

The Effectiveness of Intraoperative Ketamine and Fentanyl as Preemptive Analgesia Assessed with qNOX Score

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ABSTRACT

Background: Inadequate management of intraoperative pain poses a risk of postoperative chronic pain complications. The use of preemptive analgesia before the onset of surgical incision stimulation was considered to prevent central sensitization. Clinical research around the terms of preemptive analgesia needs to be proven by nociception-based intraoperative monitoring. An objective modality with EEG guidance can provide information on noxious stimuli.

Objective: To determine the effectiveness of ketamine and fentanyl administration as preemptive analgesia measured by qNOX scores through the CONOX tool.

Methods: This study is a single-blinded randomized experiment with the division of two groups: control and treatment. The control group received preemptive fentanyl, and the treatment group received preemptive ketamine and fentanyl. Then the qNOX score was assessed during operation.

Result: The qNOX score of the treatment group in minute-15 and 30 was lower than the control group ($p = 0.007$; $p = 0.025$), while in the minute-90 it was higher than the control group ($p = 0.001$). The mean first 1-hour qNOX score was lower in the treatment group ($p < 0.001$), while in the second 1-hour was higher in the treatment group ($p = 0.003$). The mean total dose of fentanyl supplementation in the treatment group was lower than in the control group (71.3 ± 25.1 grams vs. 92.0 ± 28.3 grams; $p = 0.044$).

Conclusion: The administration of combined ketamine and fentanyl as preemptive analgesia is more effective in the first hour of surgery compared to single preemptive fentanyl measured by qNOX score. Preemptive ketamine and fentanyl decrease the total dose of intraoperative fentanyl supplementation compared with single-dose preemptive fentanyl administration.

Keywords: fentanyl; ketamine; pain management; preemptive analgesia; qNOX

INTRODUCTION

Inadequate management of intraoperative pain raises the risk of postoperative complications, and this is also associated with the incidence of chronic pain. One resolution is to use preemptive analgesia, which aims to provide analgesia before the onset of surgical incision stimulation, to prevent the process of central sensitization. Strong noxious stimuli can induce tissue damage and cause hypersensitivity, hyperalgesia, allodynia, and abnormal paresthesia.¹ Furthermore, the concept of preemptive analgesia can reduce the risk of acute pain progressing into chronic pain.²

Ketamine, a derivative of phencyclidine or known as CI-581, was first synthesized in the early 1960s as an anesthetic agent with unique properties because it has minimal effects on cardiorespiratory organs. Since 1980, investigations regarding the role of NMDA receptors in the pathophysiology of pain have begun to develop.³ A subanesthetic dose of ketamine of 0.3 mg/kg, functions as analgesia with minimal effects on awareness and cognition.² There is sufficient clinical evidence from previous studies regarding ketamine use in the management of perioperative pain. In Cochrane review, which examined 37 randomized controlled trial studies of surgery procedures in adults who received perioperative ketamine or placebo.⁴ Twenty-seven out of 37 studies showed a decrease in pain scores and analgesia needs. A subgroup of ten studies examining the use of 24-hour patient-controlled analgesia (PCA) with morphine showed a decrease in morphine consumption in 24 hours.⁴

Although not fully understood, the pathogenesis of hyperalgesia and opioid tolerance is associated with sensitization

to nociceptive stimuli.⁵ The concept of ketamine analgesia is due to blockade of NMDA receptors, which play an essential role in the nociception process in the spinal dorsal horn ganglia.⁴ Fentanyl is a synthetic opioid agonist that produces analgesic effects by binding to specific receptors which involved in transmitting and modulating pain. Biochemically, fentanyl acts selectively on μ -receptors but also potentially on other receptors such as delta and kappa.⁶ Ketamine potentiates the antinociceptive effect of fentanyl by not changing the sedation index. This potentiation suggests that ketamine can be combined with μ -opioid agonists to enhance its analgesic effect in the clinical setting.⁷

Monitoring nociception is still a challenge towards a more automated approach to analgesia and anesthesia. Also, nociception is different from the pain that it is not a subjective feeling but is a physiological code of the process of nociceptive stimulation. To date, some devices ensure a more accurate reflection of nociception monitoring than traditional assessments that just based on vital signs, such as blood pressure and heart rate.⁸

