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Research Article

Suppressing Postoperative Inflammation with Intravenous Ketamine as an Adjunct in Epidural Hysterectomy: A Clinical Study of C-Reactive Protein and Neutrophil–Lymphocyte Ratio

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ABSTRACT

Background: Hysterectomy often triggers a systemic inflammatory response, increasing biomarkers like C-reactive protein (CRP) and the neutrophil-lymphocyte ratio (NLR), which can delay recovery and raise complication risks. Ketamine, a common anesthetic, possesses anti-inflammatory properties that may modulate this postoperative response. This study aimed to further examine the effects of ketamine on CRP and NLR levels in patients undergoing hysterectomy.

Methods: This double-blind randomized clinical trial included 28 adult female patients (ASA I–II) undergoing elective abdominal hysterectomy under epidural anesthesia. Patients were randomized to receive either 0.5 mg/kg intravenous ketamine (intervention group) or no ketamine (control group). Serum CRP and NLR were measured preoperatively and at 8 and 24 hours postoperatively. The visual analog scale was used to evaluate pain level, data were processed with the appropriate statistical test, and a p-value < 0.05 is considered significant.

Results: Our study discovers that intravenous ketamine reduced postoperative inflammatory markers significantly. Postoperative measurements at 8 and 24 ours proved that the ketamine group had lower CRP and NLR levels significantly ($p<0.05$). Patients receiving ketamine showed a non-significant reduction in VAS pain scores compared with controls. No participant in either group needed additional opioids for pain control.

Conclusion: Intravenous ketamine decreased postoperative inflammatory response significantly in hysterectomy patients receiving epidural anesthesia, as proved by lower CRP and NLR. Ketamine seemed to improve patient comfort by lowering pain intensity. Combining epidural anesthesia with ketamine may be a viable strategy to suppress inflammation and enhance recovery after hysterectomy.

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Introduction

Hysterectomy ranks among the most frequently conducted surgical procedures in women and is typically recommended for conditions like uterine fibroids, uterine cancer, uterine prolapse, and uterine atony that do not respond to other forms of treatment [1–3]. In certain cases, an abdominal approach is preferred because it allows comprehensive evaluation of the pelvic organs and lymphatic nodes [4]. In addition to being a curative procedure, hysterectomy can also play a preventive role in reducing the risk of ovarian and breast cancer in high-risk patients [5]. The complexity of these patient conditions makes postoperative management, including inflammation control, particularly important.

Ketamine is a nonbarbiturate cyclohexanone-derivative general anesthetic widely used, particularly for procedures that do not require skeletal muscle relaxation [6–8]. Ketamine has a mechanism of action that inhibits N-methyl-D-aspartate (NMDA) receptors and the NLRP3 inflammasome, both of which play roles in the inflammatory response [9]. Accordingly, ketamine serves not only as an anesthetic but also has potential anti-inflammatory effects. Post-hysterectomy inflammation responses are influenced by tissue trauma and tumor-related mechanisms as well [10]. A key marker of acute inflammation is C-reactive protein (CRP), which reflects activation of proinflammatory cytokines and rises after tissue trauma [11]. CRP production is triggered by recognition of molecules from damaged tissue (damage-associated molecular patterns, DAMPs) and pathogens (pathogen-associated molecular patterns, PAMPs) by pattern recognition receptors such as toll-like receptors and NOD-like receptors [12].

Therefore, CRP is an important parameter in evaluating the effectiveness of postoperative anti-inflammatory interventions. Besides CRP, the neutrophil-lymphocyte ratio (NLR) serves as a significant marker of inflammation [13-14]. An increased NLR suggests an acute inflammatory response, which increases neutrophil levels and decreases lymphocyte counts induced by surgical trauma and blood loss. The decrease in lymphocytes impairs immune function, therefore increasing the risk of sepsis and multiple organ failure. Combined measurement of NLR and CRP provides comprehensive picture of a patient's postoperative inflammatory status. Recent studies have suggested that the low dose ketamine (0.5 mg/kg) administered before induction of anesthesia can significantly reduce the levels of IL-6 and CRP comparing with controls. These findings suggest that ketamine may be used as a perioperative anti-inflammatory medication, particularly for major surgeries like hysterectomy. Therefore, the aim of this study was to analyze how ketamine use affected the postoperative CRP and NLR levels in individuals who undergoing hysterectomy.

