

Original Article

EFFECTIVITY COMPARISON OF KETAMINE AND MORPHINE AS POST-OPERATIVE ANALGESIC IN SPINAL SURGERYNenden Suliadiana Fajarini¹, Nancy Margarita Rehatta², Arie Utariani^{2a}¹ Resident of Department of Anesthesiology and Reanimation, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Academy Hospital Surabaya² Consultant of Department of Anesthesiology and Reanimation, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Academy Hospital Surabaya^a Corresponding author: arieutariani1995@gmail.com**ABSTRACT**

Introduction: Patients who undergo spinal procedure, experience the post-operative pain as the major problem. From the Visual Analog Scale (VAS), patients scale their pain around 8. An inadequate pain management could fasten the healing process and reduce patient life quality. Opioid group as the gold standard still inflicts several problems, such as respiratory depression. Moreover, the combination NSAID and opioid which used to suppress the side effect, still burden the healthcare cost. In a research of analgesic, through the discovery of N-Methyl D Aspartate receptor, researchers found an explanation of the ketamine effect in relieve chronic and intense pain which safer and cheaper. **Method and Material:** This research using single blind randomized control trial. Comparing 0.25mg/kg ketamine IV followed by ketamine 0,1mg/kg/h for the intervention group and 0.02mg/kg/h of morphine for the control group to manage the first 24 hours pain sensation. If patient VAS was more than 4, patient would get additional 0.5mg/kg ketamine (intervention group) and 25µg fentanyl (control group). **Result and Discussion:** From 17 patients each groups, the VAS values were better in control group rather than on intervention group. Low dose ketamine can't be compared with morphine to manage post spinal procedure pain. There were no hemodynamic changes, respiratory rate depression, loss of consciousness and hallucination, nystagmus, vomiting and hyper salivation. Even though 11.8% of the subject were nausea. The morphine group tends to experience hemodynamic changes and loss of consciousness in the first 12 hours but still within normal range. In the control group, 47.1 % patients were having nausea in the first hour, but only 17.6% of them who actually vomited. **Conclusion:** The analgesic effect of morphine is higher than ketamine, but the amount effect of ketamine is lower than morphine so that ketamine is more effective and safer given in the room.

Keywords: Post Spinal Procedure Pain; VAS; Low Dose Ketamine; Morphine**ABSTRAK**

Pendahuluan: Pasien yang menjalani operasi tulang belakang, sering kali mengeluhkan nyeri pasca-operasi sebagai masalah utama. Berdasarkan Visual Analog Scale, pasien mengaku nyeri yang dirasakannya berada pada skala 8. Penanganan nyeri yang tidak adekuat yang dapat mengganggu penyembuhan nyeri dan menurunkan kualitas hidup pasien. Gold standard dari pereda nyeri yakni opioid masih menimbulkan beberapa masalah, seperti distress napas. Lebih lanjut lagi, kombinasi dari NSAID dan opioid untuk menurunkan efek samping pada dampak kenaikan biaya perawatan pasien. Dalam sebuah penelitian analgesic, melalui penemuan reseptor N-Methyl D Aspartate, menjelaskan bahwa ketamine dapat meredakan nyeri kronis dan berat dengan biaya yang lebih rendah dan efek samping yang minimal. **Metode dan Bahan:** Penelitian ini merupakan penelitian eksperimen yang menggunakan single blind randomized trial yang bertujuan untuk membandingkan manfaat ketamin IV 0,25mg/kg yang dilanjutkan dengan ketamin 0,1mg/kg/jam untuk kelompok perlakuan dan 0,02mg/kg/jam morfin pada grup kontrol untuk mengatasi nyeri 24 jam pertama. Jika pasien mengeluh VAS>4, pasien mendapatkan tambahan 0.5mg/kg ketamine untuk grup coba dan 25µg fentanyl untuk grup kontrol. **Hasil dan Pembahasan:** Jumlah sampel yang didapatkan untuk masing - masing kelompok ada 17 orang, dimana VAS pada kelompok perlakuan lebih tinggi dibandingkan pada kelompok kontrol. VAS kelompok perlakuan lebih tinggi dari kelompok kontrol Pada kelompok ketamin tidak didapatkan perubahan pada hemodinamik, seperti frekuensi napas, penurunan kesadaran, halusinasi, nystagmus, muntah dan hipersalivasi. Salah satu keluhan yang sering timbul adalah mual (11.8%). Hal yang berbeda dijumpai pada kelompok morfin dimana ditemukan kecenderungan penurunan hemodinamik, disertai penurunan kesadaran dan frekuensi napas. Kejadian mual pada hampir 24 jam pertama tertinggi pada jam ke-1 47.1% dan muntah 17.6%. **Kesimpulan:** Efek Analgetik Morfin lebih tinggi dibandingkan

