


Differences in Pain Visual Analog Scale and High-sensitivity C-reactive Protein Levels After Perioperative Fentanyl and Ketamine Administration in Post-laparotomy Patients: A Double-blind Randomized Controlled Trial

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ABSTRACT

Introduction: Postoperative pain remains a significant challenge in perioperative management. This study aims to analyze the differences in pain scores using the visual analog scale (VAS) and high-sensitivity C-reactive protein (hsCRP) levels between perioperative ketamine administration and perioperative fentanyl administration in post-laparotomy patients. **Methods:** A double-blind randomized controlled trial was conducted on 24 laparotomy patients divided into ketamine (n = 12) and fentanyl (n = 12) groups. The ketamine group received a 0.2 mg/kg bolus followed by a 0.1 mg/kg/hour infusion, while the fentanyl group received a 0.5 mcg/kg/hour infusion during surgery; drug administration was stopped immediately after extubation. VAS scores were assessed at 4 and 8 hours postoperatively, and hsCRP levels were measured preoperatively and 6 hours postoperatively. Statistical analysis used independent t-tests, Mann-Whitney U tests, and Pearson correlation. **Results:** The ketamine group showed significantly lower VAS scores at 4 hours postoperatively (2.92 vs 5.25; $p = 0.017$), but no significant difference at 8 hours (6.00 vs 5.75; $p = 0.514$). Postoperative hsCRP levels were lower in the ketamine group compared to fentanyl (4.58 vs 7.77; $p = 0.006$). A positive correlation was found between increased VAS scores and elevated hsCRP ($r = 0.566$; $p = 0.004$). **Conclusion:** Ketamine provides significantly superior early postoperative analgesia and more effectively suppresses the acute inflammatory response than fentanyl. However, its analgesic advantage diminishes by 8 hours, indicating the need for a multimodal strategy for sustained postoperative pain management.

Keywords: Fentanyl, high-sensitivity C-reactive protein, ketamine, laparotomy, postoperative pain.

ABSTRAK

Pendahuluan: Nyeri pascaoperasi masih menjadi tantangan utama tata laksana perioperatif. Penelitian ini menganalisis perbedaan skor nyeri menggunakan *visual analog scale* (VAS) dan kadar *high-sensitivity C-reactive protein* (hsCRP) antara pemberian *ketamine* perioperatif dan *fentanyl* perioperatif pada pasien pascabedah laparotomi. **Metode:** Uji klinis acak tersamar ganda pada 24 pasien laparotomi yang dibagi menjadi kelompok *ketamine* (n = 12) dan *fentanyl* (n = 12). Kelompok *ketamine* menerima bolus 0,2 mg/kg dilanjutkan infus 0,1 mg/kg/jam, kelompok *fentanyl* mendapat infus 0,5 mcg/kg/jam selama operasi; pemberian obat dihentikan segera setelah ekstubasi. VAS dinilai pada jam ke-4 dan ke-8 pascaoperasi, kadar hsCRP diukur sebelum operasi dan 6 jam pascaoperasi. Analisis statistik menggunakan uji-t independen, Mann-Whitney U, dan korelasi Pearson. **Hasil:** Kelompok *ketamine* menunjukkan skor VAS lebih rendah signifikan pada jam ke-4 pascaoperasi (2,92 vs 5,25; $p = 0,017$), namun tidak ada perbedaan signifikan pada jam ke-8 (6,00 vs 5,75; $p = 0,514$). Kadar hsCRP pascaoperasi kelompok *ketamine* lebih rendah dibandingkan *fentanyl* (4,58 vs 7,77; $p = 0,006$). Terdapat korelasi positif antara peningkatan skor VAS dan kenaikan hsCRP ($r = 0,566$; $p = 0,004$). **Simpulan:** *Ketamine* memberikan analgesia superior pada periode awal pascaoperasi dan lebih efektif menekan respons inflamasi dibandingkan *fentanyl*. Namun, efek analgesik *ketamine* menurun setelah 8 jam, menunjukkan perlunya strategi multimodal untuk manajemen nyeri pascaoperasi yang berkelanjutan. **Adiptya Cahya Mahendra, Muhammad Husni Thamrin, Bambang Novianto Putro, Dykall Naf'an Dzikri. Perbedaan Nilai *Visual Analog Scale* Nyeri dan Kadar *High-sensitivity C-reactive Protein* Setelah Pemberian *Fentanyl* dan *Ketamine* Perioperatif pada Pasien Pasca-laparotomi: Uji Acak Terkendali Tersamar Ganda.**

Kata Kunci: *Fentanyl*, *high-sensitivity C-reactive protein*, *ketamine*, laparotomi, nyeri pascaoperasi.

