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RESEARCH

Efficacy Of Preemptive Analgesic Ketamine On Postoperative Pain At Universitas Gadjah Mada Academic Hospital

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ABSTRACT

Background: Postoperative pain remains a problem in anesthesia services. Preemptive analgesics are known to reduce postoperative pain due to noxious stimuli during the perioperative period. Ketamine can be used as a preemptive analgesic because it has the ability to prevent central sensitization. However, studies on ketamine as a preemptive analgesic have not reached a conclusion. So further research is needed to prove the effectiveness of ketamine as a preemptive analgesic

Objective: This study aims to evaluate the efficacy of preemptive intravenous ketamine 0.5 mg/kgBW in reducing postoperative pain.

Method: This research is an experimental study with double-blind randomized controlled trials. The inclusion criteria for this study are oncology surgery patients, aged 18-65 years, ASA physical status 1 or 2, BMI 18-30, and willing to sign informed consent. Exclusion criteria include patients with contraindications to ketamine, chronic pain, long-term analgesic consumption, hypertension, diabetes mellitus, cerebrovascular disease, and a history of recurrent malignancy. Meanwhile, withdrawal criteria include withdrawing from the study and experiencing ketamine hypersensitivity. The research sample is randomly divided into 2 groups, namely Group A (ketamine preemptive) and Group B (control). Both groups receive the same anesthesia procedure, namely premedication with intravenous midazolam 0.05 mg/kg body weight (BW), fentanyl 2 mcg/kg BW intravenously, rocuronium 0.6 mg/kg BW intravenously (if intubation is performed), then after a confirmed onset, the LMA (laryngeal mask airway) or ETT (endotracheal tube) airway device is inserted. After that, for Group A, preemptive analgesic ketamine 0.5 mg/kg BW intravenously is administered 10 minutes before surgical incision. The assessment performed is pain scale using the numerical rating scale (NRS) at rest and with movement, total intraoperative rescue fentanyl, total postoperative rescue fentanyl requirement, onset of postoperative rescue fentanyl requirement, and side effects. Observation is conducted for up to 12 hours postoperatively. All variables except side effects are analyzed with independent t-tests, but if the data distribution is not evenly spread, the Mann-Whitney test is conducted. The confidence interval in this study is 95%, with significance set at $p < 0.05$.

Results: A total of 65 subjects were studied, but 3 subjects dropped out of the study. Therefore, 62 subjects remained, with 31 subjects in each Group A and B. Statistically, Group A had lower NRS pain scores at rest compared to Group B at hours 0, ½, 1, and 2 postoperatively ($p<0.05$). For NRS on movement, Group A had lower NRS pain scores compared to Group B at hours 0, ½, 1, 2, 6, and 12 postoperatively ($p<0.05$). Group A had a longer onset of postoperative rescue fentanyl requirement compared to Group B ($p<0.05$). However, there was no significant difference in total intraoperative rescue fentanyl and total postoperative rescue fentanyl requirement ($p>0.05$).

Conclusion: Preemptive ketamine analgesic dose of 0.5 mg/kgBW intravenously is effective in reducing postoperative pain better than the control group. This is evidenced by lower NRS pain scores at rest and on movement, as well as a longer onset of postoperative rescue fentanyl requirement compared to the control group.

Keywords: preemptive analgesics, ketamine, general anesthesia, NRS

Background

Postoperative pain remains a problem in anesthesia services. Although pain management has made significant progress, the percentage of postoperative pain is still quite high. Around 80% of surgical patients experience acute postoperative pain, with 86% of them experiencing moderate to severe pain.1

One effort to reduce postoperative pain is through preemptive analgesic administration, which involves administering analgesics before the surgical incision begins. Preemptive analgesia was first introduced into clinical practice by Crile in 1913, then developed by Wall and Woolf. The results of these experimental studies indicate that preventive analgesia is more effective when administered before and during painful stimuli, rather than just postoperatively. Woolf concluded that the timing of analgesic administration greatly affects the degree of postoperative pain.2

