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Duloxetine combined with intra-articular injection versus intra-articular injection alone for pain relief in knee osteoarthritis: a study protocol for a randomised controlled trial

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ABSTRACT

Introduction Intra-articular (IA) injection of hyaluronic acid (HA) and corticosteroid (CS) is a common treatment for osteoarthritis (OA) of the knee. As a drug treatment for patients with depression, duloxetine has been shown in many studies to effectively relieve the pain of OA and improve function of the knee joint. However, evidence regarding the efficacy of IA injection of HA+CS combined with duloxetine for pain management in patients with OA of the knee is lacking. The aim of this study was to test the hypothesis that IA injection of HA+CS combined with duloxetine could achieve pain management superior to that of IA injection of HA+CS alone in patients experiencing knee OA pain.

Methods This study will adopt a prospective, randomised, open-label blind endpoint study design. In total, 150 patients with OA of the knee will be enrolled in the study. The participants will be randomly allocated to receive either a single IA injection of HA+CS combined with duloxetine or a single IA injection of HA+CS alone, and both groups will complete a 24-week follow-up to assess pain and functional improvements. The primary outcome measure is the change in the weekly mean of the 24 hours average pain scores from baseline to the end of 24 weeks in patients with OA of the knee, and the secondary outcomes include the response to treatment, changes from baseline in the brief pain inventory, improvement in the Western Ontario and McMaster Universities Osteoarthritis index scores, patient global impression of improvement scale, Hospital Anxiety and Depression Scale and adverse events during the 24-week follow-up. The data will be analysed by the intention-to-treat principle.

Ethics approval and dissemination This study was approved by the institutional ethics committee of the Beijing Tiantan Hospital (approval number: KY 2019-086-02). The results of the study will be published in peer-reviewed journals, and the findings will be presented at scientific meetings.

Trial registration number ClinicalTrials.gov Identifier: NCT04117893; Pre-results.

Strengths and limitations of this study

- To the best of our knowledge, this study will be the first investigation to compare the efficacy of intra-articular (hyaluronic acid+corticosteroid) alone and combined with duloxetine for the management of pain in patients with knee osteoarthritis (OA).
- This study may provide a new treatment strategy and enrich the knowledge base of the research field of combined therapies for OA of the knee.
- This trial will be conducted using rigorous methods, including a prospective,randomised, open-label blind endpoint design, the implementation of interventions using clearly prespecified approaches and the blinding of the assessors of outcomes, to increase the accuracy of the outcomes.
- This study is a single-centre trial, which could be a limitation.
- Patients receiving oral placebo as a control group were not included in our study design because of limited funding.

INTRODUCTION

Osteoarthritis (OA) is an increasingly common degenerative joint disease worldwide due to the ageing population and increase in obesity.[1–3] This disease mainly occurs in the older population and affects approximately 15% of adults older than 45 years and approximately 50% of those older than 75 years.[4] All joints can be affected, especially weight-bearing joints, such as the knee.[5] The symptoms include pain, movement limitation and functional impairment, rendering OA a leading cause of disability in the older population.[6 7] With the ageing of the population and increasing prevalence of obesity, OA of the knee has a significant negative impact from a socioeconomic perspective, including substantial healthcare costs and loss of productivity.[8 9] Therefore, it is essential to develop effective treatments that can relieve symptoms, slow disease progression and consequently reduce healthcare resource needs.[3]

Disability due to OA of the knee is more closely related to the level of pain experienced by the patient than the radiographical severity of the disease.[10] Consequently, the management of OA of the knee should focus on pain reduction to improve functionality. To manage chronic pain due to OA, the current treatment guidelines recommend a combination of pharmacological and non-pharmacological therapies, which are often applied using a multimodal approach.[11 12] Pharmacological therapies can be summarised as oral paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and drugs for slowing the progression of the disease (glucosamine and chondroitin sulfate). However, many of the above treatments, particularly NSAIDs and opioids, are associated with significant safety risks.[13]

In addition to oral medication, treatments include topical NSAIDs, intra-articular (IA) hyaluronic acid (HA), IA corticosteroids (CS) and so on. IA injection is the preferred effective non-surgical modality.[14 15] IA injection treatments have fewer systemic adverse events (AEs), and depositing the medication inside the joint has a more direct effect, especially in older patients and those at a greater risk for NSAID-induced AEs.[16 17] HA has been proposed to reduce pain through several mechanisms of action, including the restoration of the viscoelastic properties of the synovial fluid and reductions in friction within the joint.[18] CS have both anti-inflammatory and immunosuppressive effects that affect protein expression, inhibit the expression of pro-inflammatory proteins and enhance the expression of anti-inflammatory proteins within the structures of the knee.[19] IA injections of CS and HA individually demonstrate efficacy in patients with severe OA.[20] CS provide shorter term pain relief than HA, which provides longer term pain relief with the onset of pain reduction occurring over several weeks.[21 22] The combination of CS+HA for the management of OA of the knee may provide superior improvement in symptomatic relief for patients who are candidates for IA therapy.[23 24] However, recent studies have shown adverse effects on cartilage and joints, and acceleration of OA progression following repeated injections of triamcinolone acetonide (TA) administered over an extended period.[25 26] Infection, post-injection flare, crystal-induced synovitis, tendinopathy, steroid arthropathy and systemic hyperglycaemia were noted as complications after repeated IA injections of CS.[27 28] Therefore, further studies are needed to identify a new strategy to reduce the frequency of IA injections to potentially lower the incidence of adverse reactions.

Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, has been demonstrated to have a centrally acting analgesic effect in addition to its antidepressant properties.[29 30] Several studies have reported a significant improvement in pain in patients with OA of the knee treated with duloxetine compared with placebo.[5 13 31] Duloxetine is effective and well tolerated without severe or life-threatening events in patients with OA.[13 32] However, to date, no study has investigated the benefits of IA injections of CS+HA combined with oral duloxetine in patients with OA of the knee.

Based on the current literature, we hypothesise that compared with IA injection of CS and HA alone in the knee, IA injection of CS+HA combined with oral duloxetine could further relieve pain and improve the physical function and quality of life of patients with OA of the knee. Thus, this prospective, randomised, controlled study is proposed to optimise the current treatment scheme.

METHODS

Trial design

This prospective, randomised, open-label blind endpoint (PROBE) study is designed to compare the efficacy and safety of IA injection of either HA+CS combined with oral duloxetine (experimental group) or HA+CS (control group) alone for patients with OA of the knee. All OA of the knee participants will be randomly assigned to the experimental group or the control group at a 1:1 ratio (figure 1). The investigation will be performed at Beijing Tiantan Hospital Affiliated with Capital Medical University from October 2020 to December 2022. The study plan has been approved by the Ethics Committee of Beijing Tiantan Hospital (KY 2019-086-02). This study is in accordance with the World Medical Association's Declaration of Helsinki. All patients will sign written informed consent to participate in the study, and all participants will have sufficient time to decide whether to participate in this study. The patients who participate in the study will have the right to obtain the relevant information and will be allowed to withdraw their consent or discontinue participation without restrictions at any time point during the study. The confidentiality of the participant records will be protected.

Objectives

The purpose of the IA (HA+CS) combined with duloxetine versus the IA (HA+CS) alone trial is to determine whether the efficacy of duloxetine combined with IA (HA+CS) is superior to that of conventional IA (HA+CS) alone in the treatment of knee OA pain in patients who are candidates for IA therapy.

Patient population

Eligibility criteria

The patients must meet all following criteria to be eligible:

- Male and female outpatients aged 50 to 75 years who meet the American College of Rheumatology clinical and radiographical criteria for the diagnosis of OA of the knee with knee pain (pain for ≥14 days per month for ≥3 months before the study entry with a mean score ≥4 on the 24 hours average pain score (0 to 10) using the average of daily ratings before the trial[33]).
- Body mass index (BMI) <40 kg/m^2.
- Radiographical criteria including Kellgren-Lawrence grades II to III.

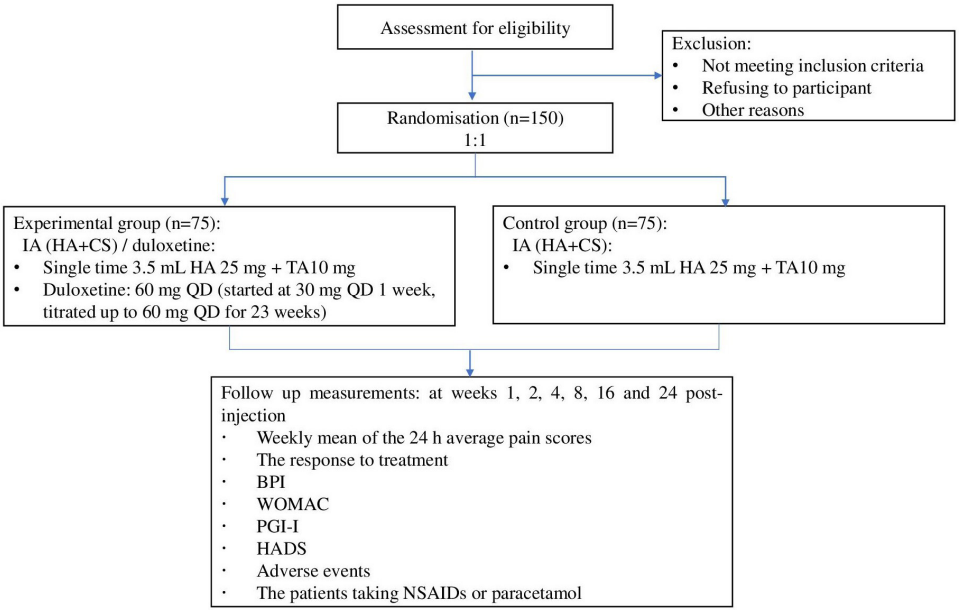

Figure 1 Trial design of the treatment for knee osteoarthritis. BPI, brief pain inventory; CS, corticosteroids; HA, hyaluronic acid; HADS, hospital anxiety and depression scale; IA, intra-articular; NSAID, non-steroidal anti-inflammatory drug; PGI-I, patient global impression of improvement scale; QD, once per day; TA, triamcinolone acetonide; WOMAC, western Ontario and McMaster universities osteoarthritis index.

