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Research Article

Comparative Analysis of Two Celecoxib Regimens for Postoperative Pain Management Following Bi-malleolar Fracture Surgery

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ABSTRACT

Background: Bimalleolar fractures, which often necessitate surgery due to instability, are linked to considerable postoperative pain. Selective cyclooxygenase-2 (COX-2) inhibitors, like celecoxib, have demonstrated potential in alleviating pain and decreasing the need for opioids. However, the optimal dosing regimen remains unclear. This study compares the efficacy of two celecoxib regimens in reducing postoperative pain after ankle fracture surgery.

Methods: A double-blind, randomized controlled trial was carried out with 240 patients undergoing bimalleolar fracture surgery under spinal anesthesia. The participants were split into three groups: a placebo group, a group receiving 400 mg of celecoxib (Group 400), and a group receiving 600 mg of celecoxib (Group 600). Pain levels were evaluated using the Visual Analog Scale (VAS) at specific time points (0, 6, 24, and 72 hours after surgery). Additionally, total morphine consumption, the time until first analgesic use, patient satisfaction, and side effects were documented.

Results: Patients in Group 600 experienced significantly lower pain scores and delayed morphine use compared to the placebo group ($P < 0.05$). Both celecoxib groups consumed less morphine overall, with higher patient satisfaction scores reported in Group 600. Adverse events were minimal and comparable across all groups.

Conclusion: The preemptive use of celecoxib, particularly at a 600 mg dose, significantly reduces postoperative pain and opioid use while enhancing patient satisfaction with minimal side effects. These results suggest that COX-2 inhibitors are a practical alternative to opioids for managing pain after ankle fracture surgery.

Introduction

Effective management of pain following surgery, while minimizing adverse effects, is key to achieving positive surgical results, boosting patient satisfaction, and reducing the length of hospital stays. Conversely, when pain is poorly managed, patients may experience decreased mobility, which can impede their recuperation and elevate the likelihood of serious complications like deep vein thrombosis, pneumonia, and pulmonary embolism [1-2]. Bimalleolar fractures, involving both the lateral and medial malleoli, are a common orthopedic injury requiring surgical intervention due to their instability. These fractures happen at a rate of 187 cases per 100,000 people each year in the United States, ranking them as the third most common type of fracture among individuals aged 60 and

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older [3]. Ankle surgeries, particularly those addressing bimalleolar fractures, are among the most painful orthopedic procedures. Even with progress in surgical methods, effectively managing pain after surgery continues to be a major challenge. Inadequate pain control can result in a slower recovery, a higher chance of developing chronic pain, and lower patient satisfaction [4-5]. Despite this, few studies have been conducted to assess and manage postoperative pain effectively.

Multimodal pain management frequently incorporates NSAIDs. However, non-selective NSAIDs, which inhibit both COX-1 and COX-2, are associated with potential complications such as gastrointestinal ulceration, nephrotoxicity, and a heightened risk of bleeding following surgical procedures. Selective COX-2 inhibitors, such as celecoxib, offer an alternative with a more desirable safety profile, notably reducing the incidence of bleeding and gastrointestinal side effects [6]. Despite these advantages, conflicting evidence exists regarding the effectiveness of prophylactic celecoxib use in managing postoperative pain. While some studies report improved pain control and reduced opioid requirements with higher doses of celecoxib [7].

This study aims to compare the effectiveness of two preemptive celecoxib regimens (400 mg and 600 mg) with a placebo in managing postoperative pain following bimalleolar fracture surgery. By assessing pain intensity, opioid consumption, and patient satisfaction, this research seeks to provide evidence-based guidance for improving pain management in orthopedic surgery.

Methods

This study was conducted as a double-blind, randomized controlled trial. Ethical approval was granted by the university's ethics committee (IR.SBMU.RETECH.REC.1402.077), and the trial was registered with the national registry (IRCT20120910010800N11). All participants gave both written and oral informed consent prior to their participation in the study.

This study included adult participants, defined as those 18 years of age or older, who received spinal anesthesia for surgical repair of a bimalleolar fracture between May and November of 2023. Enrollment criteria mandated that all participants be a minimum of 18 years old and possess a verified diagnosis of a bimalleolar fracture necessitating operative intervention. Additionally, they had to possess the capacity to provide informed consent and demonstrate an understanding of the study's purpose and procedures.

