

Randomized Trial

Pain Management Using Perioperative Administration of Parecoxib for Total Hip Arthroplasty: A Randomized, Double-Blind, Placebo-Controlled Trial

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Disclaimer: Authors Ke Xiao and Lingjia Yu contributed equally. This work was supported by the Program of Beijing Municipal Science and Technology Commission, China (D12110700420000).

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 05-21-2018
Revised manuscript received:
04-09-2019
Accepted for publication:
04-12-2019

Free full manuscript:
www.painphysicianjournal.com

Background: Controlling postoperative pain and improving outcomes after total hip arthroplasty (THA) remain an important challenge, which affects the functional recovery of the hip.

Objectives: To assess the effect of preemptive administration of the selective cyclooxygenase-2 inhibitor parecoxib sodium (PS) after THA.

Study Design: A prospective, randomized, double-blinded clinical trial.

Setting: An academic medical center.

Methods: This randomized double-blind clinical trial compared postoperative analgesia intervention for unilateral primary THA. Patients were assigned in a 1:1 ratio to the PS group and the control group. The PS group received 40 mg dose of PS 30 minutes before incision, 12 hours after THA, and every 12 hours for 2 days postoperatively, and the control group received normal saline solution at the same time point. In addition, both groups received patient-controlled intravenous analgesia of morphine. Perioperative visual analog scale (VAS) scores, cumulative morphine consumption, functional recovery, perioperative bleeding risk, and the selected indicators of the inflammatory response were compared between the PS group and the control group.

Results: From October 2014 to June 2015, 180 patients undergoing unilateral primary THA were screened for this prospective clinical trial. A total of 141 patients were enrolled and randomly assigned into the PS group (n = 69) and the control group (n = 72). Compared with the control group, VAS scores at rest were significantly lower in the PS group at 4, 12, and 24 hours after surgery, and VAS scores during movement were also lower in the PS group at 4, 12, 24, 36, and 48 hours after surgery (all $P < 0.001$). Both the cumulative morphine consumption and its associated nausea and vomiting were reduced in the PS group ($P < 0.001$ and $P = 0.021$, respectively). The length of hospitalization in the PS group was shorter than the control group (PS group 5.91 ± 1.15 days, control group 6.41 ± 1.49 days; $P = 0.019$). The PS group had lower body temperature than the control group at postoperative day (POD) 1 ($P = 0.003$) and POD 3 ($P = 0.001$), and the levels of high-sensitivity C-reactive protein in the PS group at POD 3 ($P = 0.016$) and POD 6 ($P = 0.006$) were also lower than those in the control group. The concentration of interleukin (IL)-6 and IL-10 were significantly different between the 2 groups (IL-6, $P = 0.007$; IL-10, $P = 0.006$) on the first day postoperatively. The PS group was not significantly different from the control group with respect to any outcomes: blood loss, postoperative blood drainage and blood transfusion, and number of days needed to accomplish straight-leg raising and off-bed exercise.

Limitations: PS was used only until POD 2, and there was no long-term follow-up.

Conclusions: Perioperative administration of PS is an effective addition to a multimodal regimen that alleviates postoperative pain, reduces the cumulative morphine consumption, length of hospitalization, and perioperative inflammatory response, without increasing perioperative bleeding risk.

Key words: Parecoxib sodium, multimodal analgesia, total hip arthroplasty, inflammatory response

