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Comparison of Changes in Cortisol Values Before and After Administration of a Combination of Continuous Fentanyl and Paracetamol Drip in Post-Craniotomy Patients in ICU of Haji Adam Malik General Hospital Medan

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Abstract

Introduction: Post-craniotomy surgical pain can trigger an inflammatory response and release various stress response mediators. Prolonged stress response to pain can increase cortisol secretion which will eventually be resulted in cortisol dysfunction and widespread inflammation. Opioids have been shown to provide pain management after craniotomy. Fentanyl is a commonly used opioid analgesic to manage postoperative pain. The addition of paracetamol is often used as multimodal analgesia which aims to reduce postoperative pain and to minimize the stress response that occurs. The aim of the study was to obtain a comparison of changes in cortisol values before and after the administration of a combination of continuous fentanyl and paracetamol in post-craniotomy patients in the ICU of Haji Adam Malik General Hospital Medan.
Subject and Methods: This research design used a cross sectional test with pretest and posttest design, with primary data sources obtained directly from examinations on patients in the ICU. This study involved 15 post-craniotomy patients in the ICU with mechanical ventilation. The cortisol levels in the patient's blood were checked before and after administration continuous fentanyl and paracetamol drip.
Results: There was a decrease in cortisol levels after being given a combination of continuous fentanyl and paracetamol drip in post-craniotomy patients by 18% with a p-value of 0.001 ($p < 0.05$).
Conclusion: Combination of continuous fentanyl and paracetamol drip can provide analgesia effects that can reduce the stress response, namely cortisol.

Keywords: Craniotomy, ICU, Fentanyl, Paracetamol, Cortisol

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I. Introduction

Craniotomy is a neurosurgical technique performed by opening or removing part of the skull as a surgical procedure with a specific purpose. Indications are including biopsy or resection of intracranial mass lesions, treatment of intracranial vascular pathology and trauma management.[1,2] Stress response to prolonged pain can increase cortisol secretion which will eventually be resulted in cortisol dysfunction and widespread inflammation.[3,4] The physiological response to stress is to produce sympathetic catecholamines (epinephrine and norepinephrine) and neuroendocrine hormones (cortisol). The main mechanism responsible for the hypersecretion of cortisol as a stress response is resulted from afferent nerve signals originating from the surgical incision, which stimulates the hypothalamus to release corticotropin and arginine vasopressin. These two peptides will stimulate the secretion of adrenocorticotropic

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hormone from the anterior pituitary which will stimulate the secretion of cortisol by the adrenal cortex.[5] Prolonged stress response to pain can increase cortisol secretion which will eventually lead to cortisol dysfunction and widespread inflammation.[3] Providing adequate postoperative analgesia is an important component of the postoperative recovery procedure. Suboptimal analgesia will lead to delayed functional recovery and mobilization, increasing the risk of thromboembolism and persistent pain. Early recovery protocols recommend multimodal analgesia regimens by combining two or three drugs with different mechanisms of action to optimize analgesia, minimize side effects and use fewer opioids.[6]

Opioids have been shown to provide pain management after craniotomy. Fentanyl is an opioid analgesic that is commonly used in the field of anesthesia. Research on the clinical effects of fentanyl as an analgesic in suppressing nociception and surgical stress response with a wide dose range and or its use with anesthetic adjuvants such as dexmetomidine or other analgesics has been widely conducted. The use of fentanyl in craniotomy surgery has less favorable side effect on intracranial pressure because it can increase intracranial pressure by about 6 – 9 mmHg. This is due to decreased autoregulation of cerebral vascular resistance due to a decrease in systemic blood pressure resulting in vasodilation, increased blood volume and increased intracranial pressure.[7] The use of intravenous paracetamol in conjunction with opioids is often used for postoperative pain relief rather than orally administered paracetamol as it reaches peak plasma concentrations immediately and is thought to provide a more rapid analgesic effect.

