Randomized Trial

Preemptive Analgesia with Parecoxib in Total Hip Arthroplasty: A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Total hip arthroplasty (THA) is a well-accepted surgical treatment for terminal hip diseases.

Objective: To evaluate the effect of preemptive analgesia with parecoxib in patients undergoing primary unilateral THA.

Study Design: A randomized, double-blind, placebo-controlled study.

Setting: This study was conducted at Peking Union Medical College Hospital and Beijing Jishuitan Hospital in Beijing, China.

Methods: A total of 94 patients scheduled for primary unilateral THA in 2 centers (Peking Union Medical College Hospital and Beijing Jishuitan Hospital) were randomly assigned to receive 40 mg parecoxib (n = 48) or 0.9% normal saline solution (n = 46) 30 minutes before incision. All patients received standardized intravenous patient-controlled analgesia (PCA) postoperatively. Preoperative baseline data, surgery-related conditions, postoperative Visual Analog Scale (VAS) pain score, cumulative narcotic consumption of PCA, and complications were compared between the parecoxib group and the placebo group.

Results: There were no significant differences in postoperative VAS pain score, cumulative narcotic consumption of PCA, proportion of analgesic remedy, and complications between the 2 groups.

Limitations: Only a single dose of parecoxib was used without including a dose-dependent control group.

Conclusion: A single dose of parecoxib 30 minutes before incision did not provide effective preemptive analgesia for the management of postoperative pain after primary unilateral THA. The possible effect of preemptive analgesia with parecoxib needs further investigation.

Key words: Total hip arthroplasty, pain, parecoxib, COX-2 selective inhibitor, preemptive analgesia, clinical trial, patient-controlled analgesia, analgesics

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Total hip arthroplasty (THA) is a well-accepted surgical treatment for terminal hip diseases. It can correct deformities and effectively improve joint function and quality of life. Perioperative pain control has direct influences on patient recovery and surgical outcomes. A valid perioperative analgesic protocol can relieve pain and promote patient exercising and early rehabilitation (1).

Preemptive analgesia is an emerging analgesic mode that, according to the American Society of An-

esthesiologists (ASA), (a) starts before surgery; (b) prevents the establishment of central sensitization caused by incisional injury (covers only the period of surgery); and (c) prevents the establishment of incisional and inflammatory injuries (covers the period of surgery and the initial postoperative period) (2). Preemptive analgesia may relieve postoperative pain and reduce analgesic consumption. Parecoxib is a COX-2 selective inhibitor and has been used in preemptive analgesia with conflicting results (3,4). In one study with patients undergoing general surgery, a single preoperative intramuscular injection of parecoxib 40 mg provided good postoperative analgesia (3). However, another study with patients undergoing THA found that intravenous administration of parecoxib did not have any preemptive analgesic effect (4).

This multi-center, randomized, double-blind, placebo-controlled trial was designed to evaluate the efficacy and safety of preemptive analgesia with parecoxib for perioperative pain management after THA.

Methods

Inclusion and Exclusion Criteria

Our study was approved by the ethics committee and written informed consent was obtained from each patient. Patients scheduled for primary unilateral THA from December 2014 to June 2015 were recruited. The inclusion criteria were: age ≥ 18 years, intact cognitive function, ASA score ≤ 2, and scheduled for primary unilateral THA. Patients with any of the following conditions were excluded: allergy to parecoxib sodium; history of anaphylaxis, especially dermatological manifestations, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme; allergy to sulfonamides; active gastrointestinal bleeding or ulceration; allergy to aspirin, nonsteriod antiinflammatory drugs (NSAIDs), or COX-2 inhibitors; pregnancy or breastfeeding status; or severe liver dysfunction (serum albumin level < 25 g/L, or Child-Pugh score ≥ 10).