Pain Physician 2019; 22:575-582

Arthroplasty is the most effective treatment for severe late-stage joint diseases. It can relieve pain, restore joint function, and thus improve quality of life. The long-term effect of arthroplasty has been widely approved (1). Total hip arthroplasty (THA) is one of the most popular types of arthroplasty, but pain after the procedure during the rehabilitation stage is severe. With multimodal pain treatment starting with doses before surgery, it will alleviate pain for the first hours (2). Pain management, as the highest concern of the patients undergoing surgeries (3), is crucial for the patients undergoing THA because favorable pain management enables the patients to perform the rehabilitation exercises earlier and better after surgery (4). The analgesia protocols commonly used are regional nerve block, intraarticular injection, patient-controlled intravenous analgesia (PCIA), and patient-controlled epidural analgesia. The regional nerve block brings satisfactory analgesia results postoperatively, but requires sophisticated techniques of anesthetists, increases operation time, and possibly causes nerve injury and muscle weakness (5). The patient-controlled epidural analgesia is efficacious in terms of pain control, but requires the placement of a catheter through the spinal dura mater and should be reserved for high pain responders, and thus not used routinely (6). Intraarticular injection is effective and widely used, and the efficacy of its different ingredients are still being studied (7). Patient-controlled intravenous morphine is effective in postoperative analgesia, but it causes nausea, vomiting, and thus withdrawal in some patients (8). Therefore, better analgesia methods are being studied relentlessly.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used for perioperative analgesia after arthroplasty, which can diminish inflammation and alleviate pain (9). The main side effects of NSAIDs are nausea, vomiting, rash, headache, and drowsiness, and some other important side effects are ulcers and prolonged bleeding after injury or surgery. Highly selective inhibitors of cyclooxygenase (COX)-2 inhibit COX-2 activity, whereas they do not affect COX-1 function, resulting in a greater reduction of the bleeding risk on perioperative administration of NSAIDs (10). Studies have shown that perioperative administration of selective COX-2 inhibitors (e.g., rofecoxib and celecoxib) reduces postoperative pain and morphine consumption after orthopedic surgeries, whereas it does not increase the risk of bleeding (11,12). The water-soluble parecoxib sodium (PS) is the first selective COX-2 inhibitor that can be

administered via intravenous or intramuscular routes. It has no effect on platelet function, and therefore does not increase bleeding risk during or after surgery. Therefore, PS is suitable for patients who are unable to take oral medications postoperatively because of severe nausea and vomiting (13). Few studies have focused on perioperative administration of PS during THA (14).

We aimed to observe the effectiveness of PS better in the present investigation. We studied the effectiveness of PS in terms of pain control and morphine consumption, the anti-inflammatory influence, and the safety of its perioperative administration. Thus, we conducted a randomized controlled trial to investigate the effects of PS after THA.

METHODS

Ethics Statement

This was a prospective, randomized, double-blind, placebo-controlled study, approved by the ethics committee of Peking Union Medical College Hospital (No. S-503). Data are presented in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement. The protocol for this trial and supporting CONSORT checklist are available as supporting information. The study was registered on ClinicalTrials.gov (NCT02272660), and was conducted at the orthopedics department, Peking Union Medical College Hospital, Beijing, China, and monitored by the Peking Union Medical College Hospital Good Clinical Practice unit. All patients provided written informed consent before participation in the study.

Patients

We recruited patients scheduled for unilateral primary THA from October 2014 to June 2015. Inclusion criteria were patients diagnosed with femoral head avascular necrosis or osteoarthritis, planning to undergo unilateral primary THA under general anesthesia, with American Society of Anesthesiologists physical status I to II. Exclusion criteria included age < 18 years; prior ipsilateral hip surgery; acute trauma; exhibited sensitivity or allergy to PS, opioids, or any other drugs used in the study; alcohol or drug abuse; diabetics; knee arthritis; spinal problems such as herniated discs/stenosis; being pregnant or breastfeeding; and any other conditions that caused inability to cooperate.

Randomization and Blinding

The study medications were consecutively num-

bered in accordance with a computer-generated block randomization list (1:1 ratio, blocks of 10) as subjects were assigned consecutive numbers on enrollment. The investigators, medical staff, and patients were all blinded to the group information. The randomization key was not broken until the enrollment and statistical analyses were accomplished.

Interventions

All the THA operations were completed by a senior surgeon through the posterolateral approach at our medical center. Patients were randomly assigned into the PS group and the control group. The PS group received 40 mg PS 30 minutes before incision, 12 hours after THA, and every 12 hours for 2 days, postoperatively. The control group received normal saline solution instead of PS at the same time points. All the patients were under general anesthesia and received PCIA of morphine, postoperatively. Morphine (2 mg/bolus) was given with a lockout interval of 10 minutes. Pethidine or tramcontin were given if necessary, and the consumption was added to the total amount of morphine consumption after converted.

Data Collection

The demographic variables such as gender, age, body mass index, and surgery duration were recorded. The visual analog scale (VAS) at rest and during movement were also monitored before operation, at 4, 12, 24, 36, and 48 hours, and 3 to 6 days postoperatively. Hip functional recovery, morphine consumption, PCIA duration, and bleeding risks were also documented. Moreover, indicators of inflammatory response, such as body temperature, high-sensitivity C-reactive protein (hs-CRP) level, and serum levels of interleukin (IL)-6 and IL-10 were also collected on hospital admission and 1, 3, and 6 days postoperatively.

