Would High-Dose Corticosteroid Adjuvant To Multimodal Cocktail Periarticular Injection Contribute To Prolonged Pain Control and Better Recovery After Total Knee Arthroplasty?: Study Protocol for a Double-Blinded, Randomized, and Placebo-Controlled Trial

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Research Article

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Abstract

Background

Enhanced recovery after total knee arthroplasty (TKA) has been suggested to enhance postoperative recovery. The use of multimodal cocktail periarticular injection (MCPI) to control the pain of TKA has gained wide acceptance. MCPI containing corticosteroids is believed to be an effective solution because of its local anti-inflammatory effects and ability to reduce the local stress response postoperatively. However, there is conflicting evidence about its benefits. This trial aims to compare MCPI containing a high dose of corticosteroid, MCPI containing a normal dose of corticosteroid, and MCPI without a corticosteroid during TKA to assess the effectiveness of MCPI containing corticosteroid in postoperative pain relief, functional improvement, rescue analgesia and side effects. This will provide evidence regarding the effectiveness of high-dose corticosteroids on prolonged pain control and better recovery after total knee arthroplasty.

Methods/design

This trial is a double-blinded randomized, placebo-controlled study. A total of 234 patients will be randomized into 3 groups to receive a high dose of betamethasone MCPI (group H), a normal dose of betamethasone MCPI (group N), and a nonbetamethasone MCPI (group C). The following indexes will be recorded and analyzed: knee pain at rest and bending at 90° at 6 h, 24 h, 48 h, 72 h, 5 days, 14 days, and 30 days after surgery; 1-minute walking ability and circumference around patella at 2, 4, 7, 14, and 30 days after surgery; HSS score at 14 and 30 days after surgery; C-reactive protein and blood sedimentation as well as blood sugar at 2, 4, 7, 14, 30 days after surgery; additional morphine analgesics consumption; and side effects.

Discussion

The results from this study will provide clinical evidence on the effectiveness of MCPI-containing corticosteroids in postoperative pain relief, functional improvement, rescue analgesia, and side effects as well as evidence on the efficacy of high-dose corticosteroids for leading to prolonged pain control and better recovery after TKA.

Trial registration

Chinese Clinical Trial Registry ChiCTR2000038671. Registered on 27 September 2020

Background

Total knee arthroplasty (TKA) has been reported to be the most effective procedure for pain relief in patients with advanced osteoarthritis. Enhanced recovery after TKA has been advocated as an evidence-based perioperative care protocol to enhance postoperative recovery in several European countries [1, 2, 3]. The stress response after TKA is associated with postoperative nausea and vomiting [4], pain [5], fatigue [6], and decreased muscle strength [7]. Thus, decreasing the inflammatory response after surgery is important for the TKA-enhanced recovery protocol. The use of multimodal cocktail periarticular injection (MCPI) to control pain after TKA has gained wide acceptance [8, 9, 10]. The agents mostly used in MCPI typically include corticosteroids, local anesthetics, opioids, and nonsteroidal anti-inflammatory drugs (NSAIDs) [11]. Corticosteroids are believed to be a key component because of their local anti-inflammatory effects and their ability to reduce the local stress response to surgery [12]. However, there is conflicting evidence about its benefits. Some studies have shown that postoperative pain is improved with corticosteroids [13–16], whereas others have shown no benefit [17, 18]. The role of MCPI-containing corticosteroids in enhanced recovery after TKA remains inconclusive. Therefore, we designed a three-arm, double-blinded randomized controlled trial containing a high or normal dose of MCPI or an MCPI without corticosteroids to assess postoperative pain relief, functional improvement, rescue analgesia, and side effects, thereby evaluating whether high-dose corticosteroids MCPI contribute to prolonged pain control and better recovery.

Methods/design

Study design

This trial is a randomized, double-blinded controlled study, and was approved by the ethics committee of the Second Affiliated Hospital, Guangzhou University of Chinese Medicine (ethics number: ZF2020-031-01). The trial will be conducted in accordance with the Helsinki Declaration and monitored by the trial agency at the Guangdong Provincial Hospital of Chinese Medicine.

Recruitment and consent

Patients diagnosed with severe knee osteoarthritis (OA) and scheduled for total knee arthroplasty (TKA) will be recruited from the Department of Orthopedics, Second Affiliated Hospital, Guangzhou University of Chinese Medicine, with a target sample size of 234 subjects. All candidates will go through a standardized interview process and receive more information about the study and treatments. The participants' written consents will be obtained. The purpose, procedures, and potential risks and benefits of the study will also be explained thoroughly to the participants. Participants are able to withdraw from the study at any time without consequence. The trial will be executed from October 2020 to July 2022, including enrollment and follow-up. (see Fig. 1).

