Efficacy and safety of Shaoyang Xibi decoction in patients with knee osteoarthritis: a multi-center, single-blind, randomized controlled trial

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Purpose: To observe the efficacy and safety of Shaoyang Xibi decoction (SYXBD) in patients with knee osteoarthritis (KOA), and to verify that the theory of "Shaoyang dominating bone" in Traditional Chinese Medicine (TCM) can be applied to KOA treatment.

Methods: Participants were randomly allocated to two groups: SYXBD (treatment group, n = 66) and Meloxicam (control group, n = 66). Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and 36-item Short Form Health Survey (SF-36) were used to assess efficacy before the treatment and 8 weeks after the treatment.

Results: Baseline data before the treatment between the two groups were similar. The WOMAC scores significantly decreased and the SF-36 scores significantly increased after 8-week treatment in both groups compared with before the treatment (P < 0.05). SYXBD significantly decreased pain scores (P < 0.001), physical function scores (P < 0.001) and the total scores (P < 0.001) in WOMAC compared to Meloxicam. SYXBD significantly improved physical function (P = 0.021), bodily pain (P = 0.002) and general health (P = 0.014), with no significant difference in role emotional (P = 0.053), role physical (P = 0.517), vitality (P = 0.241), social function (P = 0.712) and mental health (P = 0.800).

Abstract
in SF-36 compared to Meloxicam. No adverse events were reported in the treatment group while 13 adverse events happened in the control group during the study.

CONCLUSION: SYXBD, prepared based on the theory of "Shaoyang dominating bone", has a better curative efficacy and safety in patients with KOA compared with Meloxicam. The TCM theory of "Shaoyang dominating bone" may be useful in KOA treatment.

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Keywords: Osteoarthritis, knee; Therapeutic uses; Shaoyang dominating bone; Kidney dominating bone; Shaoyang Xibi decoction

INTRODUCTION

Knee osteoarthritis (KOA), a common degenerative and chronic disease, is becoming a social health problem. Symptoms of the disease may include pain, swelling, stiffness, limited ambulation, and declined balance function. The incidence of KOA was 40% between the age of 55 and 64, among which the incidence rate of female was higher than that of male. It is believed that the etiology and pathogenesis of KOA implicate in destruction of balance between degeneration and synthesis of articular cartilage, extracellular matrix and subchondral bone. Few Western Medicine treatments are effective for KOA and most of them include side effects such as gastrointestinal adverse reaction and which can cause unfavorable effects on the recovery of patients.

Traditional Chinese Medicine (TCM) was used to treat KOA by ancients from thousands of years ago in China. Reportedly, TCM, which has almost no side effect, has favorable efficacy on KOA. Thus, it is essential to research on the clinical effects of TCM prescriptions used for KOA. In TCM, KOA is usually considered to be "Gu Bi" (bone rheumatism) which was described almost 2000 years ago in Su Wen of Huang Di Nei Jing. According to The Standard for TCM Diseases and Syndromes therapeutic results, there are three TCM syndromes in KOA: blood stasis type, Yang deficiency cold coagulation type and kidney deficiency type. However, patients’ conditions are usually more complicated than the three types above, thus, the common decoctions for KOA in TCM, which are based on syndrome differentiation, might not be that effective. Fortunately Traditional Chinese Medicine formula is probably the key to solve this problem. For instance, Li et al. used Yishentongbi formula to treat patients with KOA and got satisfactory curative effects. Kou et al. treated KOA by applying aconite decoction oral and external treatment, found that aconite decoction oral and external treatment curative effect was better than that of diclofenac sodium. As we know, most of treatments were based on the theory of "kidney dominating bone" from Huang Di Nei Jing. However, a theory of "Shaoyang dominating bone" was also mentioned in Huang Di Nei Jing which may be another theory basis for treating KOA.

In TCM, it was both mentioned in Ling Shu · Zhang Shi and Su Wen · Zhen Yao Jing Zhong Lun that "When the Hand and Foot Shaoyang Channels are severing, the patient will become deaf; his joints of the whole body will become loose and weak". An explanatory note given by Wang was that "The Qi of Shaoyang dominates bone. Hence, when Qi is used up, joint atony will occur". The TCM theory of "Shaoyang dominating bone" does have a theoretical connection with joints, which could be a theoretical support for treating arthropathy. We conducted this clinical study aiming to observe the efficacy and safety of Shaoyang Xibi decoction (SYXBD) in patients with KOA and to verify that the theory of "Shaoyang dominating bone" could be apply to KOA treatment.