The strategy of preemptive analgesic administration can be carried out through several interventions targeting various pain pathways. Drugs that can be used as preemptive analgesics include NSAIDs (nonsteroidal anti-inflammatory drugs), local anesthetics, gabapentin, and pregabalin. NSAIDs work by inhibiting the enzyme cyclooxygenase (COX). NSAIDs can prevent secondary hyperalgesia due to prostaglandins and bradykinin which affect nociceptor sensitivity. Local anesthesia inhibits pain transmission by stabilizing cell membranes and controlling sodium influx. Pregabalin and gabapentin bind to the alpha subunit of calcium channels to induce analgesic effects. However, the effectiveness of these three drugs is still questionable.[3]

Ketamine has advantages as a preemptive analgesic. This is because it works as an NMDA receptor antagonist located in the dorsal spinal cord. Sensitization in this area is responsible for pain related to touch or movement of injured body parts. Administered ketamine can inhibit pain signals, thus preventing central sensitization that exacerbates postoperative pain.[4]

Satiyah, U., Basuki, D.R., and Laksono, R.M., in 2015 investigated the effects of preemptive ketamine administration at a dose of 0.15 mg/kgBW on major oncology surgery postoperative pain at RSUD Dr. Saiful Anwar Malang. The results of the study showed that acute postoperative pain in the treatment

group was lower at 1, 2, and 3 hours postoperatively compared to the control group.[5]

Meanwhile, Raharjo, L., and Budiono, U. in 2009 assessed the effectiveness of ketamine as preemptive analgesia for postoperative oncology pain, comparing ketamine doses of 0.5 mg/kgBW/IV and placebo given before surgical incision. The results showed that preemptive ketamine administration at a dose of 0.5 mg/kgBW/IV did not reduce the need for opioids for postoperative analgesia in oncology patients at Dr. Kariadi Hospital Semarang, but it prolonged the time for postoperative analgesia requirement.[6]

Postoperative pain management is important to improve patient comfort and prevent acute pain from progressing to persistent chronic pain. Preemptive analgesia is known to be more effective than postoperative analgesia in some studies. Ketamine plays an important role in suppressing central sensitization. Research on the efficacy of preemptive ketamine analgesia is still limited. Therefore, further research is needed to determine the efficacy of preemptive ketamine analgesia at a dose of 0.5 mg/kgBW for postoperative pain.

Literature Review

Tissue trauma and nerve damage during surgical procedures can elicit pain stimuli. Poorly modulated pain stimuli can lead to chronic pain due to peripheral sensitization or hypersensitivity. The primary goal of preemptive analgesia is to prevent peripheral sensitization. Figure 1 illustrates the degree of pain stimulus and hypersensitivity during surgery and postoperatively, in conditions without analgesics (A), with postoperative analgesics (B), with preoperative analgesics (C), and with preoperative and postoperative analgesics (D).[7]

