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# The effectiveness of Patient Controlled Analgesia (PCA) morphine-ketamine compared to Patient Controlled Analgesia (PCA) morphine to reduce total dose of morphine and Visual Analog Scale (VAS) in postoperative laparotomy surgery



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## ABSTRACT

**Background:** Laparotomy may cause moderate to severe after surgery pain, thus adequate pain management is needed. The addition of ketamine in patient controlled analgesia (PCA) morphine after surgery can be the option. This study aims to evaluate the effectiveness of PCA morphine-ketamine compared to PCA morphine in patient postoperative laparotomy surgery to reduce total dose of morphine requirement and pain intensity evaluated with visual analog scale (VAS).

**Methods:** This study was a double-blind RCT in 58 patients of ASA I and II, age 18-64 years, underwent an elective laparotomy at Sanglah General Hospital. Patients were divided into 2 groups. Group A, got addition of ketamine (1mg/ml) in PCA morphine (1mg/ml) and patients in group B received morphine (1mg/ml) by PCA. Prior to surgical incision both group were given a bolus ketamine 0,15mg/

kg and ketorolac 0,5mg/kg. The total dose of morphine and VAS were measured at 6, 12, and 24 hours postoperatively.

**Result:** Total dose of morphine in the first 24 hours postoperatively at morphine-ketamine group (5,1±0,8mg) is lower than morphine only group (6,5±0,9mg)  $p < 0,001$ . VAS (resting) 6 and 12 hour postoperative in morphine-ketamine group (13,4±4,8 mm) and (10,7±2,6 mm) are lower than morphine (17,9±4,1mm)  $p \leq 0,05$  and (12,8±5,3mm)  $p \leq 0,05$ . VAS (moving) 6, 12, and 24 hour postoperative morphine-ketamine group (24,8±5,1mm), (18±5,6mm) and (9±5,6mm) are lower than morphine (28,7±5,2mm)  $p \leq 0,05$ , (23,1±6,0mm)  $p \leq 0,05$ , and (12,8±5,3mm)  $p \leq 0,05$ .

**Conclusions:** Addition of ketamine in PCA morphine for postoperative laparotomy surgery reduces total morphine requirements in 24 hours compared to PCA morphine alone.

**Keywords:** general anesthesia, laparotomy, PCA ketamine-morphine, visual analog scale.

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## INTRODUCTION

Postoperative acute pain management is one of the challenges for the anesthesiologist. Acute pain post-operative with moderate-severe intensity need a good management, thus it does not increase morbidity and mortality. Acute postoperative pain management can be done by giving medication that affect the conduction of pain stimulus from the peripheral to the central accordance with a painful stimulus trip.<sup>1</sup>

Acute pain management after laparotomy surgery can be performed with a multimodal analgesia. One of the methods that can be used for rapid control of pain is patient-controlled analgesia (PCA). PCA with intravenous opioid is a well-established technique to control postoperative pain after major surgeries.

This technique adjusts the level of pain better than intravenous bolus doses and also increases patient satisfaction and cooperation.<sup>2</sup> PCA has been used since 1970. PCA pump allows the patient to have a set dose provided according to the needs in pain management as soon as possible. Intravenous opioid with patient-controlled analgesia (PCA) is a popular method to relieve postoperative pain. Morphine is the common choice for PCA.<sup>3</sup> Postoperative pain management is often limited by adverse effects to opioid, including drowsiness, nausea, and vomiting. When used alone in large dose for an extensive period, opioids can lead to acute tolerance which further impairs pain control and more seriously, respiratory and hemodynamic depression.<sup>4,5,6</sup>

A study suggests giving *N-Methyl-D-Aspartate* (NMDA) receptor antagonist and opioid analgesia produces synergistic and additive. Ketamine sub-dose as a specific NMDA receptor, modulate central sensitization and block hyperalgesic effect. Ketamine in postoperative management decreases the requirement of opioids, hence lower side effects, improves effectiveness, and produces hemodynamic and respiratory stability.<sup>4</sup> Ketamine has analgesic properties also in smaller doses. Ketamine analgesia achieved in plasma concentration of 100-150 ng/ml.<sup>7,8</sup> Some studies suggest that the analgesia achieved by administering ketamine 125-250mcg/kg. This dose is sufficient to achieve plasma concentrations 100-150ng/ml.<sup>8,9</sup> Nociceptive stimulation produces hyperexcitability by activation of the N-methyl-D-aspartate (NMDA) receptor, a process involved in pathophysiology of acute pain.<sup>10</sup>

The result of meta-analysis studies shows that PCA gives better result in the treatment of pain compared with conventional methods. The VAS scale also lower in patients with PCA.

