



Preemptive Ketorolac is as Effective as Oxycodone Decreasing Plasma Cortisol Levels in Patients Undergoing Spinal Anesthesia

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ABSTRACT

Introduction: Post-surgical pain is a complex problem, if not treated properly it can have multisystem negative effects. Hormone cortisol can be increased in stressful situations. A study on the effectiveness of ketorolac and another opioid on cortisol levels has been shown. However, a study about the effect of oxycodone on cortisol levels and its comparison with Ketorolac has never been done before. This study aimed to compare the effect of preemptive administration of 30 mg ketorolac and 5 mg oxycodone on plasma cortisol levels in patients undergoing spinal anesthesia.

Methods: A double-blind randomized clinical trial was carried out between October and December 2020 in the central operating room of dr. Mohammad Hoesin Palembang. Surgical patients according to the inclusion criteria who received spinal anesthesia were randomly given 5 mg oxycodone and 30 mg ketorolac intravenously shortly after spinal anesthesia. Cortisol levels were measured before and after the intervention. Data analysis using SPSS ver. 20 Windows with a 95% confidence interval.

Result: In total, 56 subjects were included. 29 samples in the ketorolac group and 27 samples in the oxycodone group. There were no significant differences in age, sex, nutritional status, blood sugar, and VAS score. There was no significant difference in the mean of cortisol levels before the intervention in the ketorolac group $12.9421 \pm 6.096 \mu\text{dL}$ and the oxycodone group $14.033 \pm 4.315 \mu\text{dL}$ ($p = 0.446$). The mean value of cortisol levels after intervention in the ketorolac group was $12.979 \pm 6.280 \mu\text{dL}$ and oxycodone $15.353 \pm 11.704 \mu\text{dL}$, there was no significant difference in changes in cortisol before and after intervention in the Ketorolac group ($p = 0.692$) and Oxycodone ($p = 0.552$). The comparison level of cortisol changes between the two groups was not significantly different ($p = 0.267$).

Conclusion: There was no difference in the comparison of the effect of preemptive administration of 30 mg IV ketorolac and 5 mg IV oxycodone on plasma cortisol levels in patients undergoing spinal anesthesia.

Keywords: Cortisol, Ketorolac, Oxycodone, Preemptive, Spinal Anesthesia.

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Introduction

Postoperative acute pain is a complex problem, if it is not properly treated it can harm the physiological functions of the respiratory, cardiovascular, autonomic nervous systems, gastrointestinal, renal, hepatic, neuroendocrine, immunological, and psychological of the patient. These changes lead to prolonged immobilization, delayed wound healing, increased length of stay and cost of hospitalization, and the potential to develop into chronic pain.¹

As the main glucocorticoid, cortisol is secreted by the adrenal glands which are stimulated by adrenocorticotrophic hormone (ACTH). Cortisol is known as a stress hormone involved in the response to physical and/or emotional stress. Cortisol acts as an anti-inflammatory and suppresses the immune response and almost all aspects of the inflammatory response. In the process of regulating cortisol levels, it is necessary to provide analgesic drugs to reduce pain due to post-surgical wounds.^{2,3}

Preemptive analgesics is an anesthetic treatment that is initiated before surgery to reduce the physiological consequences of nociceptive transmission provoked by the procedure, this can be general or regional anesthesia.^{1,4} Ketorolac is an NSAID that has been used since 1990 and is a parenteral NSAID indicated for postoperative pain. Ketorolac acts on the transduction pathway and inhibits the prostaglandin biosynthesis process by inhibiting the action of cyclooxygenase. Ketorolac also has an analgesic effect that can be used as a substitute for morphine in moderate to severe post-surgical conditions. El-Tahan et al showed that ketorolac was able to reduce the patient's stress response to tracheal intubation compared to placebo. Bakr et al compared the effects of ketorolac, tramadol, and morphine on the stress and immune response of patients with radical mastectomy surgery, the results showed that ketorolac was able to suppress the increase in cortisol 40 minutes better than tramadol and morphine, and reduced 24-hour cortisol levels the best compared to tramadol and morphine.^{5,6}

Oxycodone is a semisynthetic opioid analgesic formed from the opium alkaloid thebaine. Oxycodone is used to treat moderate to severe pain. Generally, oxycodone is used to treat post-surgical pain or relieve pain caused by cancer. Oxycodone induces analgesics primarily by acting as a receptor agonist κ -opioid with a lower affinity for μ -opioid receptors. operative as measured by cortisol levels.⁷ However, there are no studies related to the effect of oxycodone as an analgesic on cortisol levels. Therefore, it is necessary to conduct a study comparing the effects of ketorolac and oxycodone on plasma cortisol levels in surgical patients undergoing spinal anesthesia at RSMH Palembang.



