

Scalp Nerve Block with Ropivacaine as Pre-Emptive Analgesia: Its Effect on PGE2 Levels and Pain Intensity in Elective Craniotomy

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ABSTRACT

PGE2 is a pain mediator with the greatest effect on the process of postoperative pain. Craniotomy causes significant postoperative pain that leads to poor patient outcomes if it is insufficiently managed. Scalp nerve block with ropivacaine as pre-emptive analgesia can optimize postoperative pain management. Ropivacaine inhibits the transmission of painful stimuli from peripheral nociceptors and prevents the production of PGE2 from the surgical site. This study aimed to analyze the impact of scalp nerve block with ropivacaine, given as pre-emptive analgesia, on PGE2 levels and pain intensity among elective craniotomy patients. A prospective analytical-experimental study was conducted on elective craniotomy patients at RSUD Dr. Soetomo from October to November 2023. 40 subjects were divided equally into two groups: Scalp Nerve Block (SNB) group and Non-Scalp Nerve Block (non-SNB) group. The SNB group received a scalp injection with 0.5% ropivacaine after induction of general anesthesia, the non-SNB group only received general anesthesia. PGE2 levels were analyzed before surgical incision, 6 hours after incision, and 24 hours after the completion of surgery. Pain intensity was measured with CPOT score at 24 hours after surgery. PGE2 levels in the SNB group was significantly lower at 6 hours after incision compared to the non-SNB group [100.82 (71.38-426.490) pg/mL vs 194.98 (72.38-542.49) pg/mL; $p=0.009$]. CPOT score at 24 hours after surgery was significantly lower in the SNB group [1 (0-3) vs 2 (0-3); $p=0.017$]. There was no significant correlation between PGE2 level and CPOT score ($r=0.136$; $p=0.404$). SNB with ropivacaine as pre-emptive analgesia could suppress the elevation of PGE2 up to 6 hours after incision and reduce pain intensity up to 24 hours after surgery. PGE2 levels at 24 hours after surgery remained at high levels and were not correlated with pain intensity.

Keywords: Scalp Nerve Block, Pre-Emptive Analgesia, Ropivacaine, Craniotomy, PGE2, Pain Intensity, CPOT

INTRODUCTION

Craniotomy is a major surgical procedure, commonly performed worldwide with various indications. Tissue injury caused by surgical procedure triggers the release of pain mediators. Prostaglandin E2 (PGE2) is a pain mediator with the greatest impact on the pain processing pathway [1]. Once tissue injury occurs, there will be a rapid increase in PGE2 production around the injured tissue [2]. PGE2 will cause various effects, including directly activating the nociceptor and stimulating pain, making the nociceptor more sensitive to painful stimuli resulting in hyperalgesia, as well as increasing blood flow to the inflamed area through dilatation and increasing permeability of the arteries around the injured tissue. Thus, PGE2 causes redness, swelling, and pain; which are the classic signs of inflammation [3]. In the past, post-craniotomy pain was considered as a low-grade pain [4]. Contrary to that belief, in reality, post-craniotomy patients experience moderate to severe pain [5]. Poorly managed post-craniotomy pain will adversely affect postoperative recovery. Patients may experience depression, an increased stress response, chronic pain, and the triggering of hypertension due to the sympathetic response, with consequences including cerebral edema and cerebral hemorrhage. These things will certainly have an impact on increasing the length of hospitalization and increasing mortality [6]. Multimodal analgesia with a combination of systemic and local analgesia has demonstrated its effectiveness in providing adequate pain control, faster recovery, and better patient outcomes [7]. Ropivacaine is frequently used as the local anesthetic drug of choice in many peripheral nerve blocks, such as

