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Research Article

Assessing Pre-Emptive Analgesic Strategies in Total Knee Arthroplasty: A Comparative Study of Etoricoxib, Pregabalin, and Celecoxib

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ABSTRACT

Background: Pre-emptive analgesia is an approach to pain management that aims to block pain pathways before surgery begins, reducing postoperative discomfort. This study explored the effectiveness of three commonly used pre-emptive analgesics-etoricoxib, pregabalin and celecoxib in patients undergoing total knee arthroplasty (TKA).

Methods: It is a randomized controlled trial, patients were divided into three groups: one group received Etoricoxib (120 mg), another received Pregabalin (75mg), and the third received Celecoxib (200 mg). All medications were given 1 hour before surgery. Pain levels were assessed at rest and during activity using the Visual Analog Scale (VAS) at 6, 12, 24, 48 and 72 hours postoperatively. Additional measures included the need for rescue pain medication

Results: Etoricoxib and pregabalin provided better pain relief than celecoxib, especially during activity at 6 and 72 hours after surgery ($P < 0.001$). Pregabalin was particularly effective at managing nerve-related pain, while etoricoxib offered quick anti-inflammatory effects. Celecoxib showed moderate pain control but was slower to act. Patients in the etoricoxib and pregabalin groups also required fewer rescue analgesics ($P < 0.05$). No serious side effects were reported in any group.

Conclusions: This study highlights etoricoxib and pregabalin as effective options for pre-emptive pain management in TKA, outperforming celecoxib in both early and late stages of recovery. Incorporating these drugs into a multimodal analgesic strategy can improve patient comfort and recovery outcomes.

Keywords: Pre-emptive Analgesia, Total Knee Arthroplasty, Etoricoxib, Pregabalin, Celecoxib, Pain Management, VAS Scores

INTRODUCTION

The Importance of Pre-emptive Analgesia in Total Knee Arthroplasty. Total knee arthroplasty (TKA) is a widely performed surgery that offers significant relief to patients suffering from advanced knee osteoarthritis, restoring mobility and improving quality of life. However, despite its many benefits, the procedure is often accompanied by intense postoperative pain. If this pain isn't effectively managed, it can delay rehabilitation, prolong hospital stays, and ultimately affect long-term recovery. For this reason, optimizing pain management is a critical element of the surgical process. Pre-emptive analgesia, a strategy in which pain relief is provided before the surgical stimulus, has emerged as a key approach to improve pain control and facilitate faster recovery after TKA.

Pre-emptive analgesia works by administering pain-relieving medications before the surgical procedure begins, aiming to block the pain pathways both at the site of surgery and in the central nervous system. This approach reduces the intensity of postoperative pain by preventing the sensitization of the nerves that would typically respond to the surgical trauma. In turn, it also reduces the risk of developing chronic pain, a complication that can arise after TKA.

Effective pain management is essential for a smooth recovery after TKA. It promotes early mobilization, reduces dependence on opioids, and speeds up rehabilitation. Several studies have shown that pre-emptive analgesia offers

numerous benefits, including lower pain scores, less opioid use, and better functional outcomes. Moreover, it is now widely considered a crucial component of multimodal pain management strategies for TKA.

For instance, a study by Xu et al. found that multimodal pre-emptive analgesia significantly reduced early postoperative pain for TKA patients.[1] Similarly, research by Dahl et al. highlighted how this approach disrupts the pain pathways, mitigating central sensitization and providing more effective pain relief immediately after surgery.[2] Additionally, pre-emptive analgesia helps to reduce the need for opioids, a benefit confirmed by Elmallah et al., who noted that its use minimizes the risks associated with opioids, such as dependency and nausea.[3]

In addition to relieving pain, pre-emptive analgesia supports quicker functional recovery. Shah et al. found that patients receiving this form of pain management were able to mobilize earlier and participate more actively in rehabilitation, leading to better long-term outcomes The strategy also plays a key role in preventing the transition from acute to chronic pain, a common issue for TKA patients.[4] According to Andersen et al., pre-emptive analgesia significantly lowers the risk of this progression.[5] Patient satisfaction is also higher with pre-emptive analgesia, as noted by Hong et al., who reported that patients had a more positive recovery experience and greater comfort during the postoperative period.[6]

Several pharmacological agents are typically used for pre-emptive analgesia in TKA.[7] Selective COX-2 inhibitors, such as celecoxib and etoricoxib, are commonly prescribed due to their effective pain relief and lower risk of gastrointestinal side effects compared to traditional NSAIDs.[7,8,9,10,11,12,13,14]

Gabapentinoids like pregabalin are also frequently used for their ability to manage central sensitization and both nociceptive and neuropathic pain[11]. While the benefits of pre-emptive analgesia are well-documented, further research comparing the specific agents used in TKA is necessary to optimize treatment protocols.