Statistics

A sample size of 50 cases per treatment group was sufficient to provide > 90% power to detect a 20% pain relief during the exercise, and 20% difference in morphine consumption with $\alpha = 0.05$ based on previously published data (9,11). Considering a missing rate of 20%, > 120 patients is a reasonable sample size. All data were analyzed using SPSS Version 25.0 (IBM Corporation, Armonk, NY). Continuous variables underwent testing for normality by the Shapiro–Wilk tests. Normally distributed continuous data were expressed as mean \pm standard deviation, and analyzed by the Student t

test or repeated measure analysis of variance with the Tukey post hoc test, as appropriate. Categorical data were presented as frequencies (%) and analyzed by the Pearson chi-square test or the Fisher exact test. A P value < 0.05 was considered as statistically significant.

RESULTS

Patients Characteristics

From October 2014 to June 2015, 180 patients who underwent THA were screened for study participation. A total of 141 patients met the inclusion criteria and were enrolled into our study. No patients were excluded or lost to follow-up (Fig. 1). There was no significant difference between the PS group ($n = 69$) and the control group ($n = 72$) on the patient characteristics at baseline (Table 1).

Effect Outcomes

In general, PS significantly alleviated pain better than placebo the first 2 days after THA. The postoperative VAS scores at rest were significantly lower in the PS group compared with the control group at 4, 12, and 24 hours after surgery (all $P < 0.001$), and the postoperative VAS scores during movement were also lower in the PS group than the control group at 4, 12, 24, 36, and 48 hours after surgery (all $P < 0.001$) (Fig. 2).

The cumulative morphine consumption was also significantly less in the PS group (28.7 ± 9.9 mg) than in the control group (44.9 ± 10.5 mg; $P < 0.001$). Prevalence of postoperative nausea and vomiting was higher in the control group (20.8%; $P = 0.021$). There were no differences between the PS and control groups with regard to urine retention and rashes ($P = 0.643$ and 1.000, respectively). The PS group and the control group showed no significant differences in the number of days needed to accomplish straight-leg raising, off-bed exercise ($P = 0.513$ and 0.730, respectively). The days of hospital stay were significantly shorter in the PS group than the control group ($P = 0.019$). Additionally, PS did not increase the bleeding risk in patients who underwent THA because there was no difference between the PS group and control group with respect to perioperative blood loss, blood drainage, or blood transfusion ($P = 0.306$, 0.177, and 0.563, respectively) (Table 2).

Inflammatory Response

We monitored the indicators of the inflammatory response, including body temperature, levels of hs-CRP,