Methods

This study is a double-blind randomized controlled trial to determine the comparison of the effects of oxycodone vs ketorolac through the cortisol levels of patients undergoing spinal anesthesia at Dr. Mohammad Hoesin Palembang. Conducted in the nursing ward and operating room Dr. Mohammad Hoesin Palembang from October 2020 to December 2020 or until the number of samples is met. Samples were taken from patients who were going to undergo surgical procedures with spinal anesthesia, met the inclusion criteria and signed an informed consent form.

The inclusion criteria were age 18-64 years, ASA (American Society of Anesthesiologists) PS classification of I and II, and signed an informed consent form. Patients were excluded if BMI > 30 kg / m² (Obesity), had factors that affect the circadian rhythm of cortisol such as sleep disorders, mental disorders, use of psychiatric drugs, fasting > 2 days, pituitary tumor conditions, Addison's disease, Cushing syndrome, Nelson's syndrome, Sheehan's syndrome, patients with shock or patients with contraindications to ketorolac or oxycodone and an allergic reaction during treatment. Samples were collected using consecutive sampling, that is all patients who met the inclusion criteria and exclusion criteria were included as samples until the minimum sample size of 26 every group was met.

Subjects' demographic and anthropometric data were collected such as age, gender, nutritional status (BMI), surgical procedures, length of operation, and the amount of bleeding. Random blood sugar (RBS), VAS score, and plasma cortisol levels were taken before surgery and after 40 minutes postoperatively. A randomized double-blind injection of 30 mg ketorolac or 5 mg oxycodone intravenously was carried out by an anesthetist resident who was on duty in the recovery room. After the number of samples and data have been collected, they are processed and analyzed using SPSS ver. 20 Windows with a 95% confidence interval. The normality test was conducted using the Kolgomorov Smirnov test, matching with the chi-square test and comparison of cortisol levels between the two groups using the t-test or the Mann-Whitney test.

Result

The 56 children enrolled, 29 in the ketorolac group and 27 in the oxycodone group. Subject characteristics in table 1. There were 21 (37.5%) male and 35 (62.5%) female. There was no significant difference in the number of male and female samples in the oxycodone and ketorolac groups ($p = 0.629$). The mean age in the ketorolac group was 46.9 ± 12.39 and in the oxycodone group 43.62 ± 9.8 , there was



no significant age difference in the two groups ($p = 0.318$). Nutritional status (BMI) above 35 in subjects were excluded, most nutritional status in the ketorolac and oxycodone groups was normal. There was no significant difference between the two groups (p -value = 0.27). Random blood sugar before and after the intervention was mostly at normal levels in both the oxycodone and ketorolac groups. There was no significant difference in RBC before the intervention (p -value = 0.672) and after the intervention (p -value = 0.584). VAS score before intervention in the oxycodone group with mild pain was 17 (50%), moderate pain was 10 (45.4%) and none were included as severe pain. In the Ketorolac group with mild pain as much as 10 (45.4%), moderate pain 12 (54.5%), and none were included in severe pain. There was no significant difference in the VAS score before intervention in the two groups (p -value = 0.740). The VAS scores after intervention in both groups were all in the level of mild pain. The most procedure in the two treatment groups was ORIF and there was no significant difference between all types of surgical procedures with a p -value = 0.258. The most operating time was 1 to 2 hours and most intraoperative bleeding was <500 cc in both the oxycodone and ketorolac groups, there was no significant difference in the operating time (p -value = 0.440) and the amount of intraoperative bleeding (p -value = 0.640).

