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Efficacy and safety of *P*ostoperative *I*ntravenous *P*arecoxib sodium *F*ollowed by *OR*al *CE*lecoxib (PIPFORCE) post-total knee arthroplasty in patients with osteoarthritis: a study protocol for a multicentre, double-blind, parallel-group trial

Qianyu Zhuang,[1] Yanyan Bian,[1] Wei Wang,[1] Jingmei Jiang,[2] Bin Feng,[1] Tiezheng Sun,[3] Jianhao Lin,[3] Miaofeng Zhang,[4] Shigui Yan,[4] Bin Shen,[5] Fuxing Pei,[5] Xisheng Weng[1]

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For numbered affiliations see end of article.

Correspondence to
Dr Xisheng Weng;
wengxishengpumch@126.com

ABSTRACT

Introduction: Total knee arthroplasty (TKA) has been regarded as a most painful orthopaedic surgery. Although many surgeons sequentially use parecoxib and celecoxib as a routine strategy for postoperative pain control after TKA, high quality evidence is still lacking to prove the effect of this sequential regimen, especially at the medium-term follow-up. The purpose of this study, therefore, is to evaluate efficacy and safety of postoperative intravenous parecoxib sodium followed by oral celecoxib in patients with osteoarthritis (OA) undergoing TKA. The hypothesis is that compared to placebo with opioids as rescue treatment, sequential use of parecoxib and celecoxib can achieve less morphine consumption over the postoperative 2 weeks, as well as better pain control, quicker functional recovery in the postoperative 6 weeks and less opioid-related adverse events during the 12-week recovery phase.

Methods and analysis: This study is designed as a multicentre, randomised, double-blind, parallel-group and placebo-controlled trial. The target sample size is 246. All participants who meet the study inclusion and exclusion criteria will be randomly assigned in a 1:1 ratio to either the parecoxib/celecoxib group or placebo group. The randomisation and allocation will be study site based. The study will consist of three phases: an initial screening phase; a 6-week double-blind treatment phase; and a 6-week follow-up phase. The primary end point is cumulative opioid consumption during 2 weeks postoperation. Secondary end points consist of the postoperative visual analogue scale score, knee joint function, quality of life, local skin temperature, erythrocyte sedimentation rate, C reactive protein, cytokines and blood coagulation parameters. Safety end points will be monitored too.

Ethics and dissemination: Ethics approval for this study has been obtained from the Ethics Committee, Peking Union Medical College Hospital, China (Protocol number: S-572) Study results will be available as published manuscripts and presentations at national and international meetings.

Trial registration number: NCT02198924.

Strengths and limitations of this study

- This is the first study to investigate the efficacy and safety of the sequential analgesia regimen of intravenous parecoxib followed by oral celecoxib after total knee arthroplasty surgery.
- This study will explore the benefits of prolonged sequential treatment of parecoxib and celecoxib in medium-term function recovery.
- The results will promote the non-steroidal anti-inflammatory drugs incorporation into the standard multimodal analgesic regimen for post-operative pain control.
- Potential limitations include the need for further validation studies from other institutions outside China, lack of investigation of the long-term (eg, >3 months) effects of the sequential treatment, and compromise of the test accuracy of synovial fluid cytokines.

INTRODUCTION

Osteoarthritis (OA) is a chronic degenerative joint disorder which frequently occurs in the elderly.[1 2] In mainland China, knee OA is the leading cause of disability in elderly patients. Total knee arthroplasty (TKA) is now generally regarded as an effective

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treatment for end-stage knee OA in pain alleviation, joint deformity correction and life quality improvement.[3 4]

However, TKA has been regarded as a most painful orthopaedic surgery due to the weight-bearing characteristics of knee joint and the high demand for functional exercise within 6–8 weeks postoperation.[5 6] First, TKA induces massive tissue damage and severe perioperative pain which jointly hamper early postoperative rehabilitation and exert negative effects on surgical outcome and patient satisfaction.[7] Second, postoperative pain, as the most suffering experience for patients with TKA, may prolong postoperative bedbound duration and increase the risks for pulmonary infection, deep venous thrombosis (DVT), pulmonary embolism (PE), etc.[8] Third, previous findings suggested that local inflammation triggered by tissue damage increases the central and peripheral pain sensitivity, as well as leads to acute haemorrhage and swelling, which poses greater challenges to the postoperative rehabilitation.[9 10]

The targeted treatment with a selective cyclooxygenase (COX-2) inhibitor, such as parecoxib or celecoxib, can significantly reduce the inflammatory reaction level within 2 days postoperation.[11–14] In addition, perioperative administration of celecoxib can relieve postoperative pain and improve articular function, thereby improving the life quality of the patients. Recently, sequential therapy of intravenous-to-oral COX-2 inhibitor administration has been demonstrated as effective in many postoperative pain control models.[15–19] Significant morphine sparing effect and reduction of opioid-related complications were also observed.[15–19] In China, it is becoming a routine at many institutions that 40 mg parecoxib be administered intravenously two times a day for the first 3 days after surgery, followed by 200 mg celecoxib administered orally two times a day for 2 weeks or longer. Although satisfactory results of the sequential therapy on short-term pain alleviation and functional recovery have been preliminarily observed in clinical practice, high-quality evidence is still lacking, especially at the medium-term/long-term follow-up.

