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Toward Opioid-Free Analgesia: Metamizole–Ketamine versus Metamizole–Tramadol in Orthopedic Postoperative Pain Management

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ABSTRACT

Background: Postoperative pain is a common issue among patients undergoing surgery. Inadequate management of postoperative pain can affect quality of life, prolong recovery, increase the risk of postoperative complications, and contribute to the development of persistent postoperative pain. Major orthopedic surgery is one of the procedures associated with high levels of postoperative pain; therefore, effective pain management is essential to accelerate recovery and improve postoperative quality of life. A multimodal analgesia approach has been studied to help manage postoperative pain in orthopedic patients. Limited data on the effectiveness of the metamizole–ketamine combination compared to metamizole–tramadol in postoperative pain management forms the basis for conducting this study.

Objective: To analyze the difference in pain scores at 6, 12, 18, and 24 hours postoperatively between the administration of metamizole–ketamine and metamizole–tramadol combinations in adult patients undergoing major orthopedic surgery.

Research Method: This was a prospective analytic quasi-experimental study conducted at Universitas Airlangga Hospital involving 20 patients aged 18–65 years who underwent major orthopedic surgery and met the inclusion and exclusion criteria. Data collected included baseline characteristics, pain scores evaluated using Numeric Rating Scale, and side effects following the administration of either the metamizole–ketamine or metamizole–tramadol combination. The collected data were analyzed using SPSS software.

Results: A significant difference in pain scores was found at 18 and 24 hours postoperatively, with the metamizole–ketamine group showing lower pain scores compared to the metamizole–tramadol group ($p = 0.048$ and $p = 0.038$, respectively).

Conclusion: The combination of metamizole–ketamine results in lower pain scores at 18 and 24 hours after major orthopedic surgery compared to the combination of metamizole–tramadol.

Keywords: *pain scores, major orthopedic, metamizole, ketamine, tramadol*

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1. INTRODUCTION

Postoperative pain remains a major clinical challenge, affecting over 80% of surgical patients, with most describing their pain as moderate to severe. Of these, 75% report their pain as moderate, severe, or even extreme in intensity. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja, 2006). Inadequate pain control not only impairs quality of life but also delays recovery, increases complications, and raises healthcare costs. Recognizing its impact, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) designates pain as the “fifth vital

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sign," underscoring the importance of effective management (Chunduri, 2022). Multimodal analgesia, recommended by the American Pain Society (APS) and the American Society of Anesthesiologists (ASA), has become the cornerstone of modern perioperative practice. By using concurrent use of multiple analgesic agents and techniques with different mechanism, this approach enhance analgesic efficacy while minimizing side effects associated with high doses of a single agent. Although opioid-based analgesia remains a first line choice for postoperative pain management, its use is frequently limited by side effects such as nausea, vomiting, sedation, and respiratory depression, leading to delayed patient mobilization and discharge. Consequently, a major focus of modern perioperative medicine is the development of effective opioid-sparing multimodal regiments that enhance pain control, improve patient satisfaction, and accelerate recovery (Sampognaro, 2023).

Major orthopedic surgery is particularly associated with severe postoperative pain, making effective pain management essential for facilitating early rehabilitation and optimizing functional outcomes (Helander, 2017). Various combinations of non-steroidal anti-inflammatory drugs (NSAIDs), ketamine, gabapentinoids, and other adjuvants have been investigated to address this need. Previous studies demonstrated that a combination of paracetamol and ketamine was superior to paracetamol and tramadol in reducing postoperative pain scores and agitation (Khajavi, 2016). However, evidence on metamizole-based combinations remains limited, despite its established role as a potent non-opioid analgesic. This study therefore aims to compare the analgesic efficacy and safety of metamizole–ketamine versus metamizole–tramadol in adults undergoing major orthopedic surgery. We hypothesize that the metamizole–ketamine regimen will provide superior pain relief.

