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COMPARATIVE ANALYSIS OF FUNCTIONAL OUTCOME AND PAIN CONTROL USING NSAID VERSUS NON-NSAID MULTIMODAL ANALGESIC REGIMENS IN POSTOPERATIVE TOTAL KNEE ARTHROPLASTY

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Abstract

Background: Effective postoperative pain management following total knee arthroplasty (TKA) is crucial for early mobilization, improved functional outcomes, and patient satisfaction. Multimodal analgesia is the standard of care, but the specific role and necessity of non-steroidal anti-inflammatory drugs (NSAIDs) within these protocols remain debated, particularly regarding the balance between analgesic efficacy and potential side effects.

Methods: This was a single-center, prospective, randomized, double-blind controlled trial. A total of 120 patients scheduled for unilateral TKA were randomized into two groups (n=60 per group). The NSAID group received a multimodal regimen including oral celecoxib, while the non-NSAID group received an identical regimen with a placebo. The primary outcomes were Visual Analog Scale (VAS) pain scores at 24, 48, and 72 hours, and total morphine milligram equivalent (MME) consumption in the first 72 hours. Secondary outcomes included Knee Society Score (KSS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, and knee range of motion (ROM) at 6 weeks, as well as length of hospital stay and incidence of adverse events.

Results: The NSAID group reported significantly lower mean VAS pain scores with activity at 48 hours (3.8 ± 1.1 vs. 5.2 ± 1.4; p=0.002) and 72 hours (2.9 ± 0.9 vs. 4.1 ± 1.2; p<0.001). Total opioid consumption was significantly lower in the NSAID group (48.5 ± 15.2 MME) compared to the non-NSAID group (70.1 ± 22.5 MME; p<0.001). At the 6-week follow-up, the NSAID group demonstrated superior functional outcomes, with a higher mean KSS (85.2 ± 5.4 vs. 80.1 ± 6.9; p=0.003) and better active knee flexion (112.5° ± 8.1° vs. 106.3° ± 9.5°; p=0.002). There was no statistically significant difference in the incidence of nausea (16.7% vs. 11.7%; p=0.43) or acute kidney injury (1.7% vs. 0%; p=0.31).

Conclusion: The inclusion of a selective COX-2 inhibitor in a multimodal analgesic regimen for TKA significantly improves postoperative pain control, reduces opioid consumption, and leads to

enhanced early functional recovery without a significant increase in short-term adverse events in a well-screened patient population.

Keywords: Total Knee Arthroplasty, Postoperative Pain, Multimodal Analgesia, NSAID, Celecoxib, Functional Outcome, Opioid-Sparing.

Introduction

Total knee arthroplasty (TKA) is a highly effective surgical intervention for end-stage osteoarthritis, alleviating pain and restoring function for millions of patients worldwide **[1]**. Despite high success rates, significant postoperative pain remains a primary challenge. Inadequate pain control can impede early mobilization, delay participation in physical therapy, increase the length of hospital stay, and negatively impact patient satisfaction **[2]**. Historically, postoperative analgesia relied heavily on parenteral opioids, which are associated with a range of adverse effects, including sedation, respiratory depression, nausea, vomiting, and ileus, potentially hindering the recovery process.

In recent years, the paradigm has shifted towards multimodal, opioid-sparing analgesic strategies integrated within Enhanced Recovery After Surgery (ERAS) protocols **[3]**. These protocols combine various analgesic agents and techniques with different mechanisms of action to achieve synergistic effects, thereby improving pain relief while minimizing opioid-related side effects. Core components of multimodal analgesia often include regional anesthesia (e.g., spinal anesthesia, peripheral nerve blocks), local infiltration analgesia (LIA), and scheduled administration of non-opioid analgesics like acetaminophen **[4]**.

Non-steroidal anti-inflammatory drugs (NSAIDs) are a cornerstone of many multimodal regimens. By inhibiting the cyclooxygenase (COX) enzymes, NSAIDs reduce the production of prostaglandins, key mediators of inflammation and pain at the surgical site **[5]**. Their dual anti-inflammatory and analgesic properties make them theoretically ideal for managing the significant inflammatory response associated with TKA. Selective COX-2 inhibitors, such as celecoxib, were developed to offer comparable analgesic efficacy to non-selective NSAIDs but with a potentially more favorable gastrointestinal (GI) safety profile **[6]**.