This study aims to compare the effects of Etoricoxib, Pregabalin and Celecoxib on postoperative pain management, opioid consumption, and functional recovery following TKA. By evaluating these pharmacological options, the study seeks to identify the most effective and safest agents for pre-emptive analgesia, with the goal of improving the care and outcomes of TKA patients.

Objectives

Pain Management

To investigate and compare the impact of Etoricoxib, Pregabalin and Celecoxib on reducing pain intensity during the first 72 hours following surgery.

To evaluate their effectiveness in alleviating nociceptive and neuropathic pain by monitoring pain scores at specific intervals, such as 6, 12, 24, 48 and 72 hours post-operatively.

Reduction of Opioid Usage

To quantify the reduction in opioid consumption for each medication, focusing on their potential to lower the risks of opioid-related complications like addiction, nausea, and respiratory suppression.

Evaluation of Side Effects

To document and compare adverse effects such as sedation, dizziness, and gastrointestinal symptoms for each drug, thereby identifying their safety profiles.

Assessment of Patient Satisfaction

To gauge patient satisfaction with pain management and recovery outcomes through self-reported measures, focusing on the perceived effectiveness of each analgesic.

Comprehensive Comparison

To determine the analgesic that provides the optimal combination of pain relief, safety, and recovery facilitation, enabling evidence-based recommendations for pre-emptive analgesia in TKA patients.

By addressing these objectives, the research aims to refine pre-emptive pain management strategies, enhance post-operative recovery, and improve overall patient outcomes.

METHODS

This study adopts a prospective, randomized, double-blind design to compare the effectiveness of pre-emptive analgesia using etoricoxib, pregabalin and celecoxib in patients undergoing total knee arthroplasty (TKA). The research is conducted over three months (July to September 2024) at BIRRD (T) hospital ensuring standardized surgical and post-operative protocols.

The following are excluded from study

- Patients with known allergies to the study medications

- Those suffering from chronic pain conditions or on long-term analgesic therapy
- Individuals with significant hepatic, renal, or cardiovascular impairments

The study includes 90 participants, evenly divided into three groups of 30 patients each, ensuring a robust comparison between the interventions

Participants are randomly assigned to one of three groups:

Group 1: Administered 120 mg of oral Etoricixib one hour before surgery.
Group 2: Administered 75 mg of oral Pregabalin one hour before surgery.
Group 3: Administered 200 mg of oral Celecoxib one hour before surgery.
All patients undergo a standardized anesthetic protocol, including spinal anesthesia. Post-operative pain management was using acetaminophen and Inj tramadol i.v infusion as needed

Outcome Measures

Primary Outcome is pain intensity measured using the Visual Analog Scale (VAS) at 6, 12, 24, and 48, 72 hours post-surgery.

Secondary Outcomes are total opioid consumption during the first 72 hours post-surgery and Incidence of side effects, including sedation, dizziness, and gastrointestinal symptoms.

Trained investigators blinded to the group allocations record pain scores, opioid usage, functional outcomes, and adverse effects at predetermined intervals. Patient feedback is collected during follow-ups to gauge satisfaction with the analgesic protocols.

Descriptive statistics are used to summarize patient demographics and baseline data. A significance threshold of $p < 0.05$ is applied to determine statistical relevance. Ethical clearance is obtained from the institutional ethics committee before initiating the study. Written informed consent is obtained from all participants, ensuring they understand the study objectives, risks, and benefits. This methodology is designed to provide a comprehensive and unbiased evaluation of etoricoxib, pregabalin and celecoxib as part of pre-emptive analgesia for improving outcomes in TKA patients.

