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The Effect of Ketamine on Neutrophil-Lymphocyte Ratio (NRL) Levels after Gynecological Laparotomy Surgery

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ABSTRACT

Background: *Post-surgical pain is a critical issue faced by post-surgical patients. The Neutrophil-Lymphocyte Ratio (NLR) is an index indicating the direction of inflammation. Ketamine is a general anesthetic widely used in surgical procedures that do not require skeletal muscle relaxation. Intravenous ketamine can reduce inflammation through inhibition of the N-methyl-D-aspartate (NMDA) receptor. This demonstrates kematine's anti-inflammatory properties.*
Objective: *To determine the effect of ketamine on neutrophil-lymphocyte ratio (NLR) levels after gynecological laparotomy.*
Methods: *This experimental study, a clinical trial, used a pre-post-test control design, in which variables were measured before and after the intervention. Data were analyzed using paired t-tests and independent t-tests.*
Results: *The comparison of NLR levels between the control and intervention groups after pynecological laparotomy revealed a significant difference, with a higher increase in the control group compared to the intervention group receiving ketamine ($p<0.05$).*
Conclusion: *Ketamine can reduce postoperative NLR elevations, thereby reducing inflammation.*

Keywords: *Ketamine; neutrophil lymphocyte ratio; postoperative pain*

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INTRODUCTION

Postoperative pain is a critical issue faced by postoperative patients. Although our knowledge of postoperative pain mechanisms has advanced significantly, postoperative pain management is still suboptimal and often overlooked. It is estimated that pain is inadequately managed in half of all surgical procedures. Postoperative pain is largely acute nociceptive pain resulting from tissue injury.[1]

Ketamine is general anesthetic primarily used in surgical procedurs that do not requaire skeletal muscle relaxation.[2] This substance, produced as ketamine hydrochloride, is a non-barbiturate dissociative anesthetic derived from cyclohexanone.[3] Intravenous ketamine can reduce inflammation through inhibition of the N-methyl-D-aspartate (NMDA) receptor and inhibition of the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasomes. This situation demonstrates ketamine's role as an anti-inflammatory.[4-7]

Inflammation in laparotomy hysterectomy cases includes two types of inflammation: inflammation due to tissue damage and inflammation due to cancer. These different conditions require that the use of postoperative anti-inflammatory drugs be related to the physiology of inflammation involved so that the inflammation can be reduced.8,9 Inflammation following hysterectomy surgery is an acute response to tissue damage.[10,11]

A recent study, administering low-dose ketamine (1% ketamine 0.5 mg/kg) before induction of anesthesia (propofol 2 mg/kg) to patients undergoing off-pump coronary artery bypass grafting (OPCAB), induced a statistically significant decrease in the production of the pro-inflammatory mediators IL-6 and CRP compared to controls (propofol 2 mg/kg and normal saline 0.5 mg/kg induction), measured at four different time points (before induction, immediately after surgery, 24 hours postoperatively, and 48 hours postoperatively). The findings of this study strengthen the anti-inflammatory potential of ketamine in preventing changes in immune function caused by anesthesia and cardiac surgery.[12]

The neutrophil-lymphocyte ratio (NLR) is an index indicating the direction of inflammation. An increase in the NLR indicates acute inflammation, while a decrease is associated with chronic inflammation. Concurrently, trauma and blood loss suppress T and B lymphocyte activity, thereby reducing the number of CD4+ T cells and natural killer cells and leading to impaired immunity, which significantly increases the likelihood of severe sepsis and multi-organ failure. Therefore, the observed clinical response illustrates that during the early stages of multiple traumata, there is a significant increase in neutrophil counts and a decrease in lymphocytes, accompanied by an increase in NLR levels.[13,14,15]

The anti-inflammatory effect of ketamine in gynecological hysterectomy cases can be assessed using parameters that reflect the course of inflammation. Ketamine has unique anti-inflammatory effects. Therefore, research related to the anti-inflammatory role of ketamine in gynecological laparotomy cases needs to be conducted using NLR levels.

