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ORIGINAL RESEARCH OBSTETRIC ANESTHESIA

Neuroendocrine stress, analgesic outcomes, and patient satisfaction with levobupivacaine infiltration with or without ketamine in cesarean section: a prospective randomized controlled trial

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ABSTRACT

Background: The rates of cesarean section (SC) are increasing globally, making postoperative pain management a critical issue. Post-SC pain can impair recovery and activate neuroendocrine stress responses, including elevated cortisol, which may compromise healing and immunity. Multimodal analgesia combining levobupivacaine with low-dose ketamine can optimize pain relief, reduce stress responses, and improve patient satisfaction.

Methodology: This prospective, randomized, double-blind controlled trial was conducted from May to September 2025 at Raden Mattaher General Hospital, Jambi. Forty-two patients undergoing CS under spinal anesthesia (ASA I–II) were randomly assigned into three groups: levobupivacaine alone, levobupivacaine + ketamine 0.5 mg/kg, and levobupivacaine + ketamine 1 mg/kg. Subcutaneous infiltration was performed before skin closure. Randomization was computer-generated, and both participants and outcome assessors were blinded to group allocation. Serum cortisol levels were measured pre- and postoperatively. Pain intensity (VAS and PPT), need for rescue analgesics, and patient satisfaction were recorded within 24 h postoperatively.

Results: Significant intergroup differences were found in cortisol reduction, VAS scores, pain thresholds, and satisfaction ($P < 0.05$). The levobupivacaine + ketamine 1 mg/kg group demonstrated the greatest cortisol reduction, lowest pain scores, no need for rescue fentanyl, and highest satisfaction ratings.

Conclusion: Subcutaneous infiltration with levobupivacaine combined with ketamine (1 mg/kg) provides superior analgesia, attenuates the stress response, and enhances patient satisfaction after cesarean delivery. This multimodal, opioid-sparing approach is a clinically valuable strategy for postoperative pain control.

Keywords: cesarean section; cortisol; ketamine; levobupivacaine; postoperative pain; randomized controlled trial; stress response

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1. INTRODUCTION

Approximately 18 million cesarean sections (CS) are performed annually globally, making postoperative pain management a major concern.[1] Post-CS pain affects recovery and daily activities, with 78.4%–92% of mothers experiencing moderate to severe pain; an Ethiopian study reported an incidence of 88.2%.[1-3] Factors influencing pain include preoperative anxiety, incision type, anesthesia technique, and surgical duration.[4] Post-CS pain typically peaks within 12–36 h and improves by day 3.[5] Pain is commonly assessed using the Visual Analog Scale (VAS), while the Pressure Pain Threshold (PPT) provides an objective measure of local pain response.[6,7]

Cortisol, the primary stress hormone, reflects the neuroendocrine response to surgical trauma.[8-10] Elevated cortisol may impair recovery and immune response, increasing postoperative complications.[8,11-13] Hence, cortisol control is crucial for faster recovery. Analgesic options include opioids, non-steroidal anti-inflammatory drugs, PCA, and regional blocks. Levobupivacaine, a safer S-enantiomer of bupivacaine, provides long-acting local anesthesia through sodium channel blockade.[14-16] Ketamine, an NMDA receptor antagonist, produces analgesia, sedation, and bronchodilation and reduces postoperative and chronic pain when combined with opioids.[17] Pain management influences cortisol levels. Riazanova et al found lower cortisol levels in patients receiving epidural ropivacaine analgesia compared with controls (≤ 2310.91 vs. 2673.82 nmol/L, $P < 0.05$).[19] MMA, a key ERAS component, combines techniques to enhance recovery while minimizing adverse effects. Subcutaneous ketamine infiltration (1 mg/kg), alone or with bupivacaine, significantly lowers VAS scores and opioid use.[20,21] In abdominal hysterectomy, 2 mg/kg ketamine + 0.25% bupivacaine reduced morphine consumption, delayed the first analgesic request, and decreased cortisol levels at 6 and 24 h.[22] Finally, patient satisfaction remains a key quality indicator in postoperative care, influenced not only by pain control but also by health care delivery and patient demographics.