- Knee stability, no deformity and no lumbar spondylosis with radiculopathy.
- Good cognition, the ability to understand the study protocol and willingness to participate.

Subjects with one or more of the following conditions will be excluded:

- Inflammatory arthritis, autoimmune disorder, septic arthritis or any other concomitant disease (such as liver and kidney disease).
- Prior synovial fluid analysis indicative of a diagnosis other than OA.
- Contraindications to duloxetine (current use of monoamine oxidase inhibitors or poorly controlled angle-closure glaucoma), previous exposure to duloxetine, concurrent use of other drugs acting on the central nervous system (such as benzodiazepines) and allergy to any medications used in this study.
- Metabolic diseases or anticoagulation therapy.
- History of invasive therapies to the knee during the past 6 months, joint replacement of the knee at any time or current infection in the affected limb.

Randomisation and blinding

The randomisation will be performed by permuted blocks. The allocation sequence will be generated by an independent researcher before the inclusion of the first participant.[34] After randomisation, all patients will be randomly assigned to the experimental group IA (HA+CS) combined with oral duloxetine or control group (IA (HA+CS)) in a distribution ratio of 1:1. One assessor will be responsible for the pre-trial evaluation of eligibility, and another assessor will be responsible for the post-intervention evaluation. To ensure that the blinding is maintained, the patients will be given clear instructions not to disclose the treatment they have been randomised to receive while being interviewed by the blind assessors. Information regarding the treatment allocation will be stored in a secure locker in the case emergency unblinding is needed.

Intervention

All included patients will be allocated to one of the following two study groups. The patients in the experimental group will receive a single 3.5 mL IA injection of HA+CS (25 mg of HA (Artz Dispo, Seikagaku Co, Tokyo, Japan) plus 10 mg of TA and oral duloxetine (Cymbalta; Eli Lilly and Co, Indiana, USA). The patients in the control group will receive only a 3.5 mL IA injection of HA+CS (25 mg of HA plus 10 mg of TA). These two groups will receive non-cross-linked (native) avian-derived HA with a molecular weight of 0.8 Md. In this study, HA is produced by Artz that has been available on the Chinese market since 1997. The patients will agree to maintain their usual activity level throughout the course of the study.

The patients in the experimental group assigned to receive duloxetine 60 mg once per day will start with duloxetine 30 mg once per day for 1 week and then titrate up to duloxetine 60 mg once per day for 23 weeks. The patients will be instructed to take the medication with meals. At the end of the 24-week treatment phase, the patients will enter a 1-week dose-tapering phase, followed by an observational phase of 1 week to minimise discontinuation-emergent AEs. Patients who discontinue the study early must contact the investigator to obtain discontinuation advice and will be entered into a 2-week taper phase if they received the duloxetine treatment for at least 2 weeks.

All procedures will be performed in an outpatient clinic. The injection will be performed by a physician who has experience with >500 cases of knee joint injections or aspirations per year. The patients will rest in the supine position. The knee will be flexed at approximately 60° and prepared under sterile conditions; 1 mL of 2% lidocaine hydrochloride with 1:80 000 epinephrine will be injected into the skin and subcutaneous tissue at the lateral soft spot of the knee joint just inferior to the lower pole of the patella with a 27-gauge needle for patient comfort. A 21-gauge needle (0.8·50 mm) will then be inserted through the same area into the joint capsule. The injection will be performed using the inferolateral approach under ultrasound guidance. The accuracy of the injection will be assessed by an unobstructed injection of 1 mL of air into the knee joint. If effusion is present, it will be aspirated into a separate syringe. The same needle will be left in place, and then, a syringe prefilled with the HA and TA mixture will be inserted to administer the injection. Patients will be treated and closely monitored if a severe reaction to the injections occurs or if there is evidence of an active infection in the injected joint at any point throughout the study period.

If the treatment effect is not satisfactory, the patients will be allowed to use concomitant rescue medication, including paracetamol and NSAIDs (all other pain medications will be excluded), to avoid increasing the dose of duloxetine. No pain medication will be allowed within the 48 hours before each assessment to avoid masking the symptoms of pain. All patients will receive a chart to record the number of analgesics taken daily and the use of rescue treatment during the previous weeks at each study visit.