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INTRODUCTION

Postoperative pain remains a significant challenge in healthcare, with studies reporting high prevalence rates across various settings. In a tertiary hospital in Nairobi, 58% of patients experienced pain 30 minutes after surgery, 55.3% after 24 hours, and 34.7% after 48 hours.[1] Similarly, a study in Tanzania found that 61%, 73%, 67%, and 58% of postoperative patients experienced pain at 4, 24, 36, and 48 hours after surgery, respectively.[2] These high rates of postoperative pain underscore the need for improved pain management strategies.

Opioids, particularly fentanyl, remain a cornerstone in postoperative pain management. However, their use is associated with various side effects, including urinary retention, ileus, nausea, vomiting, pruritus, and respiratory depression.[3] Because fentanyl is commonly utilized as the standard of care for intraoperative and postoperative analgesia, comparing an opioid-sparing adjuvant directly to this standard is crucial to identify alternative modalities that can mitigate opioid-related complications. As a result, there is growing interest in adjuvant therapies that can enhance pain relief while reducing opioid requirements. Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has shown promise; studies reported its ability to alleviate pain and to decrease perioperative opioid consumption.[4]

While several studies have explored the benefits of ketamine in postoperative pain management, results have been inconsistent across different surgical procedures and dosing regimens. Some studies reported significant reduction in pain scores and opioid consumption,[5,6] while others found no significant difference compared to placebo. Further research is needed to clarify the efficacy of ketamine in specific surgical contexts, particularly in laparotomy procedures.

To objectively assess the physiological impact of surgical trauma and the efficacy of pain management, evaluating inflammatory biomarkers is essential. High-sensitivity C-reactive protein (hsCRP) is a sensitive acute-phase reactant that rapidly elevates in response to tissue injury and systemic inflammation. Measuring hsCRP provides a reliable, objective parameter to evaluate whether the chosen analgesic regimen effectively suppresses the postoperative neuroendocrine inflammatory response.

This study aims to compare the effects of perioperative ketamine administration with perioperative fentanyl administration on postoperative pain, as measured by visual analog scale (VAS) scores and high-sensitivity C-reactive protein (hsCRP) levels, in patients undergoing elective laparotomy under general anesthesia.

METHODS

Design and Setting

This was a double-blind randomized controlled trial conducted at a hospital in Surakarta, Indonesia, from March to August 2024.

Sample Size, Randomization, and Blinding

Sample size was calculated a priori using the formula for hypothesis testing of two independent population means, with $\alpha = 0.05$ and $\beta = 0.20$ (power 80%). The expected difference in VAS scores was 1 point, with an estimated standard deviation of 1, yielding a minimum required sample size of 24 patients (12 per group). Eligible participants were randomized in a 1:1 ratio to the ketamine or fentanyl group using a computer-generated random allocation sequence. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes prepared by an investigator not involved in postoperative outcome assessment. To preserve blinding despite the different dosing schemes, study drugs were prepared in identical syringes by an independent anesthesiology staff member; patients, postoperative observers, and data analysts were blinded to group allocation.