METHODS

This experimental study was a clinical trial using a pre-post test control design, where variables were measured before and after the intervention. The sample was randomly divided into two groups: the ketamine group and the control group. Study procedures: Upon arrival in the operating room, patients were re-examined for identity, diagnosis, anesthetic plan, and infusion access (ensuring an 18G intravenous catheter, three-way, and smooth infusion flow), and vital signs were monitored. Blood samples were drawn to determine pre-op NLR levels before anesthesia. Patients in both groups were then given spinal anesthesia. After spinal anesthesia, both groups underwent NLR testing. Group A received 0.5 mg/kgBW intravenously, and group B received 0.9% NaCl as a placebo. NLR testing was performed postoperatively to assess inflammatory effects. NLR values were obtained from neutrophil and lymphocyte counts from routine blood tests. Blood samples were collected 2 hours preoperatively and 12 hours postoperatively to determine the neutrophil-to-lymphocyte ratio (NLR). Ethical approval was obtained from the Research Ethics Committee of Universitas Muslim Indonesia (approval number: 410/A.1/KEP-UMI/V/2026).

The data obtained were analyzed using SPSS Statistics 25.0. The data normality test used Shapiro-Wilk (sample <50) with a significance value of $p>0.05$ indicating normally distributed data. The sample size was calculated using the formula for hypothesis testing of the difference between two independent population means. The minimum calculated sample size was 14.95 participants per group, which was rounded up to 15 participants in each group, resulting in a total sample size of 30 participants. To test the baseline data of age, BMI and pre-surgery NLR, a paired T-test was performed if the data distribution was normal. If the data distribution was not normal, the Mann-Whitney U test was used. Meanwhile, to determine whether there was a significant difference between NLR levels in the ketamine group compared to the control group, an unpaired T-test was performed if the data distribution was normal. If the data distribution was not normal, the Mann-Whitney U test was used. And it was considered to have statistical significance if the p-value obtained was $p <0.05$.

RESULTS

The results of the analysis in table 1 show that there were no significant differences in age, body weight, BMI and NLR before treatment (p>0.05) between the control and intervention groups undergoing gynecological laparotomy so that the data can be said to be homogeneous.

Table 1. Characteristics of research subjects

Variable	Grup		p value
	Control	Intervention	
Age (year)	45.93 ± 7.045	50.53 ± 7.019	0.084[a]
BMI (kg/m2)	23.17± 3.99	24.68 ± 5.06	0.412[b]
NLR Pre operative	2.97 ± 2.12	2.73 ± 2.68	0.285[b]

a tested with an independent t test, b tested with a Mann Whitney test, with a significance value < 0.005

Neutrophil Lymphocyte Ratio (NLR)

The results of the analysis in table 2 show a comparison of NLR levels between the control and intervention groups after gynecological laparotomy surgery which was significantly different in the increase in NLR levels which was higher in the control group compared to the intervention group given ketamine.

Table 2. Comparison of changes in NLR levels between the control and intervention groups

Grup	NLR		Velocity of NLR	P value
	Pre operative	Post operative		
Control	2.97 ± 2.12	12.81 ± 7.69	9.85 ± 8.30	0.029[a]
Intervention	2.73 ± 2.68	7.14 ± 3.29	4.41 ± 3.17	

a was tested using an independent t test, with a significance value of <0.005

DISCUSSION

This study demonstrates that the administration of ketamine as part of the anesthetic regimen in patients undergoing gynecological laparotomy is associated with suppression of the systemic inflammatory response, as reflected in a lower postoperative increase in NLR and a trend toward faster NLR normalization compared to the no-ketamine group. Given that NLR is a simple yet sensitive marker

of the degree of systemic postoperative inflammation, these findings indicate that ketamine may act as an immunomodulatory analgesic in gynecological patients undergoing major intra-abdominal surgery.