The safety of treatment will be assessed during the study. The decision to continue treatment, continue after adjusting treatment or end the trial will be made according to the available data including the risk-benefit evaluation. The trial will be continued if the patients are satisfied with clinical outcome. If patients are unable to adhere to oral duloxetine due to side effects, the treatment plan will be modified. The dosage of duloxetine will be decreased, and analgesics will be used according to the outcome of pain evaluation. The trial will be terminated in case of complication such as infection of the knee joint or serious side effects (eg, allergy) caused by duloxetine.

Outcome measures

Baseline data

The pre-enrolment information, including age (years), gender (male or female), height, weight, BMI, pre-existing pain and duration, baseline weekly mean of the 24 hours average pain scores, Kellgren-Lawrence grade, presence of depression or anxiety, and the percentage of analgesic use preceding study entry, will be collected. The schedule of measurements is presented in table 1.

Table 1 Measurements to be taken at each point in the trial

	Enrolment	Allocation	Post allocation					
Time point	**Pre-injection**	**Day 0**	**1 week**	**2 weeks**	**4 weeks**	**8 weeks**	**16 weeks**	**24 weeks**
Enrolment:								
Eligibility screening	X							
Informed consent	X							
Allocation		X						
Interventions:								
IA (HA+CS)/duloxetine		X						
IA (HA+CS)		X						
Assessments:								
Baseline variables	X							
Weekly mean of the 24 hours average pain scores	X		X	X	X	X	X	X
Response to treatment			X	X	X	X	X	X
BPI	X		X	X	X	X	X	X
WOMAC	X		X	X	X	X	X	X
PGI-I				X	X	X	X	X
HADS	X			X	X	X	X	X
Occurrence of AEs		X	X	X	X	X	X	X
Concomitant medication use	X	X	X	X	X	X	X	X

AEs, adverse events; BPI, brief pain inventory; CS, corticosteroids; HA, hyaluronic acid; HADS, hospital anxiety and depression scale; IA, intra-articular; PGI-I, patient global impression of improvement scale; WOMAC, western Ontario and McMaster universities osteoarthritis index.

Primary outcome

The primary outcome measure is the change in the weekly mean of the 24 hours average pain scores from baseline to the end of 24 weeks in patients with OA knee pain as reported in the patients' diaries based on an 11-point Likert scale (an ordinal scale with 0 indicating 'no pain' and 10 indicating the 'worst pain imaginable').

Secondary outcomes

- Response to treatment: The response to treatment is defined as a 30% (moderate) or a 50% (substantial) reduction in the weekly mean score of the 24 hours average pain severity ratings from baseline to the endpoint on weeks 1, 2, 4, 8, 16 and 24 post-injection.
- Brief pain inventory (BPI):[35] This self-reported scale will be used to measure the severity of pain and the interference of pain in function on weeks 1, 2, 4, 8, 16 and 24 post-injection. The severity of the pain will be assessed by four questions as follows: the patients will rate their most severe pain, least severe pain, average pain over the past 24 hours and current pain. The pain scale ranges from 0 (no pain) to 10 (extreme pain). Over the past 24 hours, seven questions will be used to assess the impact of pain on daily activities, mood, walking ability, ability to work normally, relationships with others, sleep and pleasure in life. The interference level ranges from 0 (no interference) to 10 (complete interference), and the average of the interference terms is obtained as a summary interference measurement.
- Western Ontario and McMaster Universities Osteoarthritis index (WOMAC):[10 36] This instrument is designed to assess pain, stiffness, and physical function in patients with OA of the knee and will be evaluated on weeks 1, 2, 4, 8, 16 and 24 post-injection. This index consists of 24 questions as follows: five questions regarding pain, two questions regarding stiffness, and 17 questions regarding physical function; each question will be answered using a 5-point scale ranging from 0 (none) to 4 (extreme). Higher scores on the WOMAC indicate worse pain, stiffness and functional limitations.
- Patient global impression of improvement scale (PGI-I):[37] This patient-rated 7-point scale of symptomatic improvement will be assessed at all visits starting 2 weeks after the treatment. On the PGI-I scale, a rating of 1 indicates that the patient is 'very much improved', a rating of 4 indicates that the patient has experienced 'no change' and a rating of 7 indicates that the patient has 'very much worsened'.
- Hospital anxiety and depression scale (HADS):[38] This self-rating patient-reported outcome measure will be developed to assess depression and anxiety in patients. Fourteen items are equally divided in two subscales: anxiety (HADS-A) and depression (HADS-D). The HADS-A includes items such as tension, worry, fear, panic, difficulties in relaxing and restlessness. The HADS-D includes items predominantly measuring anhedonia (not experiencing joy). Responses are rated on a 4-point Likert scale and range from 0 to 3, with higher scores indicating higher severity. Anchor points for the Likert items vary depending on the item. This scale is assessed to establish the analgesic effect of duloxetine independent of the effects on mood or anxiety.