The *P*ostoperative *I*ntravenous *P*arecoxib Sodium *F*ollowed by *OR*al *CE*lecoxib (PIPFORCE) study (Trial registration number: ClinicalTrails.gov identifier: NCT02198924) aims to investigate the sequential analgesia regimen with intravenous parecoxib followed by oral celecoxib for postsurgical analgesic treatment in patients with OA undergoing TKA surgery. Participants will receive a double-blinded study medication consisting of parecoxib injection in analgesic doses or matching placebo followed by oral celecoxib in acute pain doses or matching placebo. The hypothesis is that participants treated with parecoxib/celecoxib will consume less morphine during the postoperative 2 weeks, achieve better pain control and quicker functional recovery during the postoperative 6 weeks, and have less opioid adverse events than those treated with opioids alone during the 12-week recovery phase.

AIM AND OBJECTIVES

Primary objectives

The primary objective of this study is to evaluate the morphine-sparing effects of the sequential treatment with parecoxib and celecoxib versus placebo in participants undergoing TKA.

Secondary objectives

- To compare the effects of the sequential treatment versus placebo on pain relief, inflammation control and functional rehabilitation after TKA.
- To compare the safety of the sequential treatment versus placebo post-TKA.

DESIGN AND METHODS

Study design

This study is an investigator initiated postmarketing study which is designed as multicentre, randomised, double blind, parallel-group, and placebo-controlled.

Study setting

This study is being conducted by Peking Union Medical College Hospital, China as the coordinating centre and three other participating centres including (1)West China Hospital of Sichuan University, Sichuan Province, China, (2) People's Hospital of Peking University, Beijing, China and (3)Second Affiliated Hospital of Zhejiang University College of Medicine, Zhejiang Province, China.

Study participants

Inclusion criteria

Participant eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before participants are included in the study.

Participants must meet all of the following inclusion criteria to be eligible for enrolment into the study:

1. The participant is scheduled to undergo elective unilateral TKA because of OA, performed under a standardised regimen of general anaesthesia, as specified in this protocol.
2. Evidence of a personally signed and dated informed consent document indicating that the participant (or a legal representative) has been informed of all pertinent aspects of the study.
3. The participant is a male or female over 18 years of age.
4. Male and female participants of childbearing potential must agree to use an effective method of contraception throughout the study and for 42 days after the last dose of assigned treatment. A participant is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.
5. Total duration of the surgical procedure is 4 hours or less.

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6. American Society of Anesthesiologists (ASA) grade 1–3 participants.
7. Participants who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, standardised rehabilitation scheme and other study procedures.
8. The participant is in satisfactory health as determined by the investigator on the basis of medical history and physical examination.
9. The participant must demonstrate sufficient psychomotor dexterity and cognitive capacity to use intravenous patient-controlled analgesia (PCA).
10. Participants who live near to the hospital may be considered prior for the concern of convenient and sufficient follow-up.

Exclusion criteria

The participants will be excluded with any condition listed below:

1. The participant requires a revision to previous knee arthroplasty and/or is having a bilateral knee arthroplasty.
2. The participant requires an emergency knee arthroplasty.
3. Addiction to using any non-steroidal anti-inflammatory drugs (NSAIDs) and opioids.
4. The participant has a known hypersensitivity to COX-2 specific inhibitors, sulfonamides, lactose, NSAIDs, opioids or acetaminophen/paracetamol. Participants who have experienced asthma, urticaria or allergic type reactions after taking aspirin or other NSAIDs.
5. The participant has a history of any of the following arthritis: (ie, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), chronic pain (eg, fibromyalgia), metastasis and Paget's disease.
6. The participant received any investigational medication within 30 days prior to the first dose of study medication or is scheduled to receive any investigational drug other than those described in the protocol during the study.
7. The participant has any known laboratory abnormality, which in the opinion of the investigator would contraindicate study participation including alanine transaminase (serum glutamic-pyruvic transaminase), aspartate aminotransferase (serum glutamic oxaloacetic transaminase), blood urea nitrogen or creatinine ≥1.5 times the upper limit of the normal reference range.
8. The participant has an active malignancy of any type, or history of a malignancy (participants who have a history of basal cell carcinoma that has been successfully treated can be entered into the study. Participants with a history of other malignancies that have been surgically removed and who have no evidence of recurrence for at least 5 years before study enrolment can also be entered into the study).
9. The participant had inflammatory bowel disease (eg, Crohn's disease or ulcerative colitis), a chronic or acute renal or hepatic disorder, a significant coagulation defect or any condition, which could preclude use of NSAIDs or COX-2 specific inhibitors.
10. The participant has active or suspected oesophageal, gastric, pyloric channel or duodenal ulceration history.
11. The participant has received warfarin or other anticoagulants during the 30 days preceding the first dose of study medication (cardioprotective aspirin ≤or 325 mg/day is permitted when the dose has been stable for at least the month prior to entering the study). Anticoagulation is permitted when related to the surgery, with such medicines as low-molecular-weight heparin including lovenox and fragmin.
12. The participant is anticipated to require or requires treatment with lithium.
13. The participant is American Society of Anesthesiologists (ASA) grade 4–5.
14. The participant has a history of a psychiatric disorder requiring new or changing treatment (A participant with a psychiatric disorder who has been stable on therapy may enter the study if they have not required any changes in their therapy for the 4 weeks prior to study entry and it is anticipated that they will not need any changes for the 2-week duration of this study).
15. The participant has a history of uncontrolled chronic disease or a concurrent clinically significant illness or medical condition, which in the investigator's opinion would contraindicate study participation or confound interpretation of the result. Including, but not exclusive to: uncontrolled hypertension, uncontrolled ischaemic heart disease, uncontrolled cardiac insufficiency, history of coronary artery bypass graft surgery, history of heart valve surgery or coronary stent implantation, history of peripheral vascular disease or cerebrovascular disease, moderate or severe hepatic impairment, fluid retention, heart failure, abdominal pain of unknown aetiology (or where study medication could mask symptoms) or any other condition which in the opinion of the investigator would contraindicate study participation or confound interpretation of the results.
16. The participant has any cognitive impairment or other characteristics that would in the investigator's opinion preclude study participation or compliance with protocol mandated procedures.
17. The participant has a history of asthma or bronchospasm, which requires treatment with glucocorticoids.
18. The participant had a history of alcohol, analgesic or narcotic abuse.
19. The participant has been previously randomised into the study.
20. Participants who are investigational site staff members or relatives of those site staff.