2. MATERIALS AND METHODS

Study Design

This prospective, quasi-experimental study was conducted at Universitas Airlangga Hospital from June to July 2025. The study protocol was approved by the Institutional Review Board, and written informed consent was obtained from all participants. A total of 20 adult patients (18–65 years) scheduled for major orthopedic surgery who met the inclusion and exclusion criteria were enrolled

Anesthetic Management and Interventions

Patients underwent either general or regional anesthesia, as deemed appropriate for surgical procedure.

- **General anesthesia:** Induction was performed with intravenous fentanyl (1–2 μg/kg) and propofol (1–2 mg/kg). Rocuronium (0.6–1.2 mg/kg, ideal body weight) was given for intubation, and anesthesia was maintained with isoflurane (1.2 vol%). Supplemental fentanyl (1 μg/kg) was administered if surgery lasted more than two hours or if pain signs appeared. At the end of surgery, neuromuscular blockade was reversed with neostigmine (0.5 mg/kg) and atropine (0.04 mg/kg).
- **Regional anesthesia:** A spinal block with 5% hyperbaric bupivacaine was performed to achieve a sensory level between T6 and T10. Intravenous midazolam (0.03–0.1 mg/kg) was given for sedation as needed.

All patients received intravenous metoclopramide (0.1–0.15 mg/kg) for antiemesis and intravenous metamizole (1 g) as baseline analgesia near the end of surgery.

In the recovery room, patients were randomly allocated into two groups:

1. **Metamizole–Ketamine Group:** Continuous IV ketamine infusion at 0.05–0.3 mg/kg/h.
2. **Metamizole–Tramadol Group:** Continuous IV tramadol infusion at 0.2 mg/kg/h.

Data Collection and Outcomes

Data were collected using standardized forms.

- **Primary outcome:** Postoperative pain intensity, assessed with the Numeric Rating Scale (NRS, 0 = no pain, 10 = worst pain) at 6, 12, 18, and 24 hours.
- **Secondary outcomes:** Incidence of side effects. Sedation, if present, was assessed with the Richmond Agitation-Sedation Scale (RASS).

Statistical Analysis

Data were analyzed using SPSS. Normality was tested with the Kolmogorov–Smirnov test. Descriptive statistics were reported as mean ± standard deviation (SD) for normally distributed variables or median (range) for non-normal data. Between-group comparisons were performed with the independent t-test (normal distribution) or Mann–Whitney U test (non-normal). A p-value <0.05 was considered statistically significant. Results were presented in tables, figures, and descriptive text.

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3. RESULT

Baseline Characteristics

A total of 20 patients were included in the final analysis, with 10 assigned to the metamizole–ketamine group and 10 to the metamizole–tramadol group. Baseline demographic and perioperative characteristics are presented in **Table 1**. Both groups were comparable in terms of gender distribution, age, body weight, height, ASA status, duration of surgery, anesthetic technique, intraoperative opioid use, and blood loss (all $p > 0.05$). No intraoperative complications occurred in either group. Reported adverse events were minimal: two patients (20%) in the ketamine group experienced dizziness, while one patient (10%) in the tramadol group reported vomiting. Overall, the two groups were well matched, minimizing the risk of confounding factors.

