days 7 and 14 after surgery. Moreover, the expression of p-Stat3 was decreased in rats with SNL and Jingshu granule treatment compared to that in with rats with SNL and vehicle treatment. They believed that Jingshu Keli attenuated SNL-induced mechanical allodynia in rats. This analgesic effect might be explained by the suppression of the activation of spinal microglia as well as p-Stat3. Jingshu Keli were found to significantly decrease mechanical allodynia in an animal model mimicking cervical radiculopathy. Oral administration of Jingshu Keli prevented the activation of pain-causing microglia, but not astrocytes in

the spinal pain pathway. A coincident reduction of Stat3 phosphorylation by Jingshu Keli was also observed in the spinal dorsal horn. Thus, Jingshu Keli might interfere with the Stat3-microglia pathway to attenuate neuropathic pain. The present study provides experimental evidence for the use of Jingshu Keli as an alternative approach to manage refractory pain in patients with cervical radiculopathy.

Safety analysis

The safety analyses demonstrated that the frequencies of total adverse events and severe adverse events after using Jingshu Keli were not significantly higher than those after using the placebo, except for a slightly increased frequency of diarrhea. The possible cause of diarrhea is the presence of artificial *C. bovis* in the drug, which is clearly stated on the package insert of the drug. Diarrhea could be alleviated in most patients by adjusting the time of the administration and by taking the drug after meals. There were no serious adverse reactions and no significant damage to organ systems based on the various follow-up laboratory test markers. Zhang et al. [13] carried out experiments on the acute and chronic toxicology of Jingshu Keli and found no significant effects on the general condition, body mass, blood, and blood biochemical markers, and no abnormal changes in organ weight, organ coefficient, histopathological tests, etc. This suggests that the long-term administration of Jingshu Keli is safe. In addition, various scientific validations of Chinese traditional patent medicine are gradually being carried out [9,20,21], and may further reveal its active components, pharmacokinetics, and toxicology in the future.

Limitations

A limitation of the present study is its small dropout rate, which was mainly because of a loss to follow-up, particularly in those who lived in remote areas, moved houses, or had other regional factors. Additionally, the present study strictly complied with the inclusion and exclusion criteria and some patients were excluded owing to concomitant medications or poor compliance. However, we attempted to maintain the number of patients for the entire study duration. Furthermore, we used placebo as a control monotherapy and 4 weeks as the observation endpoint, which may not be sufficient for the treatment of cervical spondylotic radiculopathy. In clinical practice, we often use Jingshu Keli in combination with some anti-inflammatory and analgesic drugs, along with neurotonic drugs, to obtain good results. However, further validations on the efficacy and safety of combination therapy are needed in future. In addition, information on the recurrence of symptoms after treatment lacked. We hope to obtain more interesting and meaningful information by performing a study with a longer follow-up period.

In conclusion, the present is the first prospective, multicenter, randomized, double-blind, placebo-controlled, clinical trial that confirms the clinical efficacy and safety of Jingshu Keli for treating cervical spondylotic radiculopathy. Finally, patients should be informed of possible adverse reactions during the clinical application.

Funding disclosure statement

The authors have no acknowledgements to disclose and they received no funding for the work described in this article.

Conflict of interest

The authors have no conflicts of interest to disclose in relation to this article.

Acknowledgements

We thank all the centers and staff members, statistical analysts, and quality control members who participated in the study.