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21. Participation in other studies within 3 months before the current study begins and/or during study participation.
22. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgement of the investigator, would make the participant inappropriate for entry into this study.
23. Pregnant females, breastfeeding females, or males and females of childbearing potential not using effective contraception or not agreeing to continue effective contraception from screening through 42 days after the last dose of the investigational product will not enter this study.

Withdrawal criteria

At any stage of the study, participants are free to withdraw from the study with their medication and/or treatment and their well-being ensured by the investigator/hospital without any negative impact.

The investigator may decide that a participant needs to be withdrawn from the study based on evaluations of individual conditions and balancing of the potential benefit/risk caused by the study treatment to the participant. For example, in case that even a maximal dose of oral tramadol could not provide satisfying rescue-pain control, we may withdraw the patient from the study to guarantee the pain control quality and clinical safety. These patients will be shifted to NSAIDs or acetaminophen for pain treatment, and the details of altered treatments will be documented in the study.

Intervention measures

Allocation to treatment

All participants who meet the study inclusion and exclusion criteria will be randomly assigned in a 1:1 ratio to either the parecoxib/celecoxib group or placebo group. The allocation or randomisation will be study site based.

The Electronic Data Capture (EDC) system will automatically generate participant identification numbers in sequence at baseline, which is subsequently linked to the treatment assignments at randomisation. A copy of the randomisation code will be maintained by a designated person(s) who is independent of the trial conduct. It is the responsibility of the principal investigator (PI) to ensure that the participant is eligible for participation in the study before requesting randomisation.

The study will consist of three phases: an initial screening phase which must be completed within 30 days prior to randomisation; a 6-week double-blind treatment phase; and a 6-week follow-up phase (figure 1).

In the first phase, the investigator will initiate the required screening procedures after obtaining written informed consent. All qualified patients after selection by inclusive/exclusive criteria will be assigned in the order in which they are enrolled into the study, to receive their allocated treatment sequence according to a computer-generated randomisation schedule prepared prior to the start of the study.

In the second phase, after completion of screening, participants who remain eligible will enter a 6-week double-blind randomised treatment period. All the participants will undergo standard TKA on the unilateral side under general anaesthesia. Patients in the study group are supplied sequential treatment with parecoxib 40 mg intravenously two times a day (Q12 hours) for the first 3 days postsurgery followed by celecoxib 200 mg orally two times a day (Q12 hours) for up to 6 weeks postsurgery, whereas control patients are supplied with the corresponding placebo with the same instructions. Patient-controlled intravenous analgesia with morphine is administrated to all the participants starting immediately postanaesthesia and ending at 24 hours after operation. As long as oral intake is feasible, both the groups may receive centrally acting analgesic tramadol hydrochloride in oral form as rescue analgesia if visual analogue scale (VAS) score ≥3. With the support of sufficient pain management, patients will be educated to perform functional exercise according to the standardised post-TKA exercise plan. The investigator will use a patient diary at every visit to track the patient exercise, pain score, the study medication and the rescue therapy.

- Surgical techniques: A standard medial parapatellar approach was used through a midline skin incision, and a tourniquet was used which was inflated (280 mm Hg) following limb exsanguination immediately before skin preparation. Bone cuts and soft tissue balancing were done in the same sequence. The joint capsule and wound layers were closed in layers. A wool and crepe dressing was applied to the wound from mid-calf to mid-thigh at which point the tourniquet was then released.
- Anaesthesia regimen: All four centres in this study will adopt the same anaesthesia protocol (as presented above) and the same anaesthesia drugs to minimise difference among centres and ensure the comparability between the two study groups. The general anaesthesia protocol is as follows: patients will be operated under general anaesthesia (GA) with tracheal intubation. GA induction will be conducted with intravenous administration of 1–2 μg/kg sufentanil, 0.6–0.8 mg/kg rocuronium, 0.02 mg/kg midazolam, 4 mg ondansetron and target-controlled infusion (TCI) of propofol at 4.0–6.0 μg/mL. GA will be maintained with propofol TCI at 3–5 μg/mL and continuous infusion of sufentanil at 0.1–0.2 μg/kg. Rocuronium and 1 μg/kg of sufentanil will be given when necessitated. Parecoxib or placebo drug will be dripped at suture, and neostigmine plus atropine will be given as muscle relaxant reversal before extubation. The total amount of intraoperative sufentanil consumption will be documented at GA conclusion.

In the third phase, a telephone safety follow-up visit at 12-weeks postsurgery will be taken to reveal any adverse

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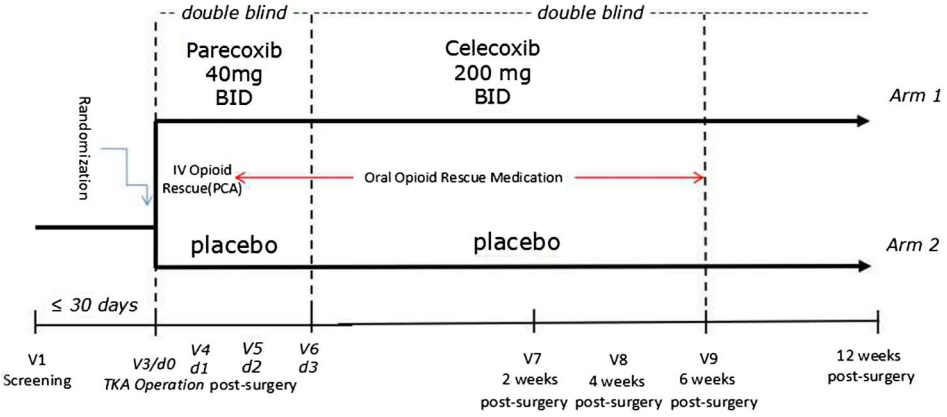

