



Oxycodone 5 Miligram is More Effective Than Ketorolac 30 Miligram in Suppressing Cortisol Levels During General Anesthesia

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ABSTRACT

Background: Preemptive analgesia is a developing clinical concept, which involves administering analgesics before pain stimulation occurs, to prevent the sensitization of the nervous system to further stimuli that can cause pain. Ketorolac has strong analgesic properties; oxycodone is a semisynthetic opioid that is synthesized from the alkaloid thebaine opiate. Pain could induce stress hormones such as cortisol. Study to compare ketorolac and oxycodone with cortisol has not been investigated. This study aimed to assess intravenous administration of ketorolac 30 mg compared with intravenous 5 mg oxycodone for pain as measured by cortisol levels post-intervention in surgery performed under general anesthesia. **Method:** A study randomized controlled trial in double-blind form for patients at dr. Mohammad Hoesin Palembang, who will undergo elective surgery with general anesthesia at the Central Surgical Installation building, with the period September-October 2020. There are 24 study samples, to anticipate dropouts, an added sample size is 10%, so the sample size is 26 for each treatment group. The selection of subjects according to the purpose of the study was carried out by simple random. Data analysis using SPSS ver 22.0 software. Data were analyzed using Independent T-Test, Mann Whitney, and Chi-Square Test. **Result:** The results showed, there was a significant difference in the effectiveness of intravenous administration of ketorolac 30 mg and intravenous oxycodone 5 mg on pain as measured by cortisol levels in patients undergoing general anesthesia at dr. Mohammad Hoesin Palembang ($p = 0.013$). The value of cortisol levels in pre-operative patients who will be given general anesthesia at dr. There was no statistically significant difference between Mohammad Hoesin in the two groups ($p = 0.107$). The value of cortisol levels in preoperative patients who were given ketorolac 30 mg intravenously at dr. Mohammad Hoesin was 9.90 ± 4.2 . The value of cortisol levels in postoperative patients who were given ketorolac 30 mg intravenously at dr. Mohammad Hoesin was 17.75 ± 6.08 . The value of preoperative cortisol levels for patients who were given oxycodone 5 mg intravenously at dr. Mohammad Hoesin was 12.03 ± 5.10 . The value of postoperative cortisol levels for patients who were given oxycodone 5 mg intravenously at dr. Mohammad Hoesin is 14.50 ± 4.75 . **Conclusion:** There was a significant difference in the effectiveness of intravenous administration of ketorolac 30 mg and oxycodone 5 mg intravenously on BSS levels ($p = 0.005$) and VAS scores ($p = 0.001$) who underwent general anesthesia at dr. Mohammad Hoesin Palembang.

Keywords: Cortisol Levels, Ketorolac, Oxycodone



Introduction

The concept of preemptive analgesics to reduce the magnitude and duration of postoperative pain was first introduced in 1983 which provided evidence for a major component of post-injury pain hypersensitivity in experimental studies. Furthermore, several experimental studies have shown that various antinociceptives established before the injury are more effective in reducing the phenomenon of central sensitivity than administration after injury.¹

The concept of preemptive analgesia (administration of analgesic drugs before surgical trauma) in patients undergoing surgery develops from central and peripheral modulation of nociception. Preemptive analgesia can reduce central and peripheral pain sensitization has been shown in several studies.² Preemptive analgesia is a developing clinical concept, which involves administering analgesics before pain stimulation occurs, to prevent the sensitization of the nervous system to subsequent stimuli that can amplify pain. The most effective preemptive analgesics are those capable of limiting the sensitization of the long nervous system throughout the perioperative period.³ Effective preemptive analgesia techniques use several pharmacological agents to reduce nociceptor activation. Preemptive analgesia can be administered via local wound infiltration, epidural or systemic administration before surgical incision. Local anesthetics, opioids, analgesic non-steroidal anti-inflammatory drugs (NSAIDs) can be administered either alone or in combination as preemptive analgesia.⁴

Pain response depends on the severity of the operation. The operation is performed with intubation general anesthesia technique, where the stress response of the operation which is assessed from the cortisol hormone levels can be reduced by administering ketorolac and oxycodone. Study on the comparison of ketorolac and oxycodone administration has not been studied. Therefore, this study aimed to assess how the effectiveness of intravenous administration of ketorolac 30 mg compared with intravenous 5 mg oxycodone on pain as measured by post-intervention cortisol levels in operations performed under general anesthesia.

