ISRCTN10047986 https://doi.org/10.1186/ISRCTN10047986

Pain-relieving plaster for the treatment of knee osteoarthritis: a multi-center, randomized, positive drug parallel-controlled clinical trial

Submission date
18/09/2024

Recruitment status
Recruiting

Registration date
27/09/2024

Overall study status
Ongoing

Last Edited
29/11/2024

Condition category
Musculoskeletal Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Knee osteoarthritis (KOA) is a chronic degenerative joint disease clinically manifested by knee pain, swelling, malformation, and limited mobility. Currently, non-surgical therapies are the first-line treatment for most patients with mild to moderate KOA, effectively alleviating pain symptoms and improving functional activities. These therapies include oral administration of acetaminophen, topical application of nonsteroidal anti-inflammatory drugs, or intra-articular injection of corticosteroids and hyaluronic acid. Pain-Relieving Plaster is a topical Tibetan medicinal plaster primarily composed of herbs such as Lamiophlomis rotate and Curcuma longa, with anti-inflammatory, blood circulation-improving, multi-target analgesic, and tissue damage repair-promoting effects. Previous clinical studies have suggested the potential positive effects of Pain-Relieving Plaster in treating KOA. The objectives of this study are to investigate and explore the efficacy and safety of Pain-Relieving Plaster in treating KOA.

Who can participate?
Patients aged between 40 and 75 years with KOA

What does the study involve?
This is an interventional study where participants will be randomly assigned to two groups in a 1:1 ratio: the experimental group and the control group. Both participants and researchers cannot preselect the group assignment. The experimental group will use Pain-Relieving Plaster (applied for 8 hours per patch, one patch per morning), while the control group will use Flurbiprofen Cataplasms (applied for 8 hours per patch, one patch in the morning and one before bedtime). The study will evaluate the effectiveness of the interventions using clinical scoring, health-related quality of life, knee circumference, and knee range of motion. Safety will be evaluated using laboratory test results, records of adverse events, and records of the severity of local skin reactions at the application site. Additionally, evaluations of patient compliance, application status, concomitant medications, and emergency management will be conducted.

What are the possible benefits and risks of participating?
Participating in this study may lead to an improvement in the participant's condition, and they

will receive attentive medical care. Their participation may help doctors gain more insights into KAO, Pain-Relieving Plaster, and Flurbiprofen Cataplasms, potentially benefiting future patients with the same or similar conditions.

Known adverse reactions of Pain-Relieving Plaster identified in previous studies and clinical applications include:
1. According to the product instructions, patients with an allergic constitution may experience allergic reactions to the adhesive tape or drug-contact itching, and even develop redness, swelling, or blisters.
2. Based on literature research results and surveys of clinicians and patients, Pain-Relieving Plaster does not have systemic adverse reactions; occasional local skin adverse reactions are mainly irritant contact dermatitis, including local itching, erythema, and papules, with rare occurrences of local blisters, pigmentation, and skin ulceration. The majority of adverse reactions occur at sites where the adhesive tape directly contacts the skin, possibly related to skin irritation caused by the tape.

Adverse reactions identified in similar drugs include:
1. Allergic reactions
2. Skin damage
3. Drug irritation

Known adverse reactions of Flurbiprofen Cataplasms identified in previous studies and clinical applications include:
1. Severe adverse reactions can induce asthma (aspirin-induced asthma): As it may induce asthma (frequency unknown), use should be discontinued if initial symptoms such as respiratory abnormalities or dyspnea occur. Furthermore, asthma induced by this product may appear several hours after application.
2. Other adverse skin reactions include itching (1.16%), redness (1.12%), rash (0.1% to less than 5%), macules, pain, etc., each occurring at a frequency of 0.1% or less.

Where is the study run from?
Peking Union Medical College Hospital, China

When is the study starting and how long is it expected to run for?
August 2024 to September 2026

Who is funding the study?
Tibet Cheezheng Tibetan Medicine Co., Ltd. (China)

Who is the main contact?
Prof. Jianping Liu, liujp@bucm.edu.cn

Contact information

Type(s)
Public, Principal Investigator

Contact name
Prof Xisheng Weng

Contact details

Peking Union Medical College Hospital, No.1 Shuaifuyuan, Dongcheng District
Beijing
China
100730
+86 010 - 69152712
drwengxsh@163.com

Type(s)
Scientific

Contact name
Prof Jianping Liu

ORCID ID
http://orcid.org/0000-0002-0320-061X

Contact details
Centre for Evidence-Based Chinese Medicine
Beijing University of Chinese Medicine
No. 11 Bei San Huan Dong Lu
Chaoyang District
Beijing
China
100029
+86 (0)10 64286760
liujp@bucm.edu.cn

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
20240605V1.0

Study information

Scientific Title
Pain-relieving plaster versus flurbiprofen cataplasms in terms of pain, stiffness, functional activities, joint swelling, quality of life, and safety for knee osteoarthritis treatment: a multi-center, randomized, controlled, non-inferiority clinical trial.