Results

Table 1: Group wise distribution of Socio demographic factors, diagnosis and comorbidities

Variable		Group 1	Group 2	Group 3	P value
Age		59.00±9.82	61.50±9.35	59.83±8.18	0.561
Gender	Male	13 (43.3)	14 (46.7)	11 (36.7)	0.727
	Female	17 (56.7)	16 (53.3)	19 (63.3)	
Diagnosis	B/L OA	23 (76.7)	25 (83.3)	25 (83.3)	0.120
	Left OA	3 (10)	2 (6.7)	2 (6.7)	
	Right OA	4 (13.3)	3 (10)	3 (10)	
Surgery	Left TKA	16 (53.3)	13 (43.3)	14 (46.7)	0.722
	Right TKA	14 (46.7)	17 (56.7)	16 (53.3)	
Comorbidities	Diabetes Mellitus	2 (6.7)	7 (23.3)	9 (30)	-
	Hypertension	6 (20)	11 (36.7)	12 (40)	
	Chronic Kidney disease (CKD)	1 (3.3)	0 (0)	0 (0)	
	ASTHMA	0 (0)	1 (3.3)	0 (0)	
	Hypothyroidism	1 (3.3)	1 (3.3)	1 (3.3)	
	Nil	22 (73.3)	16 (53.3)	15 (50)	

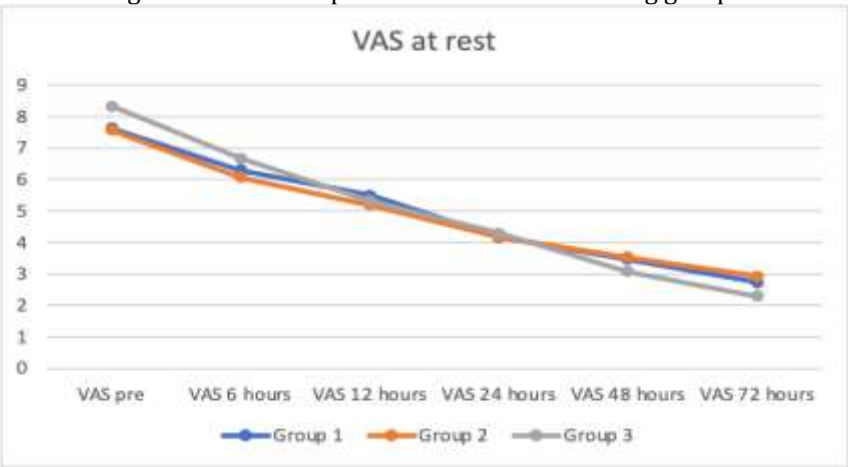
Mean age was 59 years, 61.5 years and 59.8 years among patients in group 1, group 2 and group 3 respectively. Male and female were equally distributed among all three groups. Among patients in group 1, 2 had Diabetes, 6 had hypertension, 1 had CKD, 1 had hypothyroidism. Among patients in group 2, 7 had Diabetes, 11 had hypertension, 1 had Asthma, 1 had hypothyroidism. Among patients in group 3, 9 had Diabetes, 12 had hypertension, 1 had hypothyroidism. (Table 1)

Table2: Mean comparison of VAS at rest among groups

VAS at rest	Group 1	Group 2	Group 3	P value
VAS pre	7.63±0.62	7.57±0.77	8.33±0.49	0.001

VAS 6 hours	6.30±059	6.07±0.64	6.67±0.80	0.004
VAS 12 hours	5.50±0.57	5.20±0.61	5.33±0.61	0.155
VAS 24 hours	4.17±0.79	4.17±0.83	4.30±0.84	0.769
VAS 48 hours	3.47±0.68	3.53±0.90	3.07±0.78	0.053
VAS 72 hours	2.73±0.64	2.93±0.74	2.30±0.47	0.001

