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Comparison of Changes in Cortisol Levels in the Blood of Patients Undergoing Craniotomy Using Continuous Infusion Lidocaine and Fentanyl

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Abstract

Background and Objectives: Craniotomy is a surgical procedure that involves part of the skull, temporarily removing it to expose the brain and carrying out intracranial procedures. The surgery can be considered as the standard model for assessing cortisol as a stress response. Cortisol in the blood can cause hemodynamic and physiological changes in the body such as increased heart rate, increased blood pressure, and also increased blood sugar levels. Some literature showed that continuous infusion of fentanyl and lidocaine - has an effect in maintaining the responses to stress, namely the level of cortisol in the blood. The aim aimed to determine the comparison of changes in cortisol levels in the bloodpatients undergoing craniotomy using continuous infusion lidocaine and continuous infusion fentanyl.
Subject and Method: This research used a double-blind randomized controlled trial (RCT) with a pre-test and post-test with a control group design. This study divided the samples into 2 groups. Continuous infusion of lidocaine and continuous infusion of fentanyl were then checked for cortisol levels in the patient's blood before and after undergoing craniotomy.
Results: The result of 28 samples that underwent craniotomy, 6 samples were excluded, so the total number of samples analyzed was 22 samples. Differences in mean cortisol levels before and after surgery in the lidocaine and fentanyl groups were 193.90 nmol/L and 153.90 nmol/L respectively with a P value of 0.021.
Conclusion: In the study, it was found that cortisol levels increased in both fentanyl and lidocaine groups after a craniotomy. There is a significant difference between the two groups of fentanyl and lidocaine, where statistically the fentanyl group was better at maintaining blood cortisol levels after craniotomy than the lidocaine group.

Keywords: fentanyl continuous infusion, lidocaine continuous infusion, cortisol, craniotomy

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I. Introduction

Craniotomy is a surgical procedure that involves part of the skull, temporarily removing it to expose the brain and performing intracranial procedures.[1] Dangerous stimuli associated with surgery can elicits a sympathetic stress response which has a negative impact on perioperative outcomes. Details of craniotomy starting from skin incision, placement of skull-head pin holder (Mayfield), periosteal-dural contact, closure of dura, bone and skin can cause nociceptive stimulation.[2] Stress response to surgery characterized by increased pituitary hormone secretion and activation sympathetic nervous system which will result in increased secretion of catecholamines from the adrenal medulla and release of norepinephrine from presynaptic nerve terminals. The main underlying mechanisms hypersecretion of cortisol as a stress response is executed by

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afferent nerve signals originating from the surgical incision, which in turn stimulates the hypothalamus to releasecorticotropin hormone and arginine vasopressin.[3,4] Research on the clinical effects of fentanyl as an analgesic in suppressing nociception and the surgical stress response with various dose ranges and/or its use with anesthetic adjuvants (e.g dexmedetomidine) or other analgesics has been widely carried out. The use of fentanyl in surgery, especially craniotomy, has several unfavorable side effects on intracranial pressure (ICP), which is able to increase ICP by around 6–9 mmHg.[5] Lidocaine is amide local anesthetic drugs have long been used in the field of anesthesiology. However, most of their use is still limited as a local anesthetic. Previous literature by Jean-Pierre Estebe showed that intravenous systemic lidocaine has analgesic, antihyperalgesia and anti-inflammatory properties.[6] Continuous infusion of fentanyl and lidocaine can reduce the surgical stress response as indicated by a decrease of cortisol levels in blood samples.[7]