Randomization and Power Analysis

Patients, surgeons, anesthesiologists, and investigators were all blind to the treatment allocation. A randomized sequence was generated using the RandA 1.0 software (Pulande, Beijing, China). Power analysis showed that 46 evaluable patients per treatment group were needed to achieve 90% power to detect a 2.3-point difference in Visual Analog Scale (VAS) pain scores (common standard deviation [SD 3.0]) and 0.1 mg difference in total patient-controlled analgesic (PCA) drug consumption (common SD 0.67) between the treatment groups given a one-sided .05 alpha level with sequential testing. The sample size of 46 patients per treatment group provided 96% power to detect a 2.3-point difference in VAS pain scores, 92% power to detect a 0.1 mg difference in total PCA drug consumption, and 90% power to detect both. Finally, 94 patients were recruited into our study and were randomly allocated to the parecoxib group (48 patients) or to the placebo control group (46 patients).

Surgical Procedures and Rehabilitation Exercises

The operations were completed by 4 senior surgeons at Peking Union Medical College Hospital and Beijing Jishuitan Hospital. All operations were performed using the posterolateral approach under general anesthesia. Patients were encouraged to walk with the walkers during postoperative days 1-3.

Analgesia Protocol

Patients in the parecoxib group were given 40 mg parecoxib diluted to 5 mL 0.9% normal saline 30 minutes before the incision, and 20 mg parecoxib diluted to 5 mL 0.9% normal saline every 12 hours for 2 postoperative days. Patients in the placebo group were placed on the same protocol but received normal saline instead of parecoxib.

PCA was used in both groups for 3 postoperative days with 1 mg morphine per press. There was no background or loading infusion of morphine. Other analgesics such as tramadol or pethidine were used when necessary, and their consumption was added to the total quantity after conversion to the morphine equivalent dose.

Data Collection

Demographics such as gender, age, body mass index (BMI), diagnosis, preoperative comorbidity, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores were recorded. Operation-related data were also collected including operation duration, blood loss, postoperative drainage, and blood transfusion. VAS scores at rest and during activity were recorded at the following time points: before the operation; while in the post-anesthesia care unit (PACU); 6, 12, and 24 hours post-operation; and daily during postoperative days 2-5.

Statistical Analysis

Continuous data are presented as mean ± standard deviation. Categorical data are presented as frequencies. Comparisons were made using the Student's t test or the chi-square test. All statistical analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, IL). A *P* value of less than .05 was considered statistically significant.

Results

There was no difference in baseline data between the parecoxib group and the placebo group (Table 1). The 2 groups also did not differ significantly in their operation duration, blood loss, postoperative drainage, blood transfusion, complications, and PCA consumptions (Table 2). No significant difference between the two groups was found in their postoperative VAS scores, either at rest or during activity (Table 3, Fig. 1).

The most common adverse events observed in our study were headache/dizziness (26.60%, 25/94) and nausea/vomiting (14.89%, 16/94), which did not differ significantly between the parecoxib group and the placebo group (*P* = 1.000). The adverse effects were resolved with proper treatment. All wounds achieved primary healing. The postoperative vital signs were stable; and the liver, renal, and coagulation functions were normal.

Table 1. *Baseline information of the patients.*

	Parecoxib group (n = 48)	Placebo group (n = 46)	*P*-value
Gender (male/female)	22/26	16/30	0.300
Age (year)	55.19 ± 10.97	57.22 ± 12.51	0.405
Height (cm)	163.06 ± 22.53	162.54 ± 8.30	0.884
Weight (kg)	69.24 ± 12.08	66.74 ± 10.44	0.287
BMI (kg/m^2)	24.87 ± 3.33	25.19 ± 3.17	0.640
VAS at rest	1.73 ± 1.61	1.61 ± 1.58	0.715
VAS during activity	4.54 ± 1.89	4.72 ± 1.88	0.653
WOMAC score	47.70 ± 20.96	47.08 ± 20.95	0.886
Diagnosis			
OA	18	21	0.530
ONFH	21	16	0.405
FNF	2	6	-
DDH	6	2	-
AS	1	1	-
Comorbidity			
Hypertension	9	15	0.158
Diabetes mellitus	4	9	0.142
Total	12	20	0.082

BMI, body mass index; visual analog scale, VAS; OA, osteoarthritis; ONFH, osteonecrosis of the femoral head; FNF, femoral neck fracture; DDH, developmental dysplasia of the hip; AS, ankylosing spondylitis.