Adverse events and data safety monitoring

During the trial, the treatment-related AEs reported by the patients will be recorded and evaluated at each visit. The safety and tolerability of the treatment will be assessed according to the incidence and type of AEs. Treatment-related AEs are any events that first occur or worsen during treatment compared with the baseline period. All AEs that the investigator considers causal in relation to the study drug will be recorded using a case report form. Severe AEs or adverse operation effects must be reported to the research ethics committee as soon as possible. The research ethics committee will review the AEs and determine whether termination of the study is necessary. If any patients are harmed by participating in the trial, they will be treated and closely monitored without delay by the researchers until they are healed.

Missing values

Missing data will not be replaced. Mixed models will be used in the analysis of repeated data to avoid deleting subjects with any missing values.

Sample size calculation

Based on previous research,[31] we estimate that the mean of the weekly mean of the 24 hours average pain scores after 24 weeks will be approximately −2.92±1.725 in the experimental group (IA (HA+CS) combined with oral duloxetine) and −2.08±1.745 in the control group (IA (HA+CS)). In total, 68 patients per group will be needed to achieve 80% power at a two-sided α level of 0.05. Considering a drop-out rate of 10%, in total, 75 patients per arm are needed; thus, in total, 150 patients will be needed for this trial.

Statistical analyses

The statistical analyses will be performed with SPSS software V.25 (IBM, Chicago, Illinois, USA). The Shapiro-Wilk test will be used to test whether all data are normally distributed. The normally distributed data will be expressed as the mean and SD. The data that do not follow a normal distribution will be presented as the median and IQR.

All analyses will be conducted on the intention-to-treat population. The baseline data and study outcomes of the experimental group and control group will be compared by a significance test of differences. The stratified cluster randomisation will be considered when analysing the data (multilevel analysis). If the baseline characteristics are statistically significantly different between the two treatment groups, we will perform a confounder analysis. If the effect on the outcome changes by 10% or more, the

baseline characteristic will be considered a confounder, and the analyses will be adjusted accordingly. A t-test will be used for the continuous variables with a normal distribution, and the Mann-Whitney U test will be used for the variables with a non-normal distribution. The categorical variables will be tested using the χ^2 test or Fisher's exact test. In addition, the outcomes at each postoperative time point will be compared with the preoperative data from the same group. A repeated-measures analysis of variance of the outcomes at different time points between the two groups will be performed, and Bonferroni correction will be used to correct multiple comparisons. Descriptive analyses will be used to assess the safety indicators in all randomised and treated patients. The relief of pain and functional improvement of OA of the knee after treatment may be related to BMI, effusion and use of concomitant rescue medication. The results, such as the Likert scale, BPI, WOMAC, PGI-I and AEs, will be stratified according to BMI, including normal (18.5 to 24.9), overweightness (25 to 29.9), obesity (>30), presence of effusion (negative or positive) and usage of concomitant rescue medication (yes or no) to test if the clinical effect is influenced by these confounding factors. P<0.05 will be considered indicative of statistical significance.

DISCUSSION

Consistent with a pragmatic approach, the PROBE design will be applied in the present study. Furthermore, the PROBE design can better reflect clinical practice and carry on the excellence of randomised controlled trials with randomised sequences and exact endpoint analyses by blinded experts.[39]

Chronic pain and depression often co-exist and influence each other.[29] Depressed mood has been associated with alterations in central pain processing and renders patients more sensitive to particular pain stimuli.[40] Duloxetine alleviates pain in OA by acting on serotonin and norepinephrine receptors, thereby affecting the central pain pathway.[41 42] However, patients with long-term severe symptoms may need repeated IA injections to relieve pain.[3] It is necessary for clinicians to reduce the incidence of adverse reactions caused by injections.[3] Therefore, we designed this protocol to evaluate the therapeutic effect of a single IA injection of CS and HA combined with oral duloxetine. If the combined treatment is more effective, this study will provide clinically important information regarding the pain management role of duloxetine in patients with OA of the knee receiving IA injection of CS and HA.

In addition, an analysis of the data from all placebo-controlled trials of duloxetine (52 studies involving 17 822 patients) showed that patients with OA who received duloxetine had the lowest treatment-emergent AE rate compared with other indications.[43] The dose-dependent adverse effects of duloxetine include constipation, dry mouth, decreased appetite and drowsiness.[13] Mild-to-moderate nausea may develop and be relieved within 8 days.[44] Therefore, in our study, the patients will start receiving duloxetine 30 mg once per day for 1 week and then titrate up to duloxetine 60 mg once per day to slowly improve their tolerance and reduce the occurrence of adverse reactions. The patients will be instructed to take the medication with meals.[45] In a retrospective analysis,[46] the use of duloxetine for the treatment of OA of the knee resulted in significant pain relief in both elderly and young groups (p<0.05). However, among the patients in all age groups who did not respond well to duloxetine at 7 weeks, no significant pain relief was found when the dose was increased to 120 mg/day.[46] Therefore, we chose the effective and relatively low dose of duloxetine (60 mg/day) for the treatment to avoid increasing the burden on the liver and kidney, and reducing the occurrence of adverse reactions.