Methods

Study Design

This experimental study employed a randomized controlled trial design at the surgical unit of Dr. Wahidin Sudirohusodo General Hospital, Makassar. The study was conducted from November 2024 until the required sample size was reached. This study has received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Hasanuddin University, with number 761/UN4.6.4.5.31/PP36/2024 and Wahidin Sudirohusodo Hospital Ethics with number DP.04.03/D.XIX.2.3.1/373/2024. All subjects provided informed consent prior to participation.

Participants

The study population consisted of patients scheduled for elective abdominal hysterectomy under epidural anesthesia. Patients were selected using purposive sampling based on the following inclusion criteria: adult females (≥18 years) with American Society of Anesthesiologists physical status (ASA PS) I–II who consented to participate in the entire study protocol. Patients who did not meet these criteria or who experienced severe intraoperative complications were excluded from the study.

Study procedures

Subjects were then randomized into two groups: a control group, which did not receive ketamine, and an intervention group, which received ketamine at a dose of 0.5 mg/kg intravenously during the induction of anesthesia. Serum CRP levels, the neutrophil-to-lymphocyte ratio (NLR), and the Visual Analog Scale (VAS) for measuring pain severity were among the data gathered. All variables were assessed before surgery, followong 8 and 24 hours after surgery.

Statistical Analysis

Statistical analysis was conducted with SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Both parametric and non-parametric tests were employed, depending on the data distribution, to compare CRP and NLR levels between the two groups at each time point, with a significance level set at 5% ($p < 0.05$).

Results

The ketamine and control groups were comparable in baseline characteristics (Table 1). Baseline characteristics such as age, body mass index, ASA PS status, and type of surgical procedure were not significantly different between groups (all $p > 0.05$),

indicating that both groups had comparable initial conditions (Table 1). No significant preoperative difference in NLR was found between the ketamine and control groups. However, at both 8 and 24 hours following surgery, patients receiving ketamine showed a significantly lower NLR than those in the control group ($p < 0.05$, Table 2). This implies that ketamine may reduce postoperative inflammation through inhibition of pro-inflammatory cytokines and modulation of the innate immune response. The pattern for serum CRP levels was similar. Although initial CRP levels were comparable between groups, CRP was significantly lower in the ketamine group than in the control group at both 8 and 24 hours postoperatively (Table 3). The most pronounced decrease occurred during the first 8 hours after surgery. These findings indicate a substantial early anti-inflammatory effect of ketamine and are consistent with previous studies demonstrating that ketamine can significantly reduce postoperative CRP levels in cardiac surgical patients. The increase in CRP levels between 0 to 8 hours in the ketamine group was significantly lower than that in the control group (Table 4). However, the increase in CRP levels between 8 to 24 hours showed no significant difference between the two groups. This indicates that ketamine administration can suppress the inflammatory response in the early phase after the intervention. Pain scores, as measured by VAS, decreased over time in both groups (Table 5). However, there was no statistically significant difference in VAS scores between the ketamine and control groups at any time point ($p > 0.05$), although the ketamine group tended to report slightly lower pain scores.

Table 1- Characteristics of participants

Characteristics		Control Mean± SD	Ketamine Mean± SD	P value
Age[(a)] (years)		45.14± 6.59	49.50± 5.98	0.078 [ns]
BMI[a]		23.34± 4.10	25.07± 5.01	0.325 [ns]
ASA PS[(d)] (%)	I	3 (21.4)	1 (7.1)	0.596[ns]
	II	11 (78.6)	13 (92.9)	
Action[(c)] (%)	TAH/BSO	10 (71.4)	5 (35.7)	0.058 [ns]
	TAH	4 (28.6)	9 (64.3)	

Note: [a]Independent Sample t-test, [c]Chi-Square test, [d]Fisher-Exact test, ns: not significant, *: significant, ASA PS: American Society of Anesthesiologists physical status, TAH/BSO: total abdominal hysterectomy with bilateral salpingo-oophorectomy, BMI: body mass index, TAH: total abdominal hysterectomy.