Method

This study is a randomized controlled clinical trial (*Randomized Controlled Trial*) in double disguised form in patients at dr. Mohammad Hoesin Palembang, who will undergo elective surgery under general anesthesia at the Central Surgical Installation building, with the period September-October 2020. The study was conducted after the approval of the Health Study Ethics Committee of Mohammad Hoesin



General Hospital and the Faculty of Medicine, Sriwijaya University.

The sample of the study were patients who would undergo surgery under general anesthesia in a planned operating room and met the inclusion criteria. Inclusion criteria in this sample, including patients scheduled for surgery under general anesthesia, operation time 90-180 minutes, ASA I-II physical status, patients aged 17-64 years, body mass index between 18 kg / m² to 30 kg / m², and are willing to be study subjects and sign an informed consent. In patients who have criteria including hypertension, hypotension, coronary heart disease and, AV block, hypersensitivity to study drugs used (history of drug allergy), hypovolemia, adrenal insufficiency (history of adrenal insufficiency), patients on corticosteroid therapy, Diabetes Mellitus, pregnancy, and Orthopedics were not included in the study sample. Complications during surgery such as shock, anaphylactic reactions, operation time of fewer than 90 minutes or more than 180 minutes, and additional doses of opioid drugs or inhaled anesthetics during surgery, the sample will be *drop out*.

Based on the sample calculation, the sample size is 24 samples. To anticipate dropout, the number of samples was added as much as 10%, so the sample size for each group was 26. The selection of subjects following the objectives of the study was done randomly.

In this study, 3 study variables were obtained, including dependent variable (changes in plasma cortisol hormone levels), independent variables (ketorolac 30 mg intravenously and oxycodone 5 mg intravenously), and confounding variables (age, body mass index, blood pressure and, pulse rate), *blood sugar series, Visual Analog Scale*)

Before sampling, studyers prepared several tools and materials, including: weight and height measurement. blood pressure, pulse rate, peripheral oxygen saturation monitor, end-tidal CO₂, and ECG images, anesthesia machine, general anesthesia set, general anesthetics agents: propofol, fentanyl, atracurium, sevoflurane inhalation anesthetics, syringe pump, perfusion line, 3 ml and 10 ml syringes, time measurement device, retort, cortisol reagent, ketorolac 1 ampoule 30 mg / ml, and oxycodone 1 ampoule 10 mg / ml

After the tools and materials are collected, the studyer conducts study, in the following manner: first the studyer applying for approval to the Health Study Ethics Committee of Sriwijaya University Medical Faculty, dr. Moh Hoessin Palembang, after that informed consent was performed 1 day before surgery. Studyers coordinate with the pharmacy in the process of compounding and administering ketorolac and oxycodone interventional drugs to random drug administrators, in this case, the studyer and the drug provider do not know which drug will be given to the subject. The study subjects were divided



into 2 groups randomly. In the operating room reception room, the patient was premedicated with non-pharmacology by taking venous blood for examination of the hormone cortisol just before induction. The blood sample was taken in the median cubital vein as much as 1 ml, using a 3 ml syringe, then the blood sample was inserted into a chemical tube. Group I was given ketorolac 30 mg intravenously in a 10 ml syringe dissolved with 0.9% NaCl for 10 minutes before surgery. The patient was given a titration profile until the patient was induced, fentanyl 2 $\mu\text{g/kg}$ IV, and after the patient was ventilated he was given atracurium 0.5 mg/kg intravenously. Then maintenance with sevoflurane in 50% oxygen and intraoperative ventilation with the end target of CO₂ penetration 35-40 mmHg. While group II was given 5 mg oxycodone intravenously in a 10 ml syringe dissolved with 0.9% NaCl for 10 minutes before surgery. The patient was given general anesthesia with the same steps as number 7. Hemodynamic blood pressure (MAP) and pulse rate was recorded during the operation, namely before induction, after induction, after intubation, and intraoperatively every 15 minutes until the end of the operation, and after surgery every 30 minutes. up to 2 hours. After extubation, venous blood samples were taken to check cortisol levels. A 1 ml blood sample was taken in the median cubital vein using a 3 ml syringe, then the blood sample was inserted into a chemical tube. The two blood samples are then centrifuged to separate serum and plasma. The serum that has been obtained is then stored in the refrigerator at 2-8o C. After all the samples have been collected, the cortisol level is checked using the ELISA technique. The data obtained were then analyzed. The data were analyzed using *software* SPSS ver 22.0. Data were analyzed by using Independent T-Test, Mann Whitney, and Chi-Square Test.