Figure 1 Flow chart of the 'PIPFORCE' trial design. PCA, patient-controlled analgesia; PIPFORCE, *P*ostoperative *I*ntravenous *P*arecoxib Sodium *F*ollowed by *OR*al *Ce*lecoxib; TKA, total knee arthroplasty.

events that may happen during the follow-up phase. All participants and all assessment operators are blinded to the identity of the treatments until all study data have been collated in a database.

Drug preparation and administration

Drug formulation and packaging

Parecoxib lyophilised presentation will be supplied in 40 mg per phial for intravenous administration; liquid presentation of placebo will be 0.9% saline in 2 mL per phial provided on site for intravenous administration. Two millilitre of 0.9% saline is used for reconstitution of parecoxib before administration.

Celebrex/placebo 200 mg capsule presentation will be supplied in bottles for oral administration, and the number of capsules in each bottle is 12 for the first week postsurgery, 22 for the second week and 44 for the following 2 weeks scheduled respectively.

Preparation and dispensing

Preparation of the study medication will be performed by the medicine supplier in their Good Manufacturing Practice (GMP) facility. According to the random list, a unique random code will be labelled to each phial/bottle of the medicine/placebo thus allowing no recognition of the real ingredients by the trial operating nurse and/or participants.

Dispensing of the trial medication/placebo will be based on the random code kept by the nurse for reconstitution of parecoxib or the label of the bottle for celecoxib by strictly following the sequence of the medicine identification number on the labels.

Administration

Parecoxib/placebo will be administered via the intravenous route two times a day at 12 hour intervals; the medication should not be given simultaneously with any other medication, and a bolus injection is recommended after using 1–2 mL of saline washing of the infusion route in advance. The first intravenous administration of parecoxib 40 mg or placebo will be performed at the beginning of the wound suture during the TKA surgery, followed by parecoxib 40 mg or placebo every 12 hours for three consecutive days.

Thereafter, celebrex/placebo will be administered orally, two times a day at 12 hour intervals, such as at 08:00 and 20:00, respectively, with a cup of water. When discharged from hospital, the participants are required to record the oral intake of celebrex/placebo by themselves on the diary card shown at each visit, keeping the time points of administration the same as in the ward.

Drug storage

Parecoxib and placebo will be shipped and stored at a temperature below 25°C, and celebrex and placebo will be shipped and stored at 10–25°C. Investigators and site staff are reminded to check temperatures daily and ensure that thermometers are working correctly as required for proper storage of investigational products.

Concomitant medication(s)

The use of permitted concomitant therapy must be explained in detail, including prescription and non-prescription drugs, non-drug therapy, and dietary supplements and herbal preparations, as appropriate. The name, dose, date and exact time of administration must be recorded in the case report form (CRF) and appropriate medical records as source data for each medication administered to the patient.

Prohibited medications

The following medications are prohibited for the duration of the study:

- NSAIDs and other analgesics (including steroid), by any route (ie, oral, inhaled, topical, injected, rectal), within 5 days prior to TKA until the end of the study.
- Fluconazole and/or lithium
- Hypnotics, anxiolytics, sedatives, tranquillisers, selective serotonin reuptake inhibitors selective serotonin reuptake inhibitors, tricyclic antidepressants or

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benzodiazepines unless the participant's prescribed daily dose has remained unchanged throughout the previous 4 weeks and will remain unchanged throughout the study period.
- Herbal and complementary medicines such as: garlic, ginko biloba, ginseng.
- Local infiltration of the surgical site with an anaesthetic is prohibited.

Permitted medications

- Premedication, if required, will be a short-acting benzodiazepine (eg, temazepam).
- Anaesthesia will be a standardised general anaesthesia regimen as described above.
- Midazolam and propofol are given only intraoperatively with no administration after the surgery, thereby avoiding the potential opioid sparing effect for the postoperative hours.
- Anticoagulants: low-molecular-weight heparin is permitted for postsurgical anticoagulant treatment.
- Aspirin <325 mg/day is permitted for cardiovascular prophylaxis, if used at a stable dose for the 30 days prior to randomisation.
- Antiemetic drugs may be given, if needed. The dose and total number of doses of the antiemetic treatment should be documented on the CRF.

Rescue therapy

Intravenous rescue medication—PCA

After surgery, all participants will be connected to PCA at the last stitch of wound closure. The PCA pump setting protocol is as follows: 60 mg morphine in 240 mL normal saline (morphine 1 mg/4 mL) will be prescribed for postoperative PCA. The background infusion rate of PCA is set at 4 mL/hour (morphine 1 mg/hour), and 4 mL bolus infusion (morphine 1 mg/bolus) is available with a 15 min lockout interval. A dosage limit of 60 mL within 4 hours is applied for preventing the potential adverse events.

All doses of morphine (PCA and bolus) must be recorded precisely with the date and time of administration and the amount of morphine given. If a participant is unable to use the PCA pump, he/she must be withdrawn from the study and provided with appropriate analgesia.

Oral rescue medication

After PCA is discontinued, all participants with a VAS more than 3 may take open-label oral rescue medication, tramadol 100 mg each time as needed, not to exceed 400 mg/day.