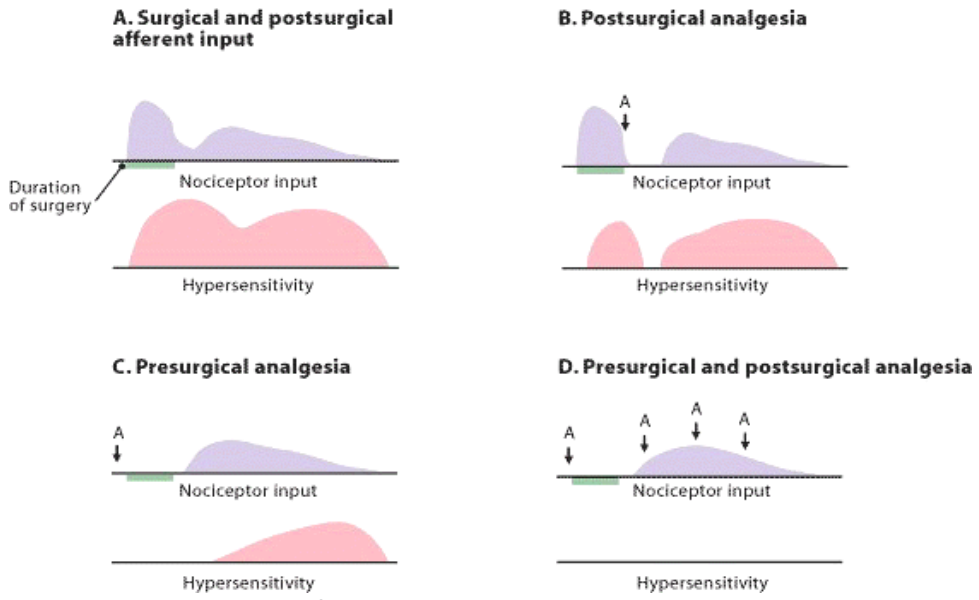

Figure 1. Timing of analgesic administration in surgical patients[7]

Spinal cord sensitization is responsible for pain related to touch or movement of injured body parts. Spinal cord sensitization is caused by the activation of NMDA receptors, which are located in the dorsal spinal cord. NMDA receptors are important glutamate-gated ion channels involved in pain processing and modulation. Glutamate, specifically, acts on NMDA receptors and plays a crucial role in the spinal nociceptive pathway. Inhibition of

NMDA receptors by drugs such as ketamine, magnesium, and dextromethorphan is useful in managing postoperative pain, including reducing analgesic consumption.[4]

Based on the concept of preemptive analgesia, ketamine is administered to inhibit pain signals, thereby preventing central sensitization, which can lead to chronic pain that significantly affects the individual's postoperative quality of life. Ketamine as preemptive analgesia can address the limitations of general anesthesia, which cannot prevent nociceptive impulse transmission from the surgical site to the spinal cord. Postoperative pain can slow down recovery and prolong hospitalization time.[8]

Methode

The research design is an experimental study using a randomized controlled trial method, with a clinical superiority trial type. The study is conducted as a double-blinded, concealed study. This research has obtained ethical approval from UGM with the number EC: KE/FK/1539/EC and permission from the research site RSA UGM with the number 230/UN1/RSA.2/AR/SB/2024.

The study population consists of all oncology surgical patients undergoing surgery with general anesthesia techniques. The inclusion criteria for this study are: oncology surgical patients aged 18-65 years, ASA physical status I-II, preoperative NRS 0-1, BMI 18-30, surgery duration < 3 hours, willing to participate in the study and sign the informed consent. The exclusion criteria for this study include: patients with contraindications to ketamine, patients with chronic pain, patients with a history of long-term analgesic drug use, patients with inability (cognitive, psychological factors) to assess pain scale, patients with a history of hypertension, heart disease, diabetes mellitus, and cerebrovascular disease, and patients with a history of recurrent oncological malignancy. Meanwhile, the dropout criteria are respondents withdrawing from the study and experiencing ketamine hypersensitivity reactions during the study.

The sample size in this study is 62 samples. All research subjects are divided into two groups, namely Group A (intervention) and Group B (control). Both groups receive the same general anesthesia procedure, including midazolam premedication 0.05 mg/kgBW IV, fentanyl 2 mcg/kgBW IV, rocuronium 0.6 mg/kgBW IV (if intubation), then after achieving onset, the LMA (laryngeal mask airway) or ETT (endotracheal tube) airway device is installed. Then, Group A is given preemptive analgesic ketamine 0.5 mg/kgBW intravenously 10 minutes before surgical incision, while Group B is not given preemptive analgesic ketamine. Group B is given Nacl 0.9% 10 cc for blinding purposes.

Subject characteristics will be analyzed descriptively. Categorical data will be presented in the form of frequency and percentage, while numerical data will be presented as mean and standard deviation. Normality testing for numerical data will be conducted using the Shapiro- Wilk test. The statistical test employed will be the independent t-test. If the data does not follow a normal distribution, the Mann-Whitney test will be used instead. A 95% confidence interval with a p-value < 0.05 will be considered statistically significant.

