Effect of laser moxibustion for knee osteoarthritis: a multi-site double-blind randomized controlled trial

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Abstract

Objective To examine the effects of laser moxibustion on pain and function in patients with knee osteoarthritis.

Methods A double-blind randomized clinical trial (4-week treatment, 20-week follow-up) was conducted. A total of 392 symptomatic knee osteoarthritis patients with moderate or greater clinically significant knee pain were randomly assigned to laser treatment or sham laser control group (1:1). Twelve sessions of laser moxibustion treatments or sham on the acupuncture points at the affected knee(s) were performed three times a week for 4 weeks. The primary outcome measurement was change in WOMAC pain score from baseline to week 4.

Results Among the 392 randomized participants, 364 (92.86%) completed the trial. The median WOMAC pain score significantly decreased at week 4 in the active group than in the sham group (2.1; 95% CI, 1.6 to 2.6; $P < .01$). At week 24, compared to the sham laser, active laser treatment resulted in significant pain reduction and function improvement (3.0; 95% CI, 2.5 to 3.6; $P < 0.01$, and 14.8; 95% CI, 11.9 to 17.6; $P < .01$, respectively). The physical component of the quality of life significantly improved in the active group than in the sham control at week 4 (3.2; 95% CI, 1.3 to 5.0; $P = 0.001$) up to week 24 (5.1; 95% CI, 3.3 to 7.0; $P < .001$). No serious adverse effects were reported.

Conclusion Laser moxibustion resulted in statistically and clinically significant pain reduction and function improvement following a 4-week treatment in patients with knee osteoarthritis.

Keywords: 10.6μm laser moxibustion, knee osteoarthritis, pain, traditional Chinese medicine, phototherapy

Osteoarthritis (OA) is the most common form of arthritis and the leading cause of disability among older adults. The knee is the joint most commonly affected by OA.[1] The prevalence of knee OA among people aged 60 years or older in the USA is 12.1%,[2-4] which is expected to increase in the next 20 years.[5] The prevalence of knee OA among elderly in China is nearly 30%.[6] Conventional treatment of knee OA mainly aims at alleviation of pain including pharmacological, such as non-steroidal anti-inflammatory drugs (NSAIDs) [7-15] and non-pharmacological managements[11, 13]. NSAIDs are associated with a moderate effect on pain relief. 9,10 However, evidence on their effectiveness is limited,[9-12, 14, 15] and often associated with undesirable side effects.[11, 14, 15] Recent review showed that appropriate treatments for knee OA included biomechanical interventions, intra-articular corticosteroids, exercise (land-based and water-based), self-management and education, strength training, and weight management. [13]

As many as 41%[16] people with OA seek out complementary and alternative medicine therapies, including traditional Chinese medicine (TCM), acupuncture, moxibustion, and laser irradiation. According to the TCM theory, joint pain is associated with coldness and dampness. Therefore, the treatment often involves thermal stimulation on acupuncture points, known as moxibustion, by burning mugwort (*Artemisia vulgaris*). The effect of moxibustion is believed mainly due to its thermal effect on the skin surface. [17] However, moxibustion therapy produces heavy smoke with unpleasant smell. The smoke of moxibustion is considered as a biological hazard to health,[18] which is therefore prohibited from use in many clinics and hospitals. Recently, low-level laser therapy has been widely used to treat musculoskeletal pain including pain in knee OA.[19-22] We have developed a laser moxibustion (LM) device of 10.6 μm wavelength, which has the thermal nature of moxibustion without smoke and smell. Our previous small studies showed that LM may be effective in alleviating the symptoms of knee OA.[23, 24] The LM device was patented in 2010 (China

Invention Patent ZL200910056991.4) and licensed by Shanghai Municipal Food and Drug Administration, China (20162210783). The purpose of this placebo controlled clinical trial was to validate whether a 4-week LM treatment is effective and safe in reducing pain and improving function among patients with knee OA as compared with a sham laser control.

Methods

This is a multi-site randomized double-blind sham-controlled trial (N=392; 1:1). The trial protocol adhered to CONSORT guidelines (Supplementary material 1).[25] ISRCTN registry trial identifier: 15030019; URL: https://doi.org/10.1186/ISRCTN15030019. It was conducted in the outpatient clinics in six hospitals in Shanghai, China, and was approved by Institutional Review Board (IRB) at each site: IRB of Shuguang hospital affiliated to Shanghai University of traditional Chinese medicine (ref: 2014-341-37-01), IRB of Shanghai East Hospital affiliated to Tongji University (ref: 2013-24), IRB of Renji Hospital affiliated to Shanghai Jiaotong University (ref: 2015-001), IRB of Shanghai Changning Tianshan Traditional Chinese Medicine Hospital (2017TSKY04) and IRB of Shanghai Tongren Hospital affiliated to Shanghai Jiaotong University (ref: 2017-32). Shanghai Hudong hospital accepted the ethics approval of Shuguang hospital. We have obtained the patient's written informed consents to publish the materials. We established an international data and safety monitoring board (DSMB) to monitor data safety to ensure the quality of the trial and safety of patients in the trial.

