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

Ling Zhao

Shanghai University of Traditional Chinese Medicine

Ke Cheng

Shanghai University of Traditional Chinese Medicine

Fan Wu

Shanghai University of Traditional Chinese Medicine

Jiong Du

Shuguang Hospital

Yue Chen

Tongren Hospital Shanghai Jiaotong University School of Medicine

Ming T. Tan

Georgetown University Medical Center

Lixing Lao

University of Hong Kong

Xueyong Shen (✉ sxy1@shutcm.edu.cn)

Shanghai University of Traditional Chinese Medicine <https://orcid.org/0000-0003-4177-8970>

Research article

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

Posted Date: January 13th, 2020

DOI: <https://doi.org/10.21203/rs.2.20523/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background A laser device that mimics traditional moxibustion without smoke may be effective and safe for treating patients with knee osteoarthritis.

Methods A double-blind randomized clinical trial was conducted. A total of 392 patients with osteoarthritis of the knee were randomly assigned to receive laser treatment or sham control three times a week for 4 weeks with 20-week follow-up. Primary outcomes were changes in the WOMAC pain scores at 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 (2.2; 95% CI, 1.7 to 2.8; $P < .01$). At week 24, compared to the sham laser, active laser treatment resulted in significant pain reduction and function improvement (3.3; 95% CI, 2.7 to 3.9; $P < 0.01$, and 15.7; 95% CI, 12.8 to 18.8; $P < .01$, respectively). The physical component of the quality of life significantly improved in the active group than in the sham control at week 4 (3.0; 95% CI, 1.1 to 4.9; $P = 0.002$) up to week 24 (5.1; 95% CI, 3.2 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.

Background

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*). However, moxibustion therapy produces heavy smoke with unpleasant smell. The smoke of moxibustion is considered as a biological hazard to health,¹⁷ 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.¹⁸⁻²¹ 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.²²⁻²⁴ 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 [*in press*] adhered to CONSORT guidelines (Supplementary material 1). It was conducted in the outpatient clinics in six hospitals (Shuguang Hospital, Renji Hospital, Shanghai East Hospital, Shanghai Changning Tianshan Traditional Chinese Medicine Hospital, Shanghai Tongren Hospital, and Shanghai Hudong hospital) in Shanghai, China. The institutional review board at each site approved the trial protocol. 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 Rheumatism Association classification criteria.²⁵ Kellgren-Lawrence grade ≥ 1 in the tibiofemoral joint on radiograph was also an inclusion requirement.⁵

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/cm² 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.^{22,23} The treatments lasted 20 minutes and were performed 3 times a week for 4 weeks with a total of 12 sessions.

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.^{27,28} The primary outcomes were the change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)²⁹ pain scores from baseline to 4 weeks. The index of WOMAC consists of 3 subscales (5 questions on pain, 2 questions on stiffness, and 17 questions on functional status). The total score ranges from 0 (best) to 98 (worst). 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 (Short Form 36 Health Survey [SF-36]³⁰); VAS; and use of medication and patients' global

assessment³¹⁻³³ (1=very good; 2=good; 3=fair; 4=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)-1 β , IL-2, IL-6, IL-8, monocyte chemoattractant protein 1 (MCP-1), matrix metalloproteinase (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,^{22-24, 35,36} 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.³⁷ 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 an intention-to-treat analysis to compare the 4-week improvement in WOMAC pain score between the treated and the control in all randomized patients whose 4-week improvement was available. 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

Between January 2015 and November 2017, we screened 603 participants for eligibility and 211 were excluded because of unmet eligibility criteria (Figure 1). Thus, 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). 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 2.6 (39.4%) compared with those receiving sham LM of 0.1 (1.5%). A significant difference was found between the two groups (2.2; 95% confidence interval [CI], 1.7 to 2.8; $P < 0.01$) (Table 2).

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.