Despite their widespread use, the inclusion of NSAIDs in TKA protocols is not universal. Concerns persist regarding potential adverse effects, including GI bleeding, renal dysfunction, and cardiovascular events, particularly in the elderly population with multiple comorbidities who frequently undergo TKA **[7]**. This has led some institutions to adopt non-NSAID-based protocols, relying more heavily on other adjuncts. While numerous studies have demonstrated the opioid-sparing benefits of NSAIDs, there is a relative paucity of high-quality, prospective trials directly comparing a modern, comprehensive NSAID-based multimodal regimen against a well-defined non-NSAID regimen within the same ERAS framework. The existing evidence is often confounded by variations in other components of the analgesic protocol, making it difficult to isolate the specific contribution of NSAIDs to both pain control and functional recovery.

This research gap highlights the need for a rigorous comparative analysis. Understanding the precise benefits and risks of incorporating an NSAID can help clinicians optimize pain management protocols, balance efficacy with safety, and ultimately improve patient outcomes. Therefore, the primary aim of this study was to compare the efficacy of a selective COX-2 inhibitor-based multimodal analgesic regimen against a non-NSAID regimen in controlling postoperative pain and improving functional outcomes following primary TKA. We hypothesized that the NSAID group would demonstrate superior analgesia, reduced opioid consumption, and better early functional scores compared to the non-NSAID group.

Materials and Methods

Study Design and Setting

This study was a prospective, single-center, randomized, double-blind, placebo-controlled trial conducted at a tertiary academic medical center.

Participants and Sample Size

Patients between 50 and 80 years of age with a diagnosis of Kellgren-Lawrence grade III or IV primary knee osteoarthritis scheduled for unilateral TKA were eligible for inclusion. A power analysis was performed based on a pilot study, which indicated that a sample size of 55 patients per group would be required to detect a clinically significant difference of 1.5 points on a 10-point VAS pain scale with 80% power and a two-sided alpha of 0.05. To account for a potential 10% dropout rate, we aimed to enroll 120 patients (60 per group).

Inclusion criteria were: (1) undergoing primary, unilateral TKA; (2) age 50-80 years; (3) American Society of Anesthesiologists (ASA) physical status I-III; and (4) ability to provide informed consent and complete study questionnaires.

Exclusion criteria included: (1) known allergy or contraindication to any study medication (acetaminophen, celecoxib, opioids, ropivacaine); (2) history of chronic opioid use (defined as daily use for >3 months); (3) pre-existing renal insufficiency (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73m²); (4) history of peptic ulcer disease or upper GI bleeding within the last year; (5) congestive heart failure (New York Heart Association Class III-IV); (6) inflammatory arthritis (e.g., rheumatoid arthritis); and (7) revision TKA.

Randomization and Blinding

Eligible patients were randomized in a 1:1 ratio to either the NSAID group or the non-NSAID (placebo) group using a computer-generated block randomization sequence with a block size of four. The randomization sequence was concealed by the hospital's investigational pharmacy, which was responsible for preparing and dispensing the study medication in identical-looking capsules. Patients, surgeons, anesthesiologists, ward nurses, physical therapists, and data collectors were all blinded to the treatment allocation throughout the study period.

Surgical and Anesthetic Procedure

All patients underwent a standardized surgical procedure performed by one of three fellowship-trained arthroplasty surgeons using a medial parapatellar approach and a cemented, posterior-stabilized prosthesis. All patients received spinal anesthesia with 12.5-15 mg of 0.5% hyperbaric bupivacaine. At the end of the procedure, a standardized periarticular injection (PAI) cocktail containing 200 mg ropivacaine, 0.5 mg epinephrine, and 30 mg ketorolac in 60 mL of normal saline was administered by the surgeon. Note: The single intraoperative dose of ketorolac was administered to both groups to standardize the immediate intraoperative analgesic block, with the study intervention focusing on the postoperative oral regimen.

Postoperative Analgesic Regimen

Both groups received a baseline multimodal analgesic regimen consisting of:

- Acetaminophen 1000 mg orally every 6 hours, starting in the post-anesthesia care unit (PACU).
- Oxycodone 5 mg orally every 4-6 hours as needed (PRN) for breakthrough pain (VAS > 4).

The study intervention was as follows:

- **Group A (NSAID group):** Received celecoxib 200 mg orally twice daily, starting on the evening of surgery and continuing for 14 days.
- **Group B (Non-NSAID group):** Received a matching placebo capsule orally on the same schedule.

Outcome Measures

- **Primary Outcomes:**

1. Postoperative pain, measured using the Visual Analog Scale (VAS; 0=no pain, 10=worst imaginable pain) at rest and with active knee flexion at 24, 48, and 72 hours postoperatively.
2. Total opioid consumption during the first 72 postoperative hours, converted to oral morphine milligram equivalents (MME) for standardization.