A total of 603 patients were screened between January 2015 and November 2017 primarily through print advertisements on local newspapers and posters distributed in nearby communities (Figure 1). Participants were included if they were 50 years old or older, reported moderate or greater clinically significant knee pain on most days during the past month, had knee pain of at least 40/100 mm on a visual analogue scale

(VAS), and had been diagnosed with idiopathic knee OA according to the American College of Rheumatology classification criteria.[26] Kellgren-Lawrence grade ≥ 1 in the tibiofemoral joint on radiograph was also an inclusion requirement.[5] The included participants all have signed the informed consents to ensure the safety and confidentiality of participants according to the protocol. [25]

Patients with other diseases affecting the knee, such as rheumatoid arthritis, fibromyalgia syndrome, chronic fatigue syndrome, and ankylosing spondylitis, were excluded. Other exclusion criteria were as follows: steroid medication or acupuncture/moxibustion treatment in the previous 3 months; intra-articular hyaluronate injection during the past 6 months; arthrocentesis or arthroscopy in the past 1 year; previous history of knee/hip replacement surgery and plan to have such surgery during the trial; use of other external treatments, such as topical medication; presence of serious medical conditions including cardiac diseases, pulmonary diseases, kidney diseases, liver diseases or malignant tumors, systemic infection or contagious diseases, and psychopathy; use of trial drug in the past 30 days; previous participation in other laser therapies; recruited in other clinical trial simultaneously; and unable to fill measurement questionnaires.

Randomization and Blinding

The 392 eligible participants were randomly assigned to receive either active LM or sham control. Randomization sequence with random blocks was generated using computer software. Allocation concealment was ensured with disguised letter codes of the LM devices (either active or sham devices) that were generated and sent to the site coordinators via a central randomization system. After receiving the device code from the site coordinator, the device operator used the LM device labeled with that code for patient treatment. The operators were unaware of the active or sham device as both produced the same red light. The whole procedure was supervised by the coordinators to ensure that the protocol was followed.

Participants in the two groups were treated by trained operators. Communication among participants was discouraged and avoided as they were treated in separate rooms. Therefore, all involved personnel including participants, device operators, outcome assessors, research coordinators, and statistician were blinded to the treatment allocation.

Interventions

The LM devices (SX10-C1) were manufactured by Shanghai Wonderful Opto-Electrics Tech. Co., Ltd. (Shanghai, China) and licensed by Shanghai Municipal Food and Drug Administration, China (20162210783). The wavelength of laser irradiation was 10.6 μm, and the output power was adjusted in the range of 160-180 mW. Energy density ranged from 61.2 to 68.8 J/cm^2 for one treatment. After the patient laid supine on a treatment table, the laser irradiation tips of the two LM devices were aimed to the surface of the acupuncture points. The distance from the tips to the skin surface was 2 cm measured using a scale. Two acupuncture points were selected, namely, ST35 (Dubi; located in the depression on the lateral side of the patella and the patellar ligament) and Ashi point (tender point),[26] at the affected knee. The selection of acupuncture points was based on the TCM theory used for *Bi* syndrome at the knee joints, and was successfully used in our previous studies.[23, 24] The treatments lasted 20 minutes and were performed 3 times a week for 4 weeks with a total of 12 sessions. The procedure of the treatment was shown in Figure 2.

The sham treatment procedure was the same as the active treatment except no laser output irradiated from the device. However, in both active and sham devices, a red light-emitting diode with an output of 3 mW was used as visible indicator light on the skin to confirm accuracy of irradiation on the targeting acupoint. Participants were allowed to receive their usual care medications but were encouraged not to change to new drugs. In case of drug change, the name and dosage of the medication were documented.

Outcome Measurements

The patients were assessed at baseline and at weeks 2, 4, 8, 12, and 24. All assessment instruments were in Chinese language version and previously validated.[28, 29] The primary outcomes were the change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [30] pain scores from baseline to 4 weeks. The WOMAC was a Likert version. The WOMAC was a Likert version. The WOMAC pain subscales included five questions with a total of 20 points (0, no pain). For bilaterally eligible knees, only the most symptomatic knee was evaluated. Secondary outcomes included the change in WOMAC scores at weeks 2, 4, 8, 12, and 24; health-related quality of life (36-Item Short Form Health Survey [SF-36][31]); VAS and Patients' global assessment. The WOMAC consists of other two subscales: stiffness (two questions), 0 to 8 points; and physical function (17 questions), 0 to 68 points (The higher the scores, the worse the symptoms are). VAS was used for measuring the pain ranging from 0 mm, indicating no pain, to 100 mm, indicating worst pain. The measurements were taken at baseline, week 2, 4, 8,12 and 24, with asking patients: "How painful is your knee now?" Patients' global assessment of OA is evaluated on a five- point Likert scale [31-33] at week 4. Patients are asked to respond to the following question: 'Considering all the ways your osteoarthritis affects you, how are you doing today?' 1=very good; 2=good; 3=fair; 4=poor; and 5=very poor. Adverse events, whether related to treatment or not, reported by the participants and practitioners were documented at each visit. We also communicated each participant weekly through telephone to follow up any adverse event or side effect. Possible side effects of LM include skin rash, redness, and blisters. To assess the masking effectiveness of the trial, the treatment providers and the participants were asked to guess their group assignment after the end of treatment at week 4.

Blood samples were collected at baseline and week 4 from the first one third of the participants (n=113, 56 from the LM group and 57 from the sham control group) to examine the changes in serum biochemical levels such as cartilage oligomeric matrix protein (COMP), interleukin (IL)-1β, IL-2, IL-6, IL-8, monocyte chemoattractant protein 1 (MCP-1), matrix metallopeptidase (MMP)-3 and MMP-13 (considered as important involved in the progress of OA). Blood samples (10 ml) were drawn at 10-11:30 am from each participant and then were stored in a refrigerator at -80 °C for later analysis.

Sample Size and Statistical Analysis

A minimum of 36% improvement in WOMAC score was considered to be clinically meaningful.[34] Based on previous small-scale preliminary studies, [23-25, 36,37] a sample size of 324 participants (162 for each group) would be sufficient to detect the difference of 36% between the two groups to achieve a 2-sided 5% significance level with at least 80% power.[38] Considering possible dropout (i.e., 17% dropout) during the trial, a total of 392 patients were thus required.