Result

The sample characteristics are shown in Table 1. From the table, it can be observed that the study subjects are predominantly female, with 25 (80.6%) in Group A and 19 (61.3%) in Group B. Additionally, the most common surgical procedure is in the breast region, with 19 (61.3%) cases in Group A and

Group B. It can also be concluded from the table that there are no significant differences in sample characteristics between the two study groups in terms of age, gender, education, ethnicity, ASA physical status, BMI, surgical region, anesthesia technique, and duration of surgery (p>0.05).

Table 1. Table 1. Characteristics of the study sample in Groups A and B

Karakteristik	Group A(n=31)	Group B(n=31)	P
Age, mean ± SD, tahun	44.23 ± 13.12	47.81 ± 12.99	0,285#
BMI, mean ± SD, kg/m2	23.36 ± 3.78	23.29 ± 3.03	0,935#
Gender, n (%)			
Male	6 (19.4)	4 (12.9)	0,490x
Female	25 (80.6)	27 (87.1)	
Education, n (%)			
SD	4 (12.9)	4 (12.9)	0,877$
SMP	5 (16.1)	3 (9.7)	
SMA	11 (35.5)	13 (41.9)	
Diploma	0 (0.0)	1 (3.2)	
S1	9 (29.0)	9 (29.0)	
S2	2 (6.5)	1 (3.2)	
Ethnicity			
Jawa	29 (93.5)	30 (96.8)	1,000^
Betawi	1 (3.2)	1 (3.2)	
Papua	1 (3.2)	0 (0.0)	
ASA physical status			
ASA 1	11 (35.5)	10 (32.3)	0,788x
ASA 2	20 (64.5)	21 (67.7)	
Surgical region n (%)			
Mammae	20 (64.5)	20 (64.5)	0,621$
Colli	5 (16.1)	5 (16.1)	
Axilla	1 (3.2)	2 (6.5)	
Facialis	4 (12.9)	3 (9.7)	
Thorax	1 (3.2)	1 (3.2)	
GA tehchnique			
Intubation	21 (67.7)	20 (64.5)	0,783x
LMA	10 (32.3)	11 (35.5)	
Duration of surgery, mean ± SD, minutes	63.71 ± 11.03	67.58 ± 12.03	0,185$

Before the study began, a kappa test was conducted on 10 research assistants tasked with collecting NRS pain score data. The analysis results for the assessment of resting NRS pain obtained a Kappa value of 0.8628, and for moving NRS pain, it obtained a Kappa value of 0.8958. With Kappa values > 0.75, it can be concluded that the pain scale assessments by all research assistants showed excellent consistency or

agreement.

Table 2 below shows the results of data collection for resting and moving NRS pain scoresin Groups A and B. Based on the table, it is known that the resting NRS pain scores in Group A(preemptive ketamine) are lower and significantly different compared to Group B (control) at 0,½, 1, and 2 hours postoperatively (p<0.05). Meanwhile, at 6 and 12 hours, the resting NRS painscores in Group A are also lower than in Group B, but the difference is not significant (p>0.05). On the other hand, for the moving NRS pain scores, it can be seen that the scores in Group A (preemptive ketamine) are lower and significantly different compared to Group B (control) at allassessment times, namely 0, ½, 1, 2, 6, and 12 hours postoperatively (p<0.05).