Participants

A total of 47 patients undergoing laparotomy were assessed for eligibility. Inclusion criteria were as follows: (1) age 18–60 years; (2) scheduled for elective laparotomy under general anesthesia; (3) American Society of Anesthesiologists (ASA) physical status I–II; (4) able to provide informed consent; (5) willing to comply with postoperative evaluation protocol. Exclusion criteria were: (1) contraindications to ketamine use; (2) uncontrolled hypertension (blood pressure > 160/100 mmHg); (3) history of long-term analgesic medication use (> 3 months); and (4) pre-existing chronic pain conditions. Of the 47 eligible patients, 12 voluntarily withdrew their informed consent before randomization [pre-randomization withdrawal]. The remaining 35 patients were randomized to either the ketamine group (n = 18) or the fentanyl group (n = 17). After randomization, 11 patients were excluded from the final analysis: 6 patients in the ketamine group (3 failed to complete therapy, 3 refused postoperative evaluation) and 5 patients in the fentanyl group (2 failed to complete therapy, 3 refused postoperative evaluation) [post-randomization dropout]. The final analysis included 24 patients who completed the study protocol (ketamine n = 12; fentanyl n = 12). The participant flow was reported in a CONSORT-style sequence: assessed for eligibility (n = 47), pre-randomization withdrawal (n = 12), randomized (n = 35), post-randomization dropout (n = 11), and analyzed per protocol (n = 24). Because outcome data were unavailable for participants who withdrew or did not complete postoperative evaluation, the final analysis used a per-protocol approach without imputation. This study received ethical approval from the Hospital Ethics Committee in Surakarta (approval number 2.232/IX/HREC/2024), ensuring adherence to ethical guidelines for human subject research.

Interventions and Comparisons

The ketamine group received an intravenous bolus of 0.2 mg/kg followed by an intraoperative infusion of 0.1 mg/kg/hour.[7] The fentanyl group received an intraoperative infusion of 0.5 mcg/kg/hour during surgery.[3] Drug syringes were prepared in the same volume and appearance to maintain blinding. Both groups received 1,000 mg paracetamol and 30 mg ketorolac intravenously at the end of surgery. VAS scores were assessed at 4 and 8 hours postoperatively. Drug administration was stopped immediately after extubation.

Measurements

The primary outcome was the VAS score at 4 hours postoperatively. Secondary outcomes were VAS score at 8 hours postoperatively, change in VAS score between 4 and 8 hours,


hsCRP level at 6 hours postoperatively, pre-postoperative hsCRP change, rescue analgesia requirement, and the correlation between VAS change and hsCRP change.

- VAS Procedure: Pain intensity was assessed using a standard 10-cm VAS, with 0 indicating "no pain" and 10 indicating "the worst imaginable pain." Patients were instructed preoperatively on how to use the scale. Assessments were conducted by a blinded observer at 4 and 8 hours postoperatively.
- hsCRP Analysis: Serum from collected samples was analyzed by immunoturbidimetric assay on an automated clinical chemistry analyzer to accurately quantify the systemic inflammatory response.

Data Collection

Demographic data, type and indication for laparotomy, surgical duration, and requirement for rescue analgesia were recorded. Blood samples for hsCRP analysis were collected preoperatively and 6 hours postoperatively. The 6-hour postoperative sampling point was selected to capture the early acute-phase inflammatory response after surgical trauma and drug exposure, rather than the expected peak hsCRP response.

Statistical Analysis

For normally distributed data, independent t-tests were used to compare means between the ketamine and fentanyl groups. When data were not normally distributed, the non-parametric Mann-Whitney U test was applied. Normality was assessed using the Shapiro-Wilk test, with $p > 0.05$ indicating normal distribution. For within-group comparisons of hsCRP levels before and after treatment, paired t-tests were utilized. To analyze the relationship between VAS score changes and hsCRP changes, Pearson correlation was employed because both variables were continuous and the change values met the assumption of normality; Spearman correlation would be used if the normality assumption was not met. Chi-square tests were used for categorical variables, including the requirement for rescue analgesia. Mean differences were presented with 95% confidence intervals when applicable. The statistical analysis was conducted on the per-protocol population, comprising participants who completed the assigned intervention and postoperative assessments. All statistical tests were conducted using IBM SPSS v.25, with a significance level set at $p < 0.05$.

RESULTS

Baseline Characteristics

The study included 24 subjects divided into two treatment groups: ketamine and fentanyl. **Table 1** shows the baseline characteristics of both groups that were homogeneous and not statistically significantly different ($p > 0.05$).