The analysis plan was determined and approved by the independent DSMB committee before the study was conducted. The primary analysis was to compare the 4-week improvement in WOMAC pain score between the treated and the control in all randomized patients. A chi-square test was used for categorical data and 2-sample t-test or Mann-Whitney U test was used for continuous data, to evaluate statistically significant differences in the distribution of different variables at baseline according to whether the data are normally distributed. Two-sample t-test or Mann-Whitney U test was performed for the primary (WOMAC pain) and secondary endpoints (WOMAC scores at other time points, SF-36, medication usage, and serum levels of different cytokines) at each time point. Chi-square test was performed for the categorical data (self-evaluation, credibility of the sham assessment, and safety assessment). For non-normally distributed

variables, 95% bootstrap confidence instead of large sample normal based interval was calculated. All statistical analyses were conducted using SPSS (version 23.0; Chicago, USA). All reported P values were two-sided and used a significance level of 0.05.

Results

After initial screening, 392 patients were randomly assigned to either the LM (n=201) or the sham LM group (n=191). Three hundred and sixty-four patients (92.86%) completed the study and available for analysis (Figure 1). 193 patients of LM group and 177 patients of sham group completed all 12 sessions of therapy. No additional missing data other than those withdrawn from the study. Missing data of withdrawn participants were replaced with the data of last observation-carried-forward. Baseline characteristics were similar between the groups (Table 1). Most study patients were women (75%). No significant difference was found between the two groups in age, sex, disease course, medication use, severity of disease, WOMAC scores for knee pain or physical function, and cytokine level. This result suggests that the two groups were comparable.

Primary Outcome: At week 4, the patients receiving LM treatment reported more pain reduction in WOMAC pain score of 2.4 (36.4%) compared with those receiving sham LM of 0.1 (1.5%). A significant difference was found between the two groups (2.1; 95% confidence interval [CI], 1.6 to 2.6; $P < 0.01$) (Table 2). At week 4, 127 patients receiving LM treatment reported more than 36% pain reduction in WOMAC pain score (63.2%) compared with 45 patients receiving sham LM (23.6%). A significant difference was found between the two groups ($P < 0.01$).

Secondary Outcomes: WOMAC total scores including pain, physical function, and stiffness at weeks 2, 4, 8, 12, and 24 improved significantly more in patients who received active LM than those who received sham LM (see Table 2 for details). The patients in the active LM group reported more VAS pain score reduction than those in the sham LM group at all time points (Table 2).

No significant difference was noted in medication usage between the two groups. For the medication intake, we counted the number of patients who did not need to take medicine as the measurement. Before treatment, 159 patients of LM group and 164 patients of sham group did not take any medicine (P=0.061). After 4 weeks treatment, 175 patients of LM group and 156 patients of sham group took no medicine (P=0.977); at week 24, 176 patients of LM group and 155 patients of sham group took no medicine (P=0.808).

Quality of life measured using SF-36 showed that the physical component summary score significantly improved by 3.2 at week 4 in the LM group compared with the sham control group (95% CI, 1.3 to 5.0; P = 0.001) up to week 24 (5.1; 95% CI, 3.3 to 7.0; $P < 0.001$). No difference was found in mental component summary score between the two groups (0.8, 95% CI, -1.0- 2.6; P＝0.378 at week 4; 1.8, 95% CI, -0.1 to 3.6, P = 0.058 at week 12; 1.1, 95% CI, -0.7 to 2.9; P = 0.238 at week 24). Among the eight components of SF-36 assessment, the active LM group showed statistically significant improvement in five components including physical functioning, role-physical, bodily pain, social functioning, and role-emotional at weeks 4, 12, and 24 (P = 0.024 - $P < 0.001$) compared with the sham LM group (Table 3). Patients' global assessment was evaluated at week 4. The rank sum test showed that the patients in the active LM group reported better overall satisfactory scores (230.09) than those in the sham control group (136.88; P<0.01).

After a 4-week treatment, among all the serum biomarkers including COMP, IL-1β, IL-2, IL-6, IL-8, MCP-1, MMP-3, and MMP-13, only COMP improved in the active LM group compared with the sham control

group. At the baseline, median (min, max) of serum COMP of the LM group was 288.3 (251.0, 340.0) pg/ml, compare with the COMP of 291.0 (253.0, 414.1) pg/ml in sham group, *P* =0.415. At week 4, COMP of the LM group was 270.2(240.7,305.9) pg/ml, while 301.0(260.2, 364.3) pg/ml in sham group, *P*=0.017 (Table 4).

Assessment of patient blinding was conducted at week 4 following treatment completion. A total of 170 patients (88.1%) in the LM group and 159 patients (89.8%) in the control group were unsure of their group allocation. Only 20 (9.95 %) in the active LM group and 5 (2.62 %) in the control group guessed their allocation correctly. The chi-square test showed *P*=0.464, suggesting successful blinding in patients. All the 21 treatment providers were unaware of the treatment types (active LM or sham LM) they had provided.

Thirty (7.65%) adverse effects (24 [11.94%] in the active LM group and 6 [3.14%] in the sham control group) were reported among the 391 participants. Skin rash was the most common adverse effect (21) reported by those who received active LM and all recovered within three days.