Ketamin, sedangkan jumlah efek samping ketamine lebih rendah dari morfin sehingga ketamine lebih efektif dan aman diberikan diruangan.

Kata kunci: Nyeri Pasca Operasi Tulang Belakang; VAS; Ketamin Dosis Rendah; Morfin.

INTRODUCTION

Pain is one of the most frequently complained by patient who have performed spinal surgery. This is supported by data that show more than 50% of patients complain of pain after surgery as their major problem. (1), the inadequate pain management will disrupt the healing process due to the activation of endocrine stress response resulting in increase in sympathetic tone and catabolic hormone. The inhibited healing process results in an increase of patient's hospitalization duration, affect mental status, and reduce the quality of life of the patient. (2)

Post spinal operative pain includes moderate to severe pain indicated by a VAS scale of more than 7. Post discectomy, patients often complain the severe pain (with VAS scale of 8). (3) This pain due to incisional pain from the skin to the bones and also the pain arise from nerve lesions. (4) Chronic pain is also felt by 80% who undergone elective lumbar puncture and received opioid drugs. The damage of nerve fibers due to spinal surgery also cause neuropathic pain that can cause interference to the somatosensory system. (5)

In 2012, 131 cases of elective spinal surgery had been carried out at Dr. Soetomo General Academic Hospital Surabaya. The most common cause of spinal surgery is fracture both trauma and non-trauma (spondylitis TB, malignancy, and idiopathic). The combination of ketorolac and tramadol is often used to relieve pain on a VAS scale of 4 – 6. On the other hand, a combination of 1 mg/hour of morphine and ketorolac can reduce pain to VAS 3. (6) This proves that analgesic

administration has not been able to completely eliminate the post-spinal surgery pain. Provision of rapid and adequate analgesics is needed to accelerate the healing process and reduce the number of diabetic ulcers caused by long time immobilization.

Nowadays, opioids are the gold standard therapeutic given to deal with acute and chronic pain. One of the opioid drugs that is often given is morphine. Morphine is a prototype of an endogenous opioid hormone that can bind with endogenous opioid receptor and cause the effects of respiratory depression, nausea, vomiting, indigestion, urinary retention, allergies, and risk of tolerance. The existence of serious side effects caused by opioid group cause the use of opioid requires strict observation. Analgesic effects can also be obtained from NSAID group. Side effects that caused by NSAID are disorders of gastrointestinal system, decreased kidney function, and affect the platelet aggregation process. (5)

N-Methyl D Aspartate (NMDA) receptors also play role in causing pain. Pain causes the excitement of glutamic acid to form NMDA-glutamic complex bonds. This complex contributes to the increasing of the intensity and amplitude of pain felt. These NMDA receptors are spread from the peripheral nerves to the central nervous system. (7)

Ketamine, the non-competitive inhibitor of glutamate will inhibit the formation of NMDA-glutamate complex bonds by binding to NMDA receptors through the binding of phencyclidine side (PSP). This complex will inhibit the excitation of pain and reduce the secretion of glutamate. (8) Ketamine giving

can be done through subcutaneous injection, intravenous injection, intramuscular injection, and intrathecal injection without the effect of respiratory depression. As an analgesic, ketamine can be given intravenously or subcutaneously at a dose of 0.2 – 0.5 mg/kg followed by intravenous administration of 0.05 – 0.2 mg/kg/hour as a maintenance dose. (9) Therefore, the use of ketamine can reduce the need of morphine, resulting in preventable side effect and tolerance of morphine.