In this study, we performed a *double-blind randomized controlled trial*. This clinical trial was designed to determine the effectiveness of PCA morphine combined with ketamine compared with PCA morphine alone, to reduce total dose of morphine requirement and reduce postoperative laparotomy surgery pain scores measured by VAS.

## MATERIAL AND METHODS

The study was a double-blind RCT in 58 patients with ASA I and II, age 18-64 years, underwent an elective laparotomy under general anesthesia at Central Operating Theatre of Sanglah General Hospital, Bali, Indonesia. The exclusion were patients refused to participate in this study, Body Mass Index <19 kg/m<sup>2</sup> or >24,9 kg/m<sup>2</sup>, patients with history of using analgetic in a long period, pregnant and breast-feeding woman, patient with allergy to morphine, ketamine, and NSAID (Non Steroid Anti Inflamasi Drugs), and also uncooperative patient. During the pre anesthetic assessment, patients were explained about visual analog scale (VAS) consists of a 100mm-long line with 0 equals to "no pain" and 100mm equals to "worst possible pain."

The patients were divided randomly into two groups, each of 29 patients. Patients in group A got ketamine (1mg/ml) in PCA morphine (1mg/ml) and patients in group B received only morphine (1mg/ml) by PCA, for acute postoperative pain. Prior to surgical incision both group were given a bolus IV ketamine 0,15 mg/kg and ketorolac 0,5mg/kg.

All patients were premedicated with midazolam 0,05 mg/kg IV. Co-induction was using fentanyl 2mcg/kg IV. Induction was achieved using propofol (2-2,5mg/kg) IV. Atracurium (0,5mg/kg) was used to facilitate insertion of endotracheal tube. For analgesia supplementation, all patients were given ketorolac 0,5mg/kg IV. Anesthesia maintained with N<sub>2</sub>O, O<sub>2</sub> and sevoflurane. Prior surgical incision both group were given a bolus i.v ketamine 0,15 mg/kg. Ringer lactate was used for fluid maintenance. The residual neuromuscular blockade was reversed using neostigmine (0,05 mg/kg) and sulfas atropine 0,5mg, and extubation was done upon complete recovery of the reflexes.

The patients were transferred to the postanesthesia unit and pain score at rest were noted immediately on arrival, 6, 12, and 24 hours postsurgery using VAS scale. At the postoperative surgery recovery room, patients were connected to PCA IV pump and were explained about using PCA unit. PCA setting mode was 1mg dose per push, loading dose of 2 mg, lock out interval every 6 minutes, with maximum dose of 10 mg every 4 hours. The patients were observed in the postoperative care unit for around 4 hours, and rescue analgesia was provided in the form of morphine 0,05 mg/kg bolus IV if pain score was more than 30/100 mm. Total requirements of morphine and total amount of morphine given in 24 hours were noted in both groups.

The results were analyzed using SPSS software. Data analysis includes descriptive analysis that aims to describe the characteristics of research subjects and assess the comparability between groups.

Comparative effectiveness analysis aims to compare the efficacy between the PCA morphine-ketamine group and PCA morphine group at 6, 12, and 24 hours postoperative. Data analysis was presented in mean ± standard deviations using unpaired t-test (parametric test) if the distribution is normal, and using Mann-Whitney if it is not normal (nonparametric test).

## RESULT

From the 58 subjects enrolled in this study, 29 were assigned to the PCA morphine-ketamine group and 29 to the PCA morphine group. The groups were compared and did not differ in distribution of age, BMI, and physical status ASA (Table 1).