Inclusion criteria

The inclusion criteria for this study will be as follows:

- Meet the diagnostic criteria for knee osteoarthritis

- American Society of Anesthesiologists (ASA) physical status I-II
- Scheduled for unilateral total knee arthroplasty
- Patients aged 50 ~ 80 years old
- Willingness to give written informed consent and to participate in and comply with the study

Exclusion criteria

Participants meeting one or more of the following criteria will be excluded:

- serious mental illness, psychological problems, and those unable to communicate
- patients with cardiovascular diseases, diabetes mellitus, and poor perioperative glycemic control (fasting plasma glucose > 8 mmol/L); severe renal dysfunction, severe hepatic dysfunction, history of gastric ulcer, and coagulation disorder
- central and peripheral nervous system problems that would not allow completion of the postoperative rehabilitation scheme
- alcohol and drug abuse
- allergies to the ingredients in a multimodal cocktail
- Previous major knee surgery, reoperation, or trauma to the knee within the study period

Interventions

All recruited patients will receive general anesthesia. Cefamandole will be administered intravenously 30 minutes before and after surgery. Low-molecular-weight heparin for thromboprophylaxis will be administered subcutaneously 8 hours postoperatively and then once daily until two weeks.

For multimodal pain management, preoperative oral doses of 400 mg celecoxib will be administered from day 1 before surgery. Postoperatively, all patients will receive 40 mg of parecoxib sodium twice intravenously until postoperative day (POD) 3, followed by oral doses of 200 mg celecoxib every 12 hours until discharge. Tramadol hydrochloride injection will be applied for rescue analgesia.

The same surgeon will perform all operations. A Depuy Attune PS prosthesis (Attune ®; DePuy Synthes, Warsaw, IN) will be inserted via a standard medial parapatellar approach in all patients.

Before wound closure, 80 ml of cocktail analgesic will be injected into the muscle and joint capsule for local infiltration analgesia, containing 300 mg 0.75% ropivacaine, 5 mg morphine, 50 mg flurbiprofen axetil, 0.4 ml 1:1000 epinephrine, and adequate saline.

Betamethasone will be mixed in the multimodal cocktail at 3 ml for high-dose betamethasone group (**group H**), 1 ml for normal-dose betamethasone group (**group N**), and a non-betamethasone group will serve as the control group (**group C**).

Randomization and blinding

Random assignment was performed before surgery by an independent assistant using a computer-generated, blocked random-allocation sequence with a 1:1:1 ratio. Computer-generated numbers will be located in a sealed envelope containing treatment information. After anesthesia, an envelope will be opened by an assisting nurse who is not involved in the study, and cocktail analgesics will be made according to the envelope. Milky white flurbiprofen axetil injection will be used as an ingredient of cocktail analgesics, which will guarantee that there are no differences in the appearance of the three groups; thus, the surgeons will be blinded. The outcome measurement will be performed by a blinded assessor who will not be involved in the randomization and blinding process. The patients will be blinded due to general anesthesia.

Primary outcome measures

The primary outcomes of this trial will be the postoperative VAS pain score at rest and the strongest pain experienced during knee flexion. The VAS score will be evaluated by an independent assessor at preoperative day 1, postoperative 6, 24, 48, and 72 hours; day 5 and 14 after the surgery.

Secondary outcome measures

Postoperative 1-minute walking ability

Physical activity is an important aspect of day-to-day life, and walking capacity is a measure of exercise tolerance requiring muscle strength. Walk tests measure the distance walked over a definite time period, with greater distances indicating better performance [19, 20]. The 1-minute walk test will be measured on preoperative days 1, POD2, 4, 7, 14, and 30.

Rescue analgesia

Tramadol injection will be used as rescue analgesia whenever the patients experience VAS exceeding 5. The application time and total amount of rescue analgesia will be recorded postoperatively.

Other rehabilitation-related outcomes

The circumference of the knee has been shown to have acceptable reliability for the determination of gross changes in knee swelling and inflammatory status in patients post-surgery [21]. Knee swelling was measured using the circumference of the knee at the mid-portion of the patella with the knee in full extension. Measurements were then taken 10 cm proximal to the superior pole of the patella (thigh) and 10 cm distal to the inferior pole of the patella (calf). The skin is marked at these points, and the tape measure is placed circumferentially around the limb. The circumference at three measurement positions will be measured on preoperative day 1, POD 2, 4, 7, 14, and 30.

The Knee Society knee score will be applied to evaluate knee function on preoperative day 1, POD14, 30.

Safety

The presence of side effects during the postoperative period will be recorded, including nausea, vomiting, constipation, wound healing status, and other adverse events. Perioperative changes in serum C-reactive protein (CRP), interleukin 6 (IL-6), erythrocyte sedimentation rate (ESR), and blood glucose (Glu) will be noted on POD1, 7, 14, and 30.