Discussion

Over a 4-week treatment period of thrice weekly treatments, 10.6-μm LM (61.2-68.8 J/cm^2) showed significant efficacy in relieving knee pain and function improvement compared with sham LM measured using WOMAC scores and VAS. The effect was prolonged up to 20 weeks after the completion of laser treatment. Our findings are similar to those of previous reports.[36, 37] In a systematic review reported by Wyszynska and Bal-Bochenska,[36] high-intensity laser therapy produces significant benefit in pain reduction and function improvement in patients with knee OA. However, most of these studies suffered from methodological flaws such as small sample size, [36,38,39] insufficient treatment time,[19] and inadequate

follow-up time.[40] The strength of our laser treatment was that our laser device used CO_2 laser, which produces a far-infrared light beam of 10.6 μm, whereas previous studies used Gal-Al-As laser with wavelengths ranging from 830 nm to 1064 nm.[41] The unique feature of 10.6-μm LM is that it produces potent superficial heat, [41] which mimics moxibustion in TCM.

According to the TCM theory, joint pain, such as in knee OA, is considered as "Bi syndrome," which is caused by wind, cold, and dampness affecting the joint. Traditionally, thermal stimulation produced by burning *A. vulgaris* is commonly used to treat "Bi syndrome" to eliminate cold and dampness in the joint.[27] However, traditional moxibustion has its limitation in clinical practice due to the nature of smoke and smell. Some studies suggested that the smoke may be hazardous for health. [43] The effect of moxibustion is believed mainly due to its thermal effect on the skin surface. In the present study, we used 10.6-μm CO_2 laser beam, which produced a thermal effect similar to that of traditional moxibustion but without smoke and smell, for treating knee arthritic pain.[22, 35, 44]

A recent systematic review [41] indicated that the best available current evidence does not support the effectiveness of laser treatment as a therapy for patients with KOA. Variation in the effectiveness of laser treatment in KOA patients could be related to a variety of dosage, treatment schedule, energy density, output and wavelength. Soleimanpour H et al performed laser therapy in knee osteoarthritis with 810 nm of 6 J/cm ^{2} dose and 890 nm of 10 J/cm^2 dose, three times a week with a total of 12 sessions, results showed laser therapy was effective in reducing pain in knee osteoarthritis. [45] While Hinman RS et al [19] used a diode laser devices (measured output 10 mW and energy output 0.2 J/point), the output and energy of which was much lower than those of both the CO_2 laser used in our trial (output 160~180 mW and energy output 192~216 J/point) and the recommended treatment dose for low level laser therapy by World Association for Laser

Therapy [46,47] (minimum energy output 1J/point for 904nm laser, minimum energy output 4J/point for 780-820nm laser). Energy outputs of most of laser treatment trials were lower than what we used. That's maybe one of the main reasons that some trials failed to detect the benefit of laser treatment.

We conducted a double-blind clinical trial ~~achieved~~ by the same appearance of active and sham laser devices; not only the patients but also the operators of the laser devices were unaware of the group allocation. Further validation test showed that the blinding was successful, and all other investigators were also blinded to the treatment allocation. Second, the patient compliance rate of the trial was high (92.86%), possibly because most of the participants were elderly and retired with more time for treatment. Most of the participants lived nearby the hospitals. Third, the incidence of side effects observed during trial was low (7.65%).

Some studies suggested that serum COMP is potentially useful to be a prognostic marker of disease progression for joint injury. [48,49] COMP is a large pentameric glycoprotein that interacts with multiple extracellular matrix proteins in the cartilage.[50] Our study suggested that the effect of the 10.6-μm laser may be associated with protecting the cartilage from degeneration in patients with knee OA.

This study has a number of limitations. First, the trial was conducted at six sites and the number of subjects recruited from each site varied, which might introduce selection bias and conditional bias. Second, the treatment only used two fixed points, whereas in real- world Chinese medicine practice, the point selections are often individualized based on the syndrome differentiation according to the Chinese medicine principles. Third, although we asked patients to document any additional medicine using a medication usage log, we did not know for sure whether all the patients complied this request. However, we hope the randomization

would address this issue as we assume both groups would have similar number of participants who may not follow our requirement.

Conclusion

A 10.6-μm LM is superior to sham laser with clinically relevant benefits for 24 weeks in treating knee OA. The effectiveness of laser treatment may be related to COMP elevation, which controls inflammation and protects the cartilage. Further research is warranted to understand the long-term efficacy and the mechanism of action of laser intervention.

Author Contributions: Professor Xueyong Shen and Professor Lixing Lao had full access to all study data and take responsibility for the integrity of the data and the accuracy of the data analysis. Ling Zhao and Ke Cheng contributed equally to this manuscript.

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Competing interests

Xueyong Shen and Ke Cheng have had a patent issued for a type of laser therapy apparatus simulating the infrared radiation spectrum of traditional Chinese moxibustion (China Invention Patent ZL 200910056991.4; issued December 1, 2010).