Table 1. Baseline Demographics of The Subjects

Characteristics	Metamizole Ketamine (n=10)	Metamizole Tramadol (n=10)	p value
Gender¶			
Male	4 (40,0%)	6 (60,0%)	0,371
Female	6 (60,0%)	4 (40,0%)	
Age^			
Median (Range)	43,00 (18 – 65)	48,00 (18 – 61)	0,924
Mean ± SD	43,50 ± 19,34	42,70 ± 17,48	
Body Weight^			
Median (Range)	60,00 (45 – 80)	67,50(53 – 85)	0,280
Mean ± SD	62,70 ± 11,13	68,30 ± 11,37	
Body Height^			
Median (Range)	158,0 (145 – 170)	160,0 (155 – 165)	0,315
Mean ± SD	157,60 ± 7,81	160,30 ± 2,71	
Operator¶			
Attending Doctor	7 (70,0%)	6 (60,0%)	1,000
Resident Doctor	3 (30,0%)	4 (40,0%)	
ASA Status¶			
ASA 1	2 (20,0%)	2 (20,0%)	0,319
ASA 2	8 (80,0%)	6 (60,0%)	
ASA 3	0 (0,0%)	2 (20,0%)	
Duration of Surgery¶			
1-2 Hours	2 (20,0%)	2 (20,0%)	0,282
2-3 Hours	4 (40,0%)	7 (70,0%)	
3-4 Hours	3 (30,0%)	0 (0,0%)	
> 4 Hours	1 (10,0%)	1 (10,0%)	
Anesthesia Technique¶			
General	8 (80,0%)	6 (60,0%)	0,628

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Spinal	2 (20,0%)	4 (40,0%)	
Opioid Administration During Surgery (Fentanyl) ¶			
Yes	8 (80,0%)	6 (60,0%)	
No	2 (20,0%)	4 (40,0%)	0,628
Surgical Complications¶			
Yes	0 (0,0%)	0 (0,0%)	-
No	10 (100%)	10 (100%)	
Adverse Events¶			
Yes	2 (20,0%)	1 (10,0%)	1,000
No	8 (80,0%)	9 (90,0%)	
Bleeding Volume#			
Median (Range)	125,0 (10 – 1800)	200,0 (20 – 1200)	0,701
Mean ± SD	304,0 ± 539,61	269,0 ± 346,36	

*declared equal/homogeneous if the p value > 0.05

¶ Using Chi Square test

^ Using independent T-test

Using Mann-Whitney test

The two groups were comparable in baseline demographics. Gender distribution was similar, with 40% male and 60% female in the metamizole–ketamine group, and 60% male and 40% female in the metamizole–tramadol group (p = 0.371). Mean age was nearly identical (43.50 ± 19.34 vs. 42.70 ± 17.48 years; p = 0.924). Body weight (62.70 ± 11.13 vs. 68.30 ± 11.37 kg; p = 0.280) and height (157.60 ± 7.81 vs. 160.30 ± 2.71 cm; p = 0.315) also showed no significant differences.

Preoperative and intraoperative variables were balanced between the two groups. ASA physical status, surgical operator (attending vs. resident), anesthetic technique (general vs. spinal), duration of surgery, intraoperative fentanyl use, and estimated blood loss showed no significant differences (all p > 0.05). No intraoperative complications occurred. Postoperative side effects were minimal and comparable, with dizziness in two patients (20%) from the metamizole–ketamine group and vomiting in one patient (10%) from the metamizole–tramadol group (p = 1.000). Overall, the two groups were well matched across baseline and perioperative characteristics, minimizing potential confounders and strengthening the validity of attributing outcome differences to the analgesic regimens.

Postoperative Pain Scores (Numeric Rating Scale)

Pain intensity was assessed at 6, 12, 18, and 24 hours using the Numeric Rating Scale (NRS). Normality testing with Shapiro–Wilk confirmed a normal distribution at all time points as shown in Table 2. (p > 0.05, **Table 2**).

Table 2. Normality Test

Groups	N	Pain Score (NRS)		p value
		Median (Range)	Mean±SD	
6 Hours				
Metamizole-Ketamine	10	5,0 (2 – 7)	4,90 ± 1,59	0,441
Metamizole-Tramadol	10	6,0 (3 – 9)	5,90 ± 2,18	0,328
12 Hours				
Metamizole-Ketamine	10	3,0 (0 – 6)	3,20 ± 1,87	0,848
Metamizole-Tramadol	10	4,5 (1 – 8)	4,60 ± 2,27	0,809

18 Hours				
Metamizole-Ketamine	10	2,0 (0 – 4)	1,90 ± 1,19	0,691
Metamizole-Tramadol	10	4,0 (0 – 7)	3,60 ± 2,17	0,513
24 Hours				
Metamizole-Ketamine	10	1,5 (0 – 3)	1,50 ± 1,27	0,061
Metamizole-Tramadol	10	3,5 (0 – 7)	3,20 ± 2,04	0,911

*declared normal if the p-value for normality > 0.05

Analysis of Pain Score Reduction

To evaluate treatment efficacy over the first 24 hours, repeated measures ANOVA was performed. This analysis assessed whether the reduction in Numeric Rating Scale (NRS) scores from 6 to 24 hours was statistically significant within each group (Table 3, Figure 1).