In this context, the present study was designed to evaluate whether adding ketamine to levobupivacaine for subcutaneous infiltration could enhance analgesic efficacy and attenuate the neuroendocrine stress response following cesarean delivery. The primary outcomes were postoperative cortisol concentration and pain intensity, and the secondary outcomes were the requirement for rescue analgesics and overall patient satisfaction.

2. METHODOLOGY

This prospective, randomized, double-blind controlled trial was conducted at Raden Mattaher General Hospital, Jambi, from May to September 2025. Ethical approval was obtained from the Hasanuddin University Health Research Ethics Committee (No. 532/UN4.6.4.5.31/PP36/2025).

The sample size was determined using Cohen's *d* formula for a paired t-test with $d = 0.8$ (large effect), $\alpha = 0.05$, and 80% power, yielding 12 participants per group. To compensate for potential dropout, 14 participants were enrolled in each. Cooperative patients with American Society of Anesthesiologists physical status I–II scheduled for elective cesarean delivery under spinal anesthesia. Exclusion criteria: known allergy to anesthetics or opioids, history of drug abuse, hypertension, cardiovascular or psychiatric disorders, body weight >100 kg, inability to comprehend the visual analog scale (VAS), or intraoperative complications.

Randomization was performed using a computer-generated sequence. Participants were assigned to three groups: Group A: levobupivacaine 0.5% 2 mg/kg (maximum 150 mg), diluted to 30 mL Group B: 0.5 mg/kg levobupivacaine + ketamine Group C: 1 mg/kg levobupivacaine + ketamine. An anesthesiologist not involved in data collection administered subcutaneous infiltration before skin closure. Both the participants and the outcome assessors were blinded to the group assignment.

2.1. Intervention Procedure

Each patient received subcutaneous wound infiltration before skin closure: Group A: levobupivacaine (0.5%), 2 mg/kg (maximum 150 mL diluted to 30 mL. Group B: the same regimen + 0.5 mg/kg ketamine. Group C: the same regimen + 1 mg/kg ketamine.

Primary outcomes: postoperative serum cortisol and visual analog scale pain scores. Secondary outcomes: PPT, time to first rescue analgesic (FRA), total fentanyl dose, and patient satisfaction (4-point Likert scale). Serum cortisol: measured 2 h preoperatively and 6 h postoperatively via ELISA. Pain intensity: assessed with Visual Analog Scale (VAS) at 0, 30, and 1 h, 6 h, 12 h, and 24 h postoperatively, and PPT, digital algometer) at 6 h postoperatively. Analgesic consumption: time to FRA and total fentanyl used. Patient satisfaction: assessed at 24 h using a 4-point scale (1 = dissatisfied to 4 = very satisfied).

2.2 Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 25. Normal data were tested using the Shapiro–Wilk test. ANOVA was applied for

normally distributed variables, Kruskal–Wallis for non-normal data, and Chi-square for categorical data. Results were reported with $P < 0.05$ considered statistically significant, along with 95% confidence intervals and effect sizes.

Table 1: Descriptive Statistics of Age, Body Weight, Height, and BMI Based on Intervention Groups

Variable	Group A (n = 14)	Group B (n = 14)	Group C (n = 14)
Age (years)	32.71 ± 7.18	29.86 ± 5.67	30.29 ± 5.00
Body Weight (kg)	69.57 ± 14.44	68.43 ± 10.73	70.29 ± 11.19
Height (cm)	157.36 ± 4.65	157.07 ± 4.31	158.07 ± 5.14
BMI (kg/m²)	27.94 ± 4.66	27.69 ± 3.95	28.08 ± 3.85

3. RESULTS

A total of 45 pregnant women scheduled for cesarean delivery were initially assessed for eligibility. Three participants were excluded due to allergy to anesthetics or opioids, body weight >100 kg, and inability to understand the visual analog scale (VAS). The remaining 42 eligible participants were randomly assigned into three groups: levobupivacaine alone, levobupivacaine + ketamine 0.5 mg/kg, and levobupivacaine + ketamine 1 mg/kg. All participants completed the study and were included in the final analysis (Table 1).