Conversely, individuals were excluded from participation if they exhibited an allergy or any contraindication to non-steroidal anti-inflammatory drugs (NSAIDs) or medications from the sulfonamide group. A history of gastrointestinal bleeding, peptic ulcers, coronary or peripheral arterial diseases, or dyspepsia also warranted exclusion. Participants who were chronically using drugs that modulate pain or opioids were not eligible for the study.

Furthermore, individuals with neuropathy, neurological diseases that could affect pain perception, or mental health disorders that might interfere with their ability to provide informed consent were excluded. A history of substance abuse, as well as the use of NSAIDs, opioids, or salicylates within the seven days before surgery, were additional grounds for exclusion. Lastly, any surgical procedure that exceeded 160 minutes in duration, involved intraoperative complications, or necessitated postoperative intensive care was grounds for exclusion from the study.

Participants were divided into three groups through a permutation block randomization method. Random numbers were created using a random number table and kept hidden in opaque, sealed envelopes by an independent third party. The first group, the placebo group, was administered two placebo capsules the evening before their surgery and an additional placebo capsule one hour before the procedure. This ensured that any observed effects could be attributed to the placebo effect rather than the active medication. Neither the participants nor the investigators were aware of group assignments. The second group, designated as Group 400, received a regimen consisting of two 200 mg celecoxib capsules the night before surgery. To maintain consistency in the administration schedule, this group was also given one placebo capsule one hour before the surgery. This approach allowed for the assessment of the effects of a 400 mg celecoxib dose on postoperative outcomes. Group 600, the third cohort in this study, received an alternative celecoxib dosing protocol. Like Group 400, participants in Group 600 ingested two 200 mg celecoxib capsules the evening prior to surgery. Unlike Group 400, however, Group 600 participants were given an additional 200 mg celecoxib capsule one hour preoperatively. This dosing strategy was implemented to assess the effects of a larger cumulative dose of 600 mg of celecoxib on postoperative analgesia and recuperation.

Spinal anesthesia using 0.5% hyperbaric bupivacaine was employed for all surgical procedures; intrathecal opioids were not utilized. The duration of each surgical intervention was documented. To maintain uniform intraoperative analgesia, patients received 0.1 mg/kg of intravenous morphine 30 minutes prior to the completion of the procedure. Postoperative monitoring included standard care in the recovery room until full recovery from spinal anesthesia, as assessed by standard recovery scores. Pain management in the recovery room utilized a fixed dose of 20 mg intravenous pethidine if required.

Postoperative pain intensity, the main outcome of interest in this study, was quantified using the Visual Analog Scale (VAS). This scale is anchored by 0,

signifying the absence of pain, and 10, denoting the most severe pain imaginable. VAS scores were recorded at specific time points—upon arrival to the operating room, prior to discharge from the postanesthesia care unit, and at 6, 24, and 72 hours postoperatively—to track changes in pain levels over time. Beyond pain intensity, several secondary endpoints were also evaluated in this study. These included the time to first analgesic request, providing an indication of the duration of effective analgesia achieved with each intervention. Furthermore, the cumulative morphine consumption for each patient during the 72 hours following surgery was quantified, serving as an indicator of the pain management strategies' success in minimizing opioid requirements.

Another important secondary outcome was patient satisfaction with pain management, measured using a Visual Analog Scale (VAS) from 0 (completely dissatisfied) to 10 (completely satisfied). This provided information about the patient's subjective experience.

Preliminary data from 55 patients informed the sample size calculation. To achieve 90% power with a 5% Type I error rate, a sample size of 220 was required. Accounting for a 20% potential dropout rate, 240 participants were recruited (Figure 1).

SPSS (version 24) was used for data analysis. Continuous variables are presented as median (IQR), and categorical variables as frequency (percentage). Group comparisons were performed using the Kruskal-Wallis and Mann-Whitney U tests. Logistic regression was used for secondary outcome analysis. Statistical significance was defined as $P < 0.05$.

Results

Initially, the study recruited 255 patients who met the eligibility criteria and gave their informed consent. However, the final analysis included only 240 participants due to the exclusion of 15 patients for various reasons. Five patients voluntarily withdrew their consent after enrollment, leading to their exclusion from the study. Additionally, six patients encountered issues with anesthesia; specifically, they experienced unsuccessful spinal anesthesia, or the anesthetic effect resolved prematurely, before the completion of the surgical procedure. These patients were excluded from the analysis as well.