Quality of life measured using SF-36 showed that the physical component summary score significantly improved by 3.0 at week 4 in the LM group compared with the sham control group (95% CI, 1.1 to 4.9; $P = 0.002$). No difference was found in mental component summary score between the two groups (1.1, 95% CI, -0.8-2.9; $P = 0.26$ at week 4; 1.3, 95% CI, -0.6 to 3.2; $P = 0.177$ at week 24). However, the mental component summary score was significantly improved by 2.0 (95% CI, 0.1 to 3.9, $P = 0.039$) at week 12. 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 ($P = 0.043$ - $P < 0.001$) 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 cytokines including COMP, IL-1 β , 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 (median 270.2 pg/ml, range 240.7-305.9 and median 301.0 pg/ml, range 260.2-364.3 respectively; $P = 0.017$).

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 (Table 4).

Discussion

Over a 4-week treatment period of thrice weekly treatments, 10.6- μm LM (61.2-68.8 J/cm²) 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.^{35,36} In a systematic review reported by Wyszynska and Bal-Bochenska,³⁵ 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,^{35,37,38} insufficient treatment time,¹⁸ and inadequate follow-up time.³⁹ The strength of our laser treatment was that our laser device used CO₂ 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.⁴⁰ 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.²⁶ 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.^{42,43} In the present study, we used 10.6- μm CO₂ laser beam, which produced a thermal effect similar to that of traditional moxibustion but without smoke and smell, for treating knee arthritic pain.^{21,34,44-47}

A recent systematic review⁴⁰ 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/cm² dose and 890 nm of 10 J/cm² dose, three times a week with a total of 12 sessions, results showed laser therapy was effective in reducing pain in knee osteoarthritis⁴⁸. While Hinman RS et al¹⁸ 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 CO₂ 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^{49,50} (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.

The other strengths of this trial are as follows. First, we conducted a double-blind clinical trial. This was 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%).

To understand the mechanisms of action, we collected peripheral blood from subjects and examined the serum biochemical components that may be associated with inflammation status of knee OA. Interestingly, no changes were observed in all cytokines; the only change we noted was COMP. Some studies suggested that serum COMP is potentially useful to be a prognostic marker of disease progression for joint injury.^{51, 52} COMP is a large pentameric glycoprotein that interacts with multiple extracellular matrix proteins in the cartilage.⁵³ Our study suggested that the effect of the 10.6- μ m 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.

Conclusion

A 10.6- μ m 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.

Abbreviations

KOA Knee osteoarthritis

NSAIDs Non-steroidal anti- inflammatory drugs

TCM traditional Chinese medicine

LM laser moxibustion

CONSORT consolidated standards of reporting trials

DSMB data and safety monitoring board

VAS Visual Analogue Scale/Score

WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

SF-36 Short Form 36 Health Survey

COMP oligomeric matrix protein

IL interleukin

MCP-1 monocyte chemoattractant protein 1

MMP matrix metalloproteinase

PCS physical component summary

MCS mental component summary

Declarations

Author Affiliations: School of Acupuncture-Moxibustion and Tuina, Shanghai University of Traditional Chinese Medicine, Shanghai, China (L. Zhao, K. Cheng, F. Wu, X. Shen); Shanghai Research Center of Acupuncture & Meridian, China (K. Cheng, X. Shen); Department of Orthopaedics and Traumatology department Shuguang Hospital, Shanghai, China (J. Du); Department of Traditional Chinese Medicine, Shanghai Tongren Traditional Chinese Medicine Hospital, Shanghai, China (Y. Chen); Department of Biostatistics, Bioinformatics & Biomathematics Georgetown University Medical Center, Washington, USA (M. Tan); School Of Chinese Medicine, University of Hong Kong, Hong Kong, China (L. Lao).

- **Ethics approval and consent to participate**

- This study was approved by Institutional Review Board (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 the major center (i.e., Shuguang hospital affiliated to Shanghai University of traditional Chinese medicine).