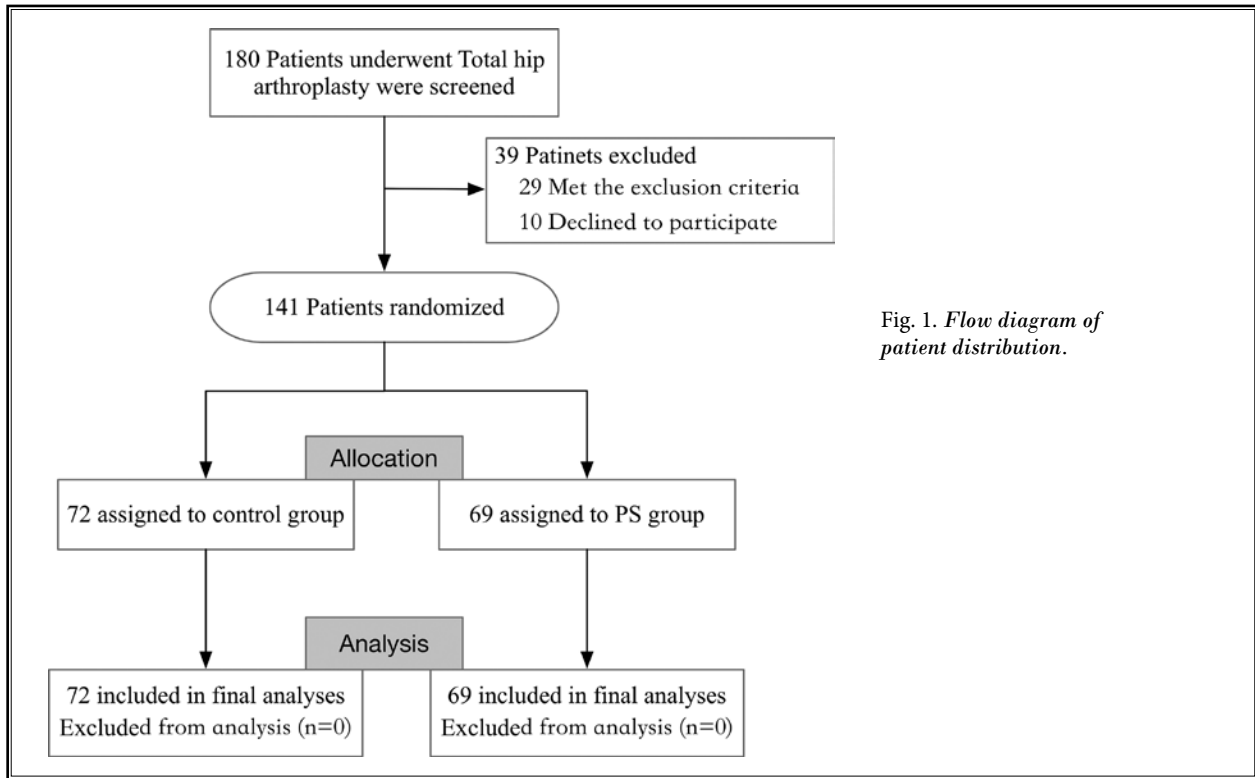


Fig. 1. Flow diagram of patient distribution.

Table 1. Baseline data of participants.

Characteristics	Control Group (n = 72)	Parecoxib Group (n = 69)	t/chi-square value	P value
Age, mean ± SD, y	54.35 ± 11.93	53.79 ± 12.46	-0.259	0.796
Sex (Female/Male), n	40/28	39/27	0.001	0.975
BMI, mean ± SD, kg/m ²	27.18 ± 4.90	27.35 ± 4.15	-0.605	0.545
Pre-OP VAS, rest	1.75 ± 0.74	1.74 ± 0.79	-0.057	0.954
Pre-OP VAS, movement	4.69 ± 0.83	4.68 ± 0.90	-0.057	0.954
Surgery Duration, mean ± SD, min	53.85 ± 1.53	54.41 ± 1.42	-0.259	0.796

SD, standard deviation; BMI, body mass index; Pre-OP, preoperative; VAS, visual analog scale

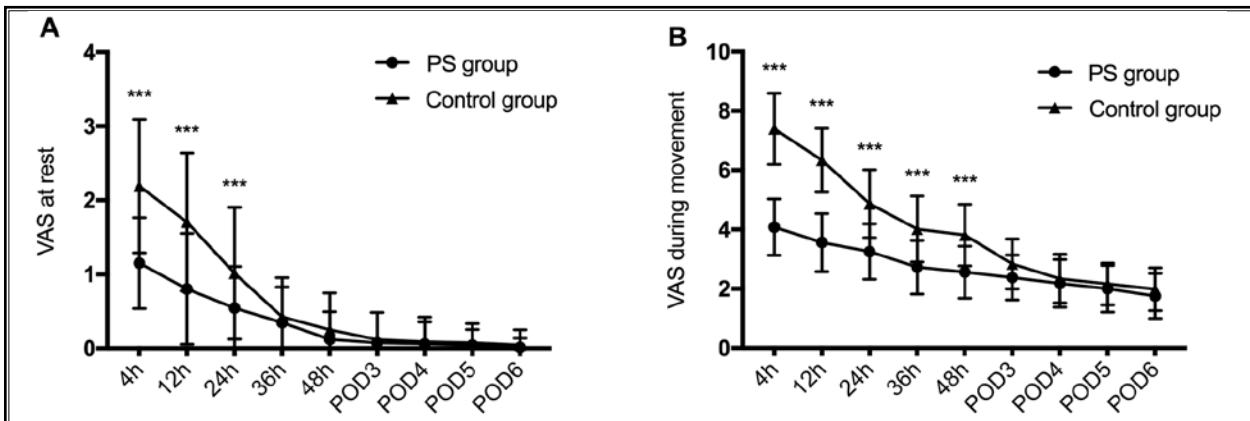


Fig. 2. Postoperative VAS scores at rest (A) and during movement (B) in the PS group and the control group. ***P < 0.001.