Furthermore, four patients required intensive care unit (ICU) support due to postoperative medical complications. As this level of care was beyond the scope of the study's protocol, these patients were rendered ineligible for continued participation and were subsequently excluded.

After applying the exclusion criteria, the remaining 240 patients were randomly assigned in equal numbers to one of three groups (n=80 per group). Group 400 received a total of 400 mg of celecoxib, while Group 600 received a total of 600 mg of celecoxib. The third group, serving as the control arm, received a placebo.

Patient demographics and baseline characteristics were well-balanced across the three study groups, with no statistically significant differences observed (Table 1). The median age of participants was 35 years (range, 18-76 years). The majority of patients (68.6%) were categorized as overweight according to their Body Mass Index (BMI). The proportion of male (48.3%) and female (51.7%) participants was similar across the groups. The median surgical time was 97.5 minutes (range, 60-160 minutes), with no significant intergroup differences ($P = 0.169$).

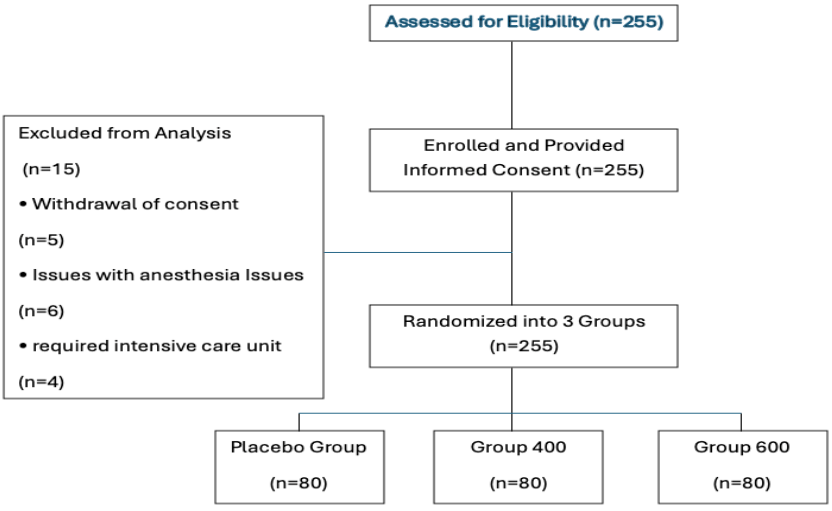

Figure 1- Patient Flow Diagram (CONSORT)

Table 1- Demographic and Baseline Characteristics of Patients by Treatment Groups, BMI: Body Mass Index, IQR: Interquartile Range

Parameters/Groups		Celecoxib 400 mg	Celecoxib 600 mg	Placebo	Total	P value
Age	Minimum	18	19	21	18	0.257
	Maximum	76	70	69	76	
	Median	33	35.5	37	35	
	IQR	23	20	22	21	
	18-30	36 (45.0%)	28 (35.0%)	28 (35.0%)	92 (38.3%)	0.497
	31-50	28 (35.0%)	40 (50.0%)	32 (40.0%)	100 (41.7%)	
	51-70	12 (15.0%)	12 (15.0%)	20 (25.0%)	44 (18.3%)	
	>70	4 (5.0%)	0 (0.0%)	0 (0.0%)	4 (1.7%)	
Gender	Male	40 (50%)	44 (55%)	32 (40.0%)	116 (48.3%)	0.156
	Female	40 (50%)	36 (45%)	48 (60%)	124 (51.7%)	
Height	Minimum	153	158	157	153	0.478
	Maximum	187	182	188	188	
	Median	174.00	174.50	173.00	174.00	
	IQR	17	9	14	10	
Weight	Minimum	61	63	58	58	0.241
	Maximum	94	91	95	95	
	Median	76.50	75.00	77.00	76.00	
	IQR	14	17	12	16	
BMI	Minimum	18.4	18.4	18.4	18.4	0.732
	Maximum	29.8	30.0	30.0	30.0	
	Median	25.572	25.823	25.838	25.747	
	IQR	2.6241	1.9800	2.4367	2.3602	
	Underweight	1 (0.2%)	1 (0.2%)	1 (0.2%)	4 (0.8%)	0.320
	Normal Weight	43 (8.9%)	33 (6.8%)	36 (7.4%)	148 (30.6%)	
	Overweight	77 (15.9%)	87 (18.0%)	84 (17.4%)	332 (68.6%)	
	Obese	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Duration of surgery	Minimum	60	70	60	60	0.169
	Maximum	160	150	160	160	
	Median	100	90	120	97.5	
	IQR	44	36	50	43	