Table 1. General characteristics of subjects

Characteristics	Group		P
	Oxycodone n (%)	Ketorolac n (%)	
Sex			
Male	11 (52.3)	10 (47.6)	0.629*
Female	16 (45.7)	19 (54.2)	
Age. years			
Mean \pm SD	43.62 \pm 9.8	46.9 \pm 12.39	0.318*
18-35	3 (42)	4 (57.1)	
35-60	22 (53.7)	19 (46.3)	
>60	2 (25)	6 (62.5)	
BMI. kg/m ²			
Wasted (<17)	2(28.6)	5(71.4)	0.270**
Normal (17-25)	22(55)	18(45)	
Overweight (>25)	3(33.3)	6(66.7)	
RBS pre operating. mg/dL			
<100	7 (43.8)	9 (56.2)	0.672**
100-199	20 (50)	20 (50)	
>200	0	0	
GDS post operating. mg/dL			
<100			0.070**
100-199	8 (72.7)	3 (27.2)	



>200	19 (44.2)	26 (57.8)	
VAS score pre-operating			
Mild pain	17 (50)	17 (50)	0.740**
Moderate pain	10 (45.4)	12 (54.5)	
Severe pain	0	0	
VAS score post operating			
Mild pain	27(48.2)	29(48.3)	
Moderate pain	0	0	
Severe pain	0	0	
Operation procedure			
ACL/PCL reconstruction	1(16.7)	5(83.3)	0.258*
Incisional biopsy	0(0)	1(100)	
Per rectal biopsy	0(0)	1(100)	
Debridement	5(71.4)	2(28.6)	
Excision of the condyloma	1(100)	0(0)	
Fistulectomy	1(100)	0(0)	
Haemorrhoidectomy	3(42.8)	4(57.1)	
Herniorrhaphy	0(0)	1(100)	
ORIF	8(57.1)	6(42.9)	
Remove implant	2(100)	0 (0)	
Remove screw	0(0)	2(100)	
Repair fistula	0(0)	1(100)	
TURP	5(62.5)	3(37.5)	
TVH	1(25)	3(75)	
Operating time, hours			
<1	8(57.1)	6(42.9)	0.440**
1-2	19(45.2)	23(54.8)	
>2	0	0	
Intraoperative bleeding, cc			
<500	18(46.1)	21(53.8)	0.640**
500-1000	9(52.9)	8(47.1)	
>1000			
Chi square, 95% CI			
* <i>t-test</i>			
** <i>Mann Whitney U-test</i>			

Before statistical analysis, the Shapiro-Wilk normality test was conducted to see differences in cortisol levels before surgery. T-test for variables with normal distribution and Mann Withney for variables with non-normal distribution. From statistical analysis, it was found that there was no difference in preoperative cortisol levels between the two groups ($p = 0.446$). So that the two groups deserve to be compared (table 2).



Table 2. Comparison of preoperative cortisol levels (T₀)

	Ketorolac	Oxycodone	P Value**
Cortisol level (T ₀)	12.9421±6.096	14.033±4.315	0.446

Independent T test

There was no significant difference in cortisol levels before and after the group which was given ketorolac surgery ($p = 0.692$). There was no significant difference in cortisol levels before and after surgery for the groups given oxycodone ($p = 0.552$). In the ketorolac group, there was an increase in cortisol levels by 0.551 points, and in the oxycodone group, there was an increase in cortisol by 1.319 points (table 3).

Table 3 Changes in pre and postoperative cortisol levels

Group	Cortisol level		Changes (T ₁ -T ₀)	P-Value
	Pre (T ₀)	Post (T ₁)		
Ketorolac	12.427 ± 5.748	12.979 ± 6.280	0.551 ± 7.423	0.692
Oxycodone	14.033 ± 4.315	15.353 ± 11.704	1.319 ± 11.388	0.552

Paired T Test

In the previous data, it is known that the changes in pre and postoperative plasma cortisol levels in the ketorolac group were 12.979 ± 6.280 and in the oxycodones group were 15.353 ± 11.704 . From the T Independent test T (table 4), it was found that there was no significant difference in changes in cortisol levels between the ketorolac and oxycodone groups ($p = 0.267$).