Table 2. NRS scores at rest and during movement postoperatively in Groups A and B

NRS at rest	Group A		Group B		p	NRS movement	Group A		Group B		p
	Mean	SD	Mean	SD			Mean	SD	Mean	SD	
NRS diam 0	2.23	.56	4.26	1.91	<0,001*	NRS bergerak 0	2.74	.73	4.55	2.20	<0,001*
NRS diam 1/2	2.74	1.61	3.97	1.68	<0,001*	NRS bergerak ½	3.39	1.76	4.29	1.90	<0,034*
NRS diam 1	2.29	1.04	3.00	.97	<0,003*	NRS bergerak 1	2.74	1.26	3.35	1.20	<0,029*
NRS diam 2	1.87	.50	2.13	.34	<0,022*	NRS bergerak 2	2.19	.70	2.58	.62	<0,034*
NRS diam 6	1.16	.37	1.35	.49	0,084	NRS bergerak 6	1.55	.57	1.97	.71	<0,018*
NRS diam 12	1.00	.00	1.03	.18	0,317	NRS bergerak 12	1.10	.30	1.39	.50	< 0,008*

The number of subjects requiring intraoperative rescue fentanyl can be seen in Table 3,with a minimal count in each group of 3 (9.7%).

Table 3. Number of subjects receiving intraoperative rescue fentanyl

Kebutuhan rescue fentanyl intraoperatif	Kelompok A	Kelompok B
Subjects receiving rescue fentanyl, n (%)	3 (9.7)	3 (9.7)
Subjects not receiving rescue fentanyl, n (%)	28 (90.3)	28 (90.3)
Total subjects, n	31	31

Meanwhile, the number of subjects requiring postoperative rescue fentanyl can be seen in Table 4, which shows that the number of subjects receiving rescue in Group A is 10 (32.3%), which is fewer than in Group B, which is 15 (48.4%).

Table 4. Number of subjects receiving postoperative rescue fentanyl in groups A and B

Postoperative rescue fentanyl requirement	Group A	Group B
Subjects receiving rescue fentanyl, n (%)	10 (32.3)	15 (48.4)
Subjects not receiving rescue fentanyl, n (%)	21 (67.7)	16 (51.6)
Total subjects, n	31	31

Table 5 presents the analysis results of three variables regarding rescue fentanyl. From the table, it can be observed that there is no significant difference in both total intraoperative and postoperative rescue fentanyl between the two groups (p<0.05). However, for the onset of postoperative rescue fentanyl, a significant difference can be observed between the two groups (p<0.05). Group A (preemptive ketamine) is found to have a longer onset of rescue fentanyl compared to Group B (control).

Table 5. Comparison of total intraoperative rescue fentanyl, onset of postoperative rescue fentanyl, and total postoperative rescue fentanyl in groups A and B

Variable	Group A	Group B	P
Total intraoperative rescue of fentanyl.mean ± SD, mcg	2.42 ± 7.51	2.42± 7.51	1.00
Onset of postoperative rescue fentanyl requirement, mean ± SD, menit	11.91±2.17	6.40± 2.06	< 0.001
Total postoperative rescue fentanyl requirement,mean ± SD, mcg	74.19±109.45	114.52± 120.55	0,117

The incidence of side effects during the study is shown in Table 6 below. In this study, the side effects observed were nausea/vomiting and dizziness. Nausea/vomiting occurred in 2 (6.5%) subjects in Group A and in 1 (3.2%) subject in Group B. Complaints of dizziness occurredin 1 (3.2%) subject in both Group A and B. Hallucinations were not found in any subjects duringthis study.

Table 6. Incidence of postoperative side effects in groups A and B

Group	A		B	
	Jumlah	%	Jumlah	%
Nausea, vomiting	2	6.5	1	3.2
Dizziness	1	3.2	1	3.2
Hallucinations	0	0	0	0

Discussion

Table 1 presents the characteristic descriptions of the study samples in both groups, indicating no significant differences (p>0.05) in terms of age, gender, education, BMI, and duration of surgery. Consequently, both groups were considered homogeneous and comparable, allowing for any differences in outcomes to be attributed to variations in treatment.

The analysis of the comparison of total intraoperative rescue fentanyl revealed no significant difference between Group A (ketamine preemptive) and Group B (control). These findings contrast with the study conducted by Gumelar et al., 2021, which reported significant differences in the administration of fentanyl supplementation during surgery with qNOX score monitoring between the combination preemptive ketamine and fentanyl group and the single preemptive fentanyl analgesic group. The results also contradict those of Setiyawan, RB, 2021, who stated that preemptive ketamine administration significantly reduced the dose of fentanyl during surgery and extubation time compared to the control group.