II. Method

This research is a double-blind-randomized controlled trial (RCT) clinical trial with a pre-test post-test with control group design. In this study, we found group A with continuous infusion of lidocaine and group B with continuous infusion of fentanyl. The next step was that blood cortisol levels were examined before and after in patients who had underwent craniotomy with continuous infusion of lidocaine and patients who had underwent craniotomy with continuous infusion of fentanyl. This means the total sample of the study population being all patients. who had underwent surgery craniotomy.The sample for this study was all patients undergoing surgery who met the inclusion and exclusion criteria. Inclusion criteria are: 1) Patients aged 18-65 years; 2) The patient will undergo elective and emergency craniotomy due to non-traumatic causes (ventriculoperitoneal shunt installation, extraventricular drainage, and twin burr hole craniotomy are not included in these criteria). Exclusion criteria are: 1) The patient or family who refuses to participate in the research; 2) Patients with heart failure, severe liver and kidney disorders, adrenal gland disorders, pregnant; 3) Patients with mean arterial pressure (MAP) before surgery <65 mmHg or >100 mmHg; 4) Patients taking beta blocker drugs, chronic use of opioids; 5) Patients with known hypersensitivity to fentanyl and/or lidocaine; 6) Operation duration >3 hours after discussion with the operator. Thus, the number of samples obtained in this study were 22 samples. Research subjects were taken using consecutive sampling technique until the number of research subjects was met. Randomization was carried out by volunteers using a computerized randomization method. The two groups were divided into groups A (continuous infusion of lidocaine) and B (continuous infusion of fentanyl) with 11 samples in each group.

This research was carried out after obtaining informed consent and approval by the Health Research Ethics Committee of the University of North Sumatra and a research permit from Haji Adam Malik Hospital Medan, RSP Prof. Dr. Chairuddin Panusunan Lubis, Haji Hospital Medan, Rumkit Tk.II Medan. Basic data were collected such as age, gender, and admission diagnosis by researchers. Patients had their serum cortisol levels checked before surgery. The patient was then prepared for general anesthesia (installation of a standard monitor) by recording heart rate, blood pressure and SpO2. Premedication was given with an intravenous bolus of fentanyl at a dose of 1 mcg/kgBW, midazolam 0.05 mg/kgBW, lidocaine 1.5 mg/kgBW, then the onset of each drug was observed simultaneously. Induction was carried out with propofol 2 mg/kgBW, and muscle relaxant rocuronium 0.6 mg/kgBW was given. After the onset was reached, then direct laryngoscopy was carried out followed by intubation with an endotracheal tube of the appropriate size. Maintenance of anesthesia was given with sevoflurane 0.8 volume % and propofol 50 mcg/kgBW/minute. Interventions according to the group were immediately provided. Groups A (continuous infusion of lidocaine 2 mg/kgBW/hour) and B (continuous infusion of fentanyl 1 mcg/kgBW/hour). Additional fentanyl as a rescue analgesic at a dose of 1 mcg/kgBW was given if there was an increase in pulse > 100 times/minute and MAP > 20% from baseline. Then the next serum cortisol examination was carried out after the operation completed.

III. Results

In this study, we evaluated changes in the comparison of serum cortisol levels in patients undergoing craniotomy, before and after craniotomy, a total of 22 samples. In table 1, sample characteristic data was obtained. Regarding gender, 16 samples were male and 6 samples were female. In the age data, the mean was 45.6 with a standard deviation value of ± 14.3. For the duration of operation, the average was 167.63 ± 4.30 minutes. For hemodynamic data, the average systolic blood pressure value was 128.44 ± 11.11 mmHg. For diastolic blood pressure data, it was found to be 71.31 ± 9.12 mmHg. For MAP data, the average was 72.13 ± 4.31 mmHg. For heart rate data, it was found to be 82.26 ± 10.15 times/minute. The cortisol value before the craniotomy procedure was found to be a mean of 215.18 nmol/L with a standard deviation value of ± 136.63 In Table 2, a normality test was carried out using the Shapiro-Wilk test in both fentanyl and lidocaine groups, in which serum cortisol levels before and after the intervention were obtained. The data was not normally distributed in the lidocaine group with p 0.038 (mean 169.72 ± 124.08) before the intervention and p 0.013 (mean 363.06 ± 346.96) after the intervention.