Pain intensity was systematically evaluated using VAS at several predetermined time points: before the surgery and at 6, 24, and 72 hours following the procedure. The results revealed notable differences in pain levels across the groups at each assessment interval.

Preoperatively, the placebo group exhibited significantly elevated median pain scores [7] relative to both Group 400 and Group 600, which presented with median pain scores of 5 ($P < 0.001$). Six hours after surgery, Group 600 showed the lowest median VAS score of 4, suggesting superior pain control compared to Group 400 and the placebo group, which both had median scores of 5 ($P < 0.001$). Twenty-four hours post-surgery, Group 600 maintained its lead in pain management, reporting the lowest median pain score of 3. Meanwhile, Group 400 and the placebo group had median scores of 3.5 and 3.34, respectively ($P < 0.001$). Seventy-two hours after surgery, Group 600 once again reported the lowest pain scores, with a median of 2, while both Group 400 and the placebo group had median scores of 3 ($P < 0.001$).

Overall, these results underscore the potential of celecoxib, especially at a 600 mg dose, to markedly decrease postoperative pain when used as part of a preemptive analgesia approach (Table 2).

The analysis of total morphine consumption over the 72-hour postoperative period revealed a significant reduction in both celecoxib groups compared to the placebo group. This finding underscores the effectiveness of celecoxib in decreasing the reliance on opioids for pain management (Table 2).

The median morphine consumption was significantly lower in the celecoxib groups. Group 600 and Group 400

both had a median morphine consumption of 15 mg, while the placebo group had a notably higher median consumption of 25 mg ($P < 0.001$) (Table 2).

The time until patients in Group 600 first requested pain relief was notably extended, with a median of 200 minutes. This was substantially longer compared to Group 400, where the median time was 120 minutes, and the placebo group, where it was only 60 minutes ($P < 0.001$) (Table 2).

Patient satisfaction scores, rated on a VAS scale from 0 (completely dissatisfied) to 10 (fully satisfied), were highest in Group 600, with a median score of 8. Group 400 reported a median score of 5, while the placebo group reported the lowest satisfaction (median: 4, $P < 0.001$) (Table 2).

Adverse events were rare and similar across groups, except for postoperative nausea and vomiting (PONV), which differed significantly. In terms of PONV, Group 600 demonstrated the most favorable outcomes, with 95% of patients reporting no symptoms. Group 400 also showed a relatively low incidence, with 85% of patients remaining free of PONV. In contrast, the placebo group had the highest rate of PONV, with only 60% of patients reporting no symptoms ($P < 0.001$). Furthermore, severe PONV was exclusively reported in the placebo group, affecting 10% of patients. Constipation rates were 5% in the 400 mg and 600 mg celecoxib groups versus 1.3% in the placebo group ($P = 0.355$). Urinary retention was uncommon, affecting only two patients in total—1.3% in the 400 mg and placebo groups and none in the 600 mg group ($P = 0.605$) (Table 2).

Discussion

Effective pain management is critical for improving outcomes in orthopedic surgery, particularly for bimalleolar fractures, which are associated with severe postoperative pain [5]. Inadequate pain control can delay recovery, impair functional outcomes, and increase the risk of chronic pain development [5]. Preemptive analgesia, a strategy to reduce pain by intervening before the onset of noxious stimuli, has gained significant attention [8-9]. This study investigated the efficacy of two celecoxib regimens (400 mg and 600 mg) compared to a placebo in managing postoperative pain following ankle fracture surgery.

Preemptive analgesia was initially conceptualized by Dr. Crile in the early twentieth century [8]. Preemptive analgesia aims to reduce postoperative pain by intervening before noxious stimuli are introduced [9]. Various medications have been tested for this strategy, including local anesthetic infiltration [10], nerve blocks [11], opioids [12], acetaminophen [13], selective cyclooxygenase-2 (COX-2) inhibitors [14], and NSAIDs [15], with varying and sometimes conflicting results.