The non-significant difference in the administration of intraoperative rescue fentanyl between Group A (ketamine preemptive) and Group B (control) in this study may be attributed to adequate administration of intraoperative analgesic regimens to prevent pain responses. In both groups, the same anesthesia procedure was administered, including intravenous fentanyl at a dose of 2 mcg/kgBB to facilitate airway device placement. This is consistent with Cummings and Naguib, MA, 2015, who stated that a dose of 2 mcg/kgBB IV fentanyl can provide analgesic effects and act as an adjuvant for inhalation anesthesia in suppressing responses to sudden changes in stimulation levels.[11]

In addition to fentanyl, subjects also received analgesic supplementation from nitrous oxide (N2O) gas. N2O gas is a potent analgesic that works by releasing endogenous opioids with actions similar to morphine. The administration of N2O may potentially address the painful stimuli during surgery, resulting in no significant difference in intraoperative rescue fentanyl between the two groups.

The analysis of the onset of postoperative rescue fentanyl requirements revealed a significant difference, with an average of 11.91 minutes in Group A and 6.40 minutes in Group B. This finding is consistent with the study by Raharjo and Budiono, 2009, which examined the effectiveness of preemptive ketamine on oncology postoperative pain at Kariadi Hospital, showing a significant difference in the first requirement for meperidine analgesia. The preemptive group required a longer time for meperidine analgesic demand compared to the control group.[6]

The result of the prolonged onset of rescue fentanyl requirement in the preemptive ketamine group may be caused by several factors, including, according to Xu, J., Li, H., Zheng, C., Wang, B., Shen, P., Xie, Z., and Qu, Y, 2019, ketamine as an NMDA antagonist can prevent central sensitization, thus reducing postoperative pain. Gottschalk and Smith, 2001, explain the timing of analgesic administration, stating that preemptive analgesic administration given before surgical incision can reduce postoperative pain hypersensitivity.[3,7]

Another factor affecting the prolonged onset of rescue fentanyl in the preemptive ketamine group is the result of ketamine metabolism, namely norketamine, which remains active with a potency of one-third to one-fifth of ketamine. Norketamine is also

known to persist for up to 5 hours after ketamine administration.[2]

Surgery causes tissue damage and results in pain. Inadequate analgesic administration can lead to patient harm, including inhibited mobilization, distress, and anxiety. This study's results show that preemptive ketamine administration significantly reduced pain scores at ½, 1, and 2 hours postoperatively compared to the control group, regardless of whether the pain was stationary or moving. Although there were no significant differences in pain scores between the preemptive ketamine and control groups at 6 and 12 hours, overall, both groups exhibited mild to moderate pain levels.

These findings are consistent with the studies by Behdad et al., 2011, and Satiyah et al., 2015, which stated that preemptive ketamine administration significantly reduced postoperative pain compared to the control group. These results also support ketamine's ability as an NMDA receptor antagonist in reducing postoperative pain, as described earlier, through the prevention of central sensitization and reduced hypersensitivity due to preemptive analgesic administration.[5,12]

Additionally, another factor contributing to ketamine's analgesic effect is its ability to work on nicotinic and muscarinic receptors. Ketamine blocks sodium channels in the human central and peripheral nervous systems and interacts with opioid receptors, μ, δ, and κ, and calcium channels. Ketamine also acts as a non-competitive antagonist at the phencyclidine site receptor complex in NMDA receptors. Low-dose ketamine can cause blockade of NMDA receptors in nociceptive input processing, resulting in non-competitive blockade. This indicates that ketamine may be "trapped" in receptor channels until the channels reopen after agonist activation.[12]