scalp nerve blocks in craniotomy cases. Its analgesia effect is obtained by inhibiting nociceptive transmission and preventing excessive PGE2 release from the surgical site [8]. The analgesia effect of ropivacaine will be even more effective when it is administered before surgical incision and acts as pre-emptive analgesia [9]. The pre-emptive analgesia concept is based on the pathophysiology of surgical pain, which includes peripheral and central sensitization. Peripheral sensitization occurs when inflammatory mediators are released from injured tissue, causing a decrease in the threshold of nociceptor, making it more easily activated by noxious stimuli. Central sensitization occurs as an advanced response triggered by the hyperexcitability of neurons in the dorsal horn of the spinal cord. This hyperexcitability itself arises due to intense afferent impulses from injured tissue. Peripheral and central sensitization clinically manifest as increased sensitivity to noxious stimuli at the surgical site and its surrounding tissue. Once central sensitization is established, prolonged postoperative hyperalgesia may occur, the patient's response to analgesics will decrease, and it takes time for improvement. Pre-emptive analgesia given before surgical incision prevents central sensitization and thus minimizes postoperative hyperalgesia [10].

Research Objective

This study aims to analyze the impact of scalp nerve block with ropivacaine, given as pre-emptive analgesia, on PGE2 levels and pain intensity among elective craniotomy patients.

Methods

Study Design and Sample Collection

This is a prospective analytical-experimental study among patients undergoing elective craniotomy at Dr. Soetomo General Academic Hospital Surabaya during October-November 2023. Patients aged 18-64 years with American Society of Anesthesiologists (ASA) classifications I-III, and Glasgow Coma Scale (GCS) scores ≥ 13 were included as subjects of the study. Meanwhile, patients with cardiovascular abnormalities, impaired renal and hepatic function, systemic and/or local scalp infections were excluded from the study. A total of 40 subjects were then randomly divided into equally two groups: the scalp nerve block (SNB) and the non-scalp nerve block (non-SNB) group.

Study Variables and Procedures

Blood samples were obtained at three consecutive times: before surgical incision, six hours after the incision, and 24 hours after the completion of surgery. Serum PGE2 concentrations were measured with an enzyme-linked immunosorbent assay (ELISA) using a Human TNF- α ELISA kit (BT Lab Bioassay Technology Laboratory, Zhejiang, China).

At 24 hours after surgery completion, pain intensity was measured using CPOT score. To induce general anesthesia, fentanyl 1-2 mcg/kg, propofol 1-2 mg/kg, and rocuronium 0.6 mg/kg were administered in sequence. One gram of intravenous paracetamol was administered to all subjects following induction. Only subjects in the SNB group

received scalp nerve block with ropivacaine 0.5% after induction. Maintenance of general anesthesia was performed with propofol target-controlled infusion (TCI) and continuous 0.15 mg/kg/hour of intravenous rocuronium using a syringe pump.

Analgesia maintenance in the non-SNB group was achieved with continuous 1 mcg/kg/hour intravenous fentanyl. The first blood samples were collected before surgical incision. Any abrupt increase in blood pressure or heart rate during surgery that was more than 20% over baseline was deemed painful, and a bolus of 1 mcg/kg fentanyl was given as rescue analgesia thereafter. Six hours following the incision, a second blood sample was taken. All subjects were given intravenous 30 mg of ketorolac every 8 hours as a form of postoperative analgesia. Every four hours, the Critical-care Pain Observational Tool (CPOT) was used to measure the pain intensity. A bolus of 1 mcg/kg fentanyl was given as rescue analgesia if the CPOT score was more than 2. The third blood sample was taken 24 hours following the completion of surgery.

Statistical Analysis

Statistical analysis was performed on all collected data using SPSS 26 (SPSS Inc., Chicago, USA). Levene's test for equality of variances was used to assess the subjects' demographic homogeneity. The Shapiro-Wilk test was used to assess data normality. PG2 levels in both groups at all sampling times were not normally distributed, thus the data will be displayed in median (min-max) form, and the comparison between the two groups was performed with Mann-Whitney test. Within the same group, changes in PGE2 levels over time were analyzed using Friedman test.

Table 1