Conox, a non-invasive anesthetic depth monitor is designed to help anesthesiologists monitor the patient's brain activity and quickly identify how anesthetic affects the patient. This tool is the only monitor that measures both hypnotic and analgesic effects.⁸ This new monitor helps identify patient's awareness during anesthesia. This tool can avoid 'too deep' anesthesia, which can cause postoperative cognitive dysfunction (POCD).⁹ The Conox monitor is equipped with a nociception index, qNOX, an index that shows the probability of responding to noxious stimuli. Lower index values mean a lower likelihood of response to surgical

stimulation. The qNOX index is based on low and high-frequency EEGs to detect changes associated with surgical excitability.⁸

Clinical research around the terms of preemptive analgesia needs to be proven in intraoperative monitoring based on nociception monitoring. Objective modalities with electroencephalography (EEG) guidance can provide information on noxious stimulation so that adequate intraoperative pain management can prevent postoperative complications.

This study aims to determine the effectiveness of ketamine and fentanyl administration as preemptive analgesia and measured by qNOX scores through Conox.

METHOD

Study Design and Setting

This study was a single-blinded randomized control trial study approved by the ethics committee and research development of Dr. Soetomo General Hospital, Surabaya. Patients undergoing elective surgery that met the inclusion criteria were recruited in March and May 2020. Thirty patients were enrolled in this study. Written informed consent was obtained from the patient or appropriate relative in the study. In this study, we allocated the samples into 2 groups, labeled as group A (ketamine group) and group B (control group). Label A was determined as patients who received preemptive ketamine and fentanyl while label B was for patients who received single preemptive fentanyl. Group coding and randomization was done before dividing the samples into two groups. The treatment group code was unknown to the patient and data collection operator.

The code was stored by researchers only.

Participant Selection Criteria

The consented patients were enrolled in the study protocol with the following inclusion criteria: (1) Adult patients aged 21 to 60 year old; (2) Patients undergoing elective orthopedic surgery and non-cardiac surgery; (3) ASA Physical Status of I-II.

The simple random sampling was done among all patients who were prepared for elective surgery. Patient selection was made at the time of pre-surgical visit, and patients who met the inclusion criteria were determined as a sample. Each patient was given information for consent, and those who agreed were included in the study as subjects. The exclusion criteria were emergency cases, pregnant or nursing women, had a history of allergy to the anesthetic drugs, intracranial surgery, transplantation surgery, patient with a difficult airway, elective surgery with local anesthesia, the duration of the surgery more than 3 hours, history of arrhythmia, the patient under beta-blocker therapy with heart rate <50 bpm, cardiac insufficiency with left ventricular ejection fraction (LVEF) <40%, history of seizure or epilepsy, patients with obstructive sleep apnea (OSA), and hepatic insufficiency (prothrombin ratio <15%).

Exposure and Outcome

We performed anamnesis, physical examination, and additional tests for each patient during the preoperative visit. Patients fasted 6 hours of food and 3 hours of clear water before the surgery and were given a 30 ml / KgBB / 24-hour crystalloid fluid in the ward.

Before the anesthesia was carried out, standard monitoring of electrocardiography, automated non-invasive arterial blood pressure (NIABP) measurement, pulse oximetry, and Conox monitor were attached to the patient. Randomization was also performed before patients' baseline data were recorded. Each patient's baseline of heart rate, respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and SpO₂ were recorded.

Induction was done with a dosage of 1 µg/kg IV Fentanyl, a dosage of 1 – 2 mg/kg IV Propofol until the loss of eyelash reflex. To facilitate tracheal intubation, IV Rocuronium was given with a dosage of 0.8 mg/kg. We recorded the heart rate, arterial blood pressure, and mean arterial pressure during and after the intubation at the 0th, 1st, 3rd, 5th minutes. After the depth of anesthesia was achieved, we maintained it using a mixture of oxygen and air (50%) with 1 minimum alveolar concentration (MAC) of isoflurane. Thirty minutes before the incision, the ketamin group (group A) received an IV bolus of ketamine and fentanyl with a dosage of 0.3 mg/kg and 0.5 mcg/kg consecutively. Meanwhile, the control group (group B) received an IV bolus of 0.5 mcg/kg of fentanyl.