Table 2. Effectiveness Outcomes

	Control Group (n = 72)	PS Group (n = 69)	Estimate Effect (95% CI)	P value
Cumulative morphine consumption, mean ± SD, mg	44.9 ± 10.5	28.7 ± 9.9	-16.18 (-19.67, -12.70)	<0.001*
Complications				
Nausea and vomiting, n (%)	15 (20.83)	5 (7.25)	13.59 (2.39, 24.79)	0.021*
Urine retention, n (%)	3 (4.17)	1 (1.45)	2.72 (-2.69, 8.13)	0.643
Rashes, n (%)	1 (1.39)	1 (1.45)	-0.06 (-3.97, 3.85)	1.000
Recovery of function				
straight-leg raising, mean ± SD, days	0.93 ± 0.26	0.89 ± 0.31	-0.033 (-0.13, 0.07)	0.513
off-bed exercise, mean ± SD, days	1.06 ± 0.24	1.05 ± 0.21	-0.013 (-0.09, 0.06)	0.730
length of hospitalization, mean ± SD, days	6.41 ± 1.49	5.91 ± 1.15	-0.503 (-0.96, -0.46)	0.019
Bleeding risk				
Blood loss, mean ± SD, mL	342.7 ± 84.7	346.9 ± 78.7	4.323 (-23.63, 32.28)	0.306
Blood transfusion, mean ± SD, mL	50.0 ± 131.0	36.4 ± 104.7	-13.636 (-54.23, 26.97)	0.177
Postoperative drainage, mean ± SD, mL	182.8 ± 86.8	162.6 ± 88.2	-20.228 (-56.80, 16.35)	0.563

SD, standard deviation; BMI, body mass index; Pre-OP, preoperative; VAS, visual analog scale

IL-6, and IL-10 preoperative and postoperative. There were no significant differences between the 2 groups with regard to all these indicators, preoperatively. However, some of the indicators of the inflammatory response were lower in the PS group postoperatively. Body temperature in the PS group was lower than that in the control group at postoperative day (POD) 1 ($P = 0.003$) and POD 3 ($P = 0.001$), and the levels of hs-CRP were also lower in the PS group than the control group at POD 3 ($P = 0.016$) and POD 6 ($P = 0.006$). There were significant differences between the 2 groups in the levels of IL-6 and IL-10 at POD 1 (IL-6, $P = 0.007$; IL-10, $P = 0.006$), but not at POD 3 (IL-6, $P = 0.140$; IL-10, $P = 0.732$) and POD 6 (IL-6, $P = 0.902$; IL-10, $P = 0.827$) (Fig. 3).