Some elderly patients with severe symptoms of OA of the knee do not want to undergo surgical treatment or have contraindications for surgical treatment. Thus, it is urgent to identify safe, effective, and persistent non-surgical treatment options with minimal side effects. Various conservative treatment modalities are used as basic methods for treating OA of the knee. If used properly, these treatments can improve the quality of life of patients. Future studies should focus on improving the efficacy of non-surgical treatment options and providing scientific and medical evidence supporting innovative non-surgical technologies as choices before surgery for patients who are reluctant or unsuitable to undergo surgical treatment.

There are several limitations in this study. First, the present study will examine the effectiveness and safety only up to 24 weeks after treatment; however, a longer follow-up period could provide more informative results. Second, additional studies will be needed to determine whether duloxetine may reduce the frequency of injections and related adverse reactions and explore the optimal dosage of duloxetine. Third, we will be use low molecular-weight (MW) HA for patients in this study; however, some authors have reported that high MW cross-linked HA may lead to better results. The effect of duloxetine combined with high or low MW HA may be different, and further study will be performed for this issue. Fourth, MRI and X-ray examinations may provide further information regarding changes in structural damage to the articular cartilage, which is worth studying in the future. Fifth, there is no oral placebo for the control group because of limited funding, and the placebo effect may not be well parcelled out. However, our primary objective will be to identify whether there is a difference between IA (HA+CS) combined with duloxetine and IA (HA+CS). Thus, IA (HA+CS) alone could serve as the primary active control. In addition, this study will be a single-centre trial, and data from a multi-centre trial may be more precise.

In summary, the results of the IA (HA+CS) combined with duloxetine versus IA (HA+CS) trial may provide an effective method for relieving pain and improving knee function in patients with OA of the knee aged over 50

years and provide guidance for patients regarding multimodal analgesia and treatment.

Patient and public involvement

The patients and public were not involved in the planning and design of this study.

Ethics and dissemination

Ethical considerations

The study plan has been approved by the Ethics Committee of Beijing Tiantan Hospital (KY 2019-086-02). A Standard Protocol Items: Recommendations for Interventional Trials checklist is available for this protocol (online supplemental file 1). All patients will sign written informed consent to participate in the study (online supplemental file 2), and all participants will have sufficient time to decide whether to participate in this study. The subjects will be informed of the objectives of the project and the risks and benefits of the explorations to be carried out, including data collection. None of the tests will pose risks that could endanger the lives of the participants. The patients who participate in the study will have the right to obtain the relevant information and will be allowed to withdraw their consent or discontinue participation without restrictions at any time point during the study. The confidentiality of the participant records will be protected.

Dissemination plan

Scientific statements and reports corresponding to the study will be written under the responsibility of the coordinating investigator of the study with the consent of the principal investigators and the methodologist. The co-authors of the report and publications will be the investigators and clinicians involved on a pro rata basis of their contribution in the study and the biostatistician and associated researchers. The aggregated research findings will be presented at national and international scientific conferences and will be submitted for publication in peer-reviewed journals.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P3, P6
	2b	All items from the World Health Organization Trial Registration Data Set	P3, P6
Protocol version	3	Date and version identifier	P6
Funding	4	Sources and types of financial, material, and other support	P20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1, P19-20
	5b	Name and contact information for the trial sponsor	P1, P6
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P14

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P4-6
	6b	Explanation for choice of comparators	P4
Objectives	7	Specific objectives or hypotheses	P7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P9-10,
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	P14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P9-10, P14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P11-13

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	P6, P11
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P6-10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P8, P15-16
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P8
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P9-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P14-16
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P14-16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P14-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P14-16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	P14-16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P17-18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	P13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P6

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P6
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P19-20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P6, P19-20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	P14
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P19-20
	31b	Authorship eligibility guidelines and any intended use of professional writers	P19-20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P6

Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	P19
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" licens

Version：v1.1, Date：2019/12/1

INFORMED CONSENT FORM

Study title: Duloxetine combined with intra-articular injection versus intra-articular injection alone for pain relief in knee osteoarthritis: a study protocol for a randomized controlled trial

Organization： Beijing Tiantan Hospital, Capital Medical University

CRO： Fang Luo, M.D.

Version： V1.1

Date： 2019.12.1

Version：v1.1, Date：2019/12/1

Duloxetine combined with intra-articular injection versus intra-articular injection alone for pain relief in knee osteoarthritis: a study protocol for a randomized controlled trial

This Informed Consent Form has two parts:

- **Information Sheet (to share information about the study with you)**
- **Certificate of Consent (for signatures if you agree may participate)**

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

Introduction

Dear patients:

I am a doctor conducting a research regarding "Duloxetine combined with intra-articular injection versus intra-articular injection alone for pain relief in knee osteoarthritis: a study protocol for a randomized controlled trial". I am going to give you information and request you to participate in this treatment. The trial will be conducted in Beijing Tiantan Hospital, Capital Medical University, and it is estimated that 150 patients will voluntarily participate in this study. The study plan has been approved by the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University （KY 2019-086-02）.