- **Consent for publication**

- All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. All authors read and approved the final manuscript.

- **Availability of data and materials**

- Data are available on reasonable request.

- **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).
- **Funding**
- This trial was supported by National Natural Science Foundation of China (81320108028) and National Program on Key Basic Research Project of China (2015CB554505). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.
- **Authors' contributions**
- Prof. Xueyong Shen and 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.
- *Concept and design:* X. Shen and L. Lao.
- *Acquisition, analysis, or interpretation of data:* L. Zhao, K. Cheng, F. Wu, and M. Guo.
- *Statistical analysis:* M. Tan.
- *Critical revision of the manuscript for important intellectual content:* All authors.
- *Obtained funding:* Shen and L. Lao.
- *Administrative, technical, or material support:* Zhao, K. Cheng, X. Shen, and L. Lao.
- *Supervision:* Shen and L. Lao.
- **Acknowledgements**
- We would like to thank Drs. Jinghua Ge, Chenhuan Ding, and Feng Yin for their assistance in patient recruitment, Ms. Lin Lin for part of the statistical analysis, and Dr. Yang Mingxiao for editorial support. The DSMB members include an epidemiologist, Professor Jianping Liu (Chair) from Beijing University of Chinese Medicine, a biophysicist, Professor Wolfgang Schwarz from Goethe-University Frankfurt, an acupuncturist, Professor Bing Zhu from China Academy of Chinese Medical Sciences, a rheumatologist, Professor Mac C. Hochberg from University of Maryland School of Medicine, and a statistician, Professor Guoliang Tian from University of Hong Kong. We would also like to thank Editage (editge.com) for English language editing.

References

1. Wallace IJ, Worthington S, Felson DT, et al. Knee osteoarthritis has doubled in prevalence since the mid-20th century. *Proceedings of the National Academy of Sciences*. 2017;114(35):9332-9336.
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis and rheumatism*. Jan 2008;58(1):26-35.
3. Neogi T, Zhang Y. Epidemiology of osteoarthritis. *Rheum Dis Clin North Am*. Feb 2013;39(1):1-19.
4. Nelson AE. Osteoarthritis year in review 2017: clinical. *Osteoarthritis and Cartilage*. 2018/03/01/ 2018;26(3):319-325.
5. Glyn-Jones S, Palmer AJ, Agricola R, et al. Osteoarthritis. *Lancet*. Jul 25 2015;386(9991):376-387.
6. Tang X, Wang S, Zhan S, et al. The Prevalence of Symptomatic Knee Osteoarthritis in China: Results From the China Health and Retirement Longitudinal Study. *Arthritis & Rheumatology*. 2016;68(3):648-653.
7. Ausiello JC, Stafford RS. Trends in medication use for osteoarthritis treatment. *The Journal of rheumatology*. May 2002;29(5):999-1005.
8. Wegman A, van der Windt D, van Tulder M, Stalman W, de Vries T. Nonsteroidal antiinflammatory drugs or acetaminophen for osteoarthritis of the hip or knee? A systematic review of evidence and guidelines. *The Journal of rheumatology*. Feb 2004;31(2):344-354.
9. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med*. 2015;162(1):46-54.
10. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet*. 2017;390(10090):e21-e33.
11. Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society*. Apr 2010;18(4):476-499.
12. Newberry SJ, FitzGerald J, SooHoo NF, et al. Treatment of osteoarthritis of the knee: an update review. <https://effectivehealthcare.ahrq.gov/topics/osteoarthritis-knee-update/research-2017>. Accessed November 20, 2018.
13. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, Hawker GA, Henrotin Y, Hunter DJ, Kawaguchi H, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage*. 2014 Mar; 22(3):363-88.
14. Toupin April K, Bisailon J, Welch V, Maxwell LJ, Jüni P, Rutjes AW, Husni ME, Vincent J, El Hindi T, Wells GA, Tugwell P. Tramadol for osteoarthritis. *Cochrane Database Syst Rev*. 2019 May 27;5:CD005522. doi: 10.1002/14651858.CD005522.pub3.
15. Fidahic M, Jelcic Kadic A, Radic M, Puljak L. Celecoxib for rheumatoid arthritis. *Cochrane Database Syst Rev*. 2017 Jun 9;6:CD012095. doi: 10.1002/14651858.CD012095.pub2.

