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Perioperative Outcomes of Patients Who Were Not Candidates for Additional Nonsteroidal Anti-inflammatory Drugs in a Multimodal Pain Control Regimen for Total Knee Arthroplasty

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Background: Postoperative pain following total knee arthroplasty (TKA) may hamper patients from a rapid recovery and increase perioperative blood loss and stress on the cardiovascular system. Therefore, our objective was to assess perioperative outcomes after TKA in patients who were not candidates for the additional nonsteroidal anti-inflammatory drugs (NSAIDs) in a multimodal pain control regimen.

Methods: Propensity score matching for age, sex, body mass index, American Society of Anesthesiologists class, and preoperative hemoglobin level was conducted on patients undergoing unilateral TKA, and thereby 52 patients remained in each group. The control group comprised patients who received parenteral parecoxib every 12 hours during the first 48 hours after TKA. The No-NSAIDs group did not receive NSAIDs because of known contraindications. Identical postoperative pain control including intravenous patient-controlled analgesia was applied for all patients. Visual analog scale (VAS) score for pain, knee flexion, blood loss, serum cardiac troponin-T (cTnT), and length of stay (LOS) were determined.

Results: The No-NSAIDs group had significantly higher VAS scores in 6–96 hours and consumed more morphine at 24 hours and 48 hours after the surgery than the control group. The No-NSAIDs group had significantly less knee flexion at 48 hours ($p = 0.045$) and tended to have more emesis and longer LOS than the control group. The blood loss of the No-NSAIDs and control group was 552.52 mL and 397.65 mL ($p = 0.02$), respectively, and blood transfusion rate was 23.1% and 17.3% ($p = 0.63$), respectively. The cTnT of the No-NSAIDs group rose over the first 48 hours and was significantly higher than that of the control group at 48 hours.

Conclusions: Patients who were not candidates for NSAIDs had significantly higher pain scores and consumed more morphine after TKA. They also tended to have greater blood loss and the rising of cardiac biomarkers during the first 48 hours after TKA. Hence, these patients may benefit from supplementary analgesia and appropriate perioperative monitoring.

Keywords: *Total knee arthroplasty, Non-steroidal anti-inflammatory drugs, Parecoxib, Postoperative pain*

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Total knee arthroplasty (TKA) is widely accepted as an effective procedure to relieve joint pain, increase mobility, and improve quality of life for patients with end-stage osteoarthritis of the knee.[1] However, postoperative pain following TKA that is not well controlled may hamper patients from early rehabilitation and rapid recovery and increase length of hospital stay. Such patients may also ex-

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perience complications such as lung atelectasis and venous thromboembolism.[2] Furthermore, severe postoperative pain might influence perioperative blood loss through various mechanisms such as sympathetic stimulation and increased arterial blood pressure.[3] The excruciating postoperative pain might also increase stress on the cardiovascular system and be related to ischemic cardiac events and myocardium insufficiency.[2,4]

For contemporary TKA, the multimodal pain management including neuroaxial anesthesia, periarticular injection (PAI) and/or peripheral nerve block, and opioid-sparing analgesia with multidrug regimen could be effective to control pain by avoiding side effects of high-dose single analgesia.[5] Nonsteroidal anti-inflammatory drugs (NSAIDs) have become one of the widely used agents to relieve moderate to severe pain and to reduce inflammation after orthopedic surgery. A recent randomized controlled trial (RCT) and meta-analysis demonstrated that NSAIDs administration could significantly mitigate pain intensity and opioid consumption, as well as opioid-related adverse events, after TKA.[6-8] Furthermore, some investigators reported that NSAIDs yielded equivalent analgesic effect to peripheral nerve block in TKA.[9]

