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Oral Ketamine Provides Superior Postoperative Analgesia to Tramadol and Paracetamol After Caesarean Section: A Prospective Comparative Study

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ABSTRACT

Background: Effective postoperative analgesia is essential for optimal recovery after caesarean section (CS), particularly within Enhanced Recovery After Caesarean Surgery (ERACS) pathways. Opioid-sparing strategies are increasingly prioritized, especially in breastfeeding women and in resource-limited settings where access to advanced analgesic techniques may be restricted. Although oral ketamine, tramadol, and paracetamol are widely used, comparative evidence on their postoperative effectiveness in post-CS patients remains limited.

Methods: This prospective, randomized, single-blind study included forty-five ASA I–II patients undergoing elective CS under spinal anaesthesia. Participants were randomized into three equal groups to receive oral ketamine 50 mg, tramadol 100 mg, or paracetamol 500 mg, administered 30 minutes after surgery or once oral fluids were tolerated. Subsequent doses were given every eight hours for 24 hours. Pain intensity was assessed using the 0–10 Numeric Rating Scale (NRS) at 2, 8, 16, and 24 hours by trained paramedical staff. Rescue analgesia (intravenous fentanyl) and adverse effects were recorded. Intergroup comparisons used ANOVA, and intragroup trends were analyzed using the Wilcoxon test.

Results: All forty-five participants completed the study with comparable baseline characteristics. Oral ketamine produced significantly lower NRS scores at all time points compared with tramadol and paracetamol ($p < 0.05$). No participants in the ketamine group required rescue fentanyl, whereas 13.3% in the tramadol group and 26.7% in the paracetamol group required additional analgesia. Adverse effects were mild, with no hallucinations or severe reactions observed. The safety and analgesic superiority of ketamine were not attributable to dosing inequivalence, as all drugs were administered within standard therapeutic ranges and patient BMI and ideal body weight were similar across groups.

Conclusion: Oral ketamine provides superior analgesia, lower rescue opioid requirement, and a favourable safety profile compared with oral tramadol and paracetamol in the first 24 hours after caesarean section. Its affordability, ease of administration, and compatibility with breastfeeding make it an attractive option for ERACS protocols, particularly in low-resource settings. These findings support the integration of low-dose oral ketamine into multimodal postoperative pain management for CS, although further research with extended monitoring is warranted to refine dosing and long-term safety.

KEYWORDS: caesarean section, postoperative pain, oral ketamine, tramadol, paracetamol.

CLINICAL PERSPECTIVE

• Multimodal analgesia is essential after CS.

• Oral ketamine shows superior analgesia and less rescue analgesia use.

• Useful in opioid-limited or resource-limited environments.

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INTRODUCTION

Caesarean section (CS) is one of the most performed major surgical procedures globally, and effective postoperative pain management is essential for promoting optimal maternal recovery. Inadequate analgesia after CS can hinder early mobilization, impair maternal–infant bonding, delay the initiation of breastfeeding, and negatively impact psychological well-being.

Postoperative pain control is a central component of Enhanced Recovery After Cesarean Surgery (ERACS) pathways, which have been increasingly adopted in obstetric care to improve clinical outcomes and reduce hospital length of stay [1,2]. In that way, selecting analgesic strategies that are not only effective but also safe for postpartum women is of high clinical importance.

Pain management after CS presents unique challenges compared with other postoperative settings, particularly because the postpartum period requires careful consideration of drug safety during lactation. Many commonly used analgesics, especially opioids, may be transferred into breast milk and potentially cause neonatal sedation or feeding difficulties [3,4]. Consequently, minimizing opioid exposure while maintaining adequate analgesia has become a major priority in postpartum care[5]. This clinical context underscores the importance of exploring multimodal, predominantly non-opioid analgesic regimens that are both effective for the mother and safe for the breastfeeding infant.