16. Quandt SA, Chen H, Grzywacz JG, Bell RA, Lang W, Arcury TA. Use of complementary and alternative medicine by persons with arthritis: results of the National Health Interview Survey. *Arthritis and rheumatism*. Oct 15 2005;53(5):748-755.
17. Park JE, Lee SS, Lee MS, Choi SM, Ernst E. Adverse events of moxibustion: a systematic review. *Complement Ther Med*. Oct 2010;18(5):215-223.
18. Hinman RS, McCrory P, Pirotta M, et al. Acupuncture for chronic knee pain: a randomized clinical trial. *JAMA*. Oct 1 2014;312(13):1313-1322.
19. Brosseau L, Welch V, Wells G, et al. Low level laser therapy (Classes I, II and III) for treating osteoarthritis. *The Cochrane database of systematic reviews*. 2004(3):CD002046.
20. Whittaker P. Laser acupuncture: past, present, and future. *Lasers in medical science*. 2004;19(2):69-80.
21. Ferreira RM, Duarte JA, Goncalves RS. Non-pharmacological and non-surgical interventions to manage patients with knee osteoarthritis: An umbrella review. *Acta Reumatol Port*. Jul-Sep 2018;43(3):182-200.
22. Wu F, Zhang H, Wang L, et al. Effects of CO₂ laser moxibustion on quality of life in patients with knee osteoarthritis: A double-blind randomized controlled trial. *Journal of Clinical Rehabilitative Tissue Engineering Research*. 2011;15(26):4885-4890.
23. Shen X, Zhao L, Ding G, et al. Effect of combined laser acupuncture on knee osteoarthritis: a pilot study. *Lasers in medical science*. Mar 2009;24(2):129-136.
24. Zhao L, Shen X, Cheng K, et al. Validating a nonacupoint sham control for laser treatment of knee osteoarthritis. *Photomedicine and laser surgery*. Jun 2010;28(3):351-356.
25. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis and rheumatism*. Aug 1986;29(8):1039-1049.
26. Cheng X. *Chinese Acupuncture and Moxibustion*. Beijing: Foreign Languages Press.; 1999.
27. Xie F, Li SC, Goeree R, et al. Validation of Chinese Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) in patients scheduled for total knee replacement. *Qual Life Res*. May 2008;17(4):595-601.
28. Symonds T, Hughes B, Liao S, Ang Q, Bellamy N. Validation of the Chinese Western Ontario and McMaster Universities Osteoarthritis Index in Patients From Mainland China With Osteoarthritis of the Knee. *Arthritis Care Res (Hoboken)*. Nov 2015;67(11):1553-1560.
29. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *The Journal of rheumatology*. Dec 1988;15(12):1833-1840.

30. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical care*. Jun 1992;30(6):473-483.
31. Brown MT, Murphy FT, Radin DM, Davignon I, Smith MD, West CR. Tanezumab reduces osteoarthritic knee pain: results of a randomized, double-blind, placebo-controlled phase III trial. *The journal of pain : official journal of the American Pain Society*. Aug 2012;13(8):790-798.
32. Spierings EL, Fidelholtz J, Wolfram G, Smith MD, Brown MT, West CR. A phase III placebo- and oxycodone-controlled study of tanezumab in adults with osteoarthritis pain of the hip or knee. *Pain*. Sep 2013;154(9):1603-1612.
33. Stengaard-Pedersen K, Ekesbo R, Karvonen AL, Lyster M. Celecoxib 200 mg q.d. is efficacious in the management of osteoarthritis of the knee or hip regardless of the time of dosing. *Rheumatology (Oxford)*. May 2004;43(5):592-595.
34. Scharf HP, Mansmann U, Streitberger K, et al. Acupuncture and knee osteoarthritis: a three-armed randomized trial. *Annals of internal medicine*. Jul 4 2006;145(1):12-20.
35. Wyszynska J, Bal-Bochenska M. Efficacy of High-Intensity Laser Therapy in Treating Knee Osteoarthritis: A First Systematic Review. *Photomed Laser Surg*. Jul 2018;36(7):343-353.
36. Stiglic-Rogoznica N, Stamenkovic D, Frlan-Vrgoc L, Avancini-Dobrovic V, Vrbanic TS. Analgesic effect of high intensity laser therapy in knee osteoarthritis. *Coll Antropol*. Sep 2011;35 Suppl 2:183-185.
37. Angelova A, Ilieva EM. Effectiveness of High Intensity Laser Therapy for Reduction of Pain in Knee Osteoarthritis. *Pain Res Manag*. 2016;2016:9163618.
38. Kheshie AR, Alayat MS, Ali MM. High-intensity versus low-level laser therapy in the treatment of patients with knee osteoarthritis: a randomized controlled trial. *Lasers Med Sci*. Jul 2014;29(4):1371-1376.
39. Hegedus B, Viharos L, Gervain M, Galfi M. The effect of low-level laser in knee osteoarthritis: a double-blind, randomized, placebo-controlled trial. *Photomed Laser Surg*. Aug 2009;27(4):577-584.
40. Huang Z, Chen J, Ma J, Shen B, Pei F, Kraus VB. Effectiveness of low-level laser therapy in patients with knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage*. Sep 2015;23(9):1437-1444.
41. Peng Q, Juzeniene A, Chen J, et al. Lasers in medicine. *Reports on Progress in Physics*. 2008;71:056701(056728pp).
42. Hsu YC, Chao HR, Shih SI. Human exposure to airborne aldehydes in Chinese medicine clinics during moxibustion therapy and its impact on risks to health. *J Environ Sci Health A Tox Hazard Subst Environ Eng*. 2015;50(3):260-271.
43. Mo F, Chi C, Guo M, Chu X, Li Y, Shen X. Characteristics of selected indoor air pollutants from moxibustion. *J Hazard Mater*. Apr 15 2014;270:53-60.
44. Berman BM, Lao L, Langenberg P, Lee WL, Gilpin AM, Hochberg MC. Effectiveness of acupuncture as adjunctive therapy in osteoarthritis of the knee: a randomized, controlled trial. *Annals of internal medicine*. Dec 21 2004;141(12):901-910.

45. Foster NE, Thomas E, Barlas P, et al. Acupuncture as an adjunct to exercise based physiotherapy for osteoarthritis of the knee: randomised controlled trial. *BMJ*. Sep 1 2007;335(7617):436.
46. Sangdee C, Teekachunhatean S, Sananpanich K, et al. Electroacupuncture versus diclofenac in symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. *BMC complementary and alternative medicine*. Mar 21 2002;2:3.
47. Williamson L, Wyatt MR, Yein K, Melton JT. Severe knee osteoarthritis: a randomized controlled trial of acupuncture, physiotherapy (supervised exercise) and standard management for patients awaiting knee replacement. *Rheumatology (Oxford)*. Sep 2007;46(9):1445-1449.
48. Soleimanpour H, Gahramani K, Taheri R, et al. The effect of low-level laser therapy on knee osteoarthritis: prospective, descriptive study. *Lasers Med Sci*. Sep 2014;29(5):1695-1700.
49. (WALT) WAoLT. Does Table 780- 860nm for Low Level Laser Therapy WALT 2010. 2010; http://waltza.co.za/wp-content/uploads/2012/08/Dose_table_780-860nm_for_Low_Level_Laser_Therapy_WALT.
50. (WALT) WAoLT. Dose Table 904nm for Low Level Laser Therapy WALT 2010. 2010; http://waltza.co.za/wp-content/uploads/2012/08/Dose_table_904nm_for_Low_Level_Laser_Therapy_WALT-2010.pdf.
51. Vilim V, Olejarova M, Machacek S, Gatterova J, Kraus VB, Pavelka K. Serum levels of cartilage oligomeric matrix protein (COMP) correlate with radiographic progression of knee osteoarthritis. *Osteoarthritis Cartilage*. Sep 2002;10(9):707-713.
52. Posey KL, Coustry F, Hecht JT. Cartilage oligomeric matrix protein: COMPopathies and beyond. *Matrix Biol*. Oct 2018;71-72:161-173.
53. Sharif M, Kirwan JR, Elson CJ, Granell R, Clarke S. Suggestion of nonlinear or phasic progression of knee osteoarthritis based on measurements of serum cartilage oligomeric matrix protein levels over five years. *Arthritis Rheum*. Aug 2004;50(8):2479-2488.