Table 2. *Comparison of operation data, complications, and PCA consumptions.*

	Parecoxib group (n = 48)	Placebo group (n = 46)	*P*-values
Operation duration (min)	92.33 ± 28.84	98.50 ± 29.20	0.306
Blood loss (mL)	372.71 ± 201.13	423.91 ± 219.53	0.241
Postoperative drainage (mL)	162.60 ± 157.07	138.59 ± 137.99	0.434
Blood transfusion (mL)	89.38 ± 177.97	95.65 ± 187.33	0.868
Complications			
Nausea and vomiting	11	5	0.171
Headache and dizziness	10	15	0.246
Rashes	1	0	
Constipation	3	3	
Gastrointestinal bleeding	0	0	
Cardiovascular events	0	0	
Delayed wound healing	0	0	
Total	18	17	1.000
PCA consumption (mg)	0.18 ± 0.18	0.17 ± 0.16	0.770

PCA, patient-controlled analgesia

Table 3. *The postoperative VAS scores of the 2 groups.*

VAS	Parecoxib group (n = 48)	Placebo group (n = 46)	*P*-value
PACU	1.27 ± 1.82	1.30 ± 1.70	0.927
Postoperative 6 h at rest	2.21 ± 2.02	2.46 ± 2.16	0.566
Postoperative 6 h during activity	3.54 ± 1.70	3.65 ± 1.91	0.768
Postoperative 12 h at rest	2.56 ± 2.19	2.43 ± 2.11	0.774
Postoperative 12 h during activity	3.42 ± 1.60	3.85 ± 1.69	0.206
Postoperative 24 h at rest	2.50 ± 2.27	2.54 ± 2.25	0.926
Postoperative 24 h during activity	3.58 ± 1.70	3.87 ± 1.88	0.440
Postoperative day 2 at rest	2.04 ± 1.90	2.20 ± 1.66	0.677
Postoperative day 2 during activity	3.42 ± 1.82	3.83 ± 1.94	0.293
Postoperative day 3 at rest	1.38 ± 1.47	1.67 ± 1.48	0.328
Postoperative day 3 during activity	2.69 ± 1.88	3.26 ± 1.77	0.132
Postoperative day 4 at rest	1.29 ± 1.15	1.37 ± 1.12	0.740
Postoperative day 4 during activity	2.63 ± 1.61	2.91 ± 1.56	0.381
Postoperative day 5 at rest	1.17 ± 0.91	1.24 ± 0.90	0.698
Postoperative day 5 during activity	2.52 ± 1.57	2.98 ± 1.34	0.133