Several oral analgesics are used after CS, including ketamine, tramadol, and paracetamol. Oral ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, provides analgesia by attenuating central sensitization, and its active metabolite, norketamine, contributes additional antinociceptive effects[6–8]. Despite growing interest in subanesthetic ketamine for postoperative pain, evidence on its oral formulation—particularly in obstetric patients—remains limited. Tramadol, an analgesic with weak μ-opioid agonism and monoaminergic activity, has been widely used for moderate postoperative pain but carries risks of nausea, dizziness, and potential neonatal exposure through breast milk[9,10]. Paracetamol is considered a first-line agent due to its safety profile and compatibility with breastfeeding; however, it is often insufficient as monotherapy for major abdominal surgery[11,12].

Despite the availability of these agents, direct comparative evidence on the effectiveness of oral ketamine, tramadol, and paracetamol specifically in post-CS patients remains scarce. Most existing literature focuses on neuraxial techniques or intravenous formulations, leaving a gap in knowledge regarding the relative performance of commonly accessible oral analgesics. This research gap is particularly relevant in low-resource environments where access to opioids, epidural techniques, or infusion devices may be limited.

Therefore, this study aims to compare the analgesic effectiveness, rescue analgesia requirements, and safety profiles of oral ketamine, oral tramadol, and oral paracetamol in women undergoing CS. The findings are expected to inform evidence-based decisions for postpartum pain management, especially in settings where simple, safe, and cost-effective oral analgesics are most needed.

METHODS

This prospective experimental study was conducted at Universitas Airlangga Hospital, Surabaya, Indonesia, after obtaining approval from the institutional ethics committee (ethical approval: 142/KEP/2025).
Forty-five ASA I–II patients scheduled for elective caesarean section under spinal anaesthesia, all of whom had provided written informed consent, were enrolled and randomly assigned in a single-blind design Patients with chronic analgesic use, psychiatric disorders, hepatic impairment, contraindications to ketamine, or who declined participation were excluded. All eligible participants were allocated into three groups of equal size (n=15). Each group received a different oral analgesic regimen: 50mg ketamine, 100mg tramadol, or 500mg paracetamol.The assigned medication was administered 30 minutes after completion of the surgical procedure, or once the patient was able to tolerate oral fluids without nausea or vomiting. Subsequent doses were administered at eight-hour intervals throughout the first 24 hours of hospitalization. Pain intensity was assessed using the 0–10 Numeric Rating Scale (NRS) at 2, 8, 16, and 24 hours postoperatively by trained paramedical staff. The need for rescue analgesia, defined as intravenous fentanyl administration, was documented, and all adverse effects, including nausea, vomiting, dizziness, and hallucinations, were recorded and reported descriptively. All patients received standard perioperative monitoring and care in accordance with institutional protocols. Statistical analysis was performed using ANOVA to compare NRS scores among groups, while intragroup changes over time were analysed using the Wilcoxon test. A p-value of less than 0.05 was considered statistically significant for all comparisons.

RESULTS

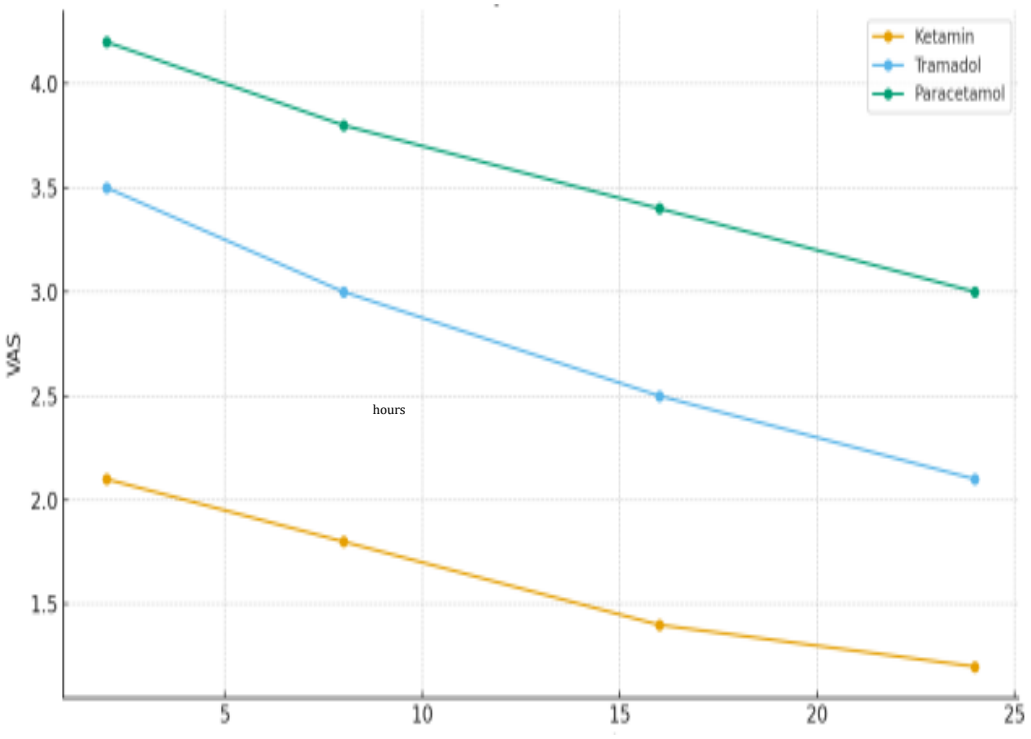
After randomization, and systematic evaluation of postoperative pain, rescue analgesia, and adverse events, the collected data were analyzed and are summarized in the Results below