METHOD AND MATERIAL

This study used a single blind randomized trial control. Held in the Surgical Center Building and Aster Ward (UPI A) Dr. Soetomo General Academic Hospital in September – October 2012. Patients who met the inclusion criteria were divided into 2 groups: the test group and the control group. The inclusion criteria are the patients have PS (Physical Status) 1 and 2, aged 15 to 55 years old, have normal BMI, elective surgery with non-trauma case. The population came from patients who were indicated for spinal surgery in September – October 2012. The test group was treated using IV ketamine at a dose of 0.25mg/kg followed by administration of 0.1mg/kg/hour, while the control group received morphine 0.02mg/kg/hour. The minimum population size is 16 patients for each group. The sample size was determined using unpaired analytical and numeric sampling formulas.

Pain scale assessed with VAS and has been conducted every 3 hours after the drug administered (3rd, 6th, 9th, 12th, 15th, 18th, and 24th hour). In addition, the hemodynamic monitoring including respiration rate, blood pressure, heart rate, and consciousness were also documented. After administering the analgesics, the side effect was also assessed at 1st and 15th minute, 1st, 3rd, 6th, 9th, 12th, 15th,

18th, and 24th hour. During the observation period, if the pain was obtained the VAS scale of 3, the patient will receive and additional analgesics using intravenous fentanyl at a dose of 25mg for the control group and ketamine 0.5mg/kg for the test group.

Patients' data were recorded including the age, sex, weight, type of surgery, and the duration of surgery. The normality of the data was tested using Kolmogorov-Smirnov sample. To compare the level of sedation and VAS in two groups, a statistical analysis was performed with the independent sample T-test if samples were normally distributed or the Mann-Whitney U test if the sample distribution was not normal.

RESULT AND DISCUSSION

From the study, there were 34 patients fulfilled the sample criteria at RSUD Dr. Soetomo and were randomized and divided into 2 groups; test and control group.

From 34 patients, the average age of patients given ketamine was 42.6 years old and 40.2 years old for patients given morphine. The average patient body weight was 58kg for the test group and 51.2kg for the control group. The normality of age and weight data was tested statistically using Kolmogorov-Smirnov test and founded the insignificant data in each group ($p > 0.05$). Chi square test was performed to analyze the homogeneity in sex and the type of surgery and showed there was not significant in both groups ($p > 0.05$). The duration of surgery in the ketamine group was 177.4 minutes and morphine group 224.1 minutes. The Kolmogorov-Smirnov test was found to be significant in both groups with $p < 0.05$.

Sedation Level

The sedation levels were evaluated using the Ramsay Sedation Scale (RSS) and analyzed using the Mann-Whitney U test.

The assessment of sedation scale in patients given ketamine shows a faster response to the stimulus. In the third observation period, there was a decrease of 1 point on the RSS scale. In addition, on 24th hour after surgery, found that the consciousness and cooperative improvement in the group of patients who received ketamine. On the other hand, in the morphine group, the patient was cooperative on 5th hour post drugs administration and the consciousness continually improved on 6th to 18th hour. The patient seemed more sensitive and anxious, but calmed down after 21st hour. Based on the results of statistical analysis, found a significant difference in the first hour and 9th to 18th hour after surgery with $p < 0.05$. However, there was no significant difference at 3rd to 6th hour and 21st to 24th hour of observational time.