Although effective in controlling pain and inflammation, NSAIDs are associated with a serious risk of gastrointestinal, renal, and cardiovascular adverse events. Currently, a selective cyclooxygenase-2 (COX-2) inhibitor, which reduces the risk of peptic ulceration and platelet inhibition, has been considered by some surgeons, including authors of the present study, as a good alternative agent for opioid-sparing strategy, particularly in elderly patients who underwent TKA.[6] However, the COX-2 inhibitor is not devoid of adverse effects entirely and their use should still be avoided for patients who have renal impairment and risk of a thromboembolic event. Even though these patients might be assumed to eventually have worse pain experience, there was sparse evidence demonstrating any exact outcome and a possible need for auxiliary pain control. Therefore, we conducted the present study to assess perioperative outcomes including pain level, recovery, blood loss, and complications of patients who underwent TKA and who were not candidates for additional NSAIDs in their multimodal pain control regimen.

METHODS

We conducted a retrospective investigation into patients diagnosed with primary osteoarthritis of the knee and underwent primary unilateral TKA. The patients who had a previous history of knee surgery, prior knee infection, and had been diagnosed with secondary osteoarthritis were excluded. The patients were divided into two groups. The control group received 40 mg of parenteral parecoxib (Dynastat, Pfizer, New York, NY, USA) every 12 hours during the first 48 hours after TKA and continued with celecoxib 200 mg twice a day until discharge to home. The second group, the No-NSAIDs group, did not receive NSAIDs during the postoperative period because of having had a diagnosis of chronic kideney disease stage ≥ 3 or preoperative serum creatinine (sCr) > 1.2, allergy to NSAIDs or sulfonamides, previous history of peptic ulceration or hemorrhage, or a cardiovascular and cerebrovascular event. Using propensity score matching, patients who underwent TKA without NSAIDs use (No-NSAIDs group) were matched 1 : 1 with the control group. The study was approved by the Institutional Review Board of Naresuan University (IRB No. P3-0016/2563).

All surgical procedures were performed by a single surgeon alone (AL) using an identical preoperative protocol and surgical technique. Aspirin therapy was discontinued at least 7 days before surgery. Premedication (gabapentin and anxiolytic drug) on the night before the surgery was applied for all cases. All procedures were carried out under regional anesthesia with bupivacaine (0.5% Marcaine, AstraZeneca, Sweden). A standard medial parapatellar arthrotomy with approximately 10 cm of skin incision was performed with tourniquet control at 250 mmHg. The bone cut was prepared with a conventional instrument by using intramedullary and extramedullary reference guides for the distal femur and the proximal tibia, respectively. The opening of the femoral medullary canal was occluded with a bone plug after finishing the femoral bone preparation. The patella was selectively resurfaced. A PAI was performed in all cases with 20 mL bupivacaine that was diluted with normal saline solution to a total volume of 75 mL. Posterior-stabilized, fixed-bearing knee prostheses were implanted with bone cement in all patients. Topical tranexamic acid was poured into the knee joint before the arthrotomy closure. A vacuum drain and compressive dressing were also applied and subsequently removed 24 hours after the surgery.

Similar postoperative care was utilized for all patients. The intravenous patient-controlled analgesia (PCA) was set to inject an on-demand bolus of 0.5 mg of morphine sulphate with a 5-minute lockout period, and the amount of morphine consumption was recorded. Acetaminophen (500 mg) was administered orally after the surgery and then every 8 hours during hospitalization. After 48 hours, the PCA, antibiotics, and all catheters were discarded. Then, 2 mg of morphine was given intravenous-

ly every 8 hours and additional 2 mg of morphine was applied as rescue analgesia every 4 hours during the patient's stay in the hospital. Postoperative pain level was assessed with a 10-cm visual analog scale (VAS) at 6, 12, 18, 24, 48, 72, and 96 hours after surgery. An identical postoperative physiotherapy protocol was conducted, a continuous passive motion device was applied, and progress was recorded daily. Chemoprophylaxis for deep vein thrombosis (DVT), consisting of low-molecular-weight heparin injection and bridging oral warfarin, was administered for all patients.