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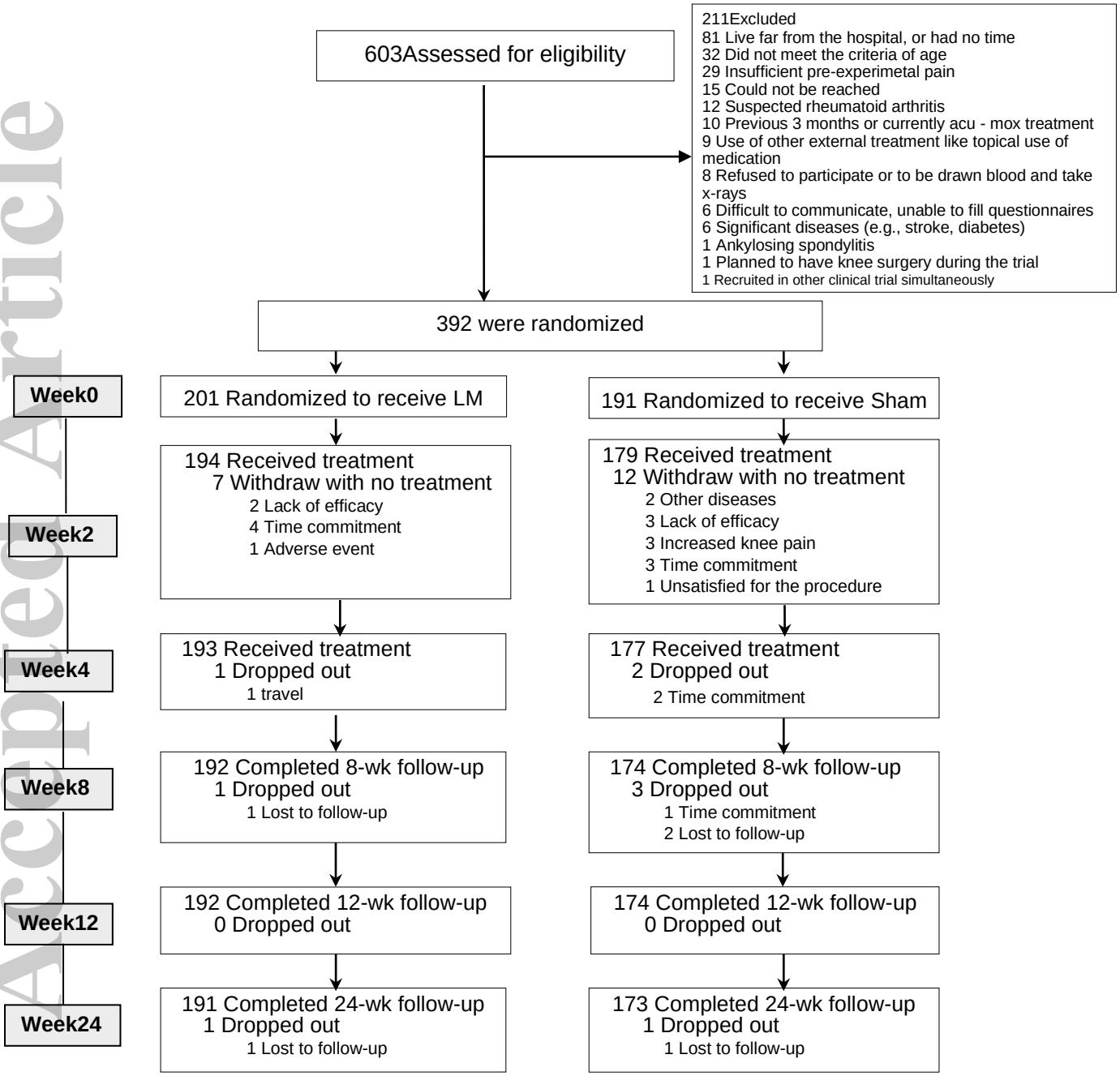

Figure 1. Participant flowchart

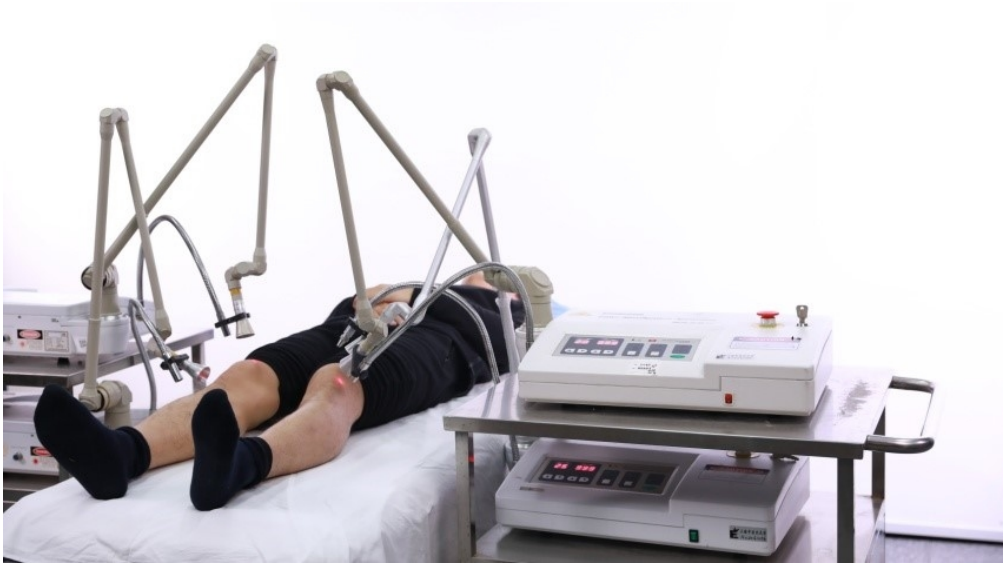

Figure 2. Laser treatment

98x55mm (220 x 220 DPI)