Our findings indicate that preemptive administration of celecoxib, particularly at a dosage of 600 mg, significantly reduces pain intensity and opioid consumption while enhancing patient satisfaction. This aligns with previous research that suggests COX-2 inhibitors offer superior pain relief compared to traditional NSAIDs and may decrease the necessity for opioid analgesics [6, 16-19]. However, it should be noted that varying results have also been reported in the literature [20].

In our study, the 600 mg celecoxib regimen consistently resulted in lower pain scores across all postoperative time points compared to the placebo group ($P < 0.001$). Similar benefits were observed in the 400 mg group, although the 600 mg dose demonstrated greater efficacy, particularly at 72 hours postoperatively. These results align with previous studies, such as Recart et al. and Pournajafian et al., which found that higher doses of celecoxib provided better pain control in minor surgeries [6, 17]. Our findings extend this knowledge to orthopedic procedures, emphasizing the importance of dosage optimization to maximize analgesic effects. Celecoxib's analgesic effects in the current study were comparable to findings by Farhanchi et al. [7], who showed that COX-2 inhibitors can be effective alternatives to traditional NSAIDs, providing pain relief with a lower risk of side effects like gastrointestinal issues. Jeffrey G. Stepan et al. conducted a study on patients undergoing soft tissue ambulatory hand surgery, showing that those who received perioperative celecoxib experienced similar postoperative pain levels and opioid intake compared to those who did not receive the medication. The limited duration and mild nature of pain associated with outpatient elective soft tissue hand surgery may explain these findings. On the contrary, another research has shown that the preemptive use of pregabalin in combination with celecoxib has beneficial effects on alleviating acute pain and reducing the cumulative opioid dosage following total knee arthroplasty [21]. Another study has demonstrated that celecoxib is non-inferior to the TAP block as a preemptive analgesic and may be administered as a simple preemptive analgesic for laparoscopic transabdominal preperitoneal hernia repair [22]. Celecoxib significantly reduced morphine consumption compared to placebo ($P < 0.001$), supporting the opioid-sparing effects of COX-2 inhibitors reported in previous studies [18,21]. A median of 200 minutes to the first analgesic request in the 600 mg group further supports its effectiveness in sustaining pain relief. Importantly, patients in the 600 mg group reported the highest satisfaction with pain control, with a median satisfaction score of 8. Research by Recart et al., Farhanchi et al., and Pournajafian et al. indicates that celecoxib, especially when used as preemptive analgesia, increases patient satisfaction [6-7,17]. Additionally, a meta-analysis indicated that the use of celecoxib reduces

the necessity for rescue analgesics following total knee arthroplasty [23].

Table 2- Postoperative Pain Intensity, Morphine Consumption, and Adverse Events by Treatment Group. VAS: visual analog scale, PONV: Postoperative Nausea and Vomiting, IQR: Interquartile Range

Parameters/Groups		Celecoxib 400 mg	Celecoxib 600	Placebo	Total	P value
Pain Intensity (VAS)						
Before Surgery, Median (IQR)	Minimum	4	4	6	4	<0.001
	Maximum	9	6	9	9	
	Median	5	5	7	6	
	IQR	2	1	1	2	
6 Hours Postop, Median (IQR)	Minimum	3	3	3	3	<0.001
	Maximum	7	6	8	8	
	Median	5	4	5	5	
	IQR	1	1	1	1	
24 Hours Postop, Median (IQR)	Minimum	3	3	3	3	<0.001
	Maximum	5	4	6	5	
	Median	3.5	3	3.34	3	
	IQR	1	0	0.645	1	
72 Hours Postop, Median (IQR)	Minimum	2	2	2	2	<0.001
	Maximum	4	3	4	4	
	Median	3	2	3	3	
	IQR	2	1	0	1	
Morphine Consumption (mg)						
Median (IQR)	Minimum	10	10	20	10	<0.001
	Maximum	30	25	60	60	
	Median	15	15	25	20	
	IQR	5	3	14	10	
PONV, n (%)						
No Symptoms		68 (85.0%)	76 (95.0%)	48 (60.0%)	192 (80%)	<0.001
Mild		4 (5.0%)	4 (5.0%)	8 (10.0%)	16 (6.7%)	
Moderate		8 (10.0%)	8 (10.0%)	16 (20%%)	24 (10.0%)	
Severe		0 (0.0%)	0 (0.0%)	8 (10.0%)	8 (3.3%)	
Constipation, n (%)						
No		76 (95.0%)	76 (95.0%)	79 (98.8%)	231 (96.3%)	0.355
Yes		4 (5.0%)	4 (5.0%)	1 (1.3%)	9 (3.8%)	
Retention, n (%)						
No		79 (98.8%)	80 (100%)	79 (98.8%)	238 (99.2%)	0.605
Yes		1 (1.3%)	0 (0.0%)	1 (1.3%)	2 (0.8%)	
Time to request analgesic, minutes						
Minimum		30	30	30	30	<0.001
Maximum		320	400	190	400	
Median		120	200	60	100	
IQR		54	184	45	120	
Satisfaction, VAS						
Minimum		0	2	0	0	<0.001
Maximum		10	10	10	10	
Median		5	8	4	5	
IQR		3	5	2	4	