Tables

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)

^aCalculated 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 95% CI	Z Value	P Value
		n	Median (Q1, Q3)	95% CI	n	Median (Q1, Q3)	95% CI			
WOMAC	2	194	1.6 (0.3, 3.0)	1.3, 1.8	179	0.04 (-0.8, 0.9)	-0.1, 0.3	1.6 (1.2, 2.0)	-6.96	< 0.01*
Pain#	4	193	2.6 (1.0, 5.0)	2.2, 3.0	177	0.1 (-0.7, 1.5)	0, 0.6	2.2 (1.7, 2.8)	-8.38	< 0.01*
	8	192	3.1 (1.2, 5.4)	2.7, 3.6	174	-0.3 (-1.2, 1.5)	-0.6, 0	3.0 (2.5, 3.6)	-9.17	< 0.01*
	12	192	3.2 (1.2, 5.7)	2.5, 3.7	174	-0.4 (-1.5, 1.3)	-0.8, 0	3.2 (2.6, 3.8)	-9.18	< 0.01*
	24	191	2.9 (1.4, 5.9)	2.5, 3.8	173	-0.5 (-1.5, 1.6)	-0.8, 0.1	3.3 (2.7, 3.9)	-9.62	< 0.01*
WOMAC	2	194	5.9 (1.1, 13.2)	4.5, 6.4	179	-0.2 (-3.9, 4.7)	-1.3, 0.6	6.4 (4.6, 8.3)	-6.88	< 0.01*
Function&	4	193	11.4 (3.8, 22.1)	9.6, 15.0	177	0.9 (-2.6, 6.5)	0.2, 1.8	10.4 (8.0, 13.1)	-8.15	< 0.01*
	8	192	13.8 (5.2, 26.5)	10.3, 17.9	174	-1.7 (-6.9, 8.4)	-2.5, -0.1	14.0 (11.2, 17.1)	-9.11	< 0.01*
	12	192	15.4 (5.2, 25.6)	11.5, 17.7	174	-2.5 (-7.8, 6.0)	-3.5, -0.8	15.9 (12.9, 18.9)	-9.90	= 0.004*
	24	191	14.8 (5.1, 26.6)	12.0, 18.3	173	-1.2 (-6.0, 7.5)	-3.2, 0.2	15.7 (12.8, 18.8)	-10.01	< 0.01*
WOMAC	2	194	1.7 (0, 4.0)	1.1, 2.3	179	0 (-0.7, 1.3)	0, 0.3	1.9 (1.3, 2.5)	-6.05	< 0.01*
Stiffness^	4	193	2.5 (0, 5.8)	2.0, 3.3	177	0.1 (-0.8, 1.8)	0, 0.4	2.7 (1.9, 3.5)	-6.15	< 0.01*
	8	192	3.0 (0, 6.7)	2.1, 4.0	174	0 (-1.6, 1.7)	-0.2, 0.1	3.6 (2.8, 4.5)	-7.48	< 0.01*
	12	192	3.0 (0, 6.5)	2.2, 4.4	174	0 (-1.6, 2.0)	-0.3, 0.3	3.6 (2.7, 4.5)	-7.15	< 0.01*
	24	191	3.6 (0, 6.7)	2.0, 4.5	173	-0.1 (-2, 1.9)	-0.5, 0	4.0 (3.0, 4.9)	-7.99	< 0.01*
VAS	2	194	17.0 (6.0, 26.5)	14.5, 18.8	179	3.0 (-4.0, 12.5)	1.0, 5.0	11.5 (9.0, 14.5)	-7.88	<0.01*
	4	193	29.5 (17.5, 41.5)	25.5, 31.8	177	5.5(-0.8, 20.0)	3.3, 8.0	19.5 (15.5, 23.0)	-8.97	<0.01*
	8	192	32.5 (21.5, 44.5)	30.0, 37.0	174	6.0 (-3.0, 20.0)	3.5, 10.0	24.5 (20.5, 28.5)	-10.19	<0.01*
	12	192	34.0 (22.5, 45.0)	30.0, 37.0	174	4.0 (-3.5, 15.3)	1.5, 8.3	26.5 (23.0, 30.0)	-10.77	<0.01*
	24	191	35.0 (23.0, 45.0)	30.5, 37.5	173	5.0 (-5.0, 20.0)	1.0, 9.0	27.5 (23.5, 31.0)	-11.24	<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)	55.0, 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, 70.0	5.0 (0, 10)	-2.817	0.005*