A total of forty-five patients completed the study, with fifteen participants in each treatment group. Baseline characteristics, including age, body mass index, parity, and duration of surgery, were comparable among the three groups, indicating successful initial group equivalence (Table 1).

Table 1. Descriptive Characteristics and Baseline Equivalence

Characteristic	Ketamine (n=15)	Tramadol (n=15)	Paracetamol (n=15)	p-value
Age (years) Mean ± SD	28.60 ± 5.578	29.60 ± 4.085	28.00 ± 3.207	0.606
Ideal Body Weight (kg), Range (Median)	47.80–56.77 (51.25)	48.72–56.69 (52.17)	47.80–56.77 (51.25)	0.769
ASA Physical Status II	15 (100%)	15 (100%)	15 (100%)	-
Induction to sign out time (hours), Range (Median)	2.0–3.5 (2.0)	2.0–3.0 (2.5)	2.0–3.0 (3.0)	0.187
Estimated blood loss (mL), Range (Median)	300–450 (350)	300–400 (350)	300–400 (350)	0.299

Postoperative pain scores demonstrated significant differences across treatment groups at all measured time points (Table 2). At 2 hours after surgery, patients receiving oral ketamine reported the lowest NRS scores, while those receiving tramadol and paracetamol experienced higher levels of pain. This trend persisted at 8, 16, and 24 hours, with the ketamine group consistently demonstrating superior analgesic effect. Statistical analysis using ANOVA confirmed significant intergroup differences at each interval ($p < 0.05$). Within-group analysis using the Wilcoxon test showed a progressive decline in NRS scores over the 24-hour postoperative period for all groups; however, the reduction was most consistent and pronounced in the ketamine group.



Picture 1. NRS trends

The requirement for rescue analgesia further distinguished the groups. None of the patients in the ketamine group required additional fentanyl, whereas two patients (13.3%) in the tramadol group and four patients (26.7%) in the paracetamol group required rescue analgesics due to inadequate pain control (Table 2).

Table 2. Rescue Analgesia and Adverse Effects

	Ketamine (n = 15)	Tramadol (n = 15)	Paracetamol (n = 15)
1. **Rescue Fentanyl**	0 (0.0%)	2 (13.3%)	4 (26.7%)
2. Adverse Effects	1 (6.7%) palpitations	1 (6.7%) nausea and vomiting	0 (0%)

Adverse effects were generally mild and did not necessitate discontinuation of therapy. Nausea and dizziness occurred more frequently in the tramadol group, while minor gastrointestinal discomfort was observed in the paracetamol group. Importantly, no hallucinations or severe adverse reactions were reported in any group, including those receiving ketamine (Table 2). Overall, oral ketamine demonstrated the most favourable analgesic profile, with lower pain scores, minimal rescue analgesia use, and a benign side-effect profile compared with oral tramadol and paracetamol

DISCUSSION

This study identified distinct differences in analgesic efficacy and adverse effect profiles among oral ketamine, tramadol, and paracetamol following caesarean section. Oral ketamine provided superior and sustained pain relief with no need for rescue fentanyl and minimal side effects, whereas tramadol and paracetamol showed higher pain scores and greater rescue analgesia use. These findings align with emerging evidence supporting NMDA-mediated analgesia and highlight the potential role of oral ketamine in postoperative pain management. The following discussion contextualizes these results within current literature and examines their clinical relevance.