Acronym
PEP

Study objectives
In terms of alleviating pain and stiffness, improving functional activities, reducing joint swelling, and enhancing quality of life, and safety, Pain-Relieving Plasters are not inferior to Flurbiprofen Cataplasms.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 05/08/2024, Ethics Review Committee of the Chinese Academy of Medical Sciences and Peking Union Medical College Hospital (No.1 Shuaifuyuan, Dongcheng District, Beijing, Beijing, 100730, China; +86 010-69156874; pumchkyc@126.com), ref: I-24PJ1637

Study design
Multicenter randomized active-controlled non-inferiority trial design

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Home, Hospital, Medical and other records

Study type(s)
Quality of life, Treatment, Safety, Efficacy

Participant information sheet
No participant information sheet available

Health condition(s) or problem(s) studied
Knee osteoarthritis

Interventions
Professional statisticians will use SAS software to generate a random number sequence and its "central code assignment" (to specify the range of treatment codes assigned to each research center) according to the blocked randomization method. Within each center, subjects will be assigned a subject number based on the chronological order of their entry into the study (determined by the random number sequence and its "central code assignment"), that is, subjects with knee osteoarthritis are randomly assigned to the experimental group (pain-relieving plaster) and the control group (Flurbiprofen Cataplasms) in a 1:1 ratio.

Allocation concealment will be achieved using sequentially coded, sealed, opaque envelopes. Personnel unrelated to the study will be responsible for allocating and packaging the study medications. Clinicians recruited subjects, and those who met the inclusion criteria and did not meet any of the exclusion criteria will be given the corresponding medication by dedicated researchers after signing the informed consent form.

Before treatment, the patient's basic information will be recorded, and a physical examination, blood routine test, and urine routine test will be conducted. Women of childbearing age will

undergo a blood pregnancy test to rule out pregnancy. Liver function tests (including ALT, AST, ALP, TBIL, γ-GT) and renal function tests (including Scr) will be performed, as well as anteroposterior X-ray examination of the knee joint. Additionally, physicians will inquire about the patient's symptoms based on the questionnaire form for primary and secondary symptoms in Traditional Chinese Medicine (TCM). Subsequently, a physician with a deputy senior professional title or with over ten years of experience in TCM will uniformly conduct TCM syndrome differentiation and typing for the patients. The Central Sensitization Inventory-9 (CSI-9) will be recorded. Record the scales for expected treatment effects and expected side effects.

Experimental group: pain-relieving plaster.
Usage and Dosage: Select the most painful area around the patient's knee joint (Ashi point) or the medial and lateral knee-eye points (EX-LE5) (surface location: located on the extensor surface of the knee joint, in the depression on both sides of the patellar ligament, the medial knee-eye point is called the inner knee-eye point, and the lateral one is called the outer knee-eye point) as the application points. Remove the plastic film, evenly apply the wetting agent in the small bag to the surface of the medicine core bag, and then directly apply it to the selected application points after wetting, pressing the surrounding adhesive tape. Each plaster is applied for 8 hours, one plaster in the morning every day, with a treatment course of 1 week.

Control group: Flurbiprofen Cataplasms.
Usage and Dosage: The selection method of the application site for the control group is the same as that for the experimental group. Remove the plastic film and directly apply the plaster to the selected application points. Each plaster is applied for 8 hours, one plaster in the morning and one before bedtime every day, with a treatment course of 1 week.

Intervention Type
Device

Pharmaceutical study type(s)
Not Applicable

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Pain-Relieving Plaster

Primary outcome measure
Pain is measured using the pain dimension of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score scale (5 items, totaling 500 points) at baseline, and at weeks 1, 2, and 3

Secondary outcome measures
1. Joint stiffness symptoms and function measured using the stiffness and joint functional dimension of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score at baseline, and weeks 1, 2, and 3
2. Quality of life measured using the EuroQol 5-dimension questionnaire (EQ-5D-5L) at baseline, and weeks 1, 2, and 3
3. Degree of knee joint swelling measured using the circumference of the knee joint at baseline, and weeks 1, 2, and 3
4. Functional mobility of the knee joint measured using the knee joint range of motion assessed

by a wearable joint range of motion measurement device at baseline, and weeks 1, 2, and 3
5. Safety measured using the laboratory test results (including blood routine, urine routine, and liver and kidney function) at baseline, and weeks 1
6. Safety measured using the adverse event records at weeks 1, 2, and 3
7. Safety measured using the severity of local skin reactions at the application site (assessed by 4 level scale, symptoms include itching, pain, burning sensation, erythema, papules, and blisters) at week 1
8. Patient compliance measured using the drug counting method and follow-up rate method at weeks 1, 2, and 3
9. Application status measured using application time, application quantity, detachment of the plaster, and medication experience at week 1
10. Application status measured using whether to use other treatment methods, and whether to engage in vigorous activities at weeks 1, 2, and 3