Intraoperatively, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), minimum alveolar concentration (MAC), and qNOX score values were recorded every 3 minutes. During surgery, titration of isoflurane was done; if there is no increase in pulse or blood pressure due to surgical stimulation within a 15-minute interval: MAC is reduced by 20%. Rescue

fentanyl of 0.5 mcg/kg was given to the patient if the qNOX score shown on the Conox monitor was >60. After the surgery, the muscle relaxant was antagonized with neostigmine. After these steps, isoflurane was discontinued, and patients ventilated with 100% oxygen at 8 l/min. The patients were then left undisturbed except for continuous verbal commands for their names to open eyes. The trachea was extubated once the patient achieved spontaneous regular respiration and followed simple commands. After extubation, we recorded the following parameters: hemodynamic parameters (HR, SBP, DBP, and MAP) before the patient left the operation theatre, the total fentanyl dose was given to the patient, and the duration of the operation.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (range) where appropriate, and categorical variables were expressed as the absolute number and proportions (%). The comparison between groups was analyzed with Student's t-test or Mann-Whitney test for continuous variables, while Chi-square test or Fisher's exact test was used to analyze categorical variables.

RESULT

30 from 32 samples were included in this single blind randomized study and grouped into control and treatment group. Two samples were excluded due to operating duration more than 180 minutes. Table 1 shows patients' demographic and preoperative clinical characteristics. There was no difference in sex, age, and body mass index (BMI) between control and treatment group (p=1.000, p=0.836, p=0.208). There was a difference in median of preoperative

respiratory rate between both group (p=0.013), but no difference in other preoperative clinical characteristic.

Median qNOX score in minute-15 and 30 was significantly lower in treatment group (p=0.007; p=0.025), however it was significantly higher in treatment group in minute-90 (p=0.001) (Table 2) (Figure 1) In treatment group, average qNOX score in first one hour was significantly lower (p<0.001), but in second one hour was significantly higher (p=0.003) (Table 3). All samples (100%) in control group were given fentanyl supplementation in one hour after

incision, meanwhile in treatment group was only 33.3% (p<0.001) (Table 4).

The baseline fentanyl dose in the control group was higher but not significantly different (p = 0.162). The frequency of fentanyl supplementation when qNOX> 60 during surgery in the two groups was also not significantly different (p = 0.714). However, there was a significant difference in the total dose of fentanyl supplementation during surgery in the two groups (p = 0.044). The mean total dose of fentanyl supplementation in the treatment group was 71.3 ± 25.1 g, lower than the control group, namely 92.0 ± 28.3 g (Table 4).

Table 1. Patients' demographic and preoperative clinical characteristics

	Control (n=15)	Treatment (n=15)	P value
Demographic			
Sex, male (n, %)	9 (60.0%)	8 (53.3%)	1.000*
Age (years)	40.73 ± 14.29	41.87 ± 15.42	0.836**
Body mass index	26.54 ± 2.12	25.53 ± 2.17	0.208**
Preoperative clinical characteristics			
Systolic blood pressure (mmHg)	125.07 ± 8.14	127.47 ± 7.50	0.408**
Diastolic blood pressure (mmHg)	71.80 ± 5.29	72.73 ± 5.28	0.633**
Mean arterial pressure (mmHg)	107.31 ± 6.64	109.22 ± 6.51	0.433**
Heart rate (beats/min)	84.73 ± 5.30	83.53 ± 4.56	0.512**
SpO2 (%)	97 (97-98)	97 (97-98)	0.264***
Respiratory rate (x/min)	18 (16-18)	16 (15-18)	0.013***
PS-ASA (I/II) (n)	8/7	8/7	1.000*
Operating time (minutes)	155 (75-175)	165 (60-175)	0.368***

Date are expressed as mean ± standard deviation or median (range)

*Chi square test

**Unpaired two tailed-t test

***Mann-Whitney test

Table 2. qNOX score every 15 minutes after incision

qNOX score	Control	Treatment	P value
15"	62 (38-65)	43.5 (38-65)	0.007*
30"	46 (44-63)	44 (42-47)	0.025*
45"	52 (43-65)	48 (44-56)	0.110*
60"	58 (48-65)	55 (46-67)	0.759*
75"	54.5 (46-64)	62 (50-65)	0.051*
90"	52 (42-62)	62 (50-65)	0.001*
105"	54.5 (48-58)	58 (49-64)	0.053*