The mean age of participants across the three groups was relatively similar, ranging from 29.86 ± 5.67 years in Group B to 32.71 ± 7.18 years in Group A. The mean body weight was also comparable among the groups, between 68.43 ± 10.73 kg and 70.29 ± 11.19 kg. The participants' mean height was consistent across the groups, approximately 157–158 cm. The mean BMI values were nearly identical among the three groups, ranging from 27.69 ± 3.95 kg/m² to 28.08 ± 3.85 kg/m². Overall, the baseline characteristics of age, weight, height, and BMI were homogeneous across the intervention groups.

Table 2 presents the results of the bivariate analysis comparing cortisol difference, first request for analgesia (FRA), total fentanyl dose, pressure pain threshold (PPT), visual analog scale (VAS) scores at various postoperative time intervals (0–24 hours), and patient satisfaction among the three intervention groups.

Significant differences were observed in several physiological and clinical outcomes between the groups. The cortisol difference showed a highly significant variation ($P = 0.000$), with Group C demonstrating the greatest reduction in cortisol levels, indicating a lower stress response following surgery. Similarly, the PPT differed significantly across groups ($P = 0.000$), with progressively higher pain thresholds observed in Groups B and C, suggesting enhanced analgesic efficacy with ketamine administration.

In terms of postoperative analgesic demand, both FRA ($P = 0.024$) and total fentanyl dose ($P = 0.024$) were significantly lower in the ketamine group than in the control group, implying that ketamine supplementation effectively prolonged analgesia and reduced opioid requirements. Pain intensity, as measured by the VAS scores, revealed significant differences between groups at 30 min, 1 h, 6 h, 12 h, and 24 h postoperatively (all $P = 0.003$), with Group C consistently reporting the lowest pain scores. However, no significant difference was found at baseline (VAS_0, $P = 0.599$), confirming that all groups had comparable initial pain levels before the intervention.

Patient satisfaction was significantly higher in the ketamine group than in the placebo group ($P = 0.000$). The majority of participants in Groups B and C were *very satisfied* with their postoperative pain management, whereas satisfaction levels were lower in the control group.

Overall, these findings indicate that the addition of ketamine—particularly at a dose of 1 mg/kg—to levobupivacaine during cesarean section provides superior postoperative analgesia, reduces stress responses and opioid consumption, and significantly enhances patient satisfaction compared to levobupivacaine alone.

4. DISCUSSION

4.1. Pre- and Post-Cortisol Differences

Cortisol is the main hormone in the stress response, secreted via the hypothalamic–pituitary–adrenal (HPA) axis. Although surgical stress is similar, cortisol responses vary among individuals due to genetic factors, glucocorticoid receptor sensitivity, and HPA activation thresholds, leading to wide individual variation despite similar group means.[25,26] Comparable pre- and post-intervention cortisol levels among groups may reflect differing physiological stress responses influenced by psychological, anxiety, and environmental factors; therefore, cortisol changes do not always match subjective reports.[27,28]

Patients with higher preoperative anxiety may show elevated baseline cortisol levels, resulting in

Table 2: Bivariate analysis of cortisol difference, FRA, fentanyl dose, PPT, VAS Score 0–24 hours, and patient satisfaction based on intervention groups