- **Secondary Outcomes:**

1. Length of hospital stay (days).
2. Time to first ambulation (hours).
3. Active knee range of motion (flexion and extension lag), measured with a goniometer at discharge and at the 6-week follow-up.
4. Functional outcomes measured at 6 weeks postoperatively using the Knee Society Score (KSS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).
5. Incidence of adverse events, including nausea/vomiting, constipation, urinary retention, symptomatic deep vein thrombosis (DVT), pulmonary embolism (PE), surgical site infection, and acute kidney injury (AKI, defined as a >50% increase in serum creatinine from baseline).

Statistical Analysis

All statistical analyses were performed using SPSS Statistics Version 27.0 (IBM Corp., Armonk, NY). An intention-to-treat analysis was conducted. Continuous variables were presented as mean ± standard deviation (SD) and compared using the independent samples t-test or Mann-Whitney U test if data were not normally distributed. Categorical variables were presented as frequencies and percentages (%) and compared using the Chi-square test or Fisher's exact test. A p-value of < 0.05 was considered statistically significant.

Results

A total of 142 patients were screened for eligibility, of whom 120 met the criteria and were randomized. Sixty patients were allocated to the NSAID group and 60 to the non-NSAID group. Two patients in the NSAID group and three in the non-NSAID group were lost to follow-up before the 6-week visit. Thus, 115 patients (58 in the NSAID group, 57 in the non-NSAID group) completed the study and were included in the final analysis.

Baseline Characteristics

There were no statistically significant differences between the two groups with respect to demographic data, including age, sex, body mass index (BMI), ASA classification, or preoperative functional scores (KSS and WOMAC), confirming successful randomization (Table 1).

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants.

Characteristic	NSAID Group (n=60)	Non-NSAID Group (n=60)	p-value
Age (years), mean ± SD	67.2 ± 7.1	68.1 ± 6.8	0.49
Sex (Female), n (%)	38 (63.3%)	35 (58.3%)	0.56
BMI (kg/m²), mean ± SD	31.5 ± 4.2	32.1 ± 4.8	0.48
ASA Class, n (%)			0.81
I	2 (3.3%)	1 (1.7%)	
II	40 (66.7%)	42 (70.0%)	
III	18 (30.0%)	17 (28.3%)	
Pre-op KSS, mean ± SD	51.4 ± 8.2	52.3 ± 7.9	0.57
Pre-op WOMAC, mean ± SD	58.9 ± 11.5	57.5 ± 12.1	0.54
SD: Standard Deviation; BMI: Body Mass Index; ASA: American Society of Anesthesiologists; KSS: Knee Society Score; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.			

Primary Outcomes

The NSAID group experienced significantly better pain control. While VAS scores at rest were similar at 24 hours, they were significantly lower in the NSAID group at 48 and 72 hours. The difference was more pronounced for pain with activity. Total opioid consumption over the first 72 hours was 30.8% lower in the NSAID group compared to the non-NSAID group ($p<0.001$) (Table 2).

Table 2. Primary Outcomes: Postoperative Pain Scores and Opioid Consumption.

Outcome	NSAID Group (n=58)	Non-NSAID Group (n=57)	p-value
VAS Pain Score (at rest)			
24 hours	3.1 ± 1.0	3.4 ± 1.2	0.21
48 hours	2.2 ± 0.8	2.9 ± 1.0	**0.001**
72 hours	1.8 ± 0.7	2.4 ± 0.9	**<0.001**
VAS Pain Score (with activity)			
24 hours	5.5 ± 1.3	5.9 ± 1.5	0.14
48 hours	3.8 ± 1.1	5.2 ± 1.4	**0.002**
72 hours	2.9 ± 0.9	4.1 ± 1.2	**<0.001**
Total Opioid Consumption (MME)			
72 hours, mean ± SD	48.5 ± 15.2	70.1 ± 22.5	**<0.001**
Data are presented as mean ± SD. VAS: Visual Analog Scale (0-10); MME: Morphine Milligram Equivalents.			

Secondary Outcomes

Patients in the NSAID group had a slightly shorter mean length of hospital stay, although this difference did not reach statistical significance. At the 6-week follow-up, the NSAID group demonstrated significantly better functional outcomes, including higher KSS and lower (better) WOMAC scores. Active knee flexion was also significantly greater in the NSAID group. There were no statistically significant differences in the rates of common adverse events between the groups (Table 3). One patient in the NSAID group developed a transient AKI that resolved with intravenous fluids, compared to none in the non-NSAID group (p=0.31).