The mean age of subjects in the ketamine group was 50.33 ± 10.37 years, while in the fentanyl group it was 51.17 ± 8.39 years. Body mass index (BMI) was similar in both groups, with a mean of 25.00 ± 3.65 in the ketamine group and 25.08 ± 3.62 in the fentanyl group. The average duration of surgery in the ketamine group was 140.17 ± 61.25 minutes, while in the fentanyl group it was 146.50 ± 55.86 minutes. Gender distribution was balanced in both groups, with 12 males and 12 females in each. The homogeneity of baseline characteristics is important to demonstrate that both groups were comparable at the start of the study. This ensures that any observed differences in outcomes can be more confidently attributed to the treatment effect (ketamine or fentanyl) rather than to initial differences between the subject groups.

Rescue analgesia was analyzed as an outcome. It was required by 2 patients (16.7%) in the ketamine group and 3 patients (25.0%) in the fentanyl group, with no statistically significant between-group difference ($p = 0.615$).

Visual Analog Scale (VAS) Scores

Table 2 presents the comparison of VAS scores between the ketamine and fentanyl groups at 4 hours, 8 hours, and the difference between 4–8 hours postoperatively.

Values are presented as mean ± SD. MD = mean difference calculated as ketamine minus fentanyl. Between-group comparisons were performed using an independent t-test or a Mann-Whitney U test, depending on the data distribution.

At 4 hours postoperatively, the ketamine group showed significantly lower VAS scores (2.92 ± 2.02) than the fentanyl group (5.25 ± 1.88), indicating a better analgesic effect ($p = 0.017$; MD -2.33; 95% CI -3.98 to -0.68). However, at 8 hours postoperatively, there was no significant difference in VAS scores between the two groups (ketamine: 6.00 ± 0.82; fentanyl: 5.75 ± 0.72; p = 0.514; MD 0.25; 95% CI -0.40 to 0.90). The difference in VAS scores between 4 and 8 hours was significantly greater in the ketamine group (3.08 ± 1.80) than in the fentanyl group (0.50 ± 1.71), $p = 0.002$; MD 2.58; 95% CI 1.09 to 4.07.

Table 1. Baseline characteristics of study subjects.

Characteristic	Ketamine (n = 12)	Fentanyl (n = 12)	*p*-value
Age (years)	50.33 ± 10.37	51.17 ± 8.39	0.829
BMI (kg/m^2)	25.00 ± 3.65	25.08 ± 3.62	0.955
Duration of surgery (min)	140.17 ± 61.25	146.50 ± 55.86	0.792
Gender			1.000
- Male	6 (50%)	6 (50%)	
- Female	6 (50%)	6 (50%)	

Table 2. VAS score data and between-group analysis.

Time Point	Ketamine (n = 12)	Fentanyl (n = 12)	*p*-value	MD (95% CI)
4 hours	2.92 ± 2.02	5.25 ± 1.88	0.017	-2.33 (-3.98 to -0.68)
8 hours	6.00 ± 0.82	5.75 ± 0.72	0.514	0.25 (-0.40 to 0.90)
Difference	3.08 ± 1.80	0.50 ± 1.71	0.002	2.58 (1.09 to 4.07)

MD = Mean Difference


High-sensitivity C-Reactive Protein (HsCRP) Levels

Table 3 presents the hsCRP levels before treatment, at 6 hours postoperatively, and the difference between pre- and post-treatment levels.

Before treatment, the ketamine group had a slightly higher mean hsCRP level (4.61 ± 2.59) compared to the fentanyl group (4.13 ± 3.34), with a narrower range for ketamine (0.39–9.00) compared to fentanyl (0.18–11.32). The independent t-test showed no significant difference between the two groups (p = 0.550), indicating comparable hsCRP levels before treatment.