Table 1. Sample Characteristics

Variable	
Gender	
Male (n,%)	16 (72.7)
Female (n,%)	6 (27.3)
Age (years)	45.6 ± 14.3
Operation Time (minutes)	167.63 ± 4.30
Systolic Blood Pressure (mmHg)	128.44 ± 11.11
Diastolic Blood Pressure (mmHg)	71.31 ± 9.12
MAP (mmHg)	72.13 ± 4.31
HR (times/minute)	82.26 ± 10.15
Cortisol before the procedure (ng/liter)	215.18 ± 136.63

Table 2. Serum Cortisol Levels in Both Groups and Data Normality Test

	Mean± SD (nmol/L)	p*
Lidocaine		
Before	169.72 ± 124.08	0.038
After	363.06 ± 346.96	0.013
Fentanyl		
Before	258.72 ± 134.67	0.982
After	412.6 ± 134.27	0.743

*Shapiro-Wilk test

Table 3. Differences in Cortisol Levels in the Lidocaine and Fentanyl Groups

		Lidocaine (Mean ± SD)	Fentanyl (Mean ± SD)	p*
Cortisol Before Intervention (nmol/L	Before	169.70 ± 124.08	258.72 ±134.6	0.188

*Mann-Whitney

Table 4. Comparison of Cortisol Levels before and after in the Lidocaine and Fentanyl Groups

	Before (Mean ± SD	After (Mean ± SD)	Different Means	P
Lidocaine (nmol/L)	169.70 ± 124.08	363.09 ± 346.96	193.90	0.003*
Fentanyl (nmol/L)	258.72 ±134.6	412.6 ± 134.27	153.90	0.145**

*Wilcoxon test, **Dependent T test

In the fentanyl group, the data was normally distributed, before and after the intervention.

In table 3 the blood cortisol values in the two groups before intervention were compared and analyzed statistically. The mean serum cortisol value in the lidocaine group was 169.70 ± 124.08 and the mean value in the fentanyl group was 258.72 ± 134.6 nmol/L. Through statistical analysis, p was found to be 0.188 (p>0.05), indicating that there was no significant difference in cortisol values in the two groups, and indicating homogeneity of the data. Table 4 Comparison of cortisol levels before and after in the lidocaine and fentanyl groups In table 4, through statistical tests, the mean

Table 5. Comparison of Changes in Cortisol Levels

	Lidocaine	Fentanyl	P
Changes in Cortisol Levels (nmol/L)	193.90	153.90	0.021*

*Mann-Whitney

blood cortisol levels before the lidocaine group were 169.70 ± 124.08 and 363.09 ± 346.96 after the intervention with an analysis result of 0.003, indicating that there was a significant difference in the lidocaine group. In the fentanyl group, the mean cortisol levels before and after the procedure were 258.72 ± 134.6 and 412.6 ± 134.27, respectively. The results of the analysis in table 5 assessed changes in cortisol levels in the lidocaine and fentanyl groups with a mean of 193.90 and 153.90 respectively with a p value of 0.021 which indicates there is a significant difference between the two groups, with changes in blood cortisol values being lower in the fentanyl group.

IV. Discussion

Previous research assessing the effects of cortisol after hip surgery found an increase in cortisol levels from a mean of 72.53 preoperatively to 92.7 after surgery.[8] This is because after surgical trauma or an accident, the nervous system activates a stress response by sending impulses from the site of injury to the hypothalamus. The hypothalamus relieves its inhibitory tone on the pituitary or releases hormones that stimulate the production and/or release of pituitary hormones. Pituitary hormones act on their respective target organs causing the release of hormones such as stress hormone and cortisol.[9] During and after surgery, high levels of ACTH and cortisol persist in the blood. In addition to the level of surgery, high cortisol levels are also influenced by anesthesia. The type of anesthesia also determines the effect on cortisol levels, with general anesthesia increasing cortisol levels higher immediately after administration and returning to normal levels after 24–48 hours after surgery without complications. Duration of surgery also seems to have an effect on daily cortisol levels. Surgical cortisol levels during later periods (i.e., evening) of the day have been reported to result in an earlier return to normal levels compared with earlier periods (i.e., morning).[10] Elevated cortisol levels in severe stress response, the rate of protein breakdown exceeds synthesis. protein, resulting in net catabolism of muscle protein to provide substrate for gluconeogenesis. Further substrates for gluconeogenesis are provided through fat breakdown.[10,11] In this study, there was an increase in cortisol levels in the blood after craniotomy with the intervention of lidocaine and fentanyl.