Table 1. Demographic and Baseline Characteristics of the Participants

Characteristics	LM group (n=201)	Sham group (n=191)
Age, mean (SD)	63.5 (7.67)	63.1 (6.0)
No (%) of woman	153 (76.1)	141 (73.8)
Affected knees (%)		
1 knee	89 (44.3)	96 (50.3)
both knees	112 (55.7)	95 (49.7)
Length of knee OA (%)		
<1y	39 (19.4)	39 (20.4)
1-5 y	96 (47.8)	82 (42.9)
5-10 y	44 (21.9)	47 (24.6)
>10 y	22 (10.9)	23 (12)
Kellgren-Lawrence grade, n (%)		
1	33 (16.4)	34 (17.1)
2	122 (60.7)	118 (61.8)
3	43 (21.4)	35 (18.3)
4	3 (1.5)	4 (2.1)
BMI [a], mean (SD)	24.7 (3.6)	24. 6 (3.2)
Medication use, No. (%)		
No medication	159 (75.7)	164 (85)
Glucosamine products	33 (15.7)	20 (10.4)
NSAIDs	2 (1)	0 (0)
TCM patent prescription	10 (4.8)	3 (1.6)
Calcium tablet	3 (1.4)	0 (0)
Analgesia	0 (0)	4 (2.1)
Alpha ossification alcohol	2 (1)	1 (0.5)
COX-2 inhibitors	1 (0.5)	1 (0.5)
WOMAC		
Pain score[#], Mean (SD)	6.6 ± 3.5	6.7 ± 3.7
Function score[&], Mean (SD)	33.7 ± 19.7	32.6 ± 19.1
Stiffness score[^], Median (Q1, Q3)	6.8 (2.4,10.0)	6.0 (2.0,10.0)
VAS, Median (Q1, Q3)	57.5 (50, 69.8)	56.0 (50.0, 71.5)

[a]Calculated as weight in kilograms divided by height in meters squared.
Abbreviations: COX-2, cyclooxygenase-2; NSAID, nonsteroidal anti-inflammatory; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
There were no differences between the groups in WOMAC and VAS scores at baseline (P>0.05).

#Range, 0–20.
&Range, 0–68.
^Range, 0–10.

Table 2. Change from Baseline in WOMAC and VAS Outcomes of the Participants

Endpoint	week	Laser group			Sham group			Difference	*Z* Value	*P* Value
		n	Median (Q1, Q3)	95% CI	n	Median (Q1, Q3)	95% CI	95% CI		
WOMAC Pain#	2	194	1.5 (0.1, 3.0)	1.2, 1.6	179	0 (-0.6, 0.8)	0, 0.2	1.4 (1.0, 1.7)	- 7.125	< 0.01*
	4	193	2.4 (0.9, 4.7)	2.0, 2.8	177	0.1 (-0.4, 1.4)	0, 0. 4	2.1 (1.6, 2.6)	- 8.616	< 0.01*
	8	192	3.0 (0.9, 5.2)	2.4, 3.5	174	-0.2 (-1.1, 1.4)	-0.4, 0	2.8 (2.2, 3.4)	- 9.446	< 0.01*
	12	192	2.8 (1.0, 5.5)	2.3, 3.6	174	-0.2 (-1.1, 1.4)	-0.6, 0	3.0 (2.4, 3.6)	- 9.455	< 0.01*
	24	191	2.9 (1.1, 5.7)	2.2, 3.6	173	-0.2 (-1.4, 1.6)	-0.6, 0	3.0 (2.5, 3.6)	- 9.771	< 0.01*
WOMAC Function&	2	194	4.9 (0.3, 12.6)	3.8, 6.3	179	0 (-3.7, 4.3)	-0.8, 0.2	5.8 (4.2, 7.5)	- 7.048	< 0.01*
	4	193	11.2 (2.4, 21.4)	8.8, 14.1	177	0.5 (-2.5, 6.0)	0, 1.5	9.8 (7.4, 12.3)	- 8.188	< 0.01*
	8	192	12.5 (3.8, 25.7)	8.9, 16.9	174	-0.8 (-6.2, 7.8)	-2.2,0	12.2 (10.5, 16.2)	- 9.309	< 0.01*
	12	192	14.4 (4.1, 25.3)	10.4, 16.6	174	-1.6 (-7.1, 5.6)	-2.8, 0	14.9 (12.1, 17.9)	- 10.147	< 0.01*
	24	191	14.7 (4.0, 25.2)	10.5, 16.5	173	-0.6 (-5.7, 6.6)	-2.4, 0	14.8 (11.9, 17.6)	- 10.121	< 0.01*
WOMAC Stiffness^	2	194	1.5 (0, 3.8)	1.0, 2.0	179	0 (-0.6, 1.1)	0, 0.1	1.4 (0.9, 2.0)	- 6.149	< 0.01*
	4	193	2.3 (0, 5.7)	1.7, 3.0	177	0 (-0.6, 1.5)	0, 0.3	2.0 (1.3, 2.7)	- 6.203	< 0.01*
	8	192	2.7 (0, 6.5)	2.0, 3.9	174	0 (-1.4, 1.5)	-0.1, 0	2.7 (2.0, 3.6)	- 7.707	< 0.01*
	12	192	2.7 (0, 6.4)	1.9, 4.0	174	0 (-1.4, 1.5)	0, 0	2.7 (2.0, 3.6)	- 7.344	< 0.01*
	24	191	3.4 (0, 6.5)	2.0, 4.3	173	0 (-1.8, 1.4)	-0.3, 0	3.1 (2.2, 4.0)	- 8.159	< 0.01*
VAS	2	194	15.5 (5.0, 26.0)	13.3, 18.3	179	2.5 (-3.0, 11.5)	0, 4.0	11.5 (9.0, 14.5)	- 8.017	<0.01*
	4	193	28.5 (15.3, 41.0)	25.0, 30.0	177	5.0(0, 20.0)	2.5,7.0	20.0 (16.0, 23.0)	- 9.120	<0.01*
	8	192	31.5 (20.0, 43.8)	30.0, 36.0	174	5.0 (-2.5, 19.0)	2.3, 10.0	24.5 (20.5, 28.0)	- 10.290	<0.01*
	12	192	32.5 (20.8, 44.8)	30.0, 35.5	174	3.0 (-3.0, 15.0)	1.0, 6.0	26.5 (22.5, 30.0)	- 10.838	<0.01*
	24	191	34.0 (22.0, 45.0)	30.0,36.5	173	3.0 (-3.5, 20.0)	0.5,6.0	26.5 (23.0, 30.0)	- 11.169	<0.01*

WOMAC index score reduction = baseline – post-treatment.
Mann-Whitney U test was used. For non-normally distributed variables, 95% bootstrap confidence was calculated.
# $P<0.01$; & $P<0.01$; ^ $P<0.01$.