After treatment (measured at 6 hours postoperatively), the ketamine group showed a slight decrease in mean hsCRP (4.58 ± 2.94), while the fentanyl group experienced a substantial increase (7.77 ± 2.93). Within-group analysis showed no significant pre-post change in the ketamine group (p = 0.982), whereas the fentanyl group showed a significant increase in hsCRP after treatment (p < 0.001). The Mann-Whitney test revealed a significant difference between the two groups (p = 0.006), with the ketamine group having a lower mean rank (8.58) compared to the fentanyl group (16.42).

The mean pre-post hsCRP change differed significantly between groups (ketamine: 0.03 ± 4.49; fentanyl: -3.64 ± 2.24; p = 0.024). Because the difference was calculated as pre-treatment minus post-treatment, the negative value in the fentanyl group indicated a postoperative increase in hsCRP.

Correlation Between VAS and hsCRP

A Pearson correlation analysis was conducted to evaluate the relationship between postoperative pain and the inflammatory response. The results demonstrated a significant positive correlation between increases in VAS scores and elevations in hsCRP levels (r = 0.566; p = 0.004), indicating that higher pain intensity was strongly associated with a greater systemic inflammatory response.

DISCUSSION

The findings of this study provide valuable insights into the comparative efficacy of ketamine and fentanyl for postoperative pain management in laparotomy patients. The results demonstrate that ketamine offers superior analgesic effects in the early postoperative period, particularly within the first 4 hours, compared to fentanyl. However, this advantage diminishes by 8 hours post-surgery, suggesting a time-dependent efficacy of ketamine. This pattern indicates that ketamine provided stronger early analgesia, whereas fentanyl maintained a more stable analgesic profile during the 4- to 8-hour interval.

The superior early analgesic effect of ketamine aligns with previous research. Gumelar, *et al*., (2021) reported that a combination of ketamine and fentanyl provided better analgesia in the first hour post-surgery compared to fentanyl alone.[8] Similarly, Yılmaz, *et al*., (2023) found ketamine to be as effective as fentanyl in managing acute pain in emergency settings.[9] The rapid onset of ketamine's analgesic effect can be attributed to its unique mechanism of action as an NMDA receptor antagonist, which plays a crucial role in pain signal transmission and central sensitization.[10] The superiority of ketamine over fentanyl in the first 4 hours is primarily attributed to this mechanism, which effectively blocks central sensitization, the "wind-up" phenomenon, and opioid-induced hyperalgesia. In addition, Jouguelet-Lacoste, *et al*., (2015) reported that low-dose ketamine infusion is effective for up to 24–48 hours postoperatively, but the effect varies with the type of surgery and the dosage regimen.[7] Furthermore, our quantitative VAS findings (2.92 for ketamine vs. 5.25 for fentanyl at 4 hours) are highly consistent with previous literature. For instance, Gumelar, *et al*., (2021) reported significantly lower early postoperative pain scores in ketamine-treated groups (VAS averaging 2–3) compared to standard opioid regimens (VAS averaging 4–5).[8] Similarly, Yılmaz, *et al*., (2023) documented mean pain scores dropping to 3.1 in ketamine groups in acute trauma settings, closely mirroring the early analgesic trajectory observed in our laparotomy cohort.[9]

The diminishing efficacy of ketamine over time, as observed in our study, is a notable finding. By 8 hours post-surgery, there was no significant difference in pain scores between the ketamine and fentanyl groups. The VAS scores in the ketamine group significantly increased from 4 to 8 hours post-surgery. This time-dependent decline in efficacy is directly related to ketamine's pharmacokinetic profile. Intravenous ketamine has a rapid distribution phase (half-life of 10–15 minutes) and a short elimination half-life (approximately 2–3 hours) due to rapid hepatic metabolism to norketamine.[11–13] Because drug administration was halted immediately following extubation, plasma concentrations of ketamine inevitably fell below the therapeutic analgesic threshold by the 8-hour mark, leading to breakthrough pain. This time-dependent effect is consistent with the pharmacokinetics of ketamine, which is rapidly metabolized into less active compound.[10,12,13] It also aligns with the report from Altirkistani, *et al*., (2023), that ketamine's analgesic effects are most pronounced in the first 15–30 minutes after administration.[14]

The correlation between VAS scores and hsCRP levels observed in this study (r = 0.566, p = 0.004) suggests a strong relationship between pain intensity and inflammatory response. This finding supports the use of hsCRP as a potential biomarker for postoperative pain, as previously suggested by Hashimoto, *et al*., (2018).[15] The lower

Table 3. High-sensitivity C-reactive protein (hsCRP) levels before and after treatment.
Within-group p-values were obtained using paired t-tests comparing pre-treatment and post-treatment hsCRP levels within each group.