	Week 12	192	75.0 (60.0,90.0)	70.0, 80.0	174	70.0 (55,75)	65.0, 70.0	10.0 (5.0, 15.0)	-4.326	<0.001*
	Week 24	191	75.0 (60.0,90.0)	75.0, 80.0	173	70.0 (55,77.5)	65.0, 70.0	10.0 (5.0, 10.0)	-4.386	<0.001*
RP (Role- Physical)	Before	201	0 (0,75.0)	0, 25.0	191	0 (0,75.0)	0, 25.0	0 (0, 0)	-0.381	0.703
	Week 4	193	50.0 (0,100.0)	50.0, 50.0	177	25.0 (0,100.0)	0, 25.0	0 (0, 25.0)	-3.335	0.001*
	Week 12	192	75.0 (0,100.0)	50.0, 75.0	174	0 (0,75.0)	0, 0	25.0 (0, 50.0)	-6.157	<0.001*
	Week 24	191	75.0 (25,100.0)	50.0,75.0	173	0 (0,75.0)	0, 25.0	25.0 (0, 25.0)	-5.413	<0.001*
BP (Body Pain)	Before	201	58.0 (45.0,68.0)	55.0, 68.0	191	58.0 (45.0,68.0)	55.0, 68.0	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)	-3.445	0.001*
	Week 12	192	68.0 (58.0,78.0)	68.0, 68.0	174	58.0 (45.0,68.0)	55.0, 68.0	10.0 (8.0, 12.0)	-4.955	<0.001*
	Week 24	191	68.0 (58.0,78.0)	68.0, 68.0	173	58.0 (45.0,68.0)	58.0, 68.0	10.0 (10.0, 12.0)	-5.191	<0.001*
GH (General Health)	Before	201	45.0 (35.0,60.0)	45.0, 50.0	191	50.0 (40.0,62.0)	45.0, 50.0	0 (-5.0, 2.0)	-7.676	0.443
	Week 4	193	50.0 (40.0,65.0)	45.0, 55.0	177	45.0 (40.0,60.0)	45.0, 50.0	2.0 (0, 5.0)	-1.296	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)	-2.112	0.035*
	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)	-2.255	0.024*
VT (Vitality)	Before	201	55.0 (40.0,65.0)	50.0, 55.0	191	55.0 (40.0,70.0)	52.5, 60.0	-5.0 (-5.0, 0)	-1.306	0.191
	Week 4	193	60.0 (50.0,70.0)	55.0, 60.0	177	55.0 (40.0,70.0)	50.0, 60.0	5.0 (0, 5.0)	-1.642	0.101
	Week 12	192	60.0 (50.0,70.0)	60.0, 65.0	174	55.0 (45.0,65.0)	50.0, 60.0	5.0 (0, 10.0)	-3.017	0.003*
	Week 24	191	60.0 (50.0,70.0)	55.0, 65.0	173	55.0 (42.5,70)	55.0, 60.0	5.0 (0, 5.0)	-1.846	0.065
SF (Social Functioning)	Before	201	75.0 (63.0,88.0)	75.0, 75.0	191	75.0 (56.5,88.0)	69.2, 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 (63.0,88.0)	63.0, 75.0	0 (0, 12.0)	-2.458	0.014*
	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)	-3.491	<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)	-3.372	0.001*
RE (Role- Emotional)	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
	Week 4	193	100.0 (33.0,100.0)	100.0,100.0	177	100.0(16.5,100.0)	67.0,100.0	0 (0, 0)	-2.025	0.043*