Blood tests including complete blood count, sCr, and cardiac troponin-T (cTnT) level were routinely performed preoperatively and then at 24 hours, 48 hours, and 72 hours after TKA. Outcome measurements for this study were postoperative VAS score, amount of morphine consumption, knee flexion angle, drain output, calculated blood loss (CBL), blood transfusion rate, and length of stay (LOS). Any complications that happened during the course of the study were also recorded. To identify patients having acute kidney disease, we compared the highest postoperative sCr obtained within 72 hours after TKA to preoperative sCr values. According to the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease criteria, (1) at-risk of acute kidney injury was defined as 1.5 × rising in sCr, (2) acute kidney injury was defined as 2 × rising in sCr, and (3) acute kidney failure was defined as 3 × rising in sCr.[10] The cTnT level > 14 ng/L was positive for myocardial infarction in our laboratory system. All outcomes were prospectively recorded.

The total blood volume (TBV) and CBL were calculated by using the equation of Nadler et al.[11] and the hemoglobin (Hb) balance method,[12] respectively:

$$\text{For men, TBV (mL)} = (0.0003669 \times \text{height}^3\ [\text{cm}]) + (32.19 \times \text{body weight}\ [\text{kg}]) + 604$$

$$\text{For women, TBV (mL)} = (0.0003561 \times \text{height}^3\ [\text{cm}]) + (33.08 \times \text{body weight}\ [\text{kg}]) + 183$$

$$\text{CBL (mL)} = \text{TBV}\ [\text{mL}] \times (Hb_i - Hb_e)/Hb_i + \text{sum of blood products transfused}\ [\text{mL}],$$

where Hb_i [g/dL] was defined as the preoperative Hb and Hb_e [g/dL] was the postoperative Hb. The difference between preoperative and 48-hour postoperative Hb was applied with the Hb balance method to determine CBL. Allogeneic blood was transfused if the Hb level was below 9.0 g/dL as our institutional cutoff values.

Statistical Analysis

Propensity score incorporating demographic data that included age, sex, body mass index, American Society of Anesthesiologists (ASA) class, and level of preoperative Hb (Hb ≥ 12 for female and ≥ 13 for male vs. Hb < 12 for female and < 13 for male) were used to match the studied group with the control group. All measured characteristics and outcomes were summarized with descriptive statistics including mean and standard deviation (SD). All outcomes

Table 1. Demographic Data of the Control and No-NSAIDs Groups before and after Propensity Score Matching

Variable	No propensity score match			Propensity match		
	Control (n = 80)	No-NSAIDs (n = 54)	*p*-value	Control (n = 52)	No-NSAIDs (n = 52)	*p*-value
Age (yr)	66.32 ± 8.16	68.09 ± 7.74	0.210	66.37 ± 8.11	67.79 ± 7.6	0.358
Sex						
Female	60 (75)	50 (92.6)	0.011*	51 (98.1)	49 (94.2)	0.618
Male	20 (25)	4 (7.4)	0.011*	1 (1.9)	3 (5.8)	0.618
Body mass index (kg/m^2)	27.44 ± 3.68	27.03 ± 3.4	0.517	27.57 ± 3.69	27.05 ± 3.43	0.453
ASA class						
1	4 (5)	0	0.148	0	0	NA
2	48 (60)	22 (40.7)	0.035*	31 (59.6)	22 (42.3)	0.116
3	28 (35)	32 (59.3)	0.008*	21 (40.4)	30 (57.7)	0.116
Preoperative Hb (g/dL)	12.49 ± 1.33	12.03 ± 1.01	0.028*	12.1 ± 1.18	12.02 ± 1.02	0.722

Values are presented as mean ± standard deviation or number (%).
NSAID: nonsteroidal anti-inflammatory drug, ASA: American Society of Anesthesiologists, NA: not available, Hb: hemoglobin.
*Statistically significant ($p < 0.05$).

were compared between groups using an independent *t*-test and Fisher's exact test for continuous and categorical variables, respectively. The sample size of 52 patients in each group would have 86.4% power to detect a difference of 1.5 of VAS for pain score with SD of 2.5, with type I error of 5%. Stata/MP 15.0 software (StataCorp., College Station, TX, USA) was used for all statistical analysis. Statistical significance was defined as $p < 0.05$.