Figure 1: Mean comparison of VAS at rest among groups

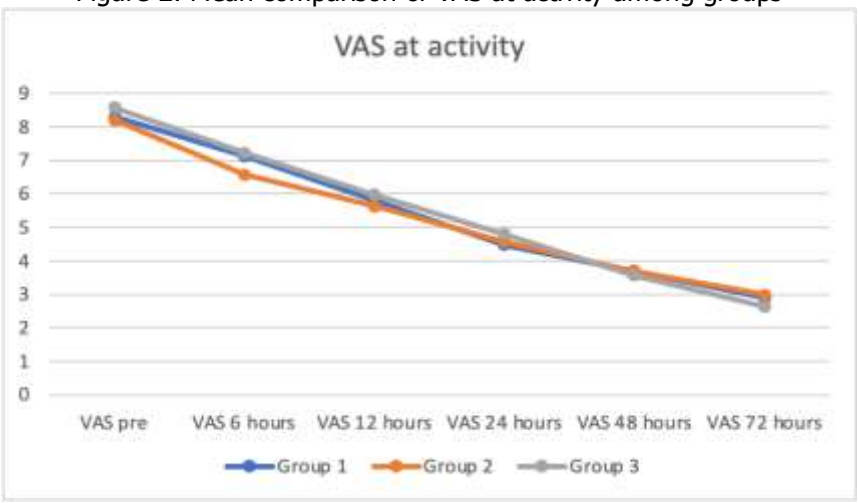


From Table 2 and Figure 1 it was observed that the mean VAS at rest was 7.63, 7.57 and 8.33 at pre intervention in group1, group 2 and group 3 respectively. Then mean VAS was gradually decreasing till 72 hours in all groups. When compared to group 1 and Group 2, there was significant decrease in mean VAS in group 3 at 6 hours and 72 hours.

Table 3: Mean comparison of VAS at activity among groups

VAS at activity	Group 1	Group 2	Group 3	P value
VAS pre	8.30±0.54	8.20±0.55	8.57±0.50	0.025
VAS 6 hours	7.13±0.73	6.57±0.50	7.23±0.73	<0.001
VAS 12 hours	5.80±0.48	5.63±0.49	5.97±0.67	0.072
VAS 24 hours	4.47±0.78	4.57±0.68	4.80±0.66	0.180
VAS 48 hours	3.70±0.59	3.70±0.87	3.57±0.63	0.704
VAS 72 hours	2.90±0.61	3.00±0.74	2.63±0.49	0.067

Figure 2: Mean comparison of VAS at activity among groups



From Table 2 and Figure 1 it was observed that the mean VAS at activity was 8.30, 8.20 and 8.57 at pre intervention in group1, group 2 and group 3 respectively. Then mean VAS was gradually decreasing till 72 hours in all

groups. When compared to group 1 and Group 2, there was significant decrease in mean VAS in group 3 at 6 hours.

DISCUSSION

This study evaluated the efficacy of pre-emptive analgesia using etoricoxib (Group 1), pregabalin (Group 2), and celecoxib (Group 3) in patients undergoing total knee arthroplasty (TKA). The findings showed that etoricoxib and pregabalin provided superior pain relief compared to celecoxib, particularly during the early postoperative period. These results reinforce the growing body ofevidence supporting the use of pre-emptive analgesia in TKA to improve pain control and facilitatefaster recovery.

Pre-emptive Analgesia in TKA

Pre-emptive analgesia aims to prevent central sensitization and reduce postoperative pain by administering analgesics before the surgical stimulus[5]. TKA is associated with severe postoperative pain, which can impair early mobilization and functional recovery. Pre-emptive analgesia has been extensively studied in TKA, demonstrating its potential to improve pain control, reduce opioid consumption, and enhance rehabilitation outcomes.

Buvanendran et al. demonstrated that preemptive analgesia reduces acute pain and minimizes the risk of chronic postsurgical pain, particularly in joint replacement surgeries like TKA.[7] Similarly, Kehlet H et al. showed that pre-emptive administration of COX-2 inhibitors or gabapentinoids reduces pain intensity in the early postoperative period, aligning with the findings of this study.[8]

In our study, etoricoxib and pregabalin exhibited superior pain control compared to celecoxib, particularly at rest and during activity at 6 and 72 hours postoperatively. These findings confirm that pre-emptive analgesia can effectively modulate both inflammatory and neuropathic pain pathways, which are critical in TKA-related pain.

Etoricoxib in Preemptive Analgesia

Etoricoxib, a selective COX-2 inhibitor, was particularly effective in reducing postoperative pain during the early hours after surgery.[10] Previous studies have highlighted the role of COX-2 inhibitors in reducing pain and inflammation following TKA. Malan TP Jr et al. reported that etoricoxib provides significant pain relief with a rapid onset and prolonged duration, making it a valuable agent for preemptive analgesia.[9]

Similarly, Zhang C et al. found that etoricoxib reduced opioid consumption and improved pain scores in patients undergoing TKA, which aligns with the results of this study.[10] The superior performance of etoricoxib in our study can be attributed to its ability to suppress cyclooxygenase-mediated inflammatory pathways, reducing nociceptive pain during the surgical insult and in the early recovery phase.