Result

The sample of this study was 52 patients who underwent elective surgery under general anesthesia and met the inclusion criteria. The sample of the study was randomized and divided into 2 groups, namely the group that was given 30 mg intravenous ketorolac for 26 patients and the group that was given 5 mg oxycodone intravenously as many as 26 patients.

The characteristics of the study subjects are shown in table 1. There were no significant difference in the patient baseline general characteristic (gender, age, weight, height, surgery time, systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse rate, respiratory rate and oxygen saturation). Hence, this study was ideal for randomized clinical trial study.



Table 1. General characteristics of study subjects

Variable	Intervention		p
	Ketorolac	Oxycodone	
Gender, n (%)			
Man	8 (44.4%)	10 (55.6%)	
Women	18 (52.9%)	16 (47.1%)	0.560 *
Age (years), n (%)	46 (18-68)	48.5 (18-68)	0.762 **
Weight (kg), n (%)	55 (45-70)	59.5 (47-75)	0.211 **
Height (m), mean \pm SD	160.96 \pm 4.85	160 \pm 4.89	0.480 ***
Body Mass Index (kg/m ²), mean \pm SD	22.21 \pm 2.61	23.67 \pm 2.74	0.704 ***
Surgery time (minutes), mean \pm SD	135 \pm 29.08	131.92 \pm 29.05	0.073 ***
Systolic blood pressure (mmHg), median (min-max)	120 (100-140)	125 (120-140)	0.260 **
Diastolic blood pressure (mmHg), median (min-max)	80 (70-90)	80 (78-90)	0.165 **
Mean Arterial Pressure, median (min-max)	93.3 (86.6-106.6)	96.6 (92-106.6)	0.115 **
Pulse rate (beats per min) , median (min-max)	80 (70-80)	80 (70-80)	0.775 **
Respiratory Rate (times per min), median (min-max)	18 (18-20)	18 (18-20)	0.717 **
Oxygen saturation (%), median (min-max)	99 (98-100)	99 (97-100)	0.143 **

Note: The mean difference is significant if p <0.05. * Chi-Square test, ** Mann-Whitney test,

*** Unpaired t-test

Preoperatively there was no significant difference in cortisol level in the subject. The mean cortisol level was 10.97 ± 4.75 .



Table 2. Pre-operative cortisol level value (T0)

	Number of Samples	Mean \pm SD Cortisol levels	p*
Value of preoperative cortisol levels (T0)	52	10.97 \pm 4.75	0.107

Note: Mean difference is significant if $p < 0.05$, * unpaired t-test

Postoperative cortisol level in ketorolac group was higher than oxycodone group (17.75 \pm 6.08 vs 14.05 \pm 4.75) while the postoperative cortisol level in ketorolac group was lower than oxycodone group (9.9 \pm 4.2 vs 12.03 \pm 5.1).

From the paired t test, it was found that there was a significant difference in the effectiveness of 30 mg of ketorolac on pain as measured by cortisol levels in pre- and post-operative patients ($p = 0.001$). Paired t-test results in the oxycodone group showed a significant difference in the effectiveness of intravenous 5 mg oxycodone on pain as measured by cortisol levels in pre and postoperative patients ($p = 0.032$). In the ketorolac group, there was an increase in cortisol levels by 7,846 points, and in the oxycodone group, there was a significant increase in cortisol levels by 2.496 points (Table 3). So it can be concluded that the administration of 5 mg oxycodone intravenously in pre and postoperative patients is more effective than the intravenous administration of 30 mg ketorolac.