*Mann-Whitney test

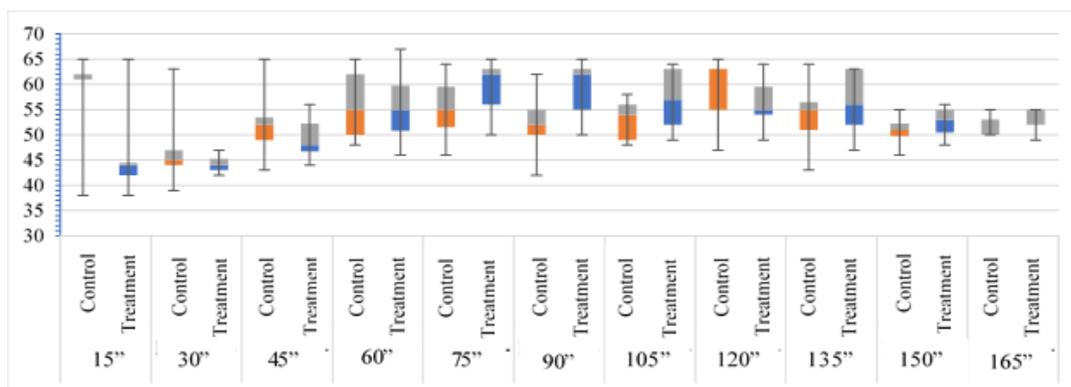


Figure 1. Boxplot diagram for qNOX score

Table 3. qNOX score average in 1st and 2nd one hour

qNOX score average	Control	Treatment	P value
First one hour	55 (48-57)	49 (44-53)	<0.001*
Second one hour	56 (45-60)	59 (54-61)	0.003*

*Mann-Whitney test

Table 4. Fentanyl supplementation

	Control	Treatment	P value
Fentanyl supplementation in one hour after incision (n, %)	15 (100%)	5 (33.3%)	<0.001*
Early dose (mcg)	150 (110-160)	130 (110-160)	0.162**
Frequency (times)	3 (1-3)	3 (0-3)	0.714**
Total dose (mcg)	92.0 ± 28.3	71.3 ± 25.1	0.044***

Date are expressed as mean ± standard deviation or median (range)

*Chi-square test

**Mann whitney test

***Independent T test

DISCUSSION

Perioperative pain is a major problem in patients undergoing surgery. Multimodal strategies are used to treat pain, primarily involving opioids and NSAID (non-steroidal anti-inflammatory drugs). NMDA receptors have an essential role in the sensitization and plasticity of the central nervous system after receiving nociceptive impulses.¹⁰ Increased activation of NMDA receptors plays a role in inflammatory and neuropathic pain that causes secondary hyperalgesia activation and exacerbation. This condition initiates translational changes from second-order neurons that may be

related to the pathogenesis of chronic pain. Analgesic interventions before the noxious stimulus, particularly preemptive analgesia, can block sensitization, thereby reducing acute pain. Although many drugs have demonstrated the benefits of preemptive analgesia, therapies that prevent the development of central excitability have great benefits.¹¹

Ketamine is an NMDA receptor antagonist and works by modulating central sensory pain processes. Research in animals and humans shows that ketamine is a potent anti-hyperalgesia agent. Ketamine can neutralize opioid-

induced hyperalgesia and prevent opioid tolerance.¹² Ketamine is an adjuvant that is useful for reducing the analgesic dose needed and reducing side effects such as nausea, dizziness, and sedation effects. This makes ketamine attractive as one of the multimodal strategies for overcoming pain.¹⁰

In this study, the qNOX score in the treatment group was significantly lower than the control group in the 15th and 30th minutes. The mean qNOX score in the first 1 hour was also significantly lower in the treatment group. This result shows that the treatment group's probability of responding to a dangerous stimulus (noxious) was lower than the control group, which means the effect of analgesia in the treatment group was better than the control group.