Commercial product RYZOLT is used in this study, which is tramadol hydrochloride extended-release tablets, a centrally acting analgesic composed of a dual-matrix delivery system with both immediate-release and extended-release characteristics. The median time to peak plasma concentrations of tramadol and O-demethylated metabolite (M1) after multiple-dose administration of RYZOLT 200 mg tablets to healthy participants are attained at about 4 and 5 hours, respectively.

Only tramadol will be used as rescue medication post-discharge from the hospital. The doctor and research nurse will give the participants very thorough and clear education on how to take tramadol as rescue medication (all participants with a VAS equal to or more than 3 may take tramadol 100 mg each time as needed, not to exceed 400 mg/day), how to record on the patient diary, and how to return the left tramadol at each visit. They will also assess the use and consumption of the participants at each follow-up visit. No other analgesics will be allowed to be taken by the participants posthospital discharge. Acetaminophen is not included in the rescue analgesia since it can inhibit cyclooxygenase-2 and thus influence the evaluation of inflammation-related end points.

Consumption of both morphine and tramadol will be calculated together and converted to morphine equivalent dosage; the conversion equivalent of tramadol to morphine is estimated as 300 mg oral administered tramadol equal to 20 mg of intravenous morphine.[20–23]

Outcome measures

Primary end point

Cumulative opioid consumption until 2 weeks postoperation can be calculated as the sum of the cumulative morphine consumption over the first 24 hours postsurgical period and the opioid drug consumption until 2 weeks postoperation. The conversion equivalent of tramadol to morphine is estimated as 300 mg tramadol equal to 20 mg of morphine.

Secondary end points

Key secondary end points

Knee Society Score (KSS) at 6 weeks postoperation.

Other secondary end points

- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) index[24] prior to operation and at 2, 4 and 6 weeks postoperation.
- KSS[25] prior to operation and at 2, 4 and 6 weeks postoperation.
- Total morphine use: The cumulative morphine consumption over the first 24 hours postsurgical period.
- Cumulative opioid consumption until 24 hours, 72 hours, 2, 4, 6 weeks postoperation. For example, total narcotic use until 72 hours postoperation will be calculated as the sum of the cumulative morphine consumption over the first 24 hours postsurgical period and the opioid drug consumption (converted to morphine equivalents) until 72 hours postoperation.
- VAS (0–10)[26] prior to operation and at 24, 48 and 72 hours, 2, 4 and 6 weeks postoperation, with 0 point representing no pain and 10 points representing the worst imaginable pain.

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- EQ-5D[27] and patient satisfaction prior to operation and 72 hours, 2, 4 and 6 weeks postoperation. EQ-5D is a standard instrument for use as a measure of health outcome. It is cognitively simple, taking only a few minutes to complete.

Exploratory end points

- Knee circumference (measured 1 cm proximal to the base of the patella) prior to operation and at 24, 48, 72 hours, 2, 4, 6 weeks postoperation. The measurements were performed in a quiet room, with a recording clerk and a physician present who measured and recorded dimensions of the knee circumference of both legs. Circumferential measurements were recorded to the nearest 0.1 cm with an ordinary tape measure.
- Knee skin temperature prior to operation and at 24, 48 and 72 hours, 2, 4, 6 weeks postoperation.
- Erythrocyte sedation rate (ESR) and C reactive protein (CRP) preoperatively and at 72 hours, 2, 4 and 6 weeks postoperation.
- Synovial fluid cytokine (including interleukin (IL)-6, IL-8, IL-10 and Prostaglandin E2 (PEG2)) concentration at 0, 24 and 48 hours postoperation.
- Peripheral blood cytokine (including IL-6, IL-8, IL-10 and PGE2) concentration prior to operation and at 24, 48 and 72 hours, 2, 4, 6 weeks postoperation.
- Blood coagulation tests prior to operation and at 72 hours, 2, 4 and 6 weeks postoperation.

Safety end points

The nature, incidence, duration and severity of adverse events (AEs); discontinuation due to adverse events; adverse events occurring during and after trial medication discontinuation; body weight, clinical safety laboratory, 12-lead ECGs, physical examinations and vital signs will be monitored in this study.

AE reporting

AE definition

An AE is any untoward medical occurrence in a clinical investigation where participants are administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to: abnormal test findings, clinically significant symptoms and signs, changes in physical examination findings, hypersensitivity, progression/worsening of underlying disease, drug abuse, drug dependency, etc.

Serious adverse events

An serious adverse event (SAE) is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.
- Lack of efficacy should be reported as an AE when it is associated with an SAE.

Medical and scientific judgement is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalisation. However, if it is determined that the event may jeopardise the participant or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported seriously.

Severity assessment

If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows: (1) MILD: Does not interfere with the participant's usual function. (2) MODERATE: Interferes to some extent with the participant's usual function. (3) SEVERE: Interferes significantly with the participant's usual function.