Ketamine's ability to consistently maintain lower NRS scores across all 24-hour assessment points aligns with previous evidence showing that subanaesthetic doses of ketamine can effectively attenuate acute postoperative pain by inhibiting central sensitisation through NMDA receptor blockade[13-15]. Oral ketamine has received less attention than intravenous administration in perioperative practice, yet available literature suggests that the oral formulation maintains clinically meaningful analgesic effects, largely attributable to its metabolite norketamine, which retains NMDA antagonistic properties[16,17]. The present findings support these pharmacologic observations and further demonstrate clinical benefit in the obstetric population.

In contrast, tramadol provided moderate but less reliable analgesia, with a portion of patients requiring additional opioids. This is consistent with previous studies reporting that tramadol's μ-opioid agonism and monoaminergic reuptake inhibition produce analgesia inferior to stronger opioids and insufficient for procedures involving both somatic and visceral pain components, such as caesarean section[18,19]. Tramadol's side-effect profile in our study, particularly nausea and dizziness, is well documented in the literature and often limits patient tolerance[20]. Paracetamol, widely accepted as a first-line analgesic, is generally recommended as part of multimodal postoperative pain strategies[21], but its utility as monotherapy in major abdominal surgery remains limited. Multiple studies have reported inadequate analgesia when paracetamol is used alone after CS, necessitating additional opioid rescue therapy[22,23], consistent with the higher rescue analgesia requirement observed in our paracetamol group.

The opioid-sparing effect observed with oral ketamine in this study is particularly important. Strategies to minimise opioid use have gained momentum due to concerns regarding opioid-related adverse effects, delayed recovery, and breastfeeding safety in postpartum patients[24-26]. Ketamine's ability to reduce or eliminate postoperative opioid requirements has been demonstrated in several surgical populations[27,28] and may offer significant benefit in regions with restricted opioid availability or stringent regulatory constraints[29]. Additionally, ketamine's favourable safety profile at low doses is supported by existing evidence indicating minimal risk of psychomimetic disturbances at subanaesthetic oral or intravenous dosages[30-32]. Our study corroborates these findings, as no participants exhibited hallucinations or severe neuropsychiatric reactions.

From a global health perspective, the findings have meaningful implications for resource-limited settings. Oral analgesics are often more feasible to administer, require minimal monitoring, and reduce the logistical burden associated with intravenous medications[33]. Given the rising global rates of caesarean section[34], developing safe, effective, and easily deployable postoperative analgesia protocols is increasingly essential. Oral ketamine's low cost, stability at room temperature, and limited need for specialised equipment position it as a viable option where epidural opioids, patient-controlled analgesia pumps, or IV infusion systems are unavailable[35].

Consideration of analgesic potency equivalence further supports the validity of the dosing strategy used in this study. Although the absolute milligram doses varied between drugs, each agent was administered within internationally accepted therapeutic ranges for postoperative analgesia. Ketamine at 50 mg orally falls within the low-dose analgesic spectrum, whereas tramadol 100 mg and paracetamol 500 mg represent standard initial doses recommended for acute postoperative pain. Importantly, BMI and ideal body weight were comparable across all groups, reinforcing that no group had a pharmacokinetic advantage based on patient size. While higher doses—such as 200 mg tramadol or 1,000 mg paracetamol—could potentially enhance analgesia, these are frequently limited by safety concerns, especially in postpartum and breastfeeding populations. Therefore, the observed superiority of ketamine is unlikely to be attributable to dose selection alone, but rather reflects true differences in intrinsic analgesic potency and mechanism of action.