Table 3. SF-36 Scale Scores Over Time

SF-36 scale		Laser group			Sham laser group			Difference 95% CI	*Z* Value	*P* Value
		n	Median (Q1, Q3)	95% CI	n	Median (Q1, Q3)	95% CI			
PF (Physical Functioning)	Before	201	60.0 (45.0,75.0)	55.0, 65.0	191	60.0 (45,75)	60.0, 65.0	0 (-5.0, 0)	-0.891	0.373
	Week 4	193	70.0 (55.0,85.0)	65.0, 75.0	177	65.0 (50,75)	60.0, 65.0	5.0 (0, 10)	-3.019	0.003*
	Week 12	192	75.0 (60.0,90.0)	70.0, 80.0	174	65.0 (55,75)	65.0, 70.0	10.0 (5.0, 15.0)	-4.553	<0.001*
	Week 24	191	75.0 (60.0,90.0)	70.0, 80.0	173	65.0 (55,75)	60.0, 70.0	10.0 (5.0, 10.0)	-4.647	<0.001*
RP (Role-Physical)	Before	201	0 (0,75.0)	0, 25.0	191	0 (0,75.0)	0, 0	0 (0, 0)	-0.381	0.703
	Week 4	193	50.0 (0,100.0)	50.0, 50.0	177	0 (0,100.0)	0, 25.0	0 (0, 25.0)	-3.440	0.001*
	Week 12	192	50.0 (0,100.0)	50.0, 75.0	174	0 (0,75.0)	0, 0	25.0 (0, 50.0)	-6.340	<0.001*
	Week 24	191	75.0 (0,100.0)	50.0,75.0	173	0 (0,75.0)	0, 25.0	25.0 (0, 25.0)	-5.589	<0.001*
BP (Body Pain)	Before	201	58.0 (45.0,68.0)	55.0, 66.5	191	58.0 (45.0,68.0)	55.0, 60.0	0 (0, 3.0)	-0.741	0.459
	Week 4	193	68.0 (55.0,78.0)	68.0, 68.0	177	58.0 (45.0,68.0)	58.0, 68.0	10.0 (0, 10.0)	-3.654	0.001*
	Week 12	192	68.0 (58.0,78.0)	68.0, 68.0	174	58.0 (45.0,68.0)	55.0, 65.0	10.0 (8.0, 12.0)	-5.206	<0.001*
	Week 24	191	68.0 (58.0,78.0)	68.0, 70.0	173	58.0 (45.0,68.0)	58.0, 68.0	10.0 (10.0, 12.0)	-5.403	<0.001*
GH (General Health)	Before	201	47.0 (35.0,61.0)	45.0, 50.0	191	50.0 (40.0,62.0)	45.0, 51.0	0 (-5.0, 2.0)	-7.676	0.443
	Week 4	193	50.0 (40.0,65.0)	46.0, 55.0	177	45.0 (40.0,60.0)	45.0, 50.0	2.0 (0, 5.0)	-1.357	0.195
	Week 12	192	50.0 (40.0,65.0)	50.0,55.0	174	50.0 (40.0,60.0)	45.0, 50.0	5.0 (0, 7.0)	-2.262	0.024*
	Week 24	191	50.0 (40.0,65.0)	50.0,55.0	173	50.0 (40.0,60.0)	45.0, 50.0	5.0 (0, 5.0)	-2.242	0.025*
VT (Vitality)	Before	201	55.0 (40.0,65.0)	50.0, 55.0	191	55.0 (40.0,70.0)	55.0, 60.0	-5.0 (-5.0, 0)	-1.306	0.191
	Week 4	193	60.0 (45.0,70.0)	55.0, 60.0	177	55.0 (40.0,70.0)	55.0, 60.0	5.0 (0, 5.0)	-1.057	0.290
	Week 12	192	60.0 (50.0,70.0)	60.0, 65.0	174	55.0 (45.0,70.0)	52.6, 60.0	5.0 (0, 10.0)	-2.442	0.015*
	Week 24	191	60.0 (50.0,70.0)	55.0, 65.0	173	55.0 (45.0,70.0)	55.0, 60.0	5.0 (0, 5.0)	-1.294	0.196
SF (Social Functioning)	Before	201	75.0 (63.0,88.0)	75.0, 75.0	191	75.0 (50.0,88.0)	63.0, 75.0	0 (0, 0)	-0.558	0.376
	Week 4	193	75.0 (63.0,88.0)	75.0, 75.0	177	75.0 (50.0,88.0)	63.0, 75.0	0 (0, 12.0)	-2.705	0.007*