The bioavailability of intravenous paracetamol is 100%, while the bioavailability of oral paracetamol is 79%. In a systemic review and a meta-analysis conducted showed that paracetamol administration in craniotomy surgery decreased postoperative pain, analgesic dose and length of stay in the intensive care unit and increased patient satisfaction. Continuous administration of fentanyl and paracetamol in post-craniotomy patients has often been done. The provision of multimodal analgesia in post-craniotomy aims to reduce pain caused after surgery and to minimize the stress response that occurs.[8,9]

II. Subject and Method

This research design used a cross sectional test with pretest and posttest design, to assess changes in cortisol values before and after the administration of a combination of continuous fentanyl and paracetamol in post-craniotomy patients at Haji Adam Malik Hospital Medan. This study was conducted in the ICU of Haji Adam Malik Hospital Medan. The study was conducted and started after ethical clearance was issued until the number of samples was met. The population of this study were all postoperative craniotomy patients in the ICU of Haji Adam Malik Hospital Medan and the sample of this study were all postoperative craniotomy patients in the ICU of Haji Adam Malik Hospital Medan who had met the inclusion and exclusion criteria and were taken by consecutive sampling technique.

The inclusion criteria for this study were patients aged 18 – 65 years who underwent non-traumatic craniotomy surgery and who were admitted to the ICU with mechanical ventilation. The exclusion criteria for this study were patients who refused to participate in this study; patients with tumors in the hypothalamic-pituitary-adrenal axis; patients who were allergic to fentanyl or paracetamol; patients who underwent VP-shunt, External Ventricular Drainage (EVD), burrhole procedures; and patients who experienced multiple traumas. Research subjects were taken using consecutive sampling technique until the number of research sampling was met.

The study was initiated after obtaining approval from the Health Research Ethics Committee of the Faculty of Medicine, University of North Sumatra/RSUP H. Adam Malik Medan and RSU Haji Medan. Upon patient arrival at the ICU after craniotomy surgery, the patient will be connected to ventilator and basic data were collected such as age, gender and admission diagnosis by

researcher and the blood samples were collected to assess blood cortisol levels (T0) as control. The patient was given paracetamol drip 1000 mg IV and fentanyl bolus 0.5 mcg/kg continuously via syringe pump. Then blood sampling and hemodynamic recording were done again at 6 hour after drug administration (T1). The results obtained were recorded on a data collection sheet and then collected and data processing and analysis were carried out.

III. Results

Data collection was carried out in the ICU room of the Medan Human Rights Hospital in the period of September – October 2023 in postoperative craniotomy patients who were intubated and met the inclusion criteria using the consecutive sampling method. This study used primary data followed by 15 samples who were given continuous fentanyl and paracetamol drip.

In Table 1, the distribution of samples according to gender in respondents with continuous fentanyl and paracetamol administration showed 8 (53.3%) samples were male and 7 (46.7%) samples were female. In the administration of continuous fentanyl and paracetamol, age characteristics were obtained with a mean value of 42.8 with a standard deviation of ± 17.33

Table 1. Samples Characteristics

Variables	Mean ± SD	P value* (p > 0.05)
Gender		
Male	8 (53.3)	0.275
Female	7 (46.7)	
Age (years)	42.8 ± 17.33	0.048
Duration of surgery (minute)	225.67 ± 43.69	0.253

years with an age range of 18 – 64 years. And the distribution of respondents according to the length of surgery in respondents with continuous fentanyl and paracetamol administration obtained a mean value of 225.67 minutes with a standard deviation of ± 43.69. In Table 2, the distribution of samples based on diagnosis was obtained,