Table 3. Secondary Outcomes: Functional Recovery and Adverse Events.

Outcome	NSAID Group (n=58)	Non-NSAID Group (n=57)	p-value
Length of Stay (days), mean ± SD	2.1 ± 0.8	2.4 ± 1.0	0.11
6-Week Follow-up			
KSS (0-100), mean ± SD	85.2 ± 5.4	80.1 ± 6.9	**0.003**
WOMAC (0-96), mean ± SD	18.3 ± 6.1	24.5 ± 8.2	**<0.001**
Active Flexion (°), mean ± SD	112.5 ± 8.1	106.3 ± 9.5	**0.002**
Extension Lag (°), mean ± SD	2.1 ± 1.5	2.8 ± 1.9	0.06
Adverse Events, n (%)			
Nausea/Vomiting	10 (16.7%)	7 (11.7%)	0.43
Constipation	8 (13.3%)	6 (10.0%)	0.60
Acute Kidney Injury	1 (1.7%)	0 (0%)	0.31
Symptomatic DVT	0 (0%)	1 (1.7%)	0.31
KSS: Knee Society Score; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; DVT: Deep Vein Thrombosis.			

Discussion

This prospective, randomized controlled trial demonstrates that incorporating a selective COX-2 inhibitor into a multimodal analgesic regimen following TKA provides significant clinical benefits. The primary findings of this study were that the NSAID-based regimen resulted in statistically significant reductions in postoperative pain, particularly with activity, and a marked decrease in total opioid consumption. Furthermore, these early analgesic benefits translated into superior functional outcomes at 6 weeks, as evidenced by better KSS, WOMAC scores, and knee flexion.

Our results align with and strengthen the existing body of evidence supporting the use of NSAIDs in the perioperative management of TKA. A meta-analysis by Zhao et al. concluded that both selective and non-selective NSAIDs effectively reduce postoperative pain and opioid consumption after

TKA **[8]**. Our study provides further granularity by isolating the effect of a scheduled oral NSAID within an otherwise identical, modern ERAS protocol that includes spinal anesthesia and PAI. The significant reduction in opioid consumption (30.8%) is particularly noteworthy, as minimizing opioid use is a key goal of ERAS pathways to reduce associated side effects and the potential for persistent postoperative opioid use **[3]**.

The observed improvement in early functional outcomes is a critical finding. The superior pain control in the NSAID group likely facilitated more effective participation in physical therapy, leading to greater gains in range of motion and overall function. Better pain relief during movement allows patients to mobilize earlier and more confidently, a cornerstone of rapid recovery protocols **[9-12]**. The 6.2-degree improvement in active knee flexion at 6 weeks in the NSAID group is a clinically meaningful difference that can impact a patient's ability to perform activities of daily living, such as climbing stairs or rising from a chair. This reinforces the concept that effective early pain management is not merely for patient comfort but is integral to the entire rehabilitation trajectory.

A primary concern limiting the routine use of NSAIDs is the risk of adverse events. In our study, we found no significant difference in the incidence of common complications. The rate of nausea and vomiting was numerically higher in the NSAID group, but this was not statistically significant and may be confounded by other factors. The single case of transient AKI in the NSAID group is an important reminder of the potential for renal toxicity, reinforcing the need for careful patient selection and exclusion of individuals with pre-existing renal disease, as was done in our trial **[7]**. The findings suggest that in a well-screened population without major contraindications, a short course of a selective COX-2 inhibitor is well-tolerated and carries a low risk of significant harm. The use of a COX-2 selective agent like celecoxib may have contributed to the low rate of GI side effects observed **[13-15]**.

This study has several strengths, including its randomized, double-blind, placebo-controlled design, which minimizes bias. We utilized a standardized surgical, anesthetic, and rehabilitation protocol, allowing us to isolate the effect of the study medication. Furthermore, we assessed a range of outcomes, from immediate pain scores to early functional recovery, providing a comprehensive view of the intervention's impact.

However, certain limitations must be acknowledged. First, this was a single-center study, which may limit the generalizability of our findings to other institutions with different patient populations or protocols. Second, the follow-up period was relatively short (6 weeks). While this is sufficient for evaluating early recovery, it does not provide insight into long-term functional outcomes or the risk of rare, delayed adverse events. Third, we studied only one specific NSAID, celecoxib. The results may not be directly applicable to other non-selective or selective NSAIDs. Finally, although we standardized the PAI, it included a single dose of ketorolac for both groups, which could have masked some of the group differences in the first 24 hours.