In this study, the qNOX score at the 90th minute in the treatment group was higher than the control group, and in the second hour, the average qNOX score in the treatment group was significantly higher. This result can be explained by the method of ketamine administration used in this study. In this study, we administered ketamine by intravenous bolus before the incision was made. Although several studies stated the administration of preemptive bolus ketamine provides analgesia to postoperative effects, several other studies mention the effectiveness of continuous low dose ketamine administration throughout the operation. Study by Miziara et al. showed that S(+)-ketamine infusion in laparoscopic cholecystectomy resulted in better postoperative pain control than the placebo group.¹⁷ Therefore, injection of a single dose of ketamine, which acts short-acting both before and after the incision, will not produce analgesia that

lasts long into the postoperative period. Besides, setting a constant serum concentration is also needed to achieve the required analgesia effect. Analysis of serum ketamine concentrations by Tucker et al. suggests that manual infusion may not always reach the required level of stability; thus, ketamine must be carefully controlled. Dosage regulation is essential in avoiding the side effects of ketamine, ensuring adequate NMDA receptor antagonism, and potentiation of analgesia resulting from the combination of ketamine with fentanyl.⁷

In a study by Jensen, an increase in qCON / qNOX indicates a response to a dangerous stimulus. Besides, there was a significant difference in qNOX before and after stimulation, and the movers' group had higher qNOX values after stimulation than the non-movers group, which indicated that this movement was associated with mild analgesia.¹³ Both the qCON and qNOX indices can detect movements in response to a noxious stimulus, even though the response in qNOX appears to be higher than qCON. This discrepancy is probably because the increase in qNOX is a direct effect of EEG on noxious stimulus, while the increase in qCON is a secondary result of the effect of awakening due to noxious stimulus.¹³

There have not been previous studies analyzing the effectiveness of ketamine administration as preemptive analgesia assessed by the qNOX score. However, research on the analgesic effect of a combination of fentanyl and ketamine by Tucker et al. in 10 healthy individuals explained an increase in pain threshold when fentanyl was combined with ketamine compared to when each drug was given individually. These results indicate that the administration of

ketamine can increase the antinociceptive effect of fentanyl. Also, additional low-dose ketamine has an analgesic effect that does not increase the effects of sedation.⁷ Previous study by Singh et al. showed that intravenous administration of low-dose ketamine before a surgical incision had a preemptive effect on postoperative pain and decreased analgesic requirements 24 hours after laparoscopic cholecystectomy surgery. The study also assessed visual analog scale (VAS) and verbal rating scale (VRS), and the results showed that the control group that received normal saline had higher VAS and VRS values, which meant the group that got preemptive ketamine experienced less pain than the group control.¹¹ Other studies have shown VAS values in the ketamine group to be lower than in the control group. These results also explain that the administration of low-dose ketamine has a preemptive analgesic effect on postoperative pain in patients undergoing appendectomy.¹¹ Studies in laparoscopic gynecological surgery compared pre-incision and postoperative ketamine addition with results showing that pre-incision ketamine statistically decreases PACU pain scores and oral opioid and analgesic consumption 1 week postoperatively.¹⁴

The central sensitization of chronic pain occurs due to secondary hyperalgesia caused by a very painful stimulus at the dorsal horn level. An increase in the receptive field of the dorsal horn neurons prolongs the stimulus. Moreover, when the stimulus is repeated, a temporal summation will occur with the subsequent stimulus causing a higher progressive response. This increased effect causes changes in

local gene expression and second messenger concentrations, ultimately causing long-lasting pain effects. NMDA is known to play a role in this mechanism, so the prevention of central sensitization is based on preemptive analgesia. If analgesia is administered before the noxious stimulus is given, then the nociceptive stimulus will not be transmitted to the dorsal horn, so that central changes can be prevented and produce lighter and shorter pains.¹⁵

Another study by Hong et al. in patients undergoing rotator cuff repair surgical arthroscopy said there were no differences in the numeric rating scale (NRS) between the ketamine groups. It was concluded that the administration of preemptive ketamine did not reduce postoperative pain or fentanyl consumption. Hong *et al.* mentioned that preemptive ketamine might depend on the intensity of the surgical pain and explained that the surgical procedure of shoulder arthroscopy has an intense noxious stimulus during and after surgery. Besides, the factor of an inadequate dose of ketamine may also contribute to these different results, but in his study, it was stated that the dose used was quite large at 0.5 mg/kg compared to other studies, so it is necessary to conduct further research related to the dose of ketamine optimal in painful surgeries.¹⁶