You do not have to decide right away, whether or not you should allow yourself to participate in the research. You can talk to anyone you feel comfortable with, and collect all the necessary information regarding this research before giving us your consent.

There may be some words that you may not understand. Please do not hesitate to ask me to stop at any point, as we go through the information and I will try my best to answer all of your questions. If you have any further questions, you can ask me, the study doctor or the staff.

1. Study purpose

Osteoarthritis (OA) is an increasingly common degenerative joint disease worldwide, and its prevalence increases with age. This disease mainly occurs in the older population and affects approximately 15% of adults older than 45 years and approximately 50% of those over 75 years. Intra-articular (IA) injection of corticosteroid (CS) and hyaluronic acid (HA) is a common treatment for osteoarthritis (OA) of the knee. As a drug treatment for patients with depression, duloxetine has been showing in many studies to effectively relieve the pain of OA and improve the function of the knee joint. However, there is no evidence regarding the efficacy of IA injection of CS and HA combined with duloxetine for pain management in patients with knee OA. The aim of the study was to test the hypothesis that IA injection of CS+HA combined with duloxetine could achieve pain management superior to that of IA injection of CS+HA alone in patients experiencing knee OA pain.

2. How many subjects are expected to take part in this study?

We will invite 150 adults to participate in this study, and the study will be conducted in Beijing Tiantan Hospital,

Capital Medical University.

3. How long will this research last?

The trial will take place over a period of 24 weeks. We will assess the weekly mean of the 24 h average pain scores, the response to treatment, the Brief Pain Inventory (BPI), the improvement of Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) scores, the Patient Global Impression of Improvement Scale (PGI-I), and adverse event during the 24-week follow-up.

4. What kind of research procedures will be received if I agree to participate in this study?

If you decide to allow to participate in this study, you will receive the following tests to further confirm their eligibility for the study:

• physical examination and medical history inquiry;

• vital signs (e.g. breathing rate, body temperature, heart rate, etc.);

• electrocardiography.

If you meet the inclusion criteria, you will be randomly divided into either the control group or the experimental group, receiving either IA injection of CS+HA alone or IA injection of CS+HA combined with duloxetine. Questionnaire and telephone interview will be used periodically for follow-up at 1, 2, 4, 8, 16, and 24 weeks. If the treatment effect is not satisfactory, patients will be allowed to use the concomitant rescue medication, including paracetamol and NSAIDs (all other pain medication was excluded), in order to avoiding to increase the dose of duloxetine. The drugs mentioned above are all routine drugs for pain treatment. This trial is to test whether the efficacy of duloxetine combined with IA(HA+CS) is superior to that of conventional IA(HA+CS) alone in the treatment of knee OA pain in patients who are candidates for IA therapy.

For an unbiased research, the groupings will not be known by the end-point evaluator involved in the study. Patients should not disclose grouping information to their doctors during follow-up. The results will only be compared after the end of data collection. We will collect the participants' responses to treatment and health status by a series of tests throughout the course of the study.

5. What exactly will be done to me in this study?

Participants will be randomly allocated to receive either IA injection of CS+HA combined with duloxetine or IA injection of CS+HA alone, and both groups will complete a 24-week follow-up.

6. Do I have any other treatment options? If I want to stop participating in the study, what should we do?

If you do not wish to participate in this study, you can also choose the following treatment: oral paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and drugs for slowing the progression of the disease (glucosamine and chondroitin sulfate)，which are effective, but there are some side effects.

Participation in this study may or may not improve your recovery process after treatment. You have the right to drop out of the study at any point throughout the study.

7.Who can take part in this study?

All willing participants who fulfill all the following criteria will be participating in this study:

Patients must meet all of the following criteria to be eligible：

- Male and female outpatients aged 50–75 years who meet the American College of Rheumatology clinical and radiographic criteria for the diagnosis of knee OA with knee pain [pain for ≥14 days of each month for ≥3

months before study entry, with a mean score ≥4 on the 24-h average pain score (0–10) using the average of daily ratings before the trial]

- Body mass index (BMI) <40 kg/m^2
- Radiographic criteria including Kellgren–Lawrence grade II–III
- Knee stability, no deformity(varus, valgus, flexion contracture, and genu recurvatum), no lumbar spondylosis with radiculopathy
- Good cognition, the ability to understand the study protocol and willingness to participate

8. Who will be excluded to take part in this study?

Patient with any of the following conditions will be excluded from participation:

- Inflammatory arthritis, autoimmune disorder, septic arthritis, or any other concomitant disease (such as liver and kidney disease)
- Patients with prior synovial fluid analysis indicative of a diagnosis other than osteoarthritis
- Patients with contraindications to duloxetine (current use of monoamine oxidase inhibitors, poorly controlled angle-closure glaucoma), previous exposure to duloxetine, concurrent use of other drugs acting on the central nervous system (such as benzodiazepines) and allergy to any of the medications used in this study
- Metabolic diseases or anticoagulation therapy
- Patients who have undergone invasive therapies to the knee during the past 6 months, joint replacement of the knee at any time or current infection in the affected limb

9. What side effects or discomfort will I face by taking part in the study? What will the researchers do to protect me against these risks?