MATERIALS AND METHODS

Subjects and protocol

The present study was a multi-center, single-blind, randomized controlled trial. A total of 140 participants were recruited from February 2015 to August 2017, and 132 KOA patients met the inclusion criteria. Yangzhou Hospital of Traditional Chinese Medicine recruited 80 participants, and Affiliated Hospital of Nanjing University of Chinese Medicine recruited 52 participants. 132 patients were selected for the study, but only 126 patients (83 women and 43 men) completed the trials, 64 of whom were in the treatment group and 62 in the control group. One patient from the treatment group declined the experiment because of concerns about security. Three patients from the control group left the experiment provided no reasons for doing so, nor did they return to the hospital. Another reason for the dropout in control group was admission to other hospitals due to other diseases (Figure 1).

Median duration of knee pain was 3 years (2 to 4 years) in the treatment group and 3 years (1 to 5 years) in the control group. According to the Kellgren/Lawrence scale, most participants had mild-to-moderate KOA. Many participants had previously tried oral western medicine and some of them had tried intra-articular injection treatment and oral TCM for KOA, but few of them had tried surgery for KOA. Including age, sex and body mass index, all demographic data which were summarized in Table 1 did not show significant difference between groups.

Diagnostic criteria

The diagnosis criteria used for KOA were based on the
criteria of the American College of Rheumatology. X-ray grading of KOA was classified according to the Kellgren-Lawrence criteria. Inclusion criteria were: fulfilling the KOA diagnostic criteria; aged between 45 and 70 years; pain in one or both knees during the previous 3 months or longer; Kellgren-Lawrence X-ray grade from Grade 0 to Grade 4 within 3 months; After a 30 days washout period if patients have been treated with other surgical procedures; adherent to treatment regimens and signed informed consent.

Exclusion criteria: with acute synovitis, osteoarticular tuberculosis, tumor, rheumatic arthritis or rheumatoid arthritis; allergic constitution; with significant trauma on knee(s); having surgery on knee(s) within 6 months or hormone therapy within 2 months with serious organic disease; pregnant or lactating; participating in clinical trials of other drugs; taking painkillers for other chronic or recurrent pain; other conditions that will reduce the likelihood of entering a group or make the study complex.

Table 1 Comparison of general data between the two groups before treatment (x ± s)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SYXBD group (n = 64)</th>
<th>Meloxicam group (n = 62)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 ± 6</td>
<td>60 ± 5</td>
<td>0.95</td>
</tr>
<tr>
<td>Sex (Male/Female)</td>
<td>25/39</td>
<td>18/44</td>
<td>0.24</td>
</tr>
<tr>
<td>Duration of knee pain (years)</td>
<td>3 ± 1</td>
<td>3 ± 2</td>
<td>0.76</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.0 ± 4.2</td>
<td>23.3 ± 2.8</td>
<td>0.29</td>
</tr>
<tr>
<td>Kellgren-Lawrence scale</td>
<td></td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td>Grade 0</td>
<td>14</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>29</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>16</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>5</td>
<td>10</td>
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</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Past experience of surgery for KOA (yes/no)</td>
<td>1/63</td>
<td>0/62</td>
<td>1.00</td>
</tr>
<tr>
<td>Past experience of oral Western Medicine for KOA (yes/no)</td>
<td>31/33</td>
<td>22/40</td>
<td>0.14</td>
</tr>
<tr>
<td>Past experience of oral TCM for KOA (yes/no)</td>
<td>11/53</td>
<td>7/55</td>
<td>0.34</td>
</tr>
<tr>
<td>Past experience of intra-articular injection treatment for knee osteoarthritis (yes/no)</td>
<td>6/58</td>
<td>9/53</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Notes: ‘The independent t-test was used for statistical analysis; ‘The Mann-Whitney U test was used for statistical analysis; ‘Fisher’s exact test was used for statistical analysis; ‘The χ² test was used for statistical analysis; KOA: knee osteoarthritis; SYXBD: Shaoyang Xibi decoction; P < 0.05 means that the difference between SYXBD group and Meloxicam group is statistically significant.
Randomization and masking
After baseline data were collected as well as written consent was provided, participants were randomly assigned to the treatment and control group at once via a computer-based random number sequence. Allocation was concealed using sequentially numbered opaque, sealed envelopes which were hidden in the safe until the trials finished. The steps above were completed by two graduate research assistants who were not involved in recruitment. The reason why we presented a “single-blind” study design was the inability to conceal two different dosage forms in the two groups from participants and physicians in trials. However, all study evaluators and statisticians were not involved throughout the duration of the study.

Ethics and statement
The protocol was approved by the ethical committee of Affiliated Hospital and informed consents were obtained from all participants. All trials were conducted in accordance with the Declaration of Helsinki, using Good Clinical Practice.