Table 3. The Effectiveness of Giving Ketorolac and Oxycodone in Pre and Post Operative Patients on Cortisol Levels

Group	Cortisol levels		Delta	p*
	Preoperative	Postoperative		
Ketorolac	9.9 \pm 4.2	17.75 \pm 6.08	7.846 \pm 6.456	0.001
Oxycodone	12.03 \pm 5.1	14.05 \pm 4.75	2.469 \pm 5.531	0.032

Note: Mean difference is significant if $p < 0.05$, paired t-test *

From the unpaired t-test, it was found that there was a significant difference in the effectiveness of intravenous administration of 30 mg of ketorolac and 5 mg of oxycodone on pain as measured by post-operative cortisol levels (p value = 0.013) where the cortisol levels in the oxycodone group were lower



than the cortisol levels in the ketorolac group.

Table 4. Ratio Effectiveness of Ketorolac and Oxycodone Post Operative Against Cortisol Levels

Variable	Group		p*
	Ketorolac	Oxycodone	
Postoperative cortisol levels ($\mu\text{g/dL}$), Mean \pm SD	17.75 \pm 6.08	13.91 \pm 4.53	0.013

Note: The mean difference is significant if $p < 0.05$. * Unpaired t-test

Discussion

This study is a randomized controlled trial in a double-blind form which was conducted in the operating room of the central surgical installation of dr. Mohammad Hoesin Palembang from October to December 2020.

This study subject had no significant difference in baseline general characteristics of both ketorolac and oxycodone groups. The value of pre-operative cortisol levels (T0), the cortisol levels of the two pre-operative groups were assessed and analyzed statistically first and there was no significant difference in the pre-operative cortisol levels in the two groups (p value = 0.107) so that it can be concluded that the two groups fulfill the randomized clinical trial criteria (Table 2)

There was a significant difference in effectiveness of giving ketorolac and oxycodone in pre and post-operative patients on cortisol Levels. the paired t test results showed that there was a significant difference in the effectiveness of 30-mg ketorolac on pain as measured by cortisol levels in pre and post operative patients (p value = 0.001). Paired t test results in the oxycodone group showed a significant difference in the effectiveness of intravenous 5-mg oxycodone on pain as measured by cortisol levels in pre and postoperative patients (p value = 0.032). In the ketorolac group there was an increase in cortisol levels by 7,846 points and in the oxycodone group there was a significant increase in cortisol levels by 2.469 points. There was a significant difference in post-operative cortisol level in ketorolac and oxycodone groups. An unpaired t test was performed and the results showed that there was a significant difference in the effectiveness of intravenous 30 mg of ketorolac and 5 mg of oxycodone on pain as measured by postoperative cortisol levels ($p = 0.013$) where cortisol levels in the oxycodone group were lower than those in the ketorolac group.

This is because oxycodone controls the stress response by inhibiting the secretion of adrenocortical hormones and β endorphins or acting on stress hormone precursors. The literature shows that oxycodone



also has a dual κ -receptor and μ -receptor agonist effect that can decrease the operative stress response. While ketorolac only works in the periphery. During surgery, activation of the hypothalamic sympathetic nervous system results in increased catecholamine secretion from the adrenal medulla and release of norepinephrine from presynaptic nerve terminals. Stimulation of the hypothalamic-pituitary-adrenal axis culminates in the release of both the anterior and posterior pituitary and adrenocortical hormones. Cortisol secretion is one of the main features of the neuroendocrine metabolic response to surgery.⁵⁻⁷

Surgical stimuli in the form of a pain response and tissue trauma will activate the central nervous system and generate a stress response through two pathways known as the "hypothalamic-pituitary and sympathetic-adrenal" axes. Preemptive analgesic oxycodone can reduce cortisol secretion. Zhang conducted a study comparing the administration of 0.1 mg / kg oxycodone with a placebo of 10 ml of normal saline in gastrointestinal surgery patients. 52 Zhang et al (2020) reported that administration of 0.1 mg / kg oxycodone in patients with heart valve replacement surgery was effective in reducing cortisol levels compared to the normal saline placebo group.⁸ Tennant et al. Reported a study of decreasing serum cortisol concentrations in patients receiving opioids (oxycodone, morphine, hydromorphone and hydrocodone).⁹