Variable	Group A (n = 14)	Group B (n = 14)	Group C (n = 14)	P-value
Cortisol Diff (ng/dl)	-12.76 ± 96.72	70.44 ± 53.37	320.69 ± 132.63	0.000
FRA (h)	1.14 ± 1.61	1.50 ± 1.83	0.00 ± 0.00	0.024
Fentanyl Doses (µg)	107 ± 128	54 ± 106	0.00 ± 0.00	0.024
• VAS_0	0.07 ± 0.27	0.07 ± 0.27	0.00 ± 0.00	0.599
• VAS_30m	2.50 ± 1.45	1.07 ± 0.92	0.79 ± 0.89	0.003
• VAS_1h	3.43 ± 1.60	1.79 ± 1.31	1.29 ± 1.38	0.003
• VAS_6h	3.43 ± 1.60	1.79 ± 1.31	1.29 ± 1.38	0.003
• VAS_12h	3.43 ± 1.60	1.79 ± 1.31	1.29 ± 1.38	0.003
• VAS_24h	2.50 ± 1.45	1.07 ± 0.92	0.79 ± 0.89	0.003
PPT	2.38 ± 0.42	3.47 ± 0.27	4.81 ± 0.90	0.000
Patient Satisfaction (n %)				
• Neutral	2 (4.8)	0 (0.0)	0 (0.0)	0.000
• Satisfied	7 (16.7)	0 (0.0)	0 (0.0)	
• Very satisfied	5 (11.9)	14 (33.3)	14 (33.3)	

FRA: first rescue analgesic; PPT: Pressure Pain Threshold; P < 0.05 considered as significant

nonhomogeneous preintervention levels and inconsistent cortisol–pain delta correlations. This aligns with prior findings that cortisol is not always a sensitive marker for nonpharmacological interventions.[29,30] Nevertheless, the overall postoperative cortisol decline across groups indicates a physiological suppression of stress responses. Similar findings were reported by Riazanova et al. (2018) and Bayazit et al. (2013), showing that effective analgesia reduces postoperative cortisol levels by inhibiting sympathetic activation.[13,19,31]

Lower cortisol levels indicate better pain control and a more stable stress response.[13] This supports the findings of Iqbal et al. (2023), who noted that early cortisol monitoring helps prevent stress-related disorders such as anxiety and metabolic and cardiovascular conditions. Thus, optimal pain management reduces endocrine stress activation and promotes faster recovery, less immunosuppression, and fewer stress-related complications.[31-33]

4.2. First Rescue Analgesic and Fentanyl Dose

Analysis of rescue analgesia (FRA) and fentanyl use showed a consistent pattern: Group A had the highest analgesic requirement, Group B had the lowest, and Group C had the lowest. This indicates superior analgesic efficacy in Group C, eliminating the need for additional opioids, reducing adverse effects, accelerating recovery, and improving comfort. Differences in the use of FRA and fentanyl among groups suggest that analgesic interventions influence both pain control and postoperative functional recovery.[34] Similar findings were reported by Podder et al. (2025) and Xavier et al. (2024), where adequate pain control enhanced mobilization, reduced complications, and improved satisfaction through the EMP.[35,36]

The absence of rescue analgesia in Group C highlights its clinical effectiveness in providing sufficient pain relief while minimizing drug-related risks, which is consistent with the findings of Kianian et al. (2024)[37] who showed that multimodal analgesia and appropriate drug combinations improve outcomes while limiting opioid exposure. Fentanyl use also differed significantly: Group A required the most (107 µg), Group B less (54 µg), and Group C none. This opioid-sparing effect is consistent has been earlier demonstrated that multimodal analgesia within ERAS pathways reduces opioid consumption. Minimizing opioid use is clinically valuable because excessive doses can cause nausea, vomiting, respiratory depression, and dependence. Overall, these results confirm that the interventions influenced not only pain intensity but also analgesic efficiency, opioid demand, and recovery quality, supporting multimodal and opioid-sparing approaches in perioperative pain management.

4.3. Visual Analog Scale Scores

At baseline (VAS0), no significant difference was observed between the groups, indicating comparable initial pain perception and eliminating baseline bias. However, pain scores diverged from 30 minutes to 24 hours postoperatively: Group A had the highest, Group B intermediate, and Group C the lowest. This pattern demonstrates that the intervention in Group C provided more stable and prolonged analgesia during the critical postoperative phase (1–12 h). The sustained pain reduction up to 24 h indicates medium-term analgesic benefits, reducing the need for rescue analgesics, and improving comfort. These results are consistent with Oham et al. (2020), who showed that wound infiltration and subcutaneous ketamine significantly prolong pain-free periods and decrease analgesic demand. Significant differences in VAS scores across time points confirm that more effective interventions resulted in better pain control and faster recovery. This emphasise on the role of MMA and regional techniques in optimizing postoperative outcomes and patient satisfaction.