RESULTS

The 134 participating patients were divided into two groups, 80 patients were in the control group, while 54 patients were in the No-NSAIDs group. After propensity score match, there were 52 patients in each group with comparable demographic data as shown in Table 1. The preoperative VAS score, range of knee motion, Hb, cTnT, and TBV were not significantly different between groups, but the baseline sCr of No-NSAIDs group was significantly higher than that of the control group (Table 2).

The VAS pain scores of the No-NSAIDs group were significantly higher than those of the control group during the entire postoperative period (Fig. 1). The No-NSAIDs group also had significantly higher cumulative morphine consumption at 24 hours and 48 hours after the surgery than the control group. The knee flexion angle of the control group was higher than that of the No-NSAIDs group and the difference was statistically significant at 48 hours postoperatively. The No-NSAIDs group had more postoperative nausea vomiting (PONV) and longer LOS than the control group, but the difference did not reach a level of statistical significance (Table 3). The CBL was 552.52 mL (interquartile range [IQR], 403.83–710.64) for the No-NSAIDs group and 397.65 mL (IQR, 266.72–622.87) for the control group ($p = 0.02$). However, the blood transfusion rate was not different between the No-NSAIDs group and control group (23.1% and 17.3%, respectively, $p = 0.63$). The drain output of the No-NSAIDs group was also significantly greater than that of the control group (Table 3).

The sCr of the No-NSAIDs group was continuously higher than that of the control group up until 72 hours after the surgery, but no patient experienced sCr elevating beyond 1.5× of baseline in both groups. The cTnT of the No-NSAIDs group was rising during the first 48 hours and significantly higher than that of the control group at 48 hours (Table 4). Each group had 2 patients with cTnT exceeding 14 ng/L during the first 72 hours postoperatively and these patients had no subsequent symptom and sign of cardiovascular event during hospitalization. Until the last follow-up, there was 1 periprosthetic fracture of

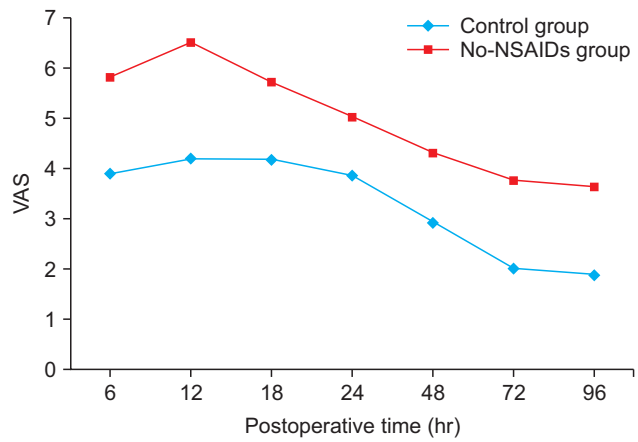

Fig. 1. Pain intensity measured by visual analog scale (VAS) at 6–96 hours after total knee arthroplasty. There was significant difference during the entire postoperative period ($p \leq 0.01$). NSAID: nonsteroidal anti-inflammatory drug.