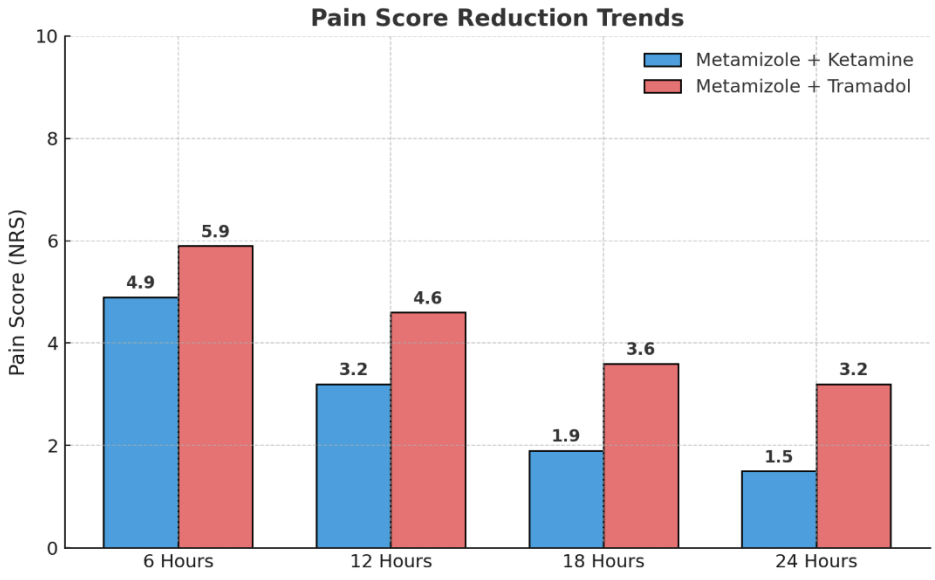
Table 3. Pain Score Reduction

Group	Mean±SD Pain Score (NRS)				p value
	6 Hours	12 Hours	18 Hours	24 Hours	
Metamizole-Ketamine	4,90 ± 1,59	3,20 ± 1,87	1,90 ± 1,19	1,50 ± 1,27	<0,01
Metamizole-Tramadol	5,90 ± 2,18	4,60 ± 2,27	3,60 ± 2,17	3,20 ± 2,04	<0,01

*declared significant if the p-value < 0.05

At 6 hours postoperatively, the metamizole–ketamine group reported a mean NRS score of 4.90 ± 1.59, compared with 5.90 ± 2.18 in the metamizole–tramadol group. This difference widened over time. By 12 hours, mean scores were 3.20 ± 1.87 versus 4.60 ± 2.27, respectively. The largest differences were observed at 18 and 24 hours, when the ketamine group had significantly lower scores (1.90 ± 1.19 and 1.50 ± 1.27) compared with the tramadol group (3.60 ± 2.17 and 3.20 ± 2.04).

Figure 1. Pain Score Reduction Trends



In the metamizole–ketamine group, pain intensity declined steadily and consistently from 4.90 ± 1.59 at 6 hours to 1.50 ± 1.27 at 24 hours, with repeated measures ANOVA confirming a highly significant reduction ($p < 0.01$). The metamizole–tramadol group also showed significant improvement, with mean NRS scores decreasing from 5.90 ± 2.18 at 6 hours to 3.20 ± 2.04 at 24 hours ($p < 0.01$). Both regimens were effective in reducing postoperative pain, but the reduction was more pronounced in the metamizole–ketamine group, which consistently achieved lower pain scores at each time point. (**Table 3, Figure 1**).