Table 2. Classification Based on Diagnosis

Variables	n (%)	P value* (p > 0.05)
Vascular (Mean ± SD) (cases)	7 (46.7)	0.000
Tumor (Mean ± SD) (cases)	8 (53.3)	0.000

namely 7 people diagnosed with vascular disease while 8 people were diagnosed with tumors.
Hemodynamic changes shown in Table 3., are characterized by T0 is the time when the group before drug administration, T1 is the time when the group 6 hours after drug administration. In the sample, the mean systolic blood pressure T0 was 133.53 ± 14.41 mmHg and T1 was 114.06 ± 10.59mmHg. While the diastolic blood pressure T0 76.93 ± 7.97 mmHg and T1 64.73 ± 10.74

Table 3. Hemodynamic Changes before and after Administration of Continuous Fentanyl and Paracetamol

Variables	Mean ± SD	P value* (p > 0.05)
Systolic (mmHg)		
Before (T0)	133.5 ± 14.4	0.879
After (T1)	114.06 ± 10.59	0.877
Diastolic (mmHg)		
Before (T0)	76.93 ± 7.97	0.485
After (T1)	64.73 ± 10.74	0.182
Heart Rate (x/ minute)		
Before (T0)	89.6 ±5.64	0.353
After (T1)	78.53± 7.52	0.272
MAP (mmHg)		
Before (T0)	95.8 ± 8.08	0.468
After (T1)	81.13 ± 7.67	0.690

* Shapiro Wilk test

mmHg so that the mean MAP T0 95.8 ± 8.08 mmHg and T1 81.13 ± 7.67 mmHg and pulse rate T0 89.6 ± 5.64 times/minute and T1 78.53 ± 7.52 times/minute. Researchers measured the variable value of cortisol levels after craniotomy surgery in samples where T0 was before drug

administration and T1 was 6 hours after drug administration. The results of the dependent T test analysis in Table 4. showed a p-value < 0.001

Table 4. Comparison of Changes in Cortisol Level before and after the Administration of Continuous Fentanyl and Paracetamol

Cortisol level	Mean ± SD	P value* (p < 0,05)
T0	551,11 ± 190,83	0,001
T1	383,44 ± 156,39	

*Dependent T test

(p-value < 0.05) which indicated that there is a significant difference between before and after the administration of continuous fentanyl and paracetamol to reduce cortisol levels.

III. Discussion

The development and implementation of safe and effective anesthetic methods to protect patients from the antinociceptive effects of acute postoperative pain is a challenge for the world of anesthesiology. The problem of postoperative pain management remains an area of further study in our country and around the world. According to the literature, about 30% – 75% of patients are sufferred from chronic post-surgical pain syndrome. Multimodal analgesia involves the use of two or more analgesics used simultaneously. These two or more analgesics work in different ways to achieve adequate pain relief, and with minimal side effects compared to the administration of a single analgesic at a high dose.[10] This study assessed cortisol levels before and after the administration of a combination of continuous fentanyl and paracetamol in post-craniotomy patients in the ICU of Haji Adam Malik Hospital Medan during September – October 2023. A total of 15 samples were obtained that met the inclusion and exclusion criteria. Samples received multimodal analgesia in the form of continuous paracetamol and fentanyl, with paracetamol drip 1000mg IV and fentanyl bolus 0.5 mcg/kg continuous via syringe pump, then cortisol levels were assessed before and after multimodal analgesia administration. Sampling was carried out 6 hours postoperatively, most of which were taken at night at 22.00 – 23.00 WIB because the patient was operated in the afternoon. The shortcoming of this study is that it cannot be ascertained that continuous fentanyl was given without a break. As we know, cortisol is one of the stress responses that can be assessed to see the effectiveness of multimodal analgesia. Prolonged stress response to pain can increase cortisol secretion which will eventually lead to cortisol dysfunction and widespread inflammation. Craniotomy causes an increase in plasma cortisol at least 25% greater than other surgeries. This high circulating cortisol level persists on the first postoperative day and then gradually falls by postoperative day.[11,12]