Causality assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. If the investigator determines that an SAE is associated with study procedures, they must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

Withdrawal due to AEs

Withdrawal due to AE should be distinguished from withdrawal due to insufficient response according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a participant withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

Study procedures

Altogether, there will be 10 visits in the study for a certain participant (table 1). Screening will be performed at visit 1, and the day for TKA operation will be considered as day 0. There is a visit on 1 day before the operation, the visit 2, when the qualification of the participant to the study will be evaluated again before the operation, and the visit right after the operation is visit 3. Those on days 1, 2 and 3 postsurgery will be regarded

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Table 1 Schedule of activities

Protocol activity	Screen	Baseline Randomisation Day 1	Surgery Day 0	Day 1	Day 2	Day 3	Day 4	Week 2	Week 4	Week 6	Week 12
Visit	*1*	*2*	*3*	*4*	*5*	*6*		*7*	*8*	*9*	*10*
Informed consent	X										
Demography	X										
Medical and surgical history	X										
Physical examination	X		X	X	X	X					
Vital signs	X	X	X	X	X	X	X	X	X	X	
Haematology	X			X				X			
Blood chemistry	X			X				X			
Urinalysis	X			X				X			
Pregnancy test*	X									X	
ECG	X			X				X			
ESR and CRP	X					X		X	X	X	
Blood coagulation	X					X		X	X	X	
Peripheral blood cytokine concentration	X			X	X	X		X	X	X	
VAS	X			X	X	X		X	X	X	
EQ-5D	X					X		X	X	X	
Knee circumference and skin temperature	X			X	X	X		X	X	X	
X-ray	X										
Echocardiogram	X										
Pulmonary function	X										
Ultrasound tests	X										
Blood transfusion tests	X										
WOMAC and KSS	X					X		X	X	X	
Inclusion/exclusion criteria	X	X									
Registration/randomisation		X	X								
Hospital admission	X										
Surgery—total knee arthroplasty			X								
Synovial fluid cytokine concentration			X	X	X						
Infusion of parecoxib or placebo 40 mg two times a day				X	X	X					
Record morphine consumption				X							
Celebrex/placebo 200 mg two times a day							X	———	———	X	
Recording the cumulative tramadol consumption					X	X	X	X	X	X	
Adverse event		X	X	X	X	X	X	X	X	X	X†

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.
CRP, C reactive protein; ESR, erythrocyte sedimentation rate; EQ-5D, Eurocol-5D; VAS, visual analogue scale.
*Pregnancy tests may be repeated as per request of Ethics Committee or if required by local regulations. † telephone follow-up.

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as visits 4, 5 and 6, respectively; then there will be visits 7, 8 and 9 at 2, 4 and 6 weeks postsurgery, and the last visit, visit 10, will be at 12 weeks postsurgery.

Screening and washout

Screening will be performed between visits 1 and 2, where the potential participants will be evaluated by inclusion/exclusion criteria, demography and medical history recording, evaluation of the background diseases as well as OA for the knee to be operated on, physical examination and laboratory examinations including routine tests of blood and urine, biochemical, X-ray (chest, two lower limbs and the knee joint), 12-lead ECG, echocardiogram, pulmonary function, ultrasound for lower extremities venous and arteria, blood transfusion test (eight items), blood type and pregnancy test for female participants, ESR and CRP, peripheral blood cytokine concentration (IL-6, IL-8, IL-10 and prostaglandin E2 (PEG2)) and blood coagulation, WOMAC index and KSS, VAS and EQ-5D, knee circumference and skin temperature at baseline.

Before any trial required assessments are conducted, a written informed consent must be signed by the participant, and a witness to the signing is needed when the participant is unable to read or write.

There is a 2-week washout period after the screening at visit 1 and before visit 2, in which participants who have been receiving any NSAIDs will be stopped from using these medicines for two weeks and asked to replace their NSAIDs with tramadol when needed.

All required data must be recorded on CRF for verification and archiving. In this study, e-CRF will be applied allowing online source data verification.

Qualification of the participant to the study will be evaluated again at visit 2, which is the day before the operation, and randomisation of the participant to receive either parecoxib or placebo in the first 3 days postsurgery, and either clebrex or placebo in the following 6 weeks, will also be determined on the same visit.

Study period

At visit 3, which is right after the operation, physical examination will be performed, infusion of parecoxib or placebo 40 mg Q12 hours in the first 3 days and recording of morphine consumption for 24 hours starts, and synovial fluid cytokine concentration will be tested. Safety evaluations are also conducted for the participants.

At visits 4 and 5, the recording of accumulative morphine consumption stops, while that for tramadol starts at visit 4, and physical examination and safety evaluations are also conducted for the participants. Synovial fluid cytokine concentration is tested at 24 and 48 hours postoperation.

At visit 6 which is 72 hours after the operation, infusion of parecoxib 40 mg Q12 hours or placebo stops, and oral administration of celebrex 200 mg Q12 hours/placebo starts on day 4, while recording of the cumulative tramadol consumption continues. Evaluations of VAS and EQ-5D will be performed, while testing of ESR, CRP, peripheral blood cytokine concentration and blood coagulation will also be performed. Safety evaluations are also conducted for the participants.

Follow-up visits

This period covers visits 7–9, where recording the cumulative tramadol consumption at 2, 4 and 6 weeks after the operation; WOMAC index and KSS at 2, 4 and 6 weeks postoperation; evaluations of VAS and EQ-5D at 2, 4 and 6 weeks postoperation; knee circumference and skin temperature at 2, 4 and 6 weeks postoperation; ESR and CRP at 2, 4 and 6 weeks postoperation; peripheral blood cytokine concentration at 2, 4 and 6 weeks postoperation; and tests of blood coagulation at 2, 4 and 6 weeks postoperation. Safety evaluations are also conducted for the participants at each visit.

Post-study subject telephone interview

At 12 weeks postsurgery, only safety evaluations will be conducted for the participants by a telephone follow-up.

All data required by the above visits must be recorded on CRF for verification and archiving.

Breaking the blind

This is a double-blind study. The participants, investigators, study coordinators, clinical site staff, clinical research associate (CRA) and staff directly involved in the study and its designees will be blinded to participant treatment assignment.

At the initiation of the study, the study site will be instructed on the method of breaking the blind. Blinding should only be broken in emergency situations for reasons of participant safety. Whenever possible, the investigator or subinvestigator consults with a member of the study team prior to breaking the blind. When the blind is broken, the reason must be fully documented and entered on the CRF.