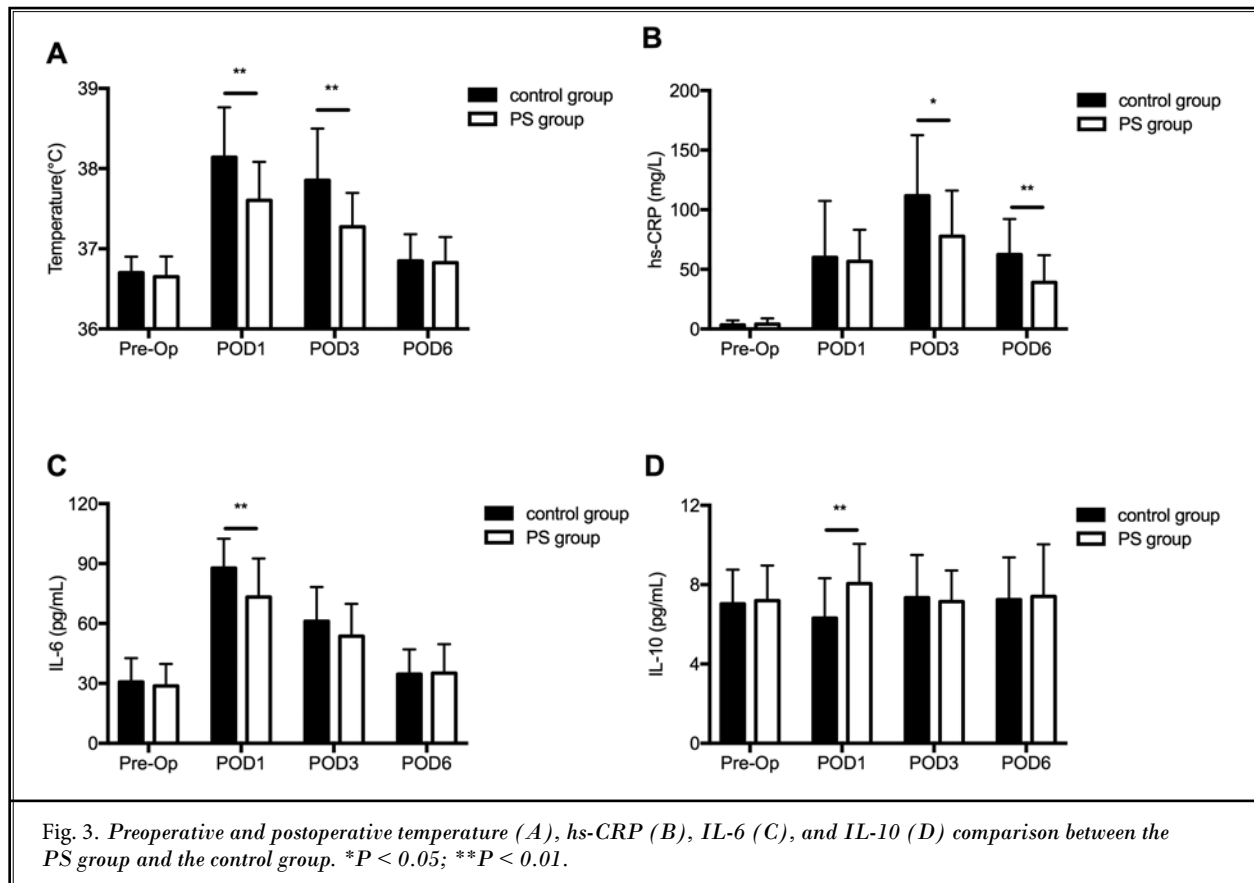
DISCUSSION

We found that multimodal perioperative administration of PS was an effective addition to a multimodal regimen, demonstrating a reduction postoperative VAS scores, cumulative morphine consumption, the nausea and vomiting complications, and the inflammatory response after THA, without increasing the risk of perioperative bleeding.

Influence on Morphine Consumption and Pain Score

PS is the first selective COX-2 inhibitor that can be administered via intravenous or intramuscular routes,

thereby suitable for patients suffering from severe nausea and vomiting postoperatively (15). Recently, additional studies focusing on the analgesic effect of PS after total knee arthroplasty (TKA) demonstrated that perioperative administration of the selective COX-2 inhibitors and PS reduced postoperative pain and morphine consumption after TKA (16-18). This phenomenon is probably due to synergism between NSAIDs and opioids because they elicit their effects at different sites during the transduction and transmission of pain (19). Thus, it is recommended to combine selective COX-2 inhibitors and opioids for pain management after arthroplasty (20). However, as far as we know, only a few studies have focused on perioperative administration of parecoxib for THA, so we performed this trial. According to our study, perioperative administration of PS combined with PCIA can reduce opioid consumption compared with the mere use of PCIA of morphine postoperatively. Also, the VAS scores of the PS group were lower than those of the control group, even on the second day after THA. This phenomenon could be the result of the preemptive analgesic effect of perioperative administration of PS (14). Additionally, PS reduced postoperative morphine consumption by approximately 35% compared with the control group, and also decreased its related adverse events, such as nausea and vomiting, which is in accordance with previous reports (9,21).



Influence on Perioperative Safety and Functional Recovery

Conventional nonselective NSAIDs inhibit COX and reversibly interfere with platelet function, thereby increasing bleeding risk, whereas selective COX-2 inhibitors such as parecoxib have fewer antiplatelet effects (22). In our study, there was no significant difference between the PS group and the control group with regard to blood loss, postoperative blood drainage, or blood transfusion. These observations are in accordance with the mechanism of selective COX-2 inhibitor action, and proved that PS was not increasing the bleeding risk during the perioperative period.

In addition, PS combined with PCIA alleviated the postoperative pain of THA, thus decreasing the length of hospitalization in the PS group. The time needed to perform active straight-leg raising and off-bed exercise of the 2 groups were all within the first 2 days after operation. Although no significant differences were found between the 2 groups, the average time needed

in the control group to perform the rehabilitation was longer than the PS group, which indicated that the use of PS may possibly promote the functional recovery after THA.