Table 1. The differences in Ramsay Sedation Scale (RSS) in the two groups

Observational time	Ketamine (n=17)	Morphine (n=17)	P value
post operation	3(2-4)	2(1-4)	0.001**
1 st	3(2-4)	2(1-4)	<0.0001**
3 rd	2(2-3)	2(1-4)	0.601*
6 th	2(1-3)	2(1-3)	0.211**
9 th	2(2-3)	3(1-4)	0.031**
12 th	2(2-3)	3(1-3)	0.073*
15 th	2(1-3)	3(1-3)	0.009**
18 th	2(2-3)	3(1-4)	0.027**
21 st	2(2-3)	2(1-3)	0.107*
24 th	2(1-3)	2(1-3)	0.491*

Note: Mann-Whitney U test

*= not significant ($p > 0.05$)

**=significant ($p < 0.05$)

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Visual Analog Scale

The comparison of Visual Analog Scale between the two groups was analyzed using the Mann-Whitney U test. This method was chosen because of the characteristic of the data.

Table 2. The Visual Analog Scale (VAS) observation in the Ketamine and Morphine groups.

Observational time	Ketamine (n=17)	Morphine (n=17)	P value
post operation	3(2-5)	2(0-3)	0.010**
1 st	3(1-5)	2(0-3)	0.044**
3 rd	2(1-4)	1(0-3)	0.030**
6 th	2(1-5)	1(0-3)	0.012**
9 th	2(1-5)	1(0-3)	<0.0001**
12 th	2(1-5)	0(0-1)	<0.0001**
15 th	2(0-3)	1(0-1)	<0.0001**
18 th	2(0-4)	0(0-1)	<0.0001**
21 st	2(0-3)	1(0-2)	0.003**
24 th	1(0-3)	1(0-1)	0.001**

Note: Mann-Whitney U test

*= not significant ($p > 0.05$)

**=significant ($p < 0.05$)

From the test group, the mean VAS at the first hour was on a scale of 3. In patients with a VAS > 4 received additional analgesics. On the other hand, in the control group with morphine, a lower VAS was obtained from the first hour (VAS < 2) and continued to improve in 3rd hour after the spinal surgery. VAS analysis between the ketamine and morphine groups showed significant differences ($p < 0.05$) at all hours of observation

a. The Effect of Giving Ketamine and Morphine on Respiration

The side effects between the ketamine and the morphine group were analyzed using the Independence T test. Observation of the respiratory rate is needed to monitor the side effects of the drug. After 24 hours of observation, data were obtained that between the ketamine and morphine groups were found to be significantly different at the 12th, 15th, and 24th hour observations. The respiratory rate on morphine administration tended to slow down from the 12th hour but was still in the normal range. Meanwhile, the respiratory rate of ketamine group remained in the normal range.

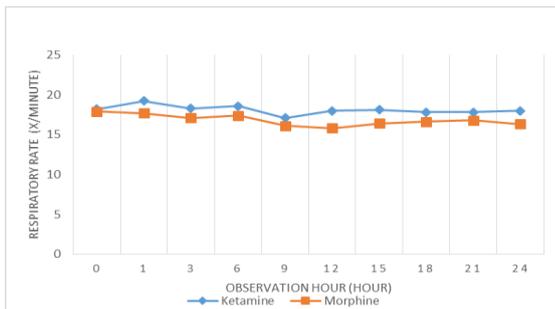


Figure 1. Respiratory rate during 24 hours of observation after ketamine and morphine administration.

b. The Effect of Ketamine and Morphine Administration on Hemodynamics

Ketamine and morphine have been known to have effects on hemodynamics. Blood pressure (systole and diastole), heart rate, and mean arterial pressure for 24 hours were recorded.

The mean systolic pressure in the ketamine group before surgery was 130mmHg and decreased to 120mmHg. In the morphine group the decrease in systolic pressure occurred significantly at 9th hour from 120mmHg to 100mmHg. Based on the results of statistical analysis on both drugs, there were no significant systolic changes. The results of systolic analysis did not show significant differences between the two groups at 9th, 21st, and 24th hour. However, there were

statistically significant differences at 12th, 15th, and 18th hour of observation.