4.4. Pressure-Pain Threshold Scores

The mean PPT values differed significantly among the groups: Group A had the lowest (2.38 ± 0.42), Group B intermediate (3.47 ± 0.27), and Group C the highest (4.81 ± 0.90). Data were normally distributed ($P > 0.05$), and ANOVA confirmed significant intergroup differences ($P < 0.001$). These results indicate that the intervention in Group C most effectively increased pain tolerance, followed by that in Group B. The findings support those of a previous study by Buhagiar et al. (2011), which showed that preoperative PPT correlates with postoperative pain and analgesic consumption.[7] The marked increase in PPT in Group C reflects the analgesic effect of ketamine as an NMDA receptor antagonist, which reduces central sensitization, prevents the wind-up phenomenon, and lowers pain intensity.[34]

4.5. Patient Satisfaction

The high satisfaction in Groups B and C reflects superior clinical outcomes, including lower cortisol levels, minimal fentanyl use, absence of rescue analgesia, and consistently lower postoperative pain scores. These factors directly contributed to improved comfort and satisfaction. This is consistent with the earlier findings reporting that multimodal analgesia and regional anesthesia improve pain control, reduce complications, and enhance patient satisfaction. The high satisfaction in Groups B and C emphasizes that the intervention not only provided physiological benefits but also supported patient-centered care, enhancing the perceived quality of service.

From a clinical perspective, this study provides practical evidence for adopting levobupivacaine–ketamine wound infiltration as a simple, cost-effective, and safe adjunct in postoperative pain management, particularly in limited-resource settings where advanced analgesic modalities may be unavailable.

Although patients were not directly involved in the design of the study, their satisfaction feedback was incorporated into data interpretation, providing valuable insights into the clinical applicability of MMA strategies. Future research should include a more direct patient involvement in the definition of meaningful recovery outcomes and satisfaction parameters.

5. LIMITATIONS

The study's observation period was limited to 24 h postoperatively, precluding the evaluation of longer-term effects. The use of a single biomarker (cortisol) and reliance on subjective pain scores may limit the comprehensiveness of stress response evaluation. A multicenter design with larger sample sizes and additional biochemical parameters, such as catecholamines or inflammatory cytokines, would enhance generalizability and mechanistic understanding.

6. CONCLUSION

This randomized controlled trial demonstrated that the addition of ketamine (1 mg/kg) to levobupivacaine for subcutaneous wound infiltration during cesarean section significantly improved analgesic outcomes, attenuated cortisol-mediated stress responses, and enhanced patient satisfaction without increasing adverse effects.

7. Scientific contribution

This study contributes to the growing evidence supporting neuroendocrine modulation through multimodal analgesia, bridging physiological stress biomarkers with clinical pain assessment and satisfaction outcomes.

8. Clinical relevance

The combination of ketamine and levobupivacaine is a practical, safe, and opioid-sparing strategy that can be easily implemented within Enhanced Recovery After Surgery (ERAS) protocols, especially in low- and middle-income healthcare settings.

9. Future research directions

Further multicenter, double-blind randomized controlled trials with larger populations and extended follow-up are warranted to validate these findings, assess long-term maternal recovery, and explore optimal dosing strategies for different surgical populations.

10. Acknowledgment

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None.

12. Conflicts of interest

There are no conflicts of interest to declare.

13. Authors' contributions

AH contributed to the study's conception and design, supervised data collection, and oversaw the research process. NSW performed the literature search, conducted data analysis, and interpreted the results. CWT performed the statistical analysis, prepared tables and figures, and critically reviewed the methodology. HH drafted and edited the manuscript, ensured proper formatting, and approved the final version for publication.

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