This suggests that ketamine may help suppress the postoperative inflammatory response. Ketamine has been shown to reduce postoperative trauma hyperalgesia by modulating the inflammatory response and reducing proinflammatory cytokine production, which is beneficial in the context of chronic postoperative pain.[16]

These results align with several clinical studies evaluating ketamine and NLR in various types of surgery (Hallikeri et al., 2024) in patients with laparoscopic inguinal hernia found that low-dose ketamine (bolus 0.5 mg/kg followed by infusion 0.2 mg/kg/hour) significantly reduced the degree of increase in NLR and PLR 2 hours postoperatively compared to saline, although on the first postoperative day, the NLR in both groups was similar. This finding is consistent with our study, which showed that the effect of ketamine is most pronounced in the early inflammatory phase (first hour–first day) after intra-abdominal surgery.[17]

In abdominal hysterectomy patients under epidural anesthesia, Wahid et al. reported that the addition of intravenous ketamine 0.5 mg/kg significantly reduced CRP and NLR levels at 8 and 24 hours postoperatively compared to controls, with no difference in the need for additional opioids. These studies are highly relevant to our study population because they both involved major gynecological surgery with significant intra-abdominal tissue trauma.[18] Gao et al. (2023) in modified radical mastectomy patients found that administration of 0.2 mg/kg bolus of ketamine followed by 0.2 mg/kg/hour infusion reduced neutrophil count, NLR, and CRP at 24 hours postoperatively compared to controls, while improving the quality of recovery without increasing side effects. Although the types of surgery differed, the similar pattern of NLR reduction reinforces the concept that ketamine's effects on perioperative inflammation are quite consistent across types of surgery.[19]

In another hysterectomy patient, a clinical trial reported that intravenous ketamine as an adjuvant to an epidural significantly reduced CRP and NLR after 8–24 hours compared to the no-ketamine group, which was interpreted as evidence of suppression of the inflammatory response after major gynecological surgery. This further supports the relevance and consistency of our findings in the context of gynecological surgery.[20] However, not all studies show the same direction of effect. Kido et al. (2019) in orthognathic surgery patients with remifentanil infusion reported that low-dose ketamine was associated with an increase in NLR on the first postoperative day. This difference is likely due to variations in the type of surgery and degree of tissue trauma, protocol design (ketamine as a preventative for opioid-induced hyperalgesia in high-remifentanil regimens), dose and duration of ketamine infusion, and timing of NLR measurement. Thus, the surgical context, other drug regimens (especially high-dose

opioids), and the timing of blood sampling are important factors in interpreting ketamine's effects on the NLR.[21]

Pharmacologically, ketamine is an NMDA receptor antagonist with analgesic and sedative effects that also possess immunomodulatory properties. Numerous experimental and clinical studies have shown that ketamine reduces the expression of pro-inflammatory cytokines such as TNF-α and IL-6, and in some cases, moderately enhances anti-inflammatory responses (e.g., IL-10). It reduces perioperative sympatho-adrenal and stress responses, thereby indirectly reducing neutrophil mobilization and lymphocyte redistribution, which contribute to the increase in NLR. It inhibits macrophage activation and the toll-like receptor pathway, and suppresses NF-κB and AP-1 activation, thereby reducing pro-inflammatory gene transcription. It reduces perioperative opioid requirements, which in turn may decrease the risk of opioid-induced hyperalgesia and secondary inflammatory responses.[22,23]

Study Limitations

This study has several limitations. First, the sample size was relatively small and the study was conducted at a single center, which may limit the generalizability of the findings. Second, the inflammatory response was assessed only using the neutrophil-to-lymphocyte ratio (NLR), without additional biomarkers such as C-reactive protein or interleukin-6. Third, NLR was measured only before surgery and 12 hours after surgery, so the longer-term inflammatory response could not be evaluated. Further studies with larger sample sizes, additional inflammatory biomarkers, and longer follow-up are recommended.

CONCLUSION

Preemptive intravenous ketamine administration can reduce the increase in NLR levels after gynecological laparotomy surgery, thereby reducing postoperative inflammation.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this research.

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