Table 2- Comparison of NLR Levels between Groups

Measurement Time	Control Mean± SD	Ketamine Mean± SD	P value
NLR 0h[b]	3.14± 2.10	2.81± 2.77	0.182 [ns]
NLR 8 hours[b]	12.95± 7.96	7.03± 3.38	0.044[*]
24-hour NLR[b]	11.14± 7.79	5.69± 3.14	0.021[*]

Note: [a]Independent Sample t-test, [b]Mann-Whitney U test, ns: not significant, *: significant, NLR: neutrophil-to-lymphocyte ratio.

Table 3- Comparison of CRP Levels between Groups

Measurement Time	Control Mean± SD	Ketamine Mean± SD	P value
CRP 0h[b]	4.21± 3.49	3.19± 1.99	0.872[ns]
CRP 8 hours[b]	29.08± 17.38	10.64± 8.44	0.005[*]
24-hour CRP[b]	81.09± 31.76	54.42± 17.90	0.027[*]

Note: [a]Independent Sample t-test, [b]Mann-Whitney U test, ns: not significant, *: significant, CRP: C-reactive protein.

Table 4- Comparison of Difference (Delta) of CRP Levels between Groups

Measurement Time	Control Mean± SD	Ketamine Mean± SD	P value
$\Delta CRP_{(T1-T0)}$ [b]	24.86± 16.19	7.45± 8.66	0.007[*]
$\Delta CRP_{(T2-T1)}$ [a]	52.02± 26.30	41.78± 14.63	0.214 [ns]

Note: [a]Independent Sample t-test, [b]Mann-Whitney U test, ns: not significant, *: significant, CRP: C-reactive protein.

Table 5- Comparison of VAS between Groups

Measurement Time	Control Mean± SD	Ketamine Mean± SD	P value
VAS 2 hours[b]	3.00± 0.00	3.00± 0.00	1.000[ns]
VAS 4 hours[b]	3.00± 0.00	3.00± 0.00	1.000[ns]
VAS 6 hours[b]	2.71± 0.47	2.43± 0.51	0.210[ns]
8-hour VAS[b]	2.43± 0.51	2.07± 0.27	0.114 [ns]
12-hour VAS[b]	2.07± 0.62	1.93± 0.27	0.423[ns]
24-hour VAS[b]	1.79± 0.43	1.71± 0.47	0.668[ns]

Note: [a]Independent Sample t-test, [b]Mann-Whitney U test, ns: not significant, *: significant, VAS: Visual Analog Scale.

Discussion

This study demonstrated that the addition of low-dose intravenous ketamine to epidural anesthesia significantly attenuated the postoperative inflammatory response in patients undergoing hysterectomy. Compared with the control group, the ketamine group showed the decreased of NLR and CRP levels significanlty at both 8 and 24 hours after surgery. This findings support the hypothesis that ketamine acts as an anti-inflammatory agent during the perioperative period, through NMDA receptor and NLRP3 inflammasome inhibition, leading to reduced cytokine production and innate immune activation.

Our results are in line with previous research. Singh et al. found that preoperative low-dose ketamine significantly lowered postoperative IL-6 and CRP levels in patients undergoing off-pump coronary artery bypass grafting [17]. Likewise, Bartoc et al. reported that ketamine reduced markers of inflammation in cardiac surgery patients [18]. These studies, together with our findings, suggest that ketamine's anti-inflammatory effects are not limited to cardiac surgery but may extend to major non-cardiac procedures such as hysterectomy.

Although ketamine is known to have analgesic effects [19], our study did not find a statistically significant difference in pain scores between groups. Pain scores decreased in both groups over time and no patients required further rescue doses of opioids, indicating that multimodal analgesia worked. The analgesic action of ketamine by NMDA receptor blockade may still be involved in the opioid-sparing effect. The lack of significant differences in pain score maybe due to the small sample size and dose used which should be investigated by prospective studies.

There are some limitations to this study such as a limited 24-h postoperative observation period and also other detailed inflammatory markers, like interleukins were unavailable which might have been helpful in understanding the effect of ketamine. Future studies with longer follow-up duration, more cases and and more various biomarkers to validate these findings.

Conclusion

The combination between epidural anesthesia with intravenous ketamine in hysterectomy patients led to significant reductions in postoperative inflammatory markers (CRP and NLR). Although pain intensity was reduced in the ketamine group, the difference was not statistically significant. These findings suggest that combining epidural anesthesia with low-dose ketamine may effectively reduce inflammation and promote postoperative recovery. Future research should focus on determining the effective ketamine dosage and evaluate additional biomarkers.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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