Anterior-posterior and lateral x-rays of hips were taken before discharge from the hospital, and no sign of radiolucent lines were observed at the bone-prosthetic contact surface in the acetabular or femoral area of the 2 groups, which indicated that the prostheses were stable, and PS did not affect bony healing, at least for the perioperative period. Long-term follow-up is still needed to detect if PS would exert a negative effect on bony incorporation around the prostheses.

Influence on Inflammatory Response

The perioperative inflammatory responses were also monitored, which have yet to be investigated in studies on THA. On inflammatory stimulation, the synthesis of COX-2 rises and the production of prostaglandins (PGs) increases. PS can decrease the produc-

tion of PGs, and therefore alleviate the postoperative inflammatory response (23). Cytokines play key roles in inflammation regulation. IL-6 is a major proinflammatory cytokine. Serum levels of IL-6 increase significantly shortly after surgery, and its concentration is in direct proportion to the trauma caused by surgery. Contrary to the function of IL-6, IL-10 can reduce IL-6 expression through the transcription factor, nuclear factor-kappa B, and thus inhibit inflammation (24). Mahdy et al (25) reported that perioperative use of NSAIDs can significantly reduce IL-6 levels in serum 12 hours after surgery, and elevate IL-10 levels in serum 6 hours after surgery. Parecoxib showed the identical effect in our study. Considering that parecoxib was administered until POD 2, the levels of IL-6 and IL-10 presented a significant difference between the PS group and the control group at POD 1, whereas no difference was shown at POD 3 and POD 6. Therefore, perioperative administration of PS can alleviate the postoperative inflammatory response and does not change the expression of IL-6 and IL-10 in the long-term after surgery, which could help keep the balance between the expression and removal of

the cytokines. Moreover, as nonspecific indicators of inflammation, the body temperatures and the hs-CRP levels usually reach the peaks on the first and third day after surgery, respectively. The use of PS reduced the peak value of body temperatures and hs-CRP levels in the PS group on POD 1 and POD 3 and accelerated these indicators to return to normal.

There are some limitations in this study. First, PS were only used for 2 days after THA in this study, and the long-term administration of PS would be done in further research. Second, we did not follow-up patients after hospital discharge. Therefore, large sample size and long-term observation of perioperative PS administration research should be carried out in the next step.

CONCLUSIONS

PS is an effective preemptive and sequential regimen that alleviates postoperative pain and inflammatory response in the early postoperative period after THA. PS also decreases the cumulative morphine consumption and associated adverse effects, without increasing perioperative bleeding risks.

REFERENCES

- Rasanen P, Paavolainen P, Sintonen H, et al. Effectiveness of hip or knee replacement surgery in terms of quality-adjusted life years and costs. *Acta Orthop* 2007; 78:108-115.
- Lunn TH, Andersen LO, Kristensen BB, et al. Effect of high-dose preoperative methylprednisolone on recovery after total hip arthroplasty: A randomized, double-blind, placebo-controlled trial. *Br J Anaesth* 2013; 110:66-73.
- Warfield CA, Kahn CH. Acute pain management. Programs in US hospitals and experiences and attitudes among US adults. *Anesthesiology* 1995; 83:1090-1094.
- Scuderi GR. The challenges of perioperative pain management in total joint arthroplasty. *Am J Orthop* 2015; 44(10 Suppl):S2.
- Njathi CW, Johnson RL, Laughlin RS, Schroeder DR, Jacob AK, Kopp SL. Complications after continuous posterior lumbar plexus blockade for total hip arthroplasty: A retrospective cohort study. *Reg Anesth Pain Med* 2017; 42:446-450.
- Golster M. Seven years of patient-controlled epidural analgesia in a Swedish hospital: A prospective survey. *Eur J Anaesthesiol* 2014; 31:589-596.
- Smith EB, Kazarian GS, Maltenfort MG, Lonner JH, Sharkey PF, Good RP. Periarthicular liposomal bupivacaine injection versus intra-articular bupivacaine infusion catheter for analgesia after total knee arthroplasty: A double-blinded, randomized controlled trial. *J Bone Joint Surg Am* 2017; 99:1337-1344.
- Radovanovic D, Radovanovic Z, Skoric-Jokic S, Tatic M, Mandic A, Ivkovic-Kapic T. Thoracic epidural versus intravenous patient-controlled analgesia after open colorectal cancer surgery. *Acta Clin Croat* 2017; 56:244-254.
- Zhu Y, Wang S, Wu H, Wu Y. Effect of perioperative parecoxib on postoperative pain and local inflammation factors PGE₂ and IL-6 for total knee arthroplasty: A randomized, double-blind, placebo-controlled study. *Eur J Orthop Surg Traumatol* 2014; 24:395-401.
- Rao P, Knaus EE. Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): Cyclooxygenase (COX) inhibition and beyond. *J Pharm Pharm Sci* 2008; 11:815-1105.
- Buvanendran A, Kroin JS, Tuman KJ, et al. Effects of perioperative administration of a selective cyclooxygenase 2 inhibitor on pain management and recovery of function after knee replacement: A randomized controlled trial. *JAMA* 2003; 290:2411-2418.
- Lin J, Zhang L, Yang H. Perioperative administration of selective cyclooxygenase-2 inhibitors for postoperative pain management in patients after total knee arthroplasty. *J Arthroplasty* 2013; 28:207-213.e2.
- Parsons B, Zhu Q, Xie L, Li C, Cheung R. Effects of parecoxib on postoperative pain and opioid-related symptoms following gynecologic surgery. *J Pain Res* 2016; 9:1101-1107.
- Zywiell MG, Prabhu A, Perruccio AV, Gandhi R. The influence of anesthesia and pain management on cognitive dysfunction after joint arthroplasty: A systematic review. *Clin Orthop Relat Res* 2014; 472:1453-1466.