When dividing the two groups into fentanyl and lidocaine, it was found that cortisol levels in the blood increased in both groups and the results showed statistically significant differences between the two groups, where the comparison of changes in cortisol levels was lower in the fentanyl group. Research in 2021 on 180 subjects who underwent craniotomy due to intracerebral hemorrhage, revealed that there was a statistically significant difference between the lidocaine group and the sufentanil and remifentanil groups, but the study did not reveal an analysis of the difference in changes in serum cortisol values.[7] Also, research in 2016 revealed a decrease in serum cortisol after intervention opioids, and this is not in line with current research. The study examined the analgesic effect of intrathecal morphine compared to continuous infusion of fentanyl on the stress hormone cortisol, where the continuous infusion group of fentanyl was as effective as the group of intrathecal morphine in caesarean section operations in reducing serum cortisol.[12]

In both our study groups, both in those receiving continuous infusion of lidocaine and fentanyl, mean serum cortisol levels were also found to increase after craniotomy surgery. This is not in line with other studies which found a decrease in cortisol levels in lung tumor patients after Video Assisted Thoracic Surgery (VATS). In this study it was found that serum cortisol values decreased with lidocaine continuous infusion intervention compared to placebo. This is due to the difference in the size of the skin incision between VATS and craniotomy, where minimally invasive surgical procedures usually do not cause significant increases in blood cortisol levels.[10] The effect of lidocaine infusion on the neuroendocrine response to surgical trauma is by inhibiting sympathetic activation and suppressing cortisol release. This may be attributed to the inhibition of chemonocireceptors by perioperative lidocaine infusion and hence a reduction in sensory nerve input leading to a central antihyperalgesic effect and decreased postoperative analgesic consumption. It should also be noted that the effects of lidocaine are associated with operations accompanied by substantial tissue trauma such as laparotomy.[13]

The postulated mechanism of intravenous lidocaine local anesthetic in inhibiting the sympathetic response appears to result from an increase in the threshold for airway stimulation, central inhibition of sympathetic transmission, and direct depression of cardiovascular response. Systemically administered lidocaine acts on voltage-gated sodium channels and provides analgesia at the spinal level, which is expected to reduce the minimum alveolar concentration of isoflurane and attenuate the stress response to surgical stimulation. However it appears that different surgeries have varying degrees of stimulating increases in stress hormones, in terms of this is cortisol.[10,12] Perioperative systemic lidocaine intervention in the literature has a profile as an adjuvant to general anesthesia in terms of reducing intraoperative opioid requirements in various types of surgery. It also has advantages in terms of reducing the incidence of ileus, post operative nausea and vomiting (PONV), antihyperalgesia effect, and in craniotomy reduces post-surgical pain, and also provides brain relaxation and reduction in the incidence of coughing during extubating which is beneficial in post-craniotomy patients.[12]

In this study, hemodynamics was relatively maintained within a safe range, where there was no change on electrocardiography during monitoring in the operating room. Nevertheless it has not statistically analyzed the other previously mentioned effects of perioperative continuous infusion of lidocaine. Statistically in this study, it was revealed that infusion continuous fentanyl was better at maintaining blood cortisol levels during craniotomy than continuous infusion of lidocaine, although in most samples the serum cortisol values were still within the normal range (138–635 nmol/L).[13]

V. Conclusion

In this study, there was an increase in cortisol levels in the blood in both fentanyl and lidocaine research groups, and statistically significant differences were found in changes in the comparison of cortisol levels in the blood between the fentanyl and lidocaine groups.

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