Table 2. Preoperative Characteristics and Blood Tests of the Control and No-NSAIDs Groups after Propensity Score Matching

Characteristic	Control (n = 52)	No-NSAIDs (n = 52)	*p*-value
VAS pain score	6.43 ± 2.30	6.31 ± 2.39	0.418
ROM (°)	106 ± 15.37	100.39 ± 23.97	0.305
Hemoglobin (g/dL)	12.1 ± 1.18	12.02 ± 1.02	0.722
Serum creatinine (mg/dL)	0.8 ± 0.23	0.95 ± 0.31	0.010*
cTnT (ng/L)	9.85 ± 8.85	10.71 ± 7.46	0.595
TBV (mL)	3,733.03 ± 449.30	3,616.19 ± 495.73	0.211

Values are presented as mean ± standard deviation.
NSAID: nonsteroidal anti-inflammatory drug, VAS: visual analog scale, ROM: range of motion, cTnT: cardiac troponin-T, TBV: total blood volume.
*Statistically significant ($p < 0.05$).

Table 3. Perioperative and Postoperative Outcomes of the Control and No-NSAIDs Groups after Propensity Score Matching

Variable	Control	No-NSAIDs	*p*-value
Operative time (min)	63.65 ± 15.59	60.74 ± 6.00	0.226
Drain output (mL)	199.78 ± 101.29	269.38 ± 140.31	0.007*
Knee flexion angle (°)			
24 hr	54.73 ± 18.57	50.1 ± 23.83	0.288
48 hr	73.43 ± 18.17	65.26 ± 21.71	0.045*
72 hr	84.5 ± 11.89	80.15 ± 18.79	0.180
96 hr	90.2 ± 12.76	88.52 ± 10.49	0.534
Morphine PCA (mg)			
24 hr	9.01 ± 8.39	15.84 ± 10.27	0.002*
48 hr	12.6 ± 11.34	25.36 ± 16.68	< 0.001*
PONV (%)	0.48 ± 1.02	0.67 ± 1.19	0.405
LOS (day)	5.16 ± 1.08	5.58 ± 1.67	0.134

Values are presented as mean ± standard deviation.
NSAID: nonsteroidal anti-inflammatory drug, PCA: patient-controlled analgesia, PONV: postoperative nausea vomiting, LOS: length of stay.
*Statistically significant ($p < 0.05$).

Table 4. Postoperative cTnT and sCr of the Control and No-NSAID Groups after Propensity Score Matching

Variable	Control	No-NSAIDs	*p*-value
cTnT (ng/L)	9.85 ± 8.85	10.71 ± 7.46	0.595
24 hr	12.05 ± 19.49	13.26 ± 9.79	0.710
48 hr	10.89 ± 10.41	17.7 ± 20.13	0.044*
72 hr	11.32 ± 9.17	13.32 ± 8.26	0.446
sCr (mg/dL)			
24 hr	0.74 ± 0.21	0.88 ± 0.24	0.004*
48 hr	0.74 ± 0.18	0.89 ± 0.26	0.003*
72 hr	0.8 ± 0.23	0.89 ± 0.28	0.211

Values are presented as mean ± standard deviation.
cTnT: cardiac troponin-T, sCr: serum creatinine, NSAID: nonsteroidal anti-inflammatory drug.
*Statistically significant ($p < 0.05$).

the distal femur in the control group. For the No-NSAIDs group, 1 patient developed DVT and was treated with anticoagulant, 1 required readmission due to wound oozing related to warfarin, and 1 had cerebrovascular disease with hemiparesis.

DISCUSSION

In this study, we found that the No-NSAIDs group had significantly higher VAS scores at any time point and consumed significantly more morphine in the first 48 hours postoperatively than the control group. The No-NSAIDs group tended to have a lower degree of knee flexion angle, a higher rate of PONV, and longer LOS than the control group. These results accord with the meta-analysis conducted by Du and Gu[6] and the RCT by Zhu et al.,[7] who reported that the patients who were postoperatively administered parenteral parecoxib had significantly less opioid use, lower pain scores, and better range of knee motion after TKA. Hence, patients who were not candidates for