Trauma to body tissues caused by surgery will cause the release of chemical mediators such as prostaglandin E2 which sensitizes pain receptors and bradykinin to interact directly with receptors and stimulate them. Therefore, the body's defense against antinociceptives should be initiated preoperatively with inhibitor agents that reduce the allogenic (transduction) effect. This function can be found in non-steroidal anti-inflammatory drugs (NSAIDs) which can decrease the sensitization of the pain receptors and thus decrease the amount of pain delivered to the segmental structures of the spinal cord. The effect of general anesthesia used in surgery aims to block pain perception in the cerebral cortex. The basis of systemic analgesics is the administration of opioid analgesics that affect the modulation process. The opioid component is the main component to counter pain stimuli at the central level (segmental and suprasegmental). Opioids activate the endogenous antinociceptive system (central analgesia), but do not reliably provide total anesthetic protection. Opioid analgesics do not affect peripheral and segmental non-opioid nociceptive mechanisms and cannot prevent central sensitization and hyperalgesia. Therefore, general anesthesia combined with strong opioids cannot fully protect patients from pain stimulation caused by post-surgical trauma, so we must use drugs with non-opioid mechanisms.[10]

The use of postoperative analgesics is an activity that is very often found in the ICU. Cortisol

levels at 6 hours postoperatively with a mean value of 12.62 ± 8.623 µg/dl in the administration of fentanyl, which indicates the effectiveness of opioids by continuous infusion where fentanyl can inhibit postoperative pain stimulants that activate the sympathetic nervous system and stimulate cortisol secretion. Opioids have been commonly used as pain management after craniotomy. Fentanyl is an opioid analgesic that is commonly used in the field of anesthesia. However, the use of fentanyl in craniotomy surgery has unfavorable side effects on intracranial pressure because it can increase intracranial pressure by about 6 – 9 mmHg. This is due to decreased autoregulation of cerebral vascular resistance due to a decrease in systemic blood pressure resulting in vasodilation, increased blood volume and increased intracranial pressure.[13,14]

Hemodynamic responses in this study were systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP) and pulse rate. This study showed a decrease in hemodynamic response after continuous fentanyl and paracetamol administration. Monitoring of hemodynamic responses in this study found a decrease, in the sample found the mean systolic blood pressure from 133.53 ± 14.41 mmHg to 114.06 ± 10.59 mmHg. While diastolic blood pressure from an average of 76.93 ± 7.97 mmHg to 64.73 ± 10.74 mmHg. So that the average MAP before was 95.8 ± 8.08 mmHg and the average after being 81.13 ± 7.67 mmHg. As well as the pulse rate before from an average of 89.6 ± 5.64 times/minute to 78.53 ± 7.52 times/minute. In one of the samples in this study, the cortisol level was higher than normal (851nmol/L). The sample profile is a patient after craniotomy surgery for spontaneous ICH evacuation with an onset of more than 24 hours and volume of ICH is 80 ml. This result was also obtained in a study conducted in 2014, a study sample of 61 samples of ICH patients with varying amounts of bleeding and onset of ICH which showed significant differences in the characteristics of these samples with high cortisol levels (1163.75 ± 522.56; $p < 0.001$). However, the results of another study did not show the same results, where the results of the study that the duration of surgery did not affect the value of cortisol.[15] Endocrine changes to the hypothalamic pituitary axis following ischemic stroke, subarachnoid hemorrhage and brain trauma have been found. Elevated stress hormones, especially cortisol, may indicate stroke severity and can be used for early risk assessment of disease severity and prognosis. Intracerebral hemorrhage (ICH) is associated with a high mortality rate. Methods often used to predict prognosis include The National Institutes of Health Stroke Scale (NIHSS) and the ICH score. The NIHSS is commonly used to predict 90-day prognosis in patients with acute cerebrovascular disease. The ICH score is a clinical measurement scale consisting of several factors related to neurologic examination (GCS), patient age and radiologic examination (ICH volume, infratentorial/supratentorial origin) that can be used as a risk stratification for ICH management but cannot be used as a detailed predictor to assess outcome. Changes in stress hormones were found in patients with intracerebral hemorrhage. Although some previous studies did not find significant changes in cortisol, it should be noted that some of these studies had limited sample sizes and heterogeneous sample groups. Research conducted in 2014, showed ICH as a stressor and stimulates the hypothalamic pituitary axis which will cause an increase in cortisol levels. The higher the cortisol level in the blood serum, the worse the functional prognosis of the patient. This is supported by previous studies that showed cortisol levels increased in proportion to the degree of stress and severity of ICH.[15]