Stop criteria

The participants involved in this study have the right to quit at any time. In addition, participants will be discontinued from the study if they meet any of the following criteria:

1. Clinical interventions (eg, systemic or topical application of glucocorticoids, other NSAIDs used within 6 weeks after TKA) which may affect the study results within the observation period;
2. Occurrence of a SAE (eg, malignant tumours, serious perioperative complications) which, in the opinion of the investigator, may complicate assessment of the effects of study drugs.

Ethical review and informed consent

The benefits and risks of participation in the trial will be explained to each patient, legal deputy or witness by the

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investigators or their designee, and written informed consent will be obtained before the trial. The informed consent with the signature of the patient, legal deputy and person who explained the benefits or risks will be preserved by the researchers. The trial will be conducted in accordance with the Declaration of Helsinki.

Sample size determination

A total of 86 participants per group would have 90% power in detecting 100 mg or more in the mean difference of cumulative opioid consumption on day 14 between the two groups, assuming a common SD of 200, and a two-sided α level of 0.05. This would result in a total of 172 participants. If 30% of participants are estimated to drop out of the study, 246 participants would be considered adequate for the study.

Owing to a lack of prospective studies for this type of end point, and in review of a retrospective evaluation of inpatient celecoxib use after total hip and knee arthroplasty[15], our assumptions in the sample size estimation are conservatively stipulated.

Data collection, management and statistical analysis

Data will be collected through the EDC system under intent-to-treat principles, that is, all the data of the participants who signed the inform consent form will be included in the study database.

Data quality assurance will be achieved through

- Online Edit Checks at the time of data entry.
- Database Edit Checks performed by Data Management (DM).
- Online query issuance/resolution among/between PI, CRA and DM.
- Medical review of data listing by the project team.

For this study, the following definitions of analysis population will be followed:

INTENT TO TREAT

All the randomised participants who signed the Informed Consent Form (ICF) and satisfied all inclusion/exclusion criteria at visit 2 will be included in the intent to treat (ITT) analysis set.

Analyses on demographics and baseline characters will be based on the ITT analysis set, and the listings of participants' information will also be based on ITT.

EFFECTIVE ANALYSIS POPULATION

All the participants in ITT who have completed demographic data and evaluable baseline morphine use, and at least one postbaseline cumulative use of tramadol.

All the analyses on efficacy will be based on effective analysis population (EAP).

PER-PROTOCOL POPULATION

All the participants in EAP who have no major protocol deviation, no forbidden concomitant use, have the data of cumulative use of tramadol in the first 2 weeks after operation, and the compliance in the treatment use during the first 2 weeks after operation is between 80% and 120%.

Per-protocol population (PP) will be only used in primary efficacy analysis.

SAFETY SET

All the randomised participants who have received at least one dose will be included in the safety set (SS). Analysis on AEs, laboratory, ECG and vital sign will be based on the SS.

All data collected at follow-up visits for patients in the study and control groups are compared by an independent statistician using SAS V.9.3 statistical analysis software. Continuous variables will be summarised by treatment groups using descriptive statistics including number of participants, mean, SD, median, Q1, Q3, minimum and maximum. The statistics of t-test, Welch-Satterthwaite t-test or Mann-Whitney U test will be used in comparison between two groups based on the results of normality test and homogeneity of variance test. Paired t-test will be used in comparison within each group if the variables are normally distributed; otherwise, the signed rank test will be used. The statistical significance level of normality test and homogeneity of variance test is 0.05. Nominal categorical variables will be presented as 'frequency (percentage)'. The statistics of Pearson χ^2 test, continuity adjusted χ^2 test or Fisher's exact test will be used in comparison between two groups based on the distribution of the variable considered. Ordinal categorical variables will be presented as 'frequency (percentage)'. The Mann-Whitney U test will be used in comparison between two groups. A two-sided p value will be used in the statistical tests, and the difference between groups will be considered statistically significant if $p<0.05$.

For primary end point analysis, statistical methods for continuous variable analysis will be used in the superiority test of the study group over the control group on reducing morphine use. Additionally, analysis of covariance will be used in primary end point analysis as supplemental analysis; the covariates include the participants' dosed days, gender, age and weight.

In additional to general statistical methods, the mixed model for repeated measures will also be used in secondary end points analysis.

For safety analysis, the AEs and abnormal findings in laboratory tests will be listed with the relationship to the study treatments. Fisher's exact test will be used to compare the rates of participants who have at least one AE between the study and control groups.

Quality control and quality assurance

During the conduct of the study, the investigator or their contracted agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may

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review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow monitors directly accessed to source documents for verification.

Each step will be performed strictly according to the trial protocol. Each step of quality control of measured outcomes will be performed according to the standard operating and quality control procedure.

DISCUSSION

TKA is associated with significant postoperative pain, which adversely affects patients' ability and desire to effectively rehabilitate their knee.[5 6] Inadequate pain control has been correlated with prolonged postoperative bed time, increased incidence of pulmonary infection, DVT, PE and poor functional recovery in some patients after TKA.[8]

Multimodal analgesia is currently recommended for postoperative pain control after TKA.[7 28–30] It basically refers to the administration, via the same route or by different routes, of multiple analgesics to provide superior analgesia and limit side effects and AE. Multimodal analgesia is achieved by combining different analgesics that act by different mechanisms (eg, NSAIDs, opioids and local anaesthetics), resulting in additive or synergistic analgesia, lower total doses of analgesics and fewer side effects.[28 29] Among multimodal analgesia modalities, NSAIDs, especially selective COX-2 inhibitors, play an important part in the postoperative pain control after TKA.[30]