MH (Mental Health)	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)	-4.557	<0.001*
	Week 24	191	100.0 (100.0,100.0)	100.0, 100.0	173	100.0 (0, 100.0)	100.0, 100.0	0 (0, 0)	-3.962	<0.001*
	Before	201	68.0 (56.0,80.0)	64.0, 72.0	191	68.0 (60.0, 76.0)	68.0, 72.0	0 (-4.0, 4.0)	-0.099	0.921
	Week 4	193	72.0 (60.0,80.0)	68.0, 76.0	177	68.0 (60.0, 80.0)	68.0, 72.0	4.0 (0, 4.0)	-1.569	0.117
	Week 12	192	68.0 (60.0,80.0)	68.0, 72.0	174	64.0 (60.0, 76.0)	64.0, 68.0	4.0 (0, 4.0)	-1.615	0.106
	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)	-1.007	0.314
	Before	201	35.8(29.5,42.9)	33.7, 37.3	191	37.2 (31.3, 43.1)	34.2, 38.5	-0.8 (-2.7, 1.0)	-0.881	0.378
	Week 4	193	41.7 (33.5,47.6)	38.9, 43.1	177	37.6 (31.2, 45.0)	36.7, 39.1	3.0 (1.1, 4.9)	-3.042	0.002*
	Week 12	192	44.7 (35.7,50.0)	42.2, 46.1	174	37.9 (31.8, 43.3)	36.3, 39.4	5.3 (3.4, 7.2)	-5.096	<0.001*
	Week 24	191	44.9 (36.4,50.3)	43.1, 46.9	173	38.5 (31.6, 45.2)	36.7, 40.3	5.1 (3.2, 7.0)	-5.060	<0.001*
SF36MCS	Before	201	51.4 (41.6,56.7)	49.7, 53.0	191	50.0 (39.8, 56.8)	48.7, 53.9	0.6 (-1.4, 2.6)	-0.570	0.568
	Week 4	193	50.7 (44.1,57.1)	49.0, 52.6	177	50.7 (42.4,55.9)	49.1,52.4	1.1 (-0.8, 2.9)	-1.126	0.260
	Week 12	192	50.7 (46.0,55.6)	48.9, 52.0	174	49.6 (39.1,55.2)	47.0, 51.0	2.0 (0.1, 3.9)	-2.064	0.039*
	Week 24	191	50.8 (45.6,55.7)	48.7, 52.4	173	50.4 (39.5,55.6)	47.4,5 2.3	1.3 (-0.6, 3.2)	-1.350	0.177

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

Adverse events	LM group (n=261)	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%)

Figures

Figure 1

flow chart