Table 4 Comparison of changes in cortisol levels between groups

Cortisol levels	Ketorolac	Oxycodone	P-Value
Changes in cortisol levels	0,551 ±7,423	1,319 + 11,388	0,267

Independent T Test

	Pre	Post
Ketorolac	12,427	12,979
Oxycodone	14,033	15,353

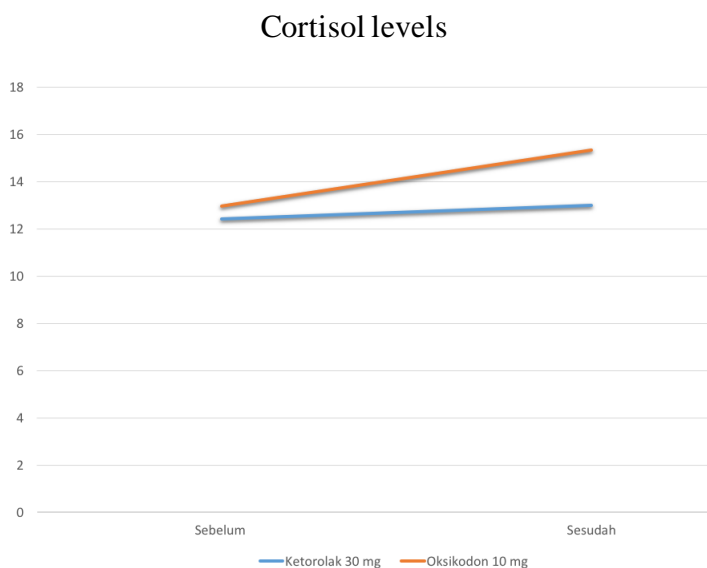


Figure 1 Cortisol levels before and after intervention

Discussion

In this randomized controlled trial study, we studied the comparison of the preemptive administration of 30 mg ketorolac and 5 mg oxycodone to plasma cortisol levels in patients undergoing spinal anesthesia in Palembang, South Sumatra. In the implementation, 56 total samples were collected, 29 samples in the ketorolac group, and 27 samples in the oxycodone group.

There was no significant difference in gender and age between the two groups (p -value = 0.629 and 0.318). The relationship between age and sex on cortisol levels is still not known with certainty, but the mechanism that is thought to influence is decreased resistance to the HPA axis associated with increased age which causes a decrease in cortisol levels. It is also known that the rate of recovery of the HPA axis from stimuli is influenced by aging, whereas the corticotropic response is increased in older women than in men of the same age in response to CRH release.⁸

Most nutritional status was normal (17-25) both in the ketorolac group as many as 22 people and oxycodone as many as 18 people. Patients with a BMI > 30 kg / m² were excluded. From the statistical analysis, there was no significant difference between the groups. Cortisol levels are also influenced by body weight, where the HPA axis changes in the condition of obesity. Cortisol levels are lower in the morning and higher at night. The cause of low cortisol in the morning is due to increased metabolism and



cortisol secretion in obesity.⁹

Random blood sugar in both groups was at normal levels. Where glucose is one of the stress markers that can increase due to suppression of insulin secretion. Both groups chose normal blood sugar levels before the procedure and intervention were one of the indicators that the patient's condition before surgery was not in a state of acute pain or stress. The ketorolac and oxycodone groups had a mean VAS score with mild and moderate degrees before treatment and mild degrees after grade. The association between VAS score and cortisol level has been assessed by several studies. However, it is not significant in the study of Flavia G et al.³⁷ The VAS score after the surgical procedure is at a mild level, possibly because the pain has been controlled by the analgesic given or the effect of spinal anesthesia is still strong. Operating time in the ketorolac and oxycodone groups all lasted less or equal to 2 hours. The maximum duration of surgery was 1 to 2 hours in both groups, there was no significant difference in the length of operation between the ketorolac and oxycodone groups ($p = 0.440$). Most of the surgical procedures were ORIF in both groups. There was no difference in operating procedures between the two groups ($p = 0.258$).^{10,11}

The mean preoperative cortisol levels in the ketorolac group were 12.9421 ± 6.096 and in the oxycodone group 14.033 ± 4.315 . Cortisol levels in both groups were not significant ($p = 0.446$). So it can be concluded that the two groups deserve to be compared. There was no significant difference in changes in cortisol levels before and after ketorolac administration ($p = 0.692$) and oxycodone administration ($p = 0.552$). There was also no significant difference in changes in cortisol levels between the ketorolac and oxycodone groups ($p = 0.267$).