VAS, visual analog scale; PACU, post-anesthesia care unit

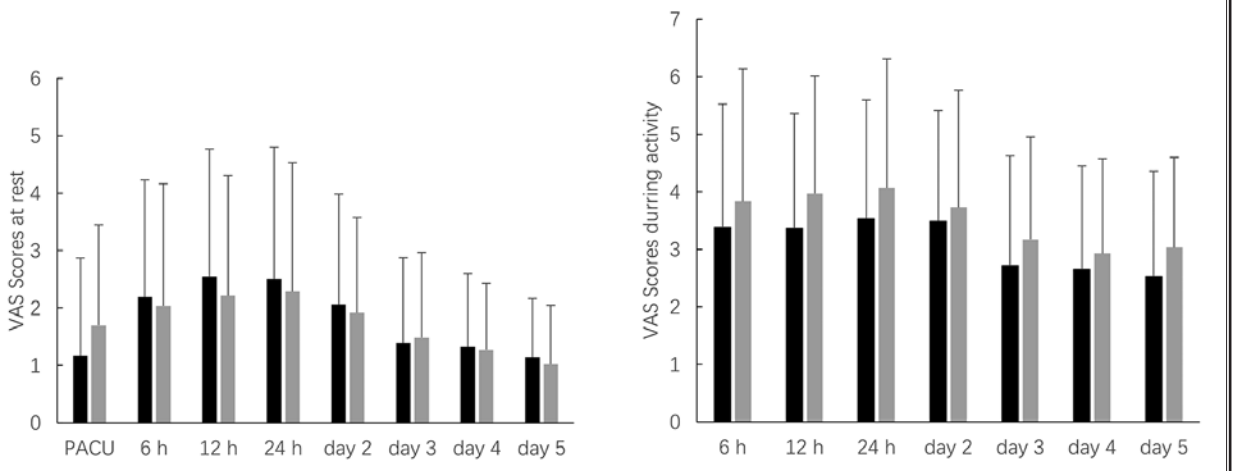

Fig. 1. *Postoperative VAS pain scores at rest (left) and during activity (right) did not differ significantly between the parecoxib group (dark columns) and the placebo group (grey columns). PACU, post-anesthesia care unit.*

Discussion

It has been shown in animals that the central nervous system enters a state of hyperalgesia after noxious stimulation (5). Therefore, the idea of pre-emptive analgesia was proposed with the purpose of blocking the pain sensation center prior to nociceptive stimulation; this process may inhibit hyperalgesia and raise the threshold of pain sensation (6). Despite the many studies investigating the preoperative use of local anesthesia agents, including opioids and NSAIDS (7-10), the value of preemptive analgesia is still controversial (4,11,12).

Opioids have severe adverse effects, and the nonselective NSAIDs are associated with high risk of bleeding due to their inhibition of COX-1. In our study, we focused on the effects of preemptive analgesia with parecoxib, a highly-selective COX-2 inhibitor. It has been suggested that parecoxib could be an alternative to the nonselective NSAID diclofenac for providing preemptive analgesia in patients undergoing general surgery because of its effective postoperative analgesic effect and minimal interference with platelet function (3). In one study, administration of parecoxib before hip arthroplasty did not provide preemptive analgesia, although perioperative parecoxib administration consisting of 2 injections spaced 12 hours apart improved postoperative analgesia over the first 24 hours (4). Another study, involving patients undergoing lumbar spinal fusion, found that preemptive analgesia using both ketorolac and parecoxib resulted in significantly better early postoperative pain control compared to the control group (4,13).

Our study found that pre-incisional administration of parecoxib in patients undergoing THA did not significantly reduce postoperative VAS scores, either at rest or during activity, in comparison with placebo. There are several possible reasons for our findings. First, COX-2 is only one of many pain mediators. In fact, animal experiments and clinical studies have suggested that COX-1 is also involved in the pain process (14,15). Parecoxib is a selective inhibitor of COX-2; therefore, its use may not effectively block the synthesis of pain mediators effected by COX-1. Second, the THA operations were performed by 4 surgeons at 2 centers. Confounding factors, such as the artificial hip joints and the negative pressure drainage, could influence the evaluation of the preemptive analgesic effect of parecoxib.

Limitations

Our study has several limitations. First, only a single dose of parecoxib was used without including a dose-dependent control group. Therefore, we could not detect the most effective and appropriate dose of parecoxib for the purpose of preemptive analgesia in THA. Second, the sample size of our study was relatively small. Third, our patients were not followed up after discharge, so VAS pain scores and data on hip function were not collected after that point. Finally, the postoperative use of tramadol may have had significant clinical effects on central sensitization and the development of hyperalgesia.

Conclusion

Preemptive analgesia with one dose of parecoxib before incision does not decrease postoperative pain and cumulative PCA consumption in comparison with placebo among patients undergoing primary unilateral THA. Further investigation is needed to elucidate the mechanisms and clinical efficacy of preemptive analgesia.

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