Oxycodone is a semisynthetic opioid that is synthesized from the alkaloid thebaine opiate. Oxycodone is available in short-acting and extended-release forms and in combination with acetaminophen or aspirin. Oxycodone undergoes a low first-pass metabolism and has a higher bioavailability (60% -87%) compared to morphine.^{10,11} Oxycodone has a 1: 2 potentiation of oxycodone morphine but one study showed a 2: 3 ratio of these drugs.¹² Oxycodone demethylates O via CYP3A4 and CYP2D6 to become oxymorphone, its main active metabolite, which is three times more potent than morphine. Oxycodone is also metabolized by CYP3A4 to noroxycodone, which has weak opioid receptor activity compared to oxycodone or oxymorphone. It has been suggested that individuals with decreased CYP2D6 activity due to genetic polymorphisms require higher oxycodone doses as a result of lower oxymorphone production, but there is limited evidence to support this claim. Oxycodone and its metabolites are mainly excreted in urine with less than 10% of the parent compound excreted unchanged.¹¹⁻¹³

Bakr et al. Compared morphine, tramadol and ketorolac in radical mastectomy patients. Sixty patients were studied with intravenous administration of morphine 5 mg (n = 20), tramadol 100 mg intravenously (n = 20) and ketorolac 60 mg intravenously (n = 20). Serum cortisol was measured immediately, 20 minutes and 24 hours after surgery. There was no significant difference between the



three groups in mean serum cortisol levels, although the increase occurred after 40 minutes and decreased after 24 hours in each group.¹⁴ Ketorolac is safe and effective in reducing maternal stress response to intubation and improving analgesic quality after cesarean delivery. El Tahan et al. Reported 15 mg ketorolac intravenous bolus 20 minutes before induction followed by 7.5 mg / hour (n = 45) compared with placebo saline (n = 45), effectively lowering plasma cortisol concentrations in patients with elective cesarean delivery.¹⁵ Varrassi et al reported that the administration of 30 mg intramuscular ketorolac followed by 2 mg / hour for 24 hours compared to 0.9% 1 ml bolus of NaCl followed by 2 ml / hour for 24 hours, was more effective at lowering the plasma cortisol concentration in abdominal surgery. This study shows that the administration of preventive ketorolac, followed by continuous infusion, is an easy, useful, and safe method for controlling pain and surgical stress following abdominal surgery.¹⁶ Ketorolac tromethamine is the first non-steroidal anti-inflammatory drug (NSAID) approved for abdominal surgery. parenteral use. Ketorolac has strong analgesic properties, with a dose of 60 mg intravenously offering the analgesic equivalent of 5 mg of morphine. Ketorolac is widely conjugated in the liver and then excreted in the urine. The time for the measurable effect was about 30 minutes, with peak effects recorded at 1 to 2 hours and duration of action of 4 to 6 hours.^{17,18}

Conclusion

In the study, there was a significant difference in the effectiveness of intravenous administration of ketorolac 30 mg and intravenous oxycodone 5 mg on pain as measured by cortisol levels in patients undergoing general anesthesia at dr. Mohammad Hoesin Palembang (p value = 0.013)

There is a significant difference in the effectiveness of 30 mg ketorolac and 5 mg oxycodone administration on pain as measured by cortisol levels in pre and post operative patients undergoing general anesthesia at dr. Mohammad Hoesin Palembang (p value = 0.001). Where postoperative cortisol level was higher in ketorolac than oxycodone group (17.75 ± 6.08 vs 13.91 ± 4.53 ; $p = 0.013$).

Intravenous administration of 5 mg oxycodone can be of practical use to lower cortisol levels in patients undergoing surgery under general anesthesia, further study can be done by comparing the effectiveness of oxycodone with other anesthetic drugs such as the opioid class (fentanyl) which can also reduce cortisol levels. Further study can be done by comparing the correlation between VAS and cortisol as an indicator of pain



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