The hormone cortisol is a hormone secreted by the adrenal cortex. Stressful conditions will provide a stimulus to the hypothalamic-pituitary axis of the adrenal cortex. Corticotropin-releasing hormone (CRH) produced by the hypothalamus will stimulate the anterior pituitary gland to release adrenocorticotrophic hormone (ACTH; corticotropin). ACTH provides stimulation to the adrenal cortex to release cortisol secretion within a few minutes. A double-blind RCT study by Varrassi et al in patients with ketorolac administration compared with 0.9% NaCl. They found that the control had higher cortisol levels, but it was significantly different after 2 hours to 6 hours postoperatively.¹² Likewise in El-Tahan et al's 2007 study on 90 samples of women who underwent elective cesarean section delivery. It was found that patients who received 15 mg of ketorolac intravenously before induction followed by a 7.5 mg/hour ketorolac infusion had a lower increase in plasma cortisol than the controls.⁵ Also in a study by Bakr et al



which compared the effects of intravenous ketorolac, tramadol, and morphine on stress and immunity response in 60 patients with radical mastectomy surgery, it was found that ketorolac was able to suppress the increased cortisol level in 40 minutes post-surgery better than tramadol and morphine and reduce cortisol levels 24 hours better than tramadol and morphine.⁶ Oxycodone provides a strong anesthetic effect such as morphine, but compared to morphine, patients receiving oxycodone have lower side effects. Despite these advantages, no specific studies have investigated the effect of adding oxycodone as an analgesic to preemptive analgesia in suppressing the MSR of operative patients.

Several previous studies demonstrated the superiority of ketorolac over the opioid class in increasing postoperative cortisol. In this study, cortisol levels were found 40 minutes postoperatively lower in the ketorolac group than oxycodone, although not significant. Several factors can be the cause. The main mechanism of action of opioids which are analgesics by blocking the pain center so that it will provide negative feedback on the HPA axis as a result, cortisol production is reduced. However, evidence from the research of Bakr et al., Opioids suppress immune function higher than NSAIDs with a direct mechanism for the production of immune cells or indirectly suppressing cortisol production which is not too strong, where it is known that the function of cortisol is also to suppress the immune system (Bakr et al, ketorolac are superior in suppressing cortisol production).

This study showed that the ketorolac group had a lower increase in cortisol levels than oxycodone although it was not significant. Subjects had received bupivacaine as a spinal anesthetic that acts locally to block sensory, motor, and autonomic nerves. In the ketorolac group, the addition of an NSAID agent had anti-inflammatory and analgesic effects by inhibiting non-selective COX and was associated with PGE2 production. The existence of two different effects of the collaboration of bupivacaine and ketorolac provides a superior analgesic effect compared to the opioid group which does not have an anti-inflammatory effect.

Different from previous studies which show the advantages of ketorolac over other opioid agents (morphine and tramadol). This can also be due to the dominant effect of spinal anesthesia where bupivacaine has an effect up to 6 hours after surgery. Longer or serial monitoring of cortisol levels such as 2 hours, 6 hours and 12 hours may be necessary to determine the effect of the two drugs without the effects of spinal anesthesia.

The limitation of this study was the time to take plasma cortisol samples at 40 minutes after surgery. The effects of spinal anesthesia can last up to 6 hours thus biasing the effects of ketorolac and



oxycodone.

Conclusion

There was no difference in the comparison of the effect of preemptive administration of 30 mg ketorolac and 5 mg oxycodone on plasma cortisol levels in patients undergoing spinal anesthesia at Dr. Mohammad Hoesin Palembang (p-value = 0.267). The mean cortisol levels in pre-operative patients in ketorolac group was $12.9421 \pm 6.096 \mu\text{dL}$ and oxycodone was $14.033 \pm 4.315 \mu\text{dL}$ (p-value = 0.446). The mean postoperative cortisol levels in patients undergoing spinal anesthesia by administering 30 mg ketorolac intravenously were $12.979 \pm 6.280 \mu\text{dL}$ and 5 mg oxycodone intravenous was $15.353 \pm 11.704 \mu\text{dL}$. Changes in pre and post-operative cortisol levels given 30 mg ketorolac were $0.551 \pm 7.423 \mu\text{dL}$ (p-value = 0.692). Changes in pre and postoperative cortisol levels given 5 mg oxycodone were $1.319 \pm 11.388 \mu\text{dL}$ (p-value = 0.552).

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