	Week 12	192	75.0 (63.0,88.0)	75.0, 75.0	174	63.0 (50.0,88.0)	63.0, 75.0	12.0 (0, 12.0)	-3.779	<0.001*
	Week 24	191	75.0 (63.0,88.0)	75.0, 75.0	173	63.0 (50.0,88.0)	63.0, 75.0	12.0 (0, 12.0)	-3.593	<0.001*
RE	Before	201	100.0 (0,100.0)	100.0, 100.0	191	100.0 (0,100.0)	67.0,100.0	0 (0, 0)	-1.126	0.260
(Role-Emotional)	Week 4	193	100.0 (33.0,100.0)	100.0,100.0	177	100.0(0,100.0)	67.0,100.0	0 (0, 0)	-1.814	0.070
	Week 12	192	100.0 (67.0,100.0)	100.0, 100.0	174	100.0 (0,100.0)	67.0, 100.0	0 (0, 0)	-4.387	<0.001*
	Week 24	191	100.0 (83.5,100.0)	100.0, 100.0	173	100.0 (0, 100.0)	100.0, 100.0	0 (0, 0)	-3.818	<0.001*
MH (Mental	Before	201	68.0 (56.0,80.0)	68.0, 72.0	191	68.0 (60.0, 76.0)	68.0, 72.0	0 (-4.0, 4.0)	-0.099	0.921
Health)	Week 4	193	72.0 (60.0,80.0)	68.0, 76.0	177	68.0 (60.0, 76.0)	68.0, 72.0	4.0 (0, 4.0)	-1.605	0.180
	Week 12	192	68.0 (60.0,80.0)	68.0, 72.0	174	68.0 (60.0, 76.0)	64.0, 68.0	4.0 (0, 4.0)	-1.72	0.081
	Week 24	191	68.0 (60.0,80.0)	68.0, 72.0	173	68.0 (60.0, 80.0)	64.0, 68.0	0 (0, 4.0)	-1.163	0.245
	Before	201	35.8(29.5,42.9)	33.8, 37.3	191	37.2 (31.3, 43.1)	34.4, 38.4	-0.8 (-2.7, 1.0)	-0.881	0.378
SF36 PCS	Week 4	193	41.6 (33.5,47.6)	39.1, 43.2	177	37.5 (31.2, 44.5)	35.0, 38.9	3.2 (1.3, 5.0)	-3.274	0.001*
	Week 12	192	44.7 (35.4,49.3)	42.1, 46.0	174	37.6 (31.8, 43.3)	35.2, 39.1	5.4 (3.5, 7.2)	-5.332	<0.001*
	Week 24	191	44.8 (36.0,50.0)	42.8, 46.7	173	38.1 (31.6, 44.3)	36.5, 40.0	5.1 (3.3, 7.0)	-5.259	<0.001*
	Before	201	51. 3(41.5,56.7)	49.3, 53.0	191	50.0 (40.0, 56.7)	48.9, 53.4	0.6 (-1.4, 2.6)	-0.570	0.568
SF36MCS	Week 4	193	50.6 (44.0,57.0)	48.6, 52.3	177	50.7 (42.5,55.9)	49.4,52.0	0.8 (-1.0, 2.6)	-0.882	0.378
	Week 12	192	50.6 (45.9,55.6)	48.9, 51.8	174	49.7 (39.4,55.2)	47.7, 50.8	1.8 (-0.1, 3.6)	-1.895	0.058
	Week 24	191	50.7 (45.9,55.7)	48.8, 52.3	173	50.4 (39.7,55.5)	48.1,52.3	1.1 (-0.7, 2.9)	-1.180	0.238

For non-normally distributed variables, 95% bootstrap confidence instead of large sample normal based interval was calculated. Comparison of different intervention methods at each time point: *P<0.05. Abbreviations: SF-36, 36-item Short Form Health Survey; MCS, mental component summary; PCS, physical component summary

Table 4. changes of serum biomarkers highly related to the progress of OA in participant serum (Med (QR))

serum biomarkers	Before treatment				after treatment			
	Laser group (n =56)	sham group (n =57)	*Z* value	*P* value	Laser group (n =56)	sham group (n =57)	*Z* value	*P* value
COMP	288.3 (251.0, 340.0)	291.0 (253.0, 414.1)	-0.815	0.415	270.2(240.7,305.9)	301.0(260.2, 364.3)	-2.398	0.017
IL-1β	3.0(0.8, 7.3)	1.5 (1.2, 13.5)	-0.830	0.460	2.5(0.8,5.7)	1.3(0.6, 3.67)	-0.166	0.868
IL-2	27.3(15.4,68.7)	19.2 (7.4, 74.9)	-1.280	0.201	33.2 (15.0, 76.8)	16.8 (8.4,68.3)	-1.108	0.268
IL-6	5.2 (2.1,11.1)	11.8 (4.8,51.1)	-1.513	0.130	4.6(2.5,9.8)	4.7(2.1,13.6)	-0.998	0.318
IL-8	61.3 (10.5,169.2)	111.2 (24.3,164.6)	-1.232	0.218	50.8 (17.0,170.4)	25.2 (10.0, 62.3)	-1.049	0.294
MCP-1	130.1(89.3,164.4)	126.6 (97.6,177.7)	-0.735	0.462	110.4 (89.1,140.5)	111.4 (82.7,150.7)	-0.235	0.814
MMP-3	62(4.2,14.3)	6.79(4.52,11.2)	-0.295	0.768	6.2 (4.1,12.3)	7.0 (4.6,9.8)	-0.027	0.979
MMP-13	162.6(50.5,267.7)	83.3(38.5,356.8)	-0.880	0.379	206.7(132.8,275.8)	120.8 (42.4,245.4)	-0.454	0.650

Mann-Whitney U test was performed for the analysis.

Table 5. Adverse Events (n=30) Reported During the Trial

Adverse events	LM group (n=201)	Sham group (n=191)
Skin rash	21	0
Increased knee pain	0	1
Weakness of the right leg	1	0
Knee swelling	0	1
Hip pain	1	0
Abdominal pain after intake of Chinese herbal medicine not related with the treatment for knee OA	0	1
Stiffness of the leg	1	0
Distension sensation in leg	0	1
Increasing BP	0	1
Abnormal sound in the knee	0	1
Total, n (%)	24 (11.94%)	6 (3.14%)