Overall study start date
01/08/2024

Completion date
01/09/2026

Eligibility

Key inclusion criteria
1. Meet the diagnostic criteria for knee osteoarthritis established by the American College of Rheumatology in 1995 (either single or both knees)
2. Age between 40 and 75 years old
3. Experience recurrent knee pain for more than 1 month
4. Kellgren-Lawrence grading scale (K-L grading): Grade II or III
5. Have at least one item with a VAS score ≥40mm among the five items of the WOMAC pain score for the study knee, and all items of the pain score for the contralateral knee osteoarthritis are <40mm
6. Provide informed consent, voluntarily participate in the study, and sign the informed consent form

Participant type(s)
Patient

Age group
Mixed

Lower age limit
40 Years

Upper age limit
75 Years

Sex
Both

Target number of participants

440 participants (220 in each group)

Total final enrolment
440

Key exclusion criteria
1. Subjects with clear surgical indications and unsuitable for conservative treatment
2. Subjects with other inflammatory pain diseases in the knee joint, such as rheumatoid arthritis, psoriatic arthritis, gout, villonodular synovitis, septic arthritis, tuberculous arthritis, or osteoarthritis caused by osteomyelitis, bone tumors, and bone tuberculosis. Or those who have undergone joint replacement surgery
3. Subjects allergic to the main components of the test drug, as well as those who have previously experienced skin allergies after using external medications
4. Subjects with skin diseases at and around the application site
5. Subjects with liver function abnormalities, specifically ALT Alanine Aminotransferase. and AST Aspartate Aminotransferase. levels exceeding twice the upper limit of normal, and renal function abnormalities, specifically Scr Serum Creatinine. levels exceeding 1.5 times the upper limit of normal, or subjects deemed by the researcher to have severe primary diseases that preclude their participation in the study. This includes patients with malignant tumors, infectious diseases, and mental illnesses.
6. Subjects who have taken non-steroidal anti-inflammatory drugs orally within 1 week before the screening period, oral hormonal drugs within 1 month, received intra-articular injection therapy within 3 months, undergone joint surgery within 1 year, or experienced a definite knee injury or open injury within 6 months
7. Women who have a positive blood pregnancy test result during the screening before enrollment; pregnant or lactating women
8. Subjects who, according to the researcher's judgment, have a low probability of enrollment or other circumstances that complicate enrollment, such as those with frequently changing work environments or frequent business trips, which may easily lead to loss of follow-up
9. Subjects who have used Chinese medicine therapies with therapeutic effects on knee osteoarthritis, such as infrared irradiation, cupping, acupuncture, proprietary Chinese medicines, or those participating in other clinical studies

Date of first enrolment
01/10/2024

Date of final enrolment
01/09/2026

Locations

Countries of recruitment
China

Study participating centre
Peking Union Medical College Hospital, Chinese Academy of Medical Sciences
No.1 Shuaifuyuan, Dongcheng District

Beijing
China
100730

Study participating centre
Beijing Friendship Hospital Affiliated to Capital Medical University
No. 95 Yong'an Road, Xicheng District
Beijing
China
100050

Study participating centre
Qilu Hospital of Shandong University
No. 107 Wenhua Xi Road, Jinan
Shandong
China
250012

Study participating centre
China-Japan Friendship Hospital
No. 2 Yinghuayuan Dongjie, Chaoyang District
Beijing
China
100029

Study participating centre
Shu Guang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine
No. 528 Zhangheng Road, Pudong New Area
Shanghai
China
201203

Study participating centre
The Second Hospital of Lanzhou University
No. 82 Cuiyingmen, Chengguan District, Lanzhou City
Gansu
China
730030

Study participating centre
Liuzhou People's Hospital
No. 8 Wenchang Road, Chengzhong District, Liuzhou City
Guangxi
China
545006

Sponsor information

Organisation
Peking Union Medical College Hospital

Sponsor details
No.1 Shuaifuyuan, Dongcheng District
Beijing
China
100730
+86 010-69151188
pumchkyc@126.com

Sponsor type
Hospital/treatment centre

Website
https://www.pumch.cn/index.html

ROR
https://ror.org/04jztag35

Funder(s)

Funder type
Industry

Funder Name
Tibet Cheezheng Tibetan Medicine Co., Ltd.

Results and Publications

Publication and dissemination plan
1. The study protocol will be submitted to a peer-reviewed journal.
2. The results will be submitted to a peer-reviewed journal.

Intention to publish date
01/09/2027

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date