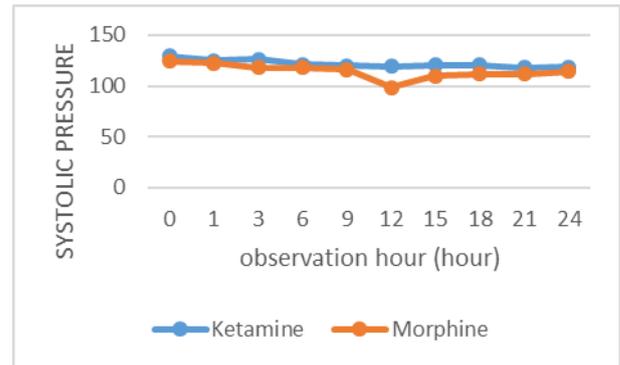


Figure 2. The changes in systolic blood pressure during 24 hours observations on ketamine and morphine administration.

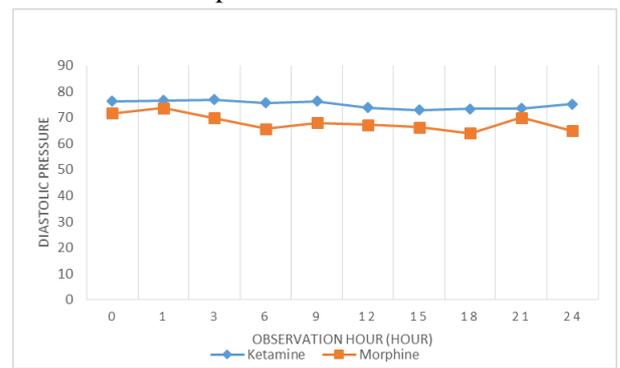


Figure 3. The diastolic changes during 24 hours of observation on the ketamine and morphine administration.

The 24-hour diastolic changes observation showed significant differences at the 3rd, 6th, 9th, 18th, and 24th hour between the ketamine and morphine groups (p<0.05). Similar diastolic pressures were obtained at all hours of observation. The diastolic of morphine group was the highest at 1st hour and lowest at 18th hour of observation. All diastolic values were within normal range (60-90mmHg).

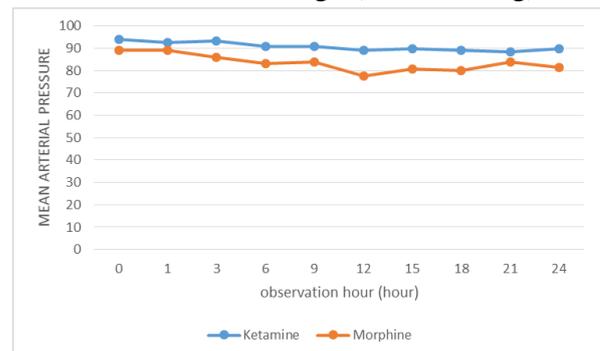


Figure 4. Mean Arterial Pressure during 24 hours of observation on ketamine and morphine administration.

There were two significant differences obtained at the 18th hour of observation (p=0.004) and the 24th hour (p=0.003). All observations in the ketamine group showed a mean arterial pressure of more than 80mmHg. Meanwhile, the administration of morphine caused a decrease in MAP below 80mmHg at the 12th hour of observation. Mean arterial pressure in the ketamine group tended to be higher than in the morphine group.

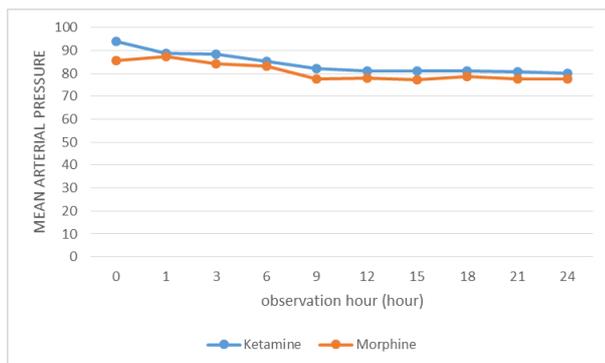


Figure 5. The average heart rate changes in the ketamine and morphine administration.