Sample size

Calculation of sample size was based on previous studies. Ikeuchi et al. [13] reported that POD3 VAS scores were 27 ± 16 mm in the steroid group and 43 ± 18 mm in the control group. Research in Kwon et al. [14] reported that POD3 VAS scores were 35 mm in the steroid group and 41 mm in the control group. We assumed that the mean difference in the visual analog scale (VAS) score between the high-dose betamethasone group and control group was 0.8, and the mean difference between the normal-dose betamethasone group and control group was 0.4. An estimated standard deviation (SD) of 1.5, significance level (α) of 0.05 (two-sided) and power of test (β) of 0.8000 will be adopted. Based on the former data, the sample size calculation will be 69 participants per group. Assuming a dropout rate of 10%, the final sample size will be 78 participants per group, and a total of 234 participants for three groups will be required.

Data analysis

Perioperative outcomes will be summarized using the mean $\pm$ SD for continuous variables and the ratio for categorical variables. All statistical analyses will be conducted using SPSS software for Windows 13.0. For continuous variables, analysis of variance (ANOVA) will be used to compare the respective differences in intragroup changes before and after surgery, and Dunnett's t test will be conducted to compare between-group differences. For categorical variables, the chi-square test will be conducted to compare intragroup differences, and partitions of chi-square methods will be used to compare between-group differences. The significance level will be set to $\alpha = 0.05$.

Discussion

In TKA, an enhanced recovery strategy requires improved patient comfort during hospital stays and accelerated discharges. Consequently, measures to control pain and accelerate rehabilitation are significant. Although the MCPI technique has been proven to be a safe and cost-effective measure, the gold standard for drug combinations has not yet been well established. Corticosteroid addition to MCPI is believed to be a key component because of its local anti-inflammatory effects and ability to reduce the local stress response after surgery. However, there is conflicting evidence about its benefits on pain control after TKA. Christensen et al.[18] conducted a randomized controlled trial that compared patients who had MCPI with 40 mg of methylprednisolone or without corticosteroids, and the only significant result was a decreased LOS in the steroid cohort (2.6 vs. 3.5 days). There was no difference in pain scores, ROM, or Knee Society Scores at any time point. Chia et al.[17] compared patients who had an MCPI containing high- or low-dose corticosteroid with patients' MCPI without corticosteroid, and they were unable to find any significant clinical effect on postoperative ROM advantage and pain relief at the

two different dosages. In contrast, Seah et al. [16], who used 40 mg of triamcinolone acetate, found a significant reduction in early postoperative pain scores as well as lasting increases in ROM in the steroid group. Wang et al.[10] found that adding corticosteroids to an analgesic cocktail can prolong the analgesic effects of local anesthetics, reduce inflammation, slightly improve immediate postoperative pain relief, and accelerate recovery in the first 24 h after TKA. They concluded that the additional analgesic effects of using corticosteroids were mild and transient, and prospective studies are still needed to determine the best cocktail of PIA. A meta-analysis by Chai et al.[22] demonstrated that cocktail analgesia containing corticosteroid periarticular injection did not contribute to pain relief within 12 hours postoperatively; from 24 to 72 hours, it significantly decreased the pain score at rest and reduced total rescue opioids. Another meta-analysis study recently by Li et al. [23] showed that adding corticosteroids to multimodal cocktail periarticular injection can relieve the POD1, POD2 and POD3 pain intensity at rest after TKA, with no significant difference in VAS score at the operation night, POD4, POD5, POD7, and two weeks after the operation. Due to these conflicting results, we plan to design a three-arm, double-blinded randomized controlled trial containing a high or normal dose of corticosteroids MCPI, and a noncorticosteroids MCPI to assess its effectiveness in postoperative pain relief, functional improvement, rescue analgesia, and side effects. This study will also provide clinical evidence on the effect of high-dose corticosteroids adjuvant to MCPI on prolonged pain control and better recovery after total knee arthroplasty.

Trial status

Recruitment commenced in October 2020, and the trial is scheduled to end in July 2022.

Abbreviations

TKA, total knee arthroplasty; MCPI, multimodal cocktail periarticular injection; POD, postoperative day; OA, knee osteoarthritis; VAS, visual analog scale; A-ROM, active range of motion; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; Glu, blood glucose.

Declarations

Ethnic approval and consent to participate

This trial was approved by the ethics committee of the Second Affiliated Hospital, Guangzhou University of Chinese Medicine (ethics number: ZF2020-031-01). Written, informed consent to participate will be obtained from all participants.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study will be available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

DG conceived the study and prepared the initial protocol and was in charge of coordination. CFZ and RH contributed equally to this work, drafted the manuscript, and participated in the study design. DKL and JL participated in the protocol and performed surgery. XML and LLZ helped to develop the study analysis. All authors read and approved the final manuscript.

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Figures

Figure 1

Study flowchart