Group A: PCA Morphine + Ketamine; Group B: PCA Morphine

Total dose of morphine required in the first 24 hours postoperative in PCA morphine-ketamine group (5,1±0,8 mg) is lower than morphine only

**Table 1** Samples characteristics for morphine-ketamine group and morphine

Variable	Category	Group A (n=29)	Group B (n=29)	P
Age	Mean±SD	44±12,6	44,5±12,4	0,876 <sup>a</sup>
BMI (kg/m <sup>2</sup> )	Mean±SD	21±1	21,5±1,1	0,829 <sup>a</sup>
Physical status	ASA 1, n(%)	11(37,9%)	13(44,8%)	0,594 <sup>b</sup>
	ASA 2, n(%)	18(62,1%)	16(55,2%)	

<sup>a</sup> = p from t-test; <sup>b</sup> = p from Chi Square test

**Table 2** Statistical value of variable based groups

Variabel	mean±SD			P
	PCA Morphine-Ketamine	PCA Morphine	Mean difference	
Morphine dose 6 hours	3.1±0.5	3.7±0.5	-0.6	<0.01
Morphine dose 12 hours	1.7±0.5	2.2±0.5	-0.5	0.001
Morphine dose 24 hours	0.3±0.5	0.6±0.8	-0.3	<b>0.469</b>
Total morphine dose	5.1±0.8	6.5±0.9	-1.4	<0.001
VAS (resting) 6 hours	13.4±4.8	17.9±4.1	-4.5	0.001
VAS (resting) 12 hours	10.7±2.6	12.8±5.3	-2.1	<b>0.050</b>
VAS (resting) 24 hours	4.8±5.1	4.1±5.0	0.7	<b>0.601</b>
VAS (moving) 6 hours	24.8±5.1	28.7±5.2	-3.9	0.009
VAS (moving) 12 hours	18±5.6	23.1±6.0	-5.1	0.002
VAS (moving) 24 hours	9±5.6	12.8±5.3	-3.8	0.013

group (6,5±0,9 mg), p<0,001. VAS (resting) at 6 hours postoperative in PCA morphine-ketamine group (13,4±4,8mm) is lower than PCA morphine group (17,9±4,1mm), p≤0,05. VAS (resting) at 12 hours postoperative in PCA morphine-ketamine group (10,7±2,6mm) is lower than PCA morphine group (12,8±5,3mm), p≤0,05. VAS (moving) at 6 hours postoperative, in PCA morphine-ketamine group (24,8±5,1 mm) is lower than PCA morphine group (28,7±5,2 mm), p≤0,05. VAS (moving) at 12 hours postoperative, in PCA morphine- ketamine group (18±5,6mm) is lower than PCA morphine group (23,1±6,0mm), p≤0,05. VAS (moving) at 24 hours postoperative, in PCA morphine-ketamine group (9±5,6mm) is lower than PCA morphine group (12,8±5,3mm), p≤0,05.

## DISCUSSION

This study demonstrates that combination of low dose ketamine with morphine, delivered via PCA IV, was superior compared with PCA morphine only. It gives better VAS when resting at 6 and 12 hours postoperative and VAS when moving at 6, 12, and 24 hours postoperative. Our results shows that the addition of ketamine in PCA morphine effectively reduces the total dose of morphine requirement in the first 24 hours and gives better visual analog scale (VAS). Total dose of morphine

24 hours and VAS when resting at 24 hours was not significantly different ( $P>0,05$ ) which it caused by the pain itself start to decreasing. Ketamine subdose 0,15 mg/kg before surgery was able to prevent wind-up, central sensitization, acute tolerance and hyperalgesia which took a role in acute and chronic pain and reduce postoperative morphine consumption up to 40 percent at 24 hours postoperatively.<sup>12</sup> Ketamine also affect inflammation by reducing the inflammatory cytokines and accelerates the resolution of inflammation.<sup>13</sup> The administration of non steroid anti-inflammatory drugs (NSAID) such as ketorolac 30 mg IV prior the surgery gives analgesia effect by inhibiting the synthesis of prostaglandin.

## CONCLUSION

From this study we can conclude that the addition of ketamine in PCA morphine in patients undergoing laparotomy surgery under general anesthesia effectively reduces total dose of morphine requirement in the first 24 hours.

In reducing postoperative pain as measured by VAS, addition of ketamine on PCA morphine effectively reducing VAS when resting, 6 hours postoperative by 4,5 mm and 12 hours postoperative by 2,1 mm.

The addition of ketamine on PCA morphine effectively reducing VAS (moving) 6 hours postoperative by 3,9mm, 12 hours postoperative by 5,1mm, and 24 hours postoperative by 3,8 mm.

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