Heart rate at 24 hours of observation showed no significant difference between administration of ketamine and morphine. The highest heart rate in the ketamine group was 88x/minute, which gradually slowed down to 80x/minute at 24th hour postoperative. The highest heart rate in the morphine group at initial observation was 85x/minute which gradually slowed down to 79x/minute. The ketamine group tended to have higher heart rate than the morphine group.

c. Nausea

The incidence of nausea in both groups was analyzed using the chi square test. A significant difference was obtained at 0 hour (p<0.05). In other observations, no significant difference was obtained. Patients who received ketamine felt nauseous at the 1st and 3rd hour as much as 11.8% of the total patients. Morphine induce nausea in 8 patients (47.1%) at 0 and 1st observational hour. Complaints of nausea gradually decreased after the 3rd to 24th

hour of observation. However, patients who received morphine did not complain for nausea started at 15th to 24th hour.

Table 3. The occurrence of nausea within 24 hours of observation

Observational time	Ketamine (n=17)	Morphine (n=17)	P value
post operation	0	8 (47.1%)	0.003**
1 st	2 (11.8%)	8 (47.1%)	0.057*
3 rd	2(11.8%)	3(17.6%)	1.000*
6 th	0	4(23.5%)	0.103*
9 th	0	3(17.6%)	0.227*
12 th	0	1(5.9%)	1.000*
15 th	0	0	0
18 th	0	1(5.9%)	1.000*
21 st	0	1(5.9%)	1.000*
24 th	0	0	0

Note: chi square test

*= significant (p>0.05)

**= not significant (p<0.05)

d. Vomiting

Vomiting was only found in the morphine group at 0 and 1st observation hour, in 3 patients. After 9 o'clock, no more complaints of vomiting were found.

Table 4. The occurrence of vomiting within 24 hours of observation

Observational time	Ketamine (n=17)	Morphine (n=17)	P value
post operation	0	3(17.6%)	0.227*
1 st	0	3(17.6%)	0.227*
3 rd	0	0	0
6 th	0	2(11.8%)	0.485*
9 th	0	1(5.9%)	1.000*
12 th	0	0	0
15 th	0	0	0
18 th	0	0	0
21 st	0	0	0
24 th	0	0	0

Note: chi square test

*= significant (p>0.05)

**= not significant (p<0.05)

e. Hyper-salivation

The ketamine administration can cause hyper-salivation. Even though, during the observational time, the incidence of hyper-salivation was not found.

f. Nystagmus and hallucination

The psycho-mimetic effect of ketamine is hallucinations and visual distortion (nystagmus). In this study, these effects were not obtained at all hours of observation.

Morphine is an effective and powerful analgesic for dealing with visceral and somatic pain. (3) On the other hand, giving bolus morphine 0.15mg/kg can cause sedation effects. (10) Administering a maintenance dose of 0.02mg/kg/hour can reduce pain to VAS 0 within 24 hours after a spinal procedure. (11) In continued administration, the effects of analgesia and sedation can be extended due to the formation of morphine glucuronate which is known as an active metabolite product. Prolonged effect of analgesia and sedation can last up to 8 hours of surgery. (2)

Ketamine works by inhibiting glutamate at the NMDA receptor through the phencyclidine side. This causes ketamine to play an indirect role in inhibiting the transmission of pain impulses, especially in central sensitization. As an analgesic, ketamine works with low doses, ranging around 0.2-0.5mg/kg. This low dose ketamine can be used to relieve acute and chronic pain. The effect of ketamine will be felt 30 minutes after administration. (12) Continuous administration will prolong the effects of analgesia. This situation can occur because metabolite products from ketamine also have an analgesic effect as much as 1/3 – 1/10 times the effect of the initial molecule. Ketamine has a stronger analgesic effect on post-spinal pain procedures. Pain caused by spinal surgery procedures is included in severe pain because it causes musculoskeletal damage and nerve pain that has the potential to cause neuropathic pain. (4)