References

[1] Corey DL, Comeau D. Cervical radiculopathy. Med Clin 2014 Jul;98(4):791–9. https://doi.org/10.1016/j.mcna.2014.04.001. xii.
[2] Childress MA, Becker BA. Nonoperative management of cervical radiculopathy. Am Fam Physician 2016 May 1;93(9):746–54.
[3] Woods BI, Hilibrand AS. Cervical radiculopathy: epidemiology, etiology, diagnosis, and treatment. J Spinal Disord Tech 2015;28:E251–9. https://doi.org/10.1097/BSD.0000000000000284.
[4] Onks CA, Billy G. Evaluation and treatment of cervical radiculopathy. Prim Care 2013 Dec;40(4):837–48. https://doi.org/10.1016/j.pop.2013.08.004. vii-viii.
[5] Deng WM, Zhang P, Huang H, Shen YG, Yang QH, Cui WL, et al. Five-year follow-up study of a kidney-tonifying herbal Fufang for prevention of postmenopausal osteoporosis and fragility fractures. J Bone Miner Metabol 2012 Sep;30(5):517–24. https://doi.org/10.1007/s00774-012-0351-7.
[6] Li ZR, Cheng LM, Wang KZ, Yang NP, Yang SH, He W, Wang YS, Wang Z, Yang P, Liu XZ, Luo YZ, Sun W, Wang HT, Zheng LZ, Wang XL, Qin L. Herbal Fufang Xian Ling Gu Bao prevents corticosteroid-induced osteonecrosis of the femoral head-A first multicentre, randomized, double-blind, placebo-controlled clinical trial. J Orthop Translat 2017 Dec 14;12:36–44. https://doi.org/10.1016/j.jot.2017.11.001.
[7] Lv QW, Zhang W, Shi Q, Zheng WJ, Li X, Chen H, Wu QJ, Jiang WL, Li HB, Gong L, Wei W, Liu H, Liu AJ, Jin HT, Wang JX, Liu XM, Li ZB, Liu B, Shen M, Wang Q, Wu XN, Liang D, Yin YF, Fei YY, Su JM, Zhao LD, Jiang Y, Li J, Tang F, Zhang FC, Lipsky PE, Zhang X. Comparison of Tripterygium wilfordii Hook F with methotrexate in the treatment of active rheumatoid arthritis (TRIFRA): a randomized, controlled clinical trial. Ann Rheum Dis 2015 Jun;74(6):1078–86. https://doi.org/10.1136/annrheumdis-2013-204807.
[8] Huang JS, Lee YH, Chuang LY, Guh JY, Hwang JY. Cinnamal-dehyde and nitricoxi deattenuate advanced glycation end products-induced the JAK/STAT signaling in human renal tubular cells. J Cell Biochem 2015;116:1028–38. https://doi.org/10.1002/jcb.25058.
[9] Ingram SL. Pain: novel analgesics from traditional Chinese medicines. Curr Biol 2014;24:R114–6. https://doi.org/10.1016/j.cub.2013.12.030.
[10] Lu X. The effect of Jingshukeli combined with computer inter-frequency therapy for patients with cervical spondylotic radiculopathy. Chin J Pract Nerv Dis 2015;10:35–6. https://doi.org/10.3969/j.ISSN.1673-5110.2015.10.021.
[11] Wu J, Mo J, Guo Y, Liang H. Observation of clinical curative effect of Jingshu granule in treatment of nerve root cervical spondylosis of Qi stagnation and blood stasis. China Med Pharm 2017;7:41–4.
[12] Zheng N, Liu X, Zhang R, Ho I, Chen S, Xu, et al. Jingshu Keli attenuates cervical spinal nerve ligation-induced allodynia in rats through inhibition of spinal microglia and Stat3 activation. Spine J 2018 Jun 30. https://doi.org/10.1016/j.spinee.2018.06.354. pii: S1529-9430(18)30633-30638.
[13] Zhang C, Chen FL, Lu YS, Ding RM, Xiao H. Experimental study on toxicity of Jingshu granule. Journal of ANHUI TCM College Aug. 2005;24(4):40–1.
[14] Tsai CM, Yen GC, Sun FM, Yang SF, Weng CJ. Assessment of the anti-invasion potential and mechanism of selectcinnamec acid derivatives on human lung adenocarcinoma cells. Mol Pharm 2013;10:1890–900. 10.1021/mp. 3006648.
[15] Huang C, Ma R, Sun S, Wei G, Fang Y, Liu R, et al. JAK2-STAT3 signaling pathway mediates thrombin-induced proin flammatory actions ofm icroglia in vitro. J Neuroimmunol 2008;204:118–25. https://doi.org/10.1016/j.jneuroim.2008.07.004.
[16] Hubbard RD, Chen Z, Winkelstein BA. Transient cervical nerve root compression modulates pain: load thresholds for allodynia and sustained changes in spinal neuropeptide expression. J Biomech 2008;41:677–85. https://doi.org/10.1016/j.jbiomech.2007.09.026.
[17] Dominguez E, Rivat C, Pommier B, Mauborgne A, Pohl M. JAK/STAT3 pathway is activated in spinal cord microglia after peripheral nerve injury and contributes to neuropathic pain development in rat. J Neurochem 2008;107:50–60. https://doi.org/10.1111/j.1471-4159.2008.05566.x.
[18] Liu X, Tian Y, Lu N, Gin T, Cheng CHK, Chan MTV. Stat3 inhibition attenuates mechanical allodynia through transcriptional regulation of chemokine expression in spinal astrocytes. PloS One 2013;8:e75804. https://doi.org/10.1371/journal.pone.0075804.
[19] Przanowski P, Dabrowski M, Ellert-Miklaszewska A, Kloss M, Mieczkowski J, Kaza B, et al. The signal transducers Stat1and Stat3 and their novel target Jmjd3 drive the expression of inflammatory genes in microglia. J Mol Med 2014;92:239–54. https://doi.org/10.1007/s00109-013-1090-5.
[20] Lee K-H. Research and future trends in the pharmaceutical development of medicinal herbs from Chinese medicine. Publ Health Nutr 2000;3:515–22. https://doi.org/10.1017/S1368980000000604.
[21] Zhang Y, Wang C, Wang L, Parks GS, Zhang X, Guo Z, et al. A novel analgesic isolated from a traditional Chinese medicine. Curr Biol 2014;24:117–23. https://doi.org/10.1016/j.cub.2013.11.039.