The drugs to be administered in this study has become a routine analgesic method for knee osteoarthritis pain. Intra-articular injection is the simplest and most effective method of knee osteoarthritis pain in the clinical practice. If you agree to participate in this clinical trial, pain and hematoma may occur as a result of puncture procedure. In addition, treatment may be ineffective, or may lead to the development of diseases or a combination of diseases. However, we will monitor you closely with regular follow ups and keep track of any unwanted side effects or problems. We will give you a telephone number to call if you notice anything out of the ordinary, or if you have any concerns or questions. You can also come to our clinic at any time. We may use some other effective and safe medication to reduce the symptoms of the side effects or reactions. If necessary, we will discuss it together with you and you will always be consulted before we move to the next step.

10. How could I benefit from this study? How could others benefit?

If you participate in this research, knee osteoarthritis pain may be relieved. There may not be any other benefit for you but your participation is likely to help us find the answer to the research question, and help other similar patients' recovery process after the same procedure in the future.

11. Do I need to pay for the study?

You will pay for the treatment/ examination expenses and registration fees during the follow-up.

If you need to perform treatment and examination as result of other complications or diseases, it may not be free.

You will not be provided any incentive to take part in this research.

12. What happens if I get hurt, become sick, or have other problems as a result of this research?

Intra-articular injection HA+CS has been found to be a minimally invasive treatment with few side effects for KOA pain. Also, duloxetine is effective and well tolerated with a lack of severe or life-threatening events in patients with osteoarthritis If you do suffer any research-related harm during the study, please immediately inform the study physician, who will provide appropriate treatment for you. Treatment costs and economic compensation according to relevant national regulations will be provided to you by Beijing Tiantan Hospital affiliated to Capital Medical University.

We intend to perform regular follow-ups to observe the possible side effects/adverse reactions caused by drug and/or treatment. While the possibility of this happening is very low, you should still be aware of them. If something unexpected happens and harm does occur, we will take measures to prevent and treat them.

Even if you have signed this informed consent, you still retain all the legal rights of yourself.

13. What information about myself could be seen by the researchers or by other people? Who might see it?

The participants' medical records will be kept in the hospital, and researchers, research authorities, and ethics committees will be allowed to access the patients' medical records. Any public report on the results of this study will not disclose your personal identity. We will, to the extent permitted by law, make every effort to protect the privacy of your personal medical data.

14. Do I have to take part in the study? Do I have the right to refuse or withdraw?

The decision to have yourself participating in this study is entirely voluntary. It is your choice whether to have yourself to participate or not. If you choose not to consent, all the services you receive at this clinic will continue and nothing will change. You may also choose to change your mind and stop participating at any point, even if you agreed earlier, and the services you receive at the clinic will continue and you could receive alternative therapies. If you choose not to consent, all the services you receive at this clinic will continue and nothing will change.

If you decide to withdraw from this study, please contact your doctor in advance. In order to ensure the safety of the participants, you may be required to carry out some related tests, which is beneficial for your health.

15. How will this affect the lives of me if participating in this study?

Some scheduled follow-up visits may be inconvenient for you, we will try our best to avoid such inconvenience. In addition, some tests may make the participants feel uncomfortable. If you have any questions about the tests or procedures, consult the study physician at any time.

The study physician will tell you what medications you may or may not take during the study. Consult with your study physician before taking any new prescribed medications.

The participants are not allowed to participate in any other clinical studies involving drugs or medical devices throughout the entire duration of this study.

16. Who to contact

If you have any questions, you may ask the researchers at any point throughout the study. If you wish to ask questions later, you may contact [Duo-Yi Li, No.119 South 4th Ring West Road, Fengtai District, Beijing, China /67096664].

This proposal has been reviewed and approved by Beijing Tiantan Hospital Affiliated to Capital Medical University of the IRB, which is a committee tasked to make sure that research participants are protected from harm. If you wish to find about more about the IRB, contact 010-59978555.

PART II: Certificate of Consent

Statement by the patient and direct relative:

I have read the foregoing information. I have had the opportunity to ask benefits or risks about the procedure and any questions that I have asked have been answered to my satisfaction. I consent voluntarily for myself to participate as a participant in this study.

I agree□ or disagree□ with the use of my medical records and pathological specimens for any other study except this study on behalf of the patient.

Signature of Participant: _____
Print Name of Participant: _____
Contact: _____

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and all the benefits or risks have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Signature of Researcher /person taking the consent_____
Print Name of Researcher/person taking the consent_____
Date _____
Day/month/year
Contact: _____