15. Paech MJ, Salman S, Ilett KF, O'Halloran SJ, Muchatuta NA. Transfer of parecoxib and its primary active metabolite valdecoxib via transitional breastmilk following intravenous parecoxib use after cesarean delivery: A comparison of naive pooled data analysis and nonlinear mixed-effects modeling. *Anesth Analg* 2012; 114:837-844.
16. Sarridou DG, Chalmouki G, Braoudaki M, Siafaka I, Asmatzi C, Vadalouka A. Parecoxib possesses anxiolytic properties in patients undergoing total knee arthroplasty: A prospective, randomized, double-blind, placebo-controlled, clinical study. *Pain Ther* 2016; 5:55-62.
17. Sarridou DG, Chalmouki G, Braoudaki M, Koutsoupaki A, Mela A, Vadalouka A. Intravenous parecoxib and continuous femoral block for postoperative analgesia after total knee arthroplasty. A randomized, double-blind, prospective trial. *Pain Physician* 2015; 18:267-276.
18. Essex MN, Choi HY, Bhadra Brown P, Cheung R. A randomized study of the efficacy and safety of parecoxib for the treatment of pain following total knee arthroplasty in Korean patients. *J Pain Res* 2018; 11:427-433.
19. Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia I: Physiological pathways and pharmacological modalities. *Can J Anaesth* 2001; 48:1000-1010.
20. Joshi GP, Schug SA, Kehlet H. Procedure-specific pain management and outcome strategies. *Best Pract Res Clin Anaesthesiol* 2014; 28:191-201.
21. Shen SJ, Peng PY, Chen HP, Lin JR, Lee MS, Yu HP. Analgesic effects of intra-articular bupivacaine/intravenous parecoxib combination therapy versus intravenous parecoxib monotherapy in patients receiving total knee arthroplasty: A randomized, double-blind trial. *Biomed Res Int* 2015; 2015:450805.
22. Marret E, Flahault A, Samama CM, Bonnet F. Effects of postoperative, non-steroidal, antiinflammatory drugs on bleeding risk after tonsillectomy: Meta-analysis of randomized, controlled trials. *Anesthesiology* 2003; 98:1497-1502.
23. Mateos JL. Selective inhibitors of cyclooxygenase-2 (COX-2), celecoxib and parecoxib: A systematic review. *Drugs Today (Barc)* 2010; 46(Suppl A):1-25.
24. Jansson K, Redler B, Truedsson L, et al. Intraperitoneal cytokine response after major surgery: Higher postoperative intraperitoneal versus systemic cytokine levels suggest the gastrointestinal tract as the major source of the postoperative inflammatory reaction. *Am J Surg* 2004; 187:372-377.
25. Mahdy AM, Galley HF, Abdel-Wahed MA, el-Korny KF, Sheta SA, Webster NR. Differential modulation of interleukin-6 and interleukin-10 by diclofenac in patients undergoing major surgery. *Br J Anaesth* 2002; 88:797-802.