There are several other mechanisms that may explain the undesirable outcomes in patients with high cortisol levels. High cortisol levels can activate the migration of pro-inflammatory cells production of cytokines and transcription activity factors in the brain that will cause necrotizing cell death that will affect the hippocampus. In normal conditions, the hippocampus inhibits the activity of the pituitary hypothalamic axis, if there is hippocampal damage then the activity that inhibits the pituitary hypothalamic axis will not occur. So, there will be continuous activation of the pituitary hypothalamic axis that causes an increase in glucocorticoid levels, which will

exacerbate hippocampal damage.[12] The deadly cycle will continue to repeat itself. In addition to hippocampal damage, hypercortisolism can also impair immune system function which is associated with a high incidence of post-stroke infectious complications, making the prognosis even worse. In addition, malfunction of the hypothalamic pituitary axis will disrupt fat and glucose metabolism which will increase mortality. Patients with ICH and high cortisol levels are more prone to cardiac disorders (arrhythmias, impaired myocardial function, or myofibril degeneration).[12]

Statistically in this study, it was found that continuous administration of fentanyl and paracetamol can reduce cortisol levels by 18%, where cortisol levels are in the normal range (138 – 635nmol/L). These results were also obtained in another study that assessed 30 research subjects to assess the effectiveness between the combination of paracetamol fentanyl and fentanyl ketorolac in reducing pain. The results of the study suggested that the combination of paracetamol fentanyl was more effective in reducing postoperative pain than the combination of fentanyl ketorolac. Postoperative pain that is not handled will cause an increase in cortisol values. With multimodal analgesia approach had an effect in reducing cortisol compared to single opioid analgesia. A multimodal analgesia approach with its effects on various pain pathways (transduction, transmission, perception, and modulation) in surgery both before, during and after surgery provides adequate results. This is achieved by balancing humoral parameters, adequate analgesia, sympathetic block, and autonomic system protection.[10]

In post-surgery, a multimodal approach to pain management with multiple mechanisms in the pain pathway is characterized by a lack of subjective pain sensation and minimal hemodynamic changes as well as humoral parameters of pain relief. A comparative evaluation of the effectiveness of multimodal analgesia showed a longer analgesic effect with minimal hemodynamic changes and better protection of the autonomic nervous system compared to morphine-based analgesics. As for the economic effect, it shows that there is a decrease in the use of narcotic analgesics by 60.8% in the perioperative period and 50% in the postoperative period. Therefore, better quality analgesia and decreased opioid analgesic consumption contributed to twice as fast recovery of gastrointestinal motility and improved renal excretory function and a 30% reduction in the incidence of postoperative pneumonia due to decreased length of stay in the intensive care unit and hospital.[10]

IV. Conclusion

There is a significant difference between cortisol levels in post-craniotomy patients in ICU before and after continuous fentanyl and paracetamol administration. There was a decrease in cortisol levels after being given a combination of continuous fentanyl and paracetamol in post-craniotomy patients by 18% with a p-value of 0.001 ($p < 0.05$).

References

1. Pasa RMA, Soemartono C, Sulistiawan SS, Utariani A. Effects of regional scalp block with ropivacaine 0,5% preincision as a preemptive analgesia after craniotomy surgery. Jurnal Widya Medika. 2020; 6(1): 1–12.