A study on the administration of ketamine in femur surgery says that at the initial dose of ketamine 0.25mg/kg followed by 0.1mg/kg

can reduce pain to VAS 1-3, by causing side effects in the form of nausea. (12) If this dose increase, ketamine can cause hallucinations, nausea, and vomiting. (13)

In this study, 0.25mg/kg ketamine was followed by 0.1mg/kg/hour given. The VAS mean obtained was 3 and gradually decreased to 1 after 24 hours of observation. When patients who had received ketamine, but still complained of pain more than VAS 3, they received analgesic resuscitation with ketamine 0.5mg/kg/hour. At the initiation dose and ketamine maintenance above, there is accumulation of ketamine and its metabolites in the blood so that it can relieve pain at 21th hour of observation. However, evidence of the need for analgesic resuscitation shows that the existing dose of ketamine is still insufficient to cope with postoperative pain.

Observations on the side effects of both drugs have been made during this study. Even though both drugs are given in low doses, the accumulation of the drug and its metabolic products can be dangerous. (2)(9) Morphine directly works in the respiratory center in the brain stem and slow down the respiratory rate. (9) Respiratory depression can be a direct result of the accumulation of morphine and its metabolites. (14) On the other hand, ketamine does not affect ventilation. The respiratory rate only decreases if ketamine is given together with other anesthetics. (15) However, things that need to be considered in the use of ketamine is an increase in salivation and secretory tracheal production which can increase the risk of aspiration. (9) Hyper-salivation in this study was not possible, this is likely due to anti-sialagogue administration during pre-surgery. Administration of morphine and ketamine during this study did not cause respiratory problems.

The impact of morphine administration on the cardiovascular system is depression in the myocardium and sympathetic nerve function.

Both of these cause a decrease in blood pressure and cardiac output. In addition morphine also has a stimulatory effect on the vagal nerve, stimulate vagal excessively, causing bradycardia. (9)(14) Meanwhile, administration of ketamine causes stimulation of the sympathetic nerve and inhibits the absorption of norepinephrine at synapses. (9)(16)

In the administration of ketamine at a dose of 0.25-0.5mg/kg IV, it can provide hypnosis effects and electroencephalographic changes. (12) In the administration of low-dose ketamine (20-40mg) for MRI procedures in patients weighing 70kg, ketamine can inhibit motor function, impulse pain, and provide psychometric effects. (17)

The percentage of nausea and vomiting during all types of surgery is 25-30%. Nausea and vomiting occur due to stimulation at the center of vomiting. Stimulation can originate from the cerebellum (pain, anxiety, senses, and vestibular disorders), cranial afferent nerve that stimulate solitary tracts (N X, N V, N VII, N IX, N XII), and stimulation of the chemoreceptor trigger zone (CTZ) at the base ventricles. (4) In addition, patient factors, type of surgery, surgical techniques, and anesthesia also increase the risk of postoperative nausea and vomiting (PONV). (18) The presence of opioid receptors on CTZ causes the administration of morphine with a low dose even though it can still cause nausea and vomiting.

Ketamine affects the dissociation center and causes 10-30% of adults to experience misperceptions, which are temporary, shown by hallucinations, delirium, and nightmares. This situation can occur in the administration of ketamine at a dose of more than 2mg/kg intravenously. (9)(16) Midazolam given just before surgery can reduce the psycho-mimetic effect of ketamine. (16)

CONCLUSION

Based on the results of the study found that the analgesic effect of morphine is higher than ketamine, but the amount effect of ketamine is lower than morphine so that ketamine is more effective and safer given in the room.

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