Group	Pre-treatment (Mean ± SD)	Post-treatment (Mean ± SD)	Difference (Mean ± SD)	Within-group p-value
Ketamine	4.61 ± 2.59	4.58 ± 2.94	0.03 ± 4.49	0.982
Fentanyl	4.13 ± 3.34	7.77 ± 2.93	-3.64 ± 2.24	< 0.001
Between-Group p-value	0.550	0.006	0.024	

hsCRP levels in the ketamine group compared to the fentanyl group at 6 hours post-surgery indicate that ketamine may have additional anti-inflammatory properties, which could contribute to its analgesic effects. Ketamine maintained relatively stable hsCRP levels, whereas fentanyl was associated with a significant postoperative increase in hsCRP. This difference was statistically significant, indicating a potential advantage of ketamine in managing early postoperative inflammation in laparotomy patients.

The 6-hour hsCRP measurement should be interpreted as an early inflammatory marker rather than the peak postoperative hsCRP response. C-reactive protein generally reaches higher postoperative values later, commonly around 24–48 hours after tissue injury; therefore, the present 6-hour measurement was intended to evaluate the early inflammatory trajectory after drug exposure. The absence of serial hsCRP measurements beyond 6 hours limits the ability to determine whether the between-group difference persisted until the expected peak inflammatory phase.

Despite these promising results, several limitations of the study should be acknowledged. The sample size of 24 patients, while statistically sufficient based on power calculations, is relatively small. A larger sample size could yield more robust findings and enable subgroup analyses. Additionally, the study was limited to patients undergoing laparotomy, which may limit the generalizability of the results to other surgical procedures. The post-randomization dropout rate was relatively high, and the final analysis used a per-protocol approach rather than an intention-to-treat analysis; therefore, attrition bias cannot be fully excluded.

The 8-hour post-surgery duration provides valuable information about the immediate postoperative period but does not capture longer-term outcomes. Future research could benefit from extended follow-up periods to assess the potential long-term benefits or risks associated with ketamine use for postoperative pain management.

Additionally, while the study focused on pain scores and hsCRP levels, other important outcomes such as opioid consumption, functional recovery, patient satisfaction, and adverse effects of ketamine and fentanyl were not extensively explored. Potential adverse effects, including nausea, vomiting, pruritus, respiratory depression, hallucination, dysphoria, hypertension, and hemodynamic instability, were not systematically recorded; therefore, safety comparisons between ketamine and fentanyl cannot be concluded from this study. Including these parameters in future studies could provide a more comprehensive understanding of the clinical benefits of ketamine versus fentanyl in postoperative pain management.

CONCLUSION

In conclusion, when comparing perioperative ketamine and fentanyl administration discontinued after extubation, ketamine provides significantly superior early postoperative analgesia (at 4 hours) and prevents an early postoperative rise in hsCRP more effectively than fentanyl in post-laparotomy patients. However, due to ketamine's rapid pharmacokinetic degradation, this analgesic advantage is not sustained at 8 hours postoperatively. This study demonstrates the potential of ketamine as an effective alternative to fentanyl for early postoperative pain management in laparotomy patients. The findings suggest that a multimodal approach, potentially combining ketamine's early analgesic effects with longer-acting agents, could optimize postoperative pain control. Future research should focus on comparing prolonged postoperative analgesic strategies, investigating the synergistic effects of combining ketamine with long-acting adjuvants, systematically recording drug-related adverse effects, and utilizing larger cohorts across diverse surgical procedures to optimize long-term postoperative pain protocols.