The total administration of postoperative fentanyl in this study showed no significant difference between group A and group B. This result differs from the studies by Behdad, A., Hosseinpour, M., and Khorasani, P. (2011) and Yang, L., Zhang, Z., Zhang, C., Zhao, D., and Li, J. (2014), which demonstrated a significant difference in postoperative opioid usage between the preemptive ketamine group and the control group.[12,13]

The differences in the NRS pain score at 6 and 12 hours and the total rescue fentanyl postoperatively, which were not significant, could be due to several factors that support the effectiveness of preemptive analgesia, including inadequate monitoring of anesthesia depth and insufficient analgesic adequacy. In this study, anesthesia depth monitoring was only based on clinical and hemodynamic parameters of the study subjects. Thus, the unstable depth of anesthesia might affect the mechanism of preemptive analgesics. Anesthesia depth monitoring would be more objective using specialized tools such as the bispectral index (BIS) or q-NOX score.

There were differences in the effects of preemptive ketamine on the NRS pain scores at rest and during movement. A significant difference between the preemptive ketamine group and the control group was observed only at 0, ½, 1, and 2 hours postoperatively for the NRS at rest, while a significant difference was observed at all measurement times, including 6 and 12 hours postoperatively, for the NRS during movement. This difference might be attributed to the distinct nature of noxious stimuli between the two types of NRS. According to Fullwood, Means, Merriwether, Chimenti, Ahluwalia, and Booker (2021), in movement-evoked pain (MEP), there are silent mechanonociceptors when there is tissue damage or acute inflammatory processes. Silent mechanonociceptors increase

hyperalgesia and individual responsiveness. This condition makes tissue or joint movements, which are normally not painful, also become painful stimuli.[14]

The additional stimulus from the movement of the painful site makes the effect of preemptive ketamine more evident in the preemptive ketamine group compared to the control group in the assessment of pain scores during movement, resulting in significance at all measurement times. Meanwhile, in the resting condition, as the wound healing process progresses, the painful stimulus becomes minimal and can be alleviated by the NSAID analgesics provided, so the pain response in both groups at 6 and 12 hours is minimal and not significantly different.

The assessment of side effects in this study found that 2 subjects in group A and 1 subject in group B experienced nausea and vomiting. Meanwhile, symptoms of dizziness were present in 1 subject each in group A and B. These results indicate minimal side effects in this study and no significant difference between the two groups. These findings are consistent with the study by Yang, L., Zhang, Z., Zhang, C., Zhao, D., and Li, J. (2014), which showed no significant difference in nausea and vomiting symptoms between the group receiving preemptive ketamine analgesia and the control group. Side effects of ketamine are reported to occur at higher doses, i.e., more than 2 mg/kg body weight.

Conclusion

1. Intravenous ketamine at a dose of 0.5 mg/kgBW is effective as preemptive analgesia with significantly lower and different NRS pain scores, both at rest and during movement, in the first 2 hours postoperatively compared to the control group ($p<0.05$).
2. There is no significant difference in NRS pain scores at rest at 6 and 12 hours between the ketamine and control groups ($p>0.05$). This could be influenced by the suboptimal monitoring of anesthesia depth during the intraoperative period.
3. Intravenous ketamine at a dose of 0.5 mg/kgBW has a longer and significantly different postoperative rescue fentanyl request time compared to the control group ($p<0.05$).
4. The total administration of postoperative rescue fentanyl between the two groups is not significantly different ($p>0.05$). This result may be because continuous fentanyl administration may not adequately reflect the difference between the two groups.
5. The occurrence of side effects in this study, both in the preemptive ketamine and control groups, was minimal and not significantly different. Nausea and vomiting were recorded in 2 subjects in the preemptive ketamine group and 1 subject in the control group, complaints of dizziness were recorded in 1 subject in each group, and no complaints of hallucinations were reported in either group.

Suggestion

1. Further research is needed using more objective anesthesia depth monitoring tools, such as the q- NOX score or BIS.
2. Pain score data collection should preferably be conducted in a dedicated room, so pain score assessments become stricter, and opioid rescue can be incrementally administered according to the predetermined pain score threshold for rescue

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