In the 600 mg group, only a small percentage experienced PONV, with 95% of patients reporting no symptoms. In contrast, the placebo group exhibited the highest incidence of severe PONV (10%, $P < 0.001$). These results support previous studies suggesting that

COX-2 inhibitors may reduce the incidence of PONV, potentially by lowering opioid requirements [19].

Other adverse events were minimal and comparable across all groups, indicating a favorable safety profile for celecoxib in both dosing regimens. Constipation was reported in 5% of patients in both celecoxib groups and 1.3% of patients in the placebo group, with no statistically significant differences (P = 0.355). Urinary retention was rare, occurring in only two patients overall (P = 0.605). Multiple studies, including those by Recart et al. [6], Farhanchi et al. [7], and Ma et al. [8], demonstrate that celecoxib, as a COX-2 inhibitor, offers effective pain relief with fewer side effects, making it a viable alternative to opioids for postoperative analgesia.

Our study supports the growing evidence for selective COX-2 inhibitors, like celecoxib, in preemptive analgesia [24]. Nonetheless, the results underscore the necessity for further research to optimize dosing strategies, evaluate long-term outcomes, and investigate potential interactions with other analgesics. Future studies should aim to assess the long-term effectiveness of preemptive analgesia with COX-2 inhibitors, particularly in high-risk patient populations or those undergoing more complex surgical procedures.

While this study provides robust evidence for the efficacy and safety of preemptive celecoxib use, some limitations warrant consideration. Firstly, the study was carried out in a single center, which could restrict the applicability of the results to broader contexts. Secondly, the follow-up period was limited to 72 hours after surgery, and long-term effects, such as the development of chronic pain or functional recovery, were not evaluated. Future research should explore the long-term benefits of COX-2 inhibitors and investigate their use in diverse patient populations and surgical contexts. Additionally, studies evaluating the cost-effectiveness of celecoxib regimens could further inform clinical decision-making.

This study boasts several key strengths, notably its double-blind, randomized controlled design, which reduces bias and enhances the reliability of its findings. The even distribution of participants across various groups and the thorough data collection on pain intensity, opioid consumption, and patient satisfaction contribute to the study's robustness. The inclusion of both objective and subjective measures, such as the time to first analgesic request and patient satisfaction scores, allows for a comprehensive assessment of the interventions.

However, the study has certain limitations. The single-center design may limit the generalizability of our findings. The short follow-up period of 72 hours hinders insights into long-term outcomes, like chronic pain development or functional recovery. Moreover, the absence of a cost-effectiveness analysis for the celecoxib regimens restricts the findings' practical relevance in resource-limited settings. Lastly, the exclusion of patients with comorbidities or those undergoing more complex surgeries limits the study's scope, highlighting the need for future research to address these variables.

Conclusion

This study demonstrates that preemptive administration of 600 mg celecoxib effectively manages postoperative pain following bimalleolar fracture surgery. This dosage reduced pain, delayed the need for additional analgesia, and decreased morphine use. Patients reported high satisfaction levels, and celecoxib had a favorable safety profile. Further studies are needed to explore long-term effects, ideal dosing, cost-effectiveness, and combined use of celecoxib with non-opioids.

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