REFERENCES

1. Mwaka G, Thikra S, Mung'ayi V. The prevalence of postoperative pain in the first 48 hours following day surgery at a tertiary hospital in Nairobi. Afr Health Sci. 2013;13(3):768–76. https://doi.org/10.4314/ahs.v13i3.36.
2. Ndebea AS, van den Heuvel SAS, Temu R, Kaino MM, van Boekel RLM, Steegers MAH. Prevalence and risk factors for acute postoperative pain after elective orthopedic and general surgery at a tertiary referral hospital in Tanzania. J Pain Res. 2020;13(1):3005–11. https://doi.org/10.2147/JPR.S258954.
3. Cheung CK, Adeola JO, Beutler SS, Urman RD. Postoperative pain management in enhanced recovery pathways. J Pain Res. 2022;15(1):123–35. https://doi.org/10.2147/JPR.S231774.
4. Brinck EC, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, et al. Perioperative intravenous ketamine for acute postoperative pain in adults. Cochrane database Syst Rev. 2018;12(12):CD012033. https://doi.org/10.1002/14651858.CD012033.pub4.
5. Doan LV, Li A, Brake L, Ok D, Jee HJ, Park H, et al. Single-dose of postoperative ketamine for postoperative pain after mastectomy: a pilot randomized controlled trial. J Pain Res. 2023;16(1):881–92. https://doi.org/10.2147/JPR.S389564.
6. Zhou D, Liu F, Jiang F, Ye X, Gong X, Zhang M. Sub-anesthesia dose of s-ketamine reduces postoperative pain and anxiety in patients receiving breast and thyroid surgery: a randomized, controlled trial. Pain Physician. 2023;26(3):257–64. https://doi.org/10.36076/ppj.2023/26/257.
7. Jouguelet-Lacoste J, La Colla L, Schilling D, Chelly JE. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. Pain Med. 2015;16(2):383–403. https://doi.org/10.1111/pme.12619.


8. Gumelar W, Hamzah H, Sumartono C. The effectiveness of intraoperative ketamine and fentanyl as preemptive analgesia with qNOX score. J Anestesiol Indones. 2021;13(2):67–77. https://doi.org/10.14710/jai.v13i2.31900.

9. Yılmaz M, Kudu E, Sanri E, Karacabey S, Akoglu H, Denizbasi A. Comparison of the analgesic effects of low-dose ketamine versus fentanyl in patients with long bone fractures in the emergency department: a prospective observational study. Cureus 2023;15(10):e46344. https://doi.org/10.7759/cureus.46344.

10. Sleigh J, Harvey M, Voss L, Denny B. Ketamine – more mechanisms of action than just NMDA blockade. Trends Anaesth Crit Care. 2014;4(2–3):76–81. https://doi.org/10.1016/j.tacc.2014.03.002

11. Nichols KA, Paciullo CA. Subdissociative ketamine use in the emergency department. Adv Emerg Nurs J. 2019;41(1):15–22. https://doi.org/10.1097/TME.0000000000000222.

12. Zhang J, Ma Q, Li W, Li X, Chen X. S-ketamine attenuates inflammatory effect and modulates the immune response in patients undergoing modified radical mastectomy: A prospective randomized controlled trial. Front Pharmacol. 2023;14(1):1128924. https://doi.org/10.3389/fphar.2023.1128924.

13. Bayable SD, Melesse DY, Lema GF, Ahmed SA. Perioperative management of patients with asthma during elective surgery: a systematic review. Ann Med Surg. 2021;70:102874. https://doi.org/10.1016/j.amsu.2021.102874.

14. Altirkistani BA, Ashqar AA, Bahathiq DM, Bougis SM, Aljabri AM, Hanafi S. The effectiveness of ketamine versus opioids in patients with acute pain in the emergency department: a systematic review and meta-analysis. Cureus 2023;15(3):e36250. https://doi.org/10.7759/cureus.36250.

15. Hashimoto K, Tsuji A, Takenaka S, Ohmura A, Ueki R, Noma H, et al. C-reactive protein level on postoperative day one is associated with chronic postsurgical pain after mastectomy. Anesthesiol Pain Med. 2018;8(4):e79331. https://doi.org/10.5812/aapm.79331.