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Comparative Analysis of Postoperative Pain Scores Between Groups

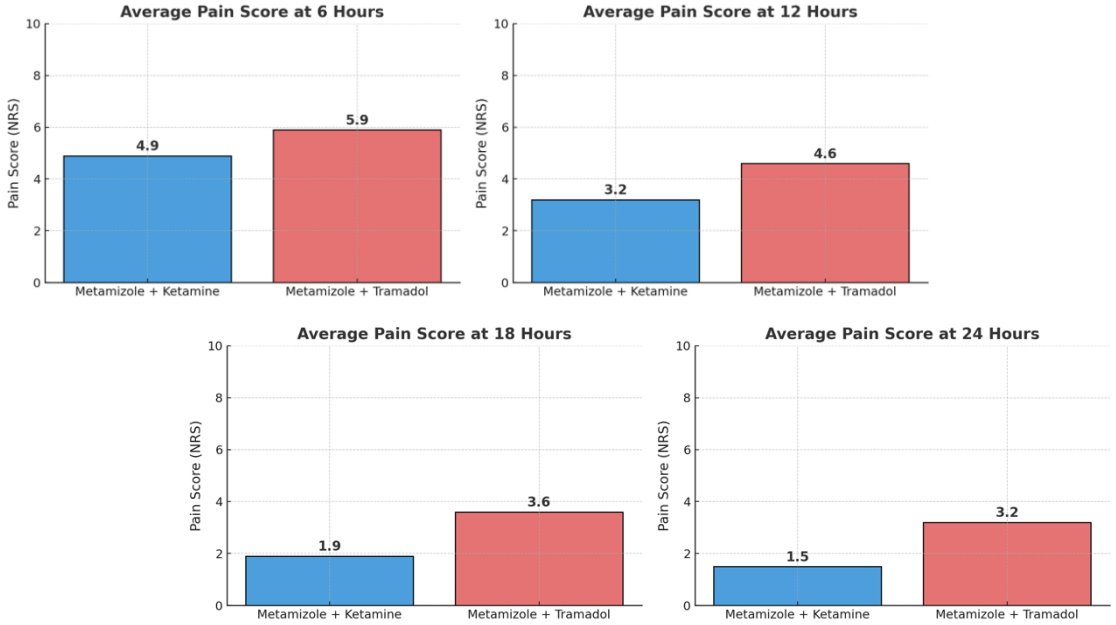
At 6 and 12 hours, the ketamine group reported lower mean NRS scores than the tramadol group, though the differences were not statistically significant (p = 0.257 and p = 0.150, respectively). By 18 hours, however, the ketamine group demonstrated significantly lower pain scores (1.90 ± 1.19 vs. 3.60 ± 2.17; p = 0.048). This difference persisted at 24 hours (1.50 ± 1.27 vs. 3.20 ± 2.04; p = 0.038) (**Table 4, Figure 2**).

Table 4. Comparison of Pain Score between Group

Pain Score (NRS)	Group		p value
	Metamizole-Ketamine	Metamizole-Tramadol	
	Mean±SD	Mean±SD	
6 Hours	4,90 ± 1,59	5,90 ± 2,18	0,257
12 Hours	3,20 ± 1,87	4,60 ± 2,27	0,150
18 Hours	1,90 ± 1,19	3,60 ± 2,17	0,048
24 Hours	1,50 ± 1,27	3,20 ± 2,04	0,038

*declared significant if the p-value < 0.05

Figure 2. Graph of Differences in Pain Scores between Group



At 6 and 12 hours postoperatively, the metamizole–ketamine group reported lower mean NRS scores than the metamizole–tramadol group (4.90 ± 1.59 vs. 5.90 ± 2.18 at 6 hours; 3.20 ± 1.87 vs. 4.60 ± 2.27 at 12 hours), but these differences were not statistically significant (p = 0.257 and p = 0.150). By 18 hours, a significant difference emerged, with the ketamine group reporting lower scores (1.90 ± 1.19 vs. 3.60 ± 2.17; p = 0.048). This advantage persisted at 24 hours (1.50 ± 1.27 vs. 3.20 ± 2.04; p = 0.038). Overall, both regimens reduced pain effectively, but metamizole–ketamine provided significantly greater analgesia during the later postoperative period (18–24 hours).