2. Vacas S, Van de Wiele B. Designing a pain management protocol for craniotomy: A narrative review and consideration of promising practices. Surg Neurol Int. 2017; 8:291. Doi: 10.4103/sni.sni_301_17

3. Sriganesh K, Syeda S, Shanthanna H, Venkataramaiah S, Palaniswamy SR. Effect of opioid versus non-opioid analgesia on surgical pleth index and biomarkers of surgical stress during neurosurgery for brain tumors: Preliminary Findings. Neurol India. 2020; 68(5); 1101-105. Doi: 10.4103/0028-3886.294559

4. Bilotta F, Guerra C, Rosa G. Update on anesthesia for craniotomy. Curr Opin Anesthesiol. 2013; 26(5):517-22. Doi:

10.1097/01.aco.0000432513.92822.c2

5. Prete A, Yan Q, Al-Tarrah K, Akturk HK, Prokop LJ, Alahdab F, et al. The cortisol stress response induced by surgery: A systematic review and meta- analysis. Clin Endocrinol. 2018; 89(5):554-67. Doi: 10.1111/cen.13820

6. Poland F, Spalding N, Gregory S, McCulloch J, Sargen K, Vicary P. Developing patient education to enhance recovery after colorectal surgery through action research: a qualitative study. BMJ Open. 2017;7(6):e134. Doi: 10.1136/bmjopen-2016-013498

7. Cummings III C K, Naguib M A. Opioid agonists and antagonists. In: Stoelting's Pharmacology and Physiology in Anesthetic Practice. Ed 6th. Wolter Kluwer:China. 2022:710-830

8. Ghaffarpasand F, Dadgostar E, Ilami G, Shoaee F, Niakan A , Aghabaklou S, Ghadimi M, et al. Intravenous acetaminophen (Paracetamol) for pascacraniotomy pain: Systemic review and meta-analysis of randomized controlled trials. Elsevier. World Neurosurg. 2020; 134: 569-76. Doi: 10.1016/j.wneu.2019.11.066\

9. Raffa RB, Pawasauskas J, Pergolizzi JV, Lu L, Chen YL, Wu S; et al. Pharmacokinetics of oral and intravenous paracetamol (acetaminophen) when co-administered with intravenous morphine in healthy adult subjects. Clin Drug Investig. 2018; 38(3):259–68. Doi: 10.1007/s40261-017-0610-4

10. Schwenk ES, Mariano ER. Designing the ideal perioperative pain management plan starts with multimodal analgesia. Korean J Anesthesiology. 2018;71(5):345-352. https://doi.org/10.4097/kja.d.18.00217

11. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson, et al. The revised International Association for the study of pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976-982. Doi: 10.1097/j.pain.0000000000001939

12. Harrewijn A, Vida-Ribas P, Clore-Gronenborn K, Jackson SM, Pisano S, Pine DS, et al. Associations between brain activity and endogenous cortisol – a systemic review. 2020. Psychoneuroendocrinology. 2020:120:1-30. Doi: http://doi.org/110.1016/j.psyneuen.2020.104775

13. Yuwono Putro PW, Nasihun T. Comparison in efficacy between fentanyl continuous infusion and intrathecal morphine for pain after caesarean section management. Sains Med J Kedokt dan Kesehat. 2018;8(2):83-87. Doi: 10.30659/sainsmed.v8i2.1842

14. Flood P, Rathmell JP, Urman RD. Opioid Agonists and Antagonists. In: Stoelting's pharmacology and physiology in anesthetic practice. 6th ed. Philadelphia: Wolter Kluwer. 2021(5):234.

15. Yang X, Ren W, Zu H, Dong Q. Evaluate the kadar cortisol and outcome in patients with intracerebral hemorrhage. Clin Neurol Neurosurg. 2014;123:127-30. Doi: 10.1016/j.clineuro.2014.05.019