Non-selective NSAIDs may cause gastrointestinal (GI) and haematological AEs, compromise platelet function,[31] and are associated with increased postoperative bleeding and increased blood transfusion requirements after joint arthroplasty surgery.[32]

Selective COX-2 inhibitors display similar anti-inflammatory properties with traditional NSAIDs, but lack many of the side effects associated with NSAIDs because they spare the COX-1 enzyme and have no clinically significant effect on platelet or GI function.[31 33 34]

Parecoxib sodium (parecoxib) is the injectable prodrug of valdecoxib and is the only parenteral formulation of a selective COX-2 inhibitor NSAID.[35] It can be rapidly hydrolysed in vivo to its active form, valdecoxib, which is ~28 000-fold more potent against COX-2 than COX-1.[36] Following intravenous injection, parecoxib is rapidly converted to valdecoxib, the pharmacologically active substance, by enzymatic hydrolysis in the liver. AUC and Cmax following two times a day administration is linear up to 50 mg intravenous and 20 mg intramuscular. Following single intravenous and Intramuscular doses of parecoxib sodium 20 mg, Cmax of valdecoxib is achieved in ~30 min and ~1 hour, respectively. After intravenous or intramuscular dosing of parecoxib sodium, the elimination half-life (t1/2) of valdecoxib is about 8 hours.[37]

Parecoxib has been demonstrated as effective in several models of postoperative pain[38] with no effect on platelet function or gastric mucosa at doses up to 40 mg two times a day.[39] Some recent literature[40 41] also revealed that 40 mg of intravenous administered parecoxib can alleviate the anxiety during the perioperative period of TKA, which consequently led to better satisfaction scores and overall experiences for the patients. Celecoxib, another oral specific COX-2 inhibitor, was shown as having short-term pain reduction and morphine sparing effect in patients undergoing TKA,[13] as well as improving functionality recovery if prolonged use up to 6 weeks postoperatively.[11]

Treatment of postoperative pain with intravenous with or without subsequent oral COX-2 specific inhibitor has been demonstrated as effective in many postoperative pain models.[15–19] Significant morphine sparing effect and reduction of opioid distressed symptoms were also observed. Combination of intravenous parecoxib and oral valdecoxib was used for <2 weeks in most of the previous studies. In these studies,[15–19] short-term postoperative pain control and morphine sparing effect were evaluated. However, to the best of our knowledge, no study has investigated the effect of prolonged (6 weeks) sequential treatment of intravenous parecoxib and oral celecoxib on the medium-term functionality recovery.

We present here the protocol of the PIPFORCE study, which aims to investigate the sequential analgesia regimen with intravenous parecoxib followed by oral celecoxib for postsurgical analgesic treatment in patients with OA undergoing TKA. Participants will receive study medication consisting of the parecoxib injection in analgesic doses or matching placebo followed by oral celecoxib in acute pain doses or matching placebo in a double-blind fashion. The hypothesis is that participants treated with parecoxib/celecoxib will consume less morphine over the 2 weeks postoperative period, achieve improved pain control over the study period, quicker return to functionality, and have less opioid adverse events than those treated with opioids alone over the 12-week recovery phase. Both treatment groups will be able to use open-label rescue medication with opioids.

The possible limitations of the PIPFORCE study are listed as follows: First, since the four study centres of this multicentre RCT study are all from mainland China, the future results of the PIPFORCE study should be explained with this concern and require further validation studies in data sets from other institutions outside China. Second, the PIPFORCE study does not investigate the long-term (eg, >3 months) effects of the sequential treatment on inflammation control and functional rehabilitation after TKA. Finally, cytokines of synovial fluid, as one of the exploratory end points, will be tested in this study with the aim of observing the trend of change of local inflammation. However, the synovial fluid tested after surgery is actually obtained from the wound drainage and inevitably contains blood, which will compromise the test accuracy. We will ensure that the same technique is used to obtain the synovial fluid sample in both groups to guarantee the comparability.

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In addition, we will also observe peripheral blood cytokines as the reference.

In spite of these possible limitations, the contribution of the PIPFORCE study is expected to provide a comprehensive understanding of how the sequential regimen with intravenous parecoxib followed by oral celecoxib affects postoperative pain relief, inflammation control and functional rehabilitation in patients with OA undergoing TKA. The completion of this study will provide solid evidence for the efficacy and safety of the clinical use of the sequential regimen of COX-2 specific inhibitors after TKA surgery. The results will assist in optimising NSAIDs use as a part of the standard multimodal analgesic regimen for managing postoperative pain. Furthermore, this project will provide insight into the benefits of prolonged sequential treatment of parecoxib and celecoxib in this population on the medium-term functionality recovery.

Author affiliations
[1]Department of Orthopaedics, Peking Union Medical College Hospital, Beijing, China
[2]Department of Epidemiology and Biostatistics, Institute of Basic Medical Sciences Chinese Academy of Medical Sciences/School of Basic Medicine, Peking Union Medical College, Beijing, China
[3]Department of Orthopaedics, Peking University People's Hospital, Beijing, China
[4]Department of Orthopaedics, The Second Affiliated Hospital of Zhejiang University, Zhejiang Province, China
[5]Department of Orthopaedics, West China Hospital, Sichuan University, Sichuan, China

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Contributors WXS contributed as the senior author and the principal investigator (PI) of this study. ZQY, as the sub PI, wrote the first draft of the manuscript and contributed to the design of the study. BYY, WW, FB, STZ and ZMF advised on the study design. LJH, YSG, SB and PFX refined the protocol. JJM, as the medical statistician for the study, contributed to the statistical design, acquisition and analysis of data for the work. All authors revised the protocol critically for important intellectual content and approved the final manuscript.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Ethics Committee, Peking Union Medical College Hospital, China (Protocol number: S-572).

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