Treatments
The treatment group was given SYXBD orally, twice per day after two infusions with warm water for two months. The ingredients of SYXBD were: Chaihu (Radix Bupleuri) 15 g; Huangqin (Radix Scutellariae) 12 g, Baishao (Radix paeoniae Alba) 10 g, Daneshen (Radix Codonopis) 6 g, Buguzhi (Fructus Poriae) 6 g, Yiyiren (Coix Seed) 10 g, Fulin (Poria cocos) 10 g, Muxiang (Radix Aucklandiae) 6 g, Chuanxiong (Rhizoma Chuanxiong) 9 g, Dazao (Jujube) 6 g, processed Gancao (liquiritin) 10 g. Drugs above were added or subtracted from the decoction according to different clinical symptoms (avoid fried granules, Anhui Jingguan Traditional Chinese Medicine Co., Ltd., Anhui, China). Participants in the control group orally took Meloxicam tablets in the control group (Jiangsu Huafeng Medicine Co., Ltd., Nanjing, China), 7.5 mg/day meal service, for two months.

Clinical evaluation
WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) score was used as a tool for primary outcome assessment. This questionnaire is a widely used instrument to measure severity of KOA, which is recognized as the best evaluation scale for KOA. It comprises three dimensions, including pain (5 items), stiffness (2 items), and difficulty of daily activities (18 items), 10 points for each item. The total WOMAC score ranges from 0 to 240, and a higher score indicates a worse knee function.

Secondary outcome measures were assessed by the 36-Item Short Form Health Survey (SF-36). This survey, including physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health, is an often applied measure of general health and health-related quality of life. All questionnaires and tests were conducted before and after the 8 week treatment by two postgraduate assistants.

Statistical analysis
The software SPSS 19.0 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0, Armonk, NY , USA) was used for data analysis. T-test and χ2 test were conducted to test the differences between the groups. A P value less than 0.05 was considered statistically significant.

RESULTS

WOMAC
There were no significant differences in WOMAC scores between the two groups before treatment (P > 0.05). The pain scores, physical function scores and the total scores in the treatment group were significantly lower than those in the control group after treatment (P < 0.05). However, the stiffness scores in the treatment group were significantly higher than that in the control group (P < 0.05) (Table 2). The WOMAC scores after treatment were significantly lower compared with those before treatment in both groups (P < 0.05) (Figure 2).

SF-36
There were no significant differences in the various indices of SF-36 score between the two groups before treatment (P > 0.05). The scores for physical function, bodily pain and general health in the treatment group were significantly higher than those in the control group after treatment (P < 0.05). The role emotional score showed a comparatively large effect size after treatment (P=0.053). However, no significant difference was observed in the scores for role physical, vitality, social function and mental health between two groups (P > 0.05). The SF-36 scores after treatment were significantly higher compared with those before treatment in both groups (P < 0.05) (Figure 2).

Adverse events
In the treatment group, no adverse events were reported during the study. No serious adverse events were reported in the control group and gastrointestinal discomfort was the most common adverse events. In the control group, 13 adverse events happened among these 62 participants, 6 participants in the control group experienced AEs at least once during the treatment period, and 2 participants experienced AEs more than 3 times.

DISCUSSION
From the results of this trial, WOMAC scores in both
Inclusion criteria and included patients according to our preliminary study. Hence, we eased the entry into our protocol, but a low participation rate was observed. Approximately 9% of participants experienced at least one AE (mostly gastrointestinal discomfort) and all the AEs merely happened in control group. This result largely indicated that the safety of the treatment group was superior to that of control group.

To be clear, we had planned to recruit patients with grades over 2 on the Kellgren/Lawrence scale according to our protocol, but a low participation rate was observed in our preliminary study. Hence, we eased the inclusion criteria and included patients according to the clinical criteria of American College of Rheumatology, regardless of Kellgren-Lawrence X-ray grade. It is necessary for us to recruit participants with merely moderate and severe KOA to evaluate the effect of SYXBD in future studies. We did not recruit more patients due to limited funds which may influence the representative of our results to some extent. Furthermore, a long-term effect of SYXBD should also be observed later.

In conclusion, it is believed that SYXBD based on the theory of "Shaoyang dominating bone" has a significant effect in treating KOA without obvious adverse events. Seen as a whole, SYXBD seems be superior to Meloxicam in the relief of knee symptoms and improvement of patients’ quality of life. Otherwise, it is necessary to state that the theory of "kidney dominating bone" is useful for KOA treatment.

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**REFERENCES**

Figure 2 Comparisons of changes in WOMAC scores and SF-36 scores before and after treatment in each group
A: comparison of WOMAC scores between baseline and week 8 in treatment group; B: comparison of WOMAC scores between baseline and week 8 in control group; C: comparison of SF-36 scores between baseline and week 8 in treatment group; D: comparison of SF-36 scores between baseline and week 8 in control group. SF-36: 36-item Short Form Health Survey, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index. *Represents comparison between baseline and week 8 outcomes in each item, assessed by paired samples t-tests. Significance at \( P < 0.05 \).