NSAIDs might benefit from additional analgesic modalities to better control their pain and enhance recovery. Currently, corticosteroid and acetaminophen are considered as useful supplements for controlling post-TKA pain. Intravenous acetaminophen has been revealed by meta-analysis as an efficacious adjunct to multimodal analgesia after total joint arthroplasty in terms of pain scores and opioid consumption in the first 72 hours.[13] Tammachote and Kanitnate[14] also revealed that administration of 0.15 mg/kg of intravenous dexamethasone can significantly relieve pain between 12 hours to 21 hours after TKA and reduce rates of PONV and level of C-reactive protein compared with placebo, but might be associated with transient hyperglycemia. On the other hand, the efficacy of PAI might also be improved by some strategies such as location of injection[15] or adding some adjuvants to the PAI mixture.[8,16] Alternatively, additional peripheral nerve block could also be considered as an analgesic supplement to overwhelm the pain after TKA.[17-20]

Our second finding was the coincidence of higher pain intensity and blood loss in the No-NSAIDs group than in the control group, even if the blood transfusion rate was not different. The cTnT of No-NSAIDs group was rising during the first 48 hours after TKA and reached a statistically significant difference from the control group at 48 hours. Some patients in both groups had postoperative cTnT exceeding 14 ng/L in the first 72 hours after the surgery, but all did not have a cardiovascular event. In a previous study, Guay[3] found a positive correlation between morphine consumption and postoperative blood loss by some mechanisms. They conjectured that postoperative pain increased blood loss through sympathetic stimulation and increased arterial blood pressure. Despite the pain not being severe enough to increase the systemic arterial blood pressure, pain rising while patient doing physiotherapy might induce muscle contraction, high venous blood pressure, and then increased blood loss of that limb. In addition, Mangano et al.[4] reported that pain, fluid shift, temperature changes, impaired pulmonary gas exchange, and sleep deprivation could alter myocardial oxygen demand and precipitate ischemia. They also revealed that postoperative pain was one of the factors that could alter the use of oxygen in the myocardium and induce myocardial ischemia during the first 48 hours after cardiac and noncardiac surgery. Nevertheless, Kim et al.[21] revealed a contrary result as pain had no effect on postoperative blood pressure and blood loss even after bilateral TKA. Other research, however, found that perioperative blood loss had an effect on neither postoperative pain nor opioid use.[22,23] To our knowledge, studies that assessed possible linking of postoperative pain with blood loss and cardiovascular complications after TKA are seldom reported and our findings might be confounded by the underlying disease of patients that precluded the use of parecoxib. Thus, the relationship between postoperative pain, blood loss, and cardiovascular complications is still inconclusive and may warrant further investigation. However, TXA, which is an antifibrinolytic agent, has been demonstrated as having an additional benefit of reducing inflammatory biomarkers and subsequently mitigating pain and morphine use after TKA when administered via intra-articular or multiple doses intravenously.[23,24] Hence, TXA administration could be an alternative approach, used to concurrently reduce blood loss and pain after TKA.

However, there are some limitations in our study. First, this study is retrospective with all the inherent limitations accorded by the study design. Therefore, we performed propensity score matching to reduce confounding between the studied and control groups who underwent TKA carried out by a single surgeon alone. Despite that, the sCr of No-NSAIDs group was significantly higher than that of the control group initially and thereafter. Second, there were predominantly female patients in the present study and sex might be associated with different pain sensitivity and blood loss after TKA.[25,26] Nevertheless, previous studies found neither sex nor ASA class as predictors of pain, function recovery, and blood loss after TKA.[27-29] Third, different thresholds or cutoff values for blood transfusion protocols between institutions may cause a variation of transfused rate. Lastly, our sample size might not be enough to assess the exact risk of cardiovascular events after TKA.

In conclusion, patients who were not candidates for NSAIDs administration had significantly higher pain scores and consumed significantly more morphine after TKA. They also tended to have greater blood loss and the rising of cardiac biomarkers during the first 48 hours after the surgery. Hence, these patients may benefit from supplementary analgesia and appropriate perioperative monitoring.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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