Another study also showed the results of a group receiving 0.5 mg/kg ketamine bolus and continued 0.25 mg/kg/hour continuous doses requiring less patient-controlled analgesia (PCA) less residual pain, and smaller areas of hyperalgesia at six months of follow-up.¹⁸ Of the various ketamine administration methods, continuous infusion of ketamine is beneficial in major surgeries that require large doses of opiate after

surgery, such as abdominal and thoracic procedures.⁸ Himmelseher and Durieux explain to prevent pathological pain; ketamine must be administered not only at the beginning of traumatic stimuli but during on-going surgery due to high-intensity noxious stimulus and inflammatory stimulation that take place during and even after surgery. This method is done to reduce central sensitization and peripheral pain pathways so that adequate administration of ketamine is a critical component in preventing pain.¹⁹

Fentanyl is often used as rescue analgesia because of its high-potential and short-acting nature so that it can be used repeatedly without causing an assessment of the drug's efficacy to be biased. Our study showed a significant difference of fentanyl supplementation within 1 hour of the incision between the ketamine and the control group. All samples in the control group received fentanyl supplementation, while only 33.3% of patients in the ketamine group. These results are in accordance with a study by Al-Maxoud Yousef and Mostafa (2013),²⁰ in patients undergoing thyroid surgery with bilateral superficial cervical plexus block (BSCP). In their study, the ketamine group (bupivacaine + ketamine) showed significantly lower intraoperative fentanyl supplementation compared to the control group (bupivacaine + normal saline) which was $40 \pm 10.5 \mu\text{g}$ vs. $90 \pm 25.5 \mu\text{g}$. The need for additional 24-hour postoperative acetaminophen was lower in the ketamine group than in the control group. Another study by Helmy et al. (2014),²¹ in pregnant women undergoing C-section under general anesthesia showed that the administration of low-dose pre-induced ketamine could reduce the need for

intraoperative fentanyl and reduce pain score 12 hours postoperatively. Another study showed no difference in the consumption of fentanyl as rescue analgesia in patients undergoing rotator cuff repair surgery between the ketamine and control groups. This discrepancy can be caused by the masked preemptive effect of ketamine by intraarticular local anesthetic injection procedures so that the difference in the use of fentanyl supplementation was not visible.¹⁶

Ketamine is known to act by blocking the supraspinal of the NMDA subunit NR2B, which has an antinociceptive effect. Moreover, ketamine also acts on the delta-opioid receptor (δ) and improves the function of your opioid receptor (μ). The interaction of ketamine with mu and delta and receptors is known to have a central antinociceptive effect. Ketamine can change the response of antinociceptive, and its analgesic effect is not influenced by naloxone, which can oppose the primary mechanism of opioids. Fentanyl itself is a receptor agonist (μ), and its analgesic properties are 100 times more potent than morphine.¹² Research by Gupta *et al.*,²² showed a synergistic effect of ketamine on selective morphine/fentanyl signaling through the ERK1/2 pathway, and ketamine was more effective in potentiating ERK1/2 phosphorylation at lower doses of opioid agonists. Synergistic interactions between the two drugs exist when the benefits of the two drugs' combined effects are higher than the effects produced when each drug is given. The ability of ketamine to increase the duration of opioid-induced analgesia explains that ketamine can modulate opioid signaling so that opioid receptors remain active for a long time. This effect can be achieved by influencing the

desensitization and resensitization time of the opioid receptor signaling so that the addition of ketamine can provide benefits in the form of prolongation of analgesia and antinociceptive effects. Preemptive ketamine as a control for postoperative pain is currently being used, although its use is still controversial. There were consensus and disagreement regarding the use of preemptive ketamine with different recommended dosages and routes of administration (intravenous or epidural), as well as different adequate perioperative times (during induction of anesthesia or upon awakening).²³

This study still has several limitations. The patients were sampled from a single health center so that it did not cover the more general population and can be biased in selecting samples. No further investigation was carried out on other confounding factors that influenced the qNOX score. The duration of some samples' operation was less than 2 hours, so the qNOX score at the third hour cannot be compared.

CONCLUSION

The administration of combined ketamine and fentanyl is effective as preemptive analgesia in the first hour of surgery compared to single preemptive fentanyl measured by qNOX score. Preemptive ketamine and fentanyl decrease the total dose of intraoperative fentanyl supplementation compared with single-dose preemptive fentanyl administration.

However, a significantly higher qNox score in the second 1 hour period is also a cause for concern. So that, using fentanyl alone can be a reasonable option. The underlying mechanism is

not yet clear, leading to the need for further research.

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