Beyond its superior analgesic performance, the findings also have important implications for Enhanced Recovery After Caesarean Surgery (ERACS), particularly in low- and middle-income countries. Oral ketamine represents a practical and cost-effective adjunct where access to opioids, neuraxial morphine, or intravenous multimodal agents may be limited. The drug is inexpensive, widely available, and does not require cold-chain storage or specialized equipment for administration, making it compatible with typical resource constraints in district hospitals. Moreover, the absence of significant neonatal or breastfeeding-related concerns supports its integration into ERACS pathways that emphasize early mobilization, maternal infant bonding, and accelerated functional recovery. In contexts where staffing shortages, supply instability, and budget limits challenge postoperative care, oral ketamine offers a feasible and scalable analgesic strategy that aligns with ERACS goals without increasing system complexity.

LIMITATIONS

This study has several limitations. First, pain assessment relied solely on subjective Numeric Rating Scale scores without incorporating objective physiological markers, such as stress hormone levels or autonomic responses, that could have provided a more comprehensive understanding of analgesic effects. The dependence on patient self-report, particularly in the immediate postoperative recovery phase, may also have limited the detection of subtle psychological symptoms. Future studies would benefit from incorporating validated neuropsychological instruments, such as the Clinician-Administered Dissociative States Scale (CADSS) or the Brief Psychiatric Rating Scale (BPRS), to better capture potential dissociative or perceptual disturbances associated with ketamine. Second, although ketamine is known to influence blood pressure, heart rate, and sympathetic activity, this study did not include serial hemodynamic monitoring, preventing evaluation of these systemic effects. Third, the 24-hour observation window captured only the acute postoperative period and may not fully reflect the duration of analgesic benefit or delayed adverse effects. Additionally, psychological factors, environmental influences, and interindividual variability in pain tolerance were not explicitly measured, despite their potential impact on pain perception and rescue analgesia use. Nonetheless, these limitations do not diminish the validity of the primary findings, and future research employing multidimensional assessment, objective physiological monitoring, and longer follow-up periods will help refine the clinical relevance and generalizability of these results.

SUGGESTIONS FOR FUTURE RESEARCH

Future research should incorporate objective physiological parameters, such as serial hemodynamic measurements, autonomic indicators, or biochemical stress markers, to complement subjective pain assessments and provide a more comprehensive evaluation of analgesic response. The inclusion of validated neuropsychological instruments, such as the Clinician-Administered Dissociative States Scale (CADSS) or the Brief Psychiatric Rating Scale (BPRS), is also recommended to better capture subtle dissociative or perceptual effects potentially associated with ketamine use. Larger, adequately powered studies with longer follow-up periods are needed to assess sustained analgesic benefit and late-onset adverse events. Additionally, future trials employing dose-equivalent comparisons across analgesics may help refine dosing strategies and better clarify the relative analgesic potency of oral ketamine. Multicenter studies conducted in diverse healthcare environments, including resource-limited settings, are warranted to evaluate feasibility, cost-effectiveness, and broader applicability within ERACS pathways.

CONCLUSION

In conclusion, this study demonstrates that oral ketamine provides superior postoperative analgesia compared with oral tramadol and paracetamol in women undergoing caesarean section, as evidenced by consistently lower pain scores, minimal need for rescue opioids, and a favourable safety profile. The analgesic superiority of ketamine was not attributable to dosing inequivalence, as all medications were administered within standard therapeutic ranges and baseline characteristics—including BMI and ideal body weight—were comparable across groups. These findings highlight the potential of low-dose oral ketamine as an effective, opioid-sparing, and well-tolerated option for post-caesarean analgesia. Its practicality, affordability, and suitability for breastfeeding women make it particularly valuable within ERACS pathways, especially in low-resource settings where access to advanced analgesic modalities is limited. Further research with broader physiological monitoring and extended follow-up is warranted to optimize dosing strategies and fully characterize its long-term safety profile, but the present results provide a strong foundation for incorporating oral ketamine into multimodal postoperative pain management after caesarean delivery.

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CONFLICT OF INTEREST
None declared.

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