4. DISCUSSION

This study compared the analgesic efficacy of continuous infusion of metamizole–ketamine versus metamizole–tramadol in adults undergoing major orthopedic surgery. Both regimens provided effective pain relief over 24 hours; however, the metamizole–ketamine group achieved significantly greater reductions in pain scores at 18 and 24 hours. Baseline demographics, ASA status, and perioperative variables were comparable between groups, minimizing potential confounding. Both groups showed a pain trajectory that improved from moderate in the early hours to mild by 24 hours, this information may help guide patient education and expectations for recovery.

The delayed onset of significant differences is noteworthy. At 6 and 12 hours, ketamine showed lower but non-significant pain scores. Ketamine's pharmacokinetic factors may play a role here. Without an initial bolus, low-dose ketamine infusion requires several hours to reach steady-state plasma concentrations (~200 ng/mL) adequate for analgesia, as described by a study in 2002 by Yanagihara et al (Yanagihara, 2002). In contrast, tramadol may exert earlier but less sustained effects. By 18–24 hours, ketamine infusion likely reached therapeutic levels, explaining its superior analgesia. Our findings align with prior studies. Khajavi et al. (2016) reported lower pain scores and reduced opioid use with paracetamol–ketamine versus paracetamol–tramadol. Similar benefits of ketamine have been observed in pediatric populations, ketamine proved to be superior in postoperative analgesia over tramadol, further reinforcing its efficacy (Putri, 2020), and in studies comparing it with other analgesic technique. A study by Jha et al. (2013), noted that ketamine infiltration provided better pain control at 24 hours compared to bupivacaine infiltration.

Several side effects were observed in both groups. In ketamine group, 20% patients experienced dizziness, all whom had undergone general anesthesia. This dizziness observed in this group cannot be conclusively attributed to ketamine, as it may also reflect side effects of general anesthesia. A 2025 study by Chin et al. reported that 42% of patients undergoing surgery with general anesthesia experienced vertigo or dizziness, which may be related to the opioid administered during anesthesia (Chin, 2025). In tramadol group, 10% patients experienced vomiting, likely due to opioid-induced activation of the chemoreceptor trigger zone, that can be partly mitigated by prophylactic antiemetics and administering tramadol slowly over at least 3 minutes has been shown to reduce the incidence of vomiting (Gan, 2024). Clinically, continuous infusion of metamizole–ketamine (0.05 mg/kg/h) appears more effective for sustained analgesia than metamizole–tramadol (0.2 mg/kg/h), particularly beyond 12 hours. Superior pain control may facilitate earlier mobilization, faster recovery, and shorter hospital stays. This study has several limitations. Group allocation was not blinded to researchers, creating potential observer bias. Pain was also assessed by using the subjective Numeric Rating Scale (NRS), which may be influenced by psychological and individual experience of pain. Preoperative baseline pain scores were not recorded, limiting comparison of pre- and postoperative changes. In addition, patients underwent different types of major orthopedic procedures, giving variability in initial pain levels. Larger, blinded studies with more homogenous surgical populations are needed to validate these findings.

5. CONCLUSIONS

In conclusion, this study shows that a multimodal regimen of continuous metamizole-ketamine infusion provides superior pain relief at 18 and 24 hours postoperatively in major orthopedic surgery compared with metamizole-tramadol. Combining metamizole and ketamine appears to be an effective opioid-sparing option for better postoperative pain management in this population.

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