Conclusion

In conclusion, for patients undergoing primary total knee arthroplasty without specific contraindications, the inclusion of the selective COX-2 inhibitor celecoxib as part of a multimodal analgesic regimen significantly improves postoperative pain control, substantially reduces the need for rescue opioids, and leads to superior functional outcomes at 6 weeks. This was achieved without a statistically significant increase in the rate of short-term adverse events. These findings support the routine use of NSAIDs as a core component of ERAS protocols for TKA to enhance the quality of recovery. Future research should focus on long-term outcomes, cost-effectiveness, and direct comparisons between different classes of NSAIDs in this patient population.

References

1. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am. 2007;89(4):780-5. DOI: 10.2106/JBJS.F.00222.

2. Pasero C, Paice JA. Postoperative pain management in the 21st century. J Perianesth Nurs. 2011;26(5):344-9. DOI: 10.1016/j.jopan.2011.07.004.
3. Husted H, Lunn TH, Troelsen A, Gaarn-Larsen L, Kristensen BB, Kehlet H. Why still in hospital after fast-track hip and knee arthroplasty? Acta Orthop. 2011;82(6):679-84. DOI: 10.3109/17453674.2011.636682.
4. Kaye AD, Urman RD, Rappaport Y, Siddaiah H, Cornett EM, Belani K. Multimodal analgesia for the orthopedic patient. Orthop Clin North Am. 2019;50(2):135-150. DOI: 10.1016 /j.ocl.2018.12.001.
5. O'Neal JB, Freiberg AA, Yelle-LaBlock E, Booth R, Bedair HS. A randomized, controlled trial of a multimodal pre-emptive analgesia protocol for total knee arthroplasty. Clin Orthop Relat Res. 2016;474(1):87-94. DOI: 10.1007/s11999-015-4497-6.
6. Chen AF, Ranawat AS, Cushner FD, Goyal N, D'Apuzzo M, Lo D. A multi-center, randomized, controlled trial of the efficacy of celecoxib on pain management after total knee arthroplasty. J Arthroplasty. 2013;28(8 Suppl):48-51. DOI: 10.1016/j.arth.2013.04.043.
7. Lee YS, Kim Y, Heo J, Park HJ, Park Y. The effect of non-steroidal anti-inflammatory drugs on the risk of acute kidney injury after total knee arthroplasty: a retrospective cohort study. J Clin Med. 2021;10(11):2333. DOI: 10.3390/jcm10112333.
8. Zhao Z, Zhang Z, He W, Wang J. Efficacy and safety of nonsteroidal anti-inflammatory drugs for pain management after total knee arthroplasty: a systematic review and meta-analysis. J Orthop Surg Res. 2021;16(1):335. DOI: 10.1186/s13018-021-02482-1.
9. Gwynne-Jones DP, Martin G, Crane T. Enhanced recovery programs for total knee arthroplasty. Orthopedics. 2017;40(3):e417-e423. DOI: 10.3928/01477447-20170306-03.
10. Wainwright TW, Gill M, McDonald DA, et al. Consensus statement for perioperative care in total hip replacement and total knee replacement surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. Acta Orthop. 2020;91(1):3-19. DOI: 10.1080/ 17453674.2019.1683790.
11. Seangleulur A, Vanasbuncha A, Piriyaprasarth P, Ratanaprasatporn S, Poajanasupawun A. The efficacy of local infiltration analgesia in the setting of multimodal analgesia for postoperative pain management in total knee arthroplasty: a systematic review and meta-analysis. Knee. 2016;23(6):917-924. DOI: 10.1016/j.knee.2016.08.008.
12. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med. 2016;375(26):2519-2529. DOI: 10.1056 /NEJMoa 1611593.
13. Huang YM, Wang CM, Wang CT, Lin WP, Horng YS, Jiang CC. Perioperative oral celecoxib for pain management after total knee arthroplasty: A systematic review and meta-analysis of randomised controlled trials. J Orthop Surg (Hong Kong). 2018;26(1):2309499018758832. DOI: 10.1177/2309499018758832.
14. Goesling J, Moser SE, Zaidi B, Hassett AL, Hilliard P, Hallstrom B, Clauw DJ, Brummett CM. Trends and predictors of opioid use after total knee and total hip arthroplasty. Pain. 2016;157(6):1259-65. DOI: 10.1097/j.pain.0000000000000511.
15. Bourne RB, Chesworth BM, Davis AM, Mahomed NN, Charron KDJ. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? Clin Orthop Relat Res. 2010;468(1):57-63. DOI: 10.1007/s11999-009-1119-9.