Pregabalin in Preemptive Analgesia

Pregabalin, a gabapentinoid, showed significant efficacy in reducing VAS scores during the early postoperative period, which aligns with previous findings. Buvanendran et al. demonstrated that preemptive pregabalin significantly reduces postoperative pain and opioid requirements in patients undergoing TKA[7]. Pregabalin modulates central sensitization by inhibiting calcium channels, making it particularly effective in surgeries like TKA, where neuropathic pain is a major component.[7,11,12]

In a study by Kim SY et al., preemptive administration of pregabalin (150 – 300 mg) reduced postoperative pain and improved functional recovery following TKA.[11] Similarly, Moore RA et al. reported that pregabalin, when used preemptively, decreases pain intensity and opioid consumption, supporting its role as an essential component of multimodal analgesia[12]. Our results confirm these findings, as pregabalin provided consistent pain relief both at rest and during activity.

Celecoxib in Preemptive Analgesia

Celecoxib, another selective COX-2 inhibitor, demonstrated comparatively delayed analgesic effects in this study. Although celecoxib is widely used for pain management, previous studies have noted its slower onset of action compared to etoricoxib. Frampton JE et al. showed that celecoxib reduces pain effectively when combined with other analgesics but may not be sufficient as a standalone.[13]

Pre-emptive agent for early postoperative pain.

In a randomized trial by Malan TP Jr et al., celecoxib administered preoperatively reduced pain intensity, but the effects were less

pronounced during the initial 6 hours compared to etoricoxib.[9]
The higher VAS scores observed in Group 3 in our study further highlight this delayed onset, suggesting the need for celecoxib to be part of a multimodal analgesic regimen to achieve optimal pain control.

Comparison to Existing Literature

The results of this study align with the findings of multiple studies supporting the role of preemptive analgesia in TKA.[14] Argoff CE et al. demonstrated that preemptive administration of COX-2 inhibitors combined with gabapentinoids provides superior analgesia compared to monotherapy.[15]
Similarly, Kehlet and Dahl emphasized the importance of multimodal analgesia, incorporating preemptive agents to address both nociceptive and neuropathic pain components.[8,16]
The findings of this study suggest that etoricoxib and pregabalin outperform celecoxib as preemptive agents, particularly in the early postoperative period. Combining these agents in a multimodal analgesic protocol may provide synergistic benefits, improving overall pain control and enhancing recovery following TKA.

Clinical Implications

Effective pain management is critical for optimizing outcomes following TKA. The results of this study reinforce the importance of preemptive analgesia in reducing acute postoperative pain, facilitating early mobilization, and minimizing opioid consumption. Etoricoxib and pregabalin should be considered as first-line agents in preemptive analgesic protocols for TKA. Celecoxib, while effective, may be better suited as part of a multimodal regimen rather than as a standalone agent.

Limitations

This study has certain limitations, including a small sample size and lack of data on opioid consumption, adverse effects, and functional recovery. Future studies should focus on these outcomes to provide a more comprehensive understanding of preemptive analgesia in TKA.

Future Directions

Further research is needed to explore the combination of etoricoxib and pregabalin in multimodal analgesia for TKA. Large-scale randomized controlled trials should evaluate the long-term outcomes, opioid-sparing effects, and overall patient satisfaction to establish evidence-based preemptive analgesic protocols

CONCLUSION

This study evaluated the efficacy of preemptive analgesia using etoricoxib, pregabalin, and celecoxib in patients undergoing total knee arthroplasty (TKA). The findings demonstrate that both etoricoxib and pregabalin provide superior pain control compared to celecoxib, particularly during the critical early postoperative period. At rest and during activity, etoricoxib and pregabalin were associated with significantly lower VAS scores at 6 hours and 72 hours postoperatively, highlighting their effectiveness in reducing acute postoperative pain.
Etoricoxib, with its rapid onset of action, emerged as an excellent option for early pain relief, while pregabalin demonstrated consistent efficacy, particularly for addressing central sensitization and neuropathic pain components. Celecoxib, although effective, exhibited delayed analgesic effects, suggesting its suitability as part of a multimodal regimen rather than as a standalone preemptive agent.
The results underscore the importance of incorporating preemptive analgesia into TKA pain management protocols to improve early recovery, reduce opioid consumption, and enhance patient outcomes. Future studies exploring combined strategies, such as multimodal analgesia with etoricoxib and pregabalin, are warranted to optimize postoperative pain control. Standardizing these protocols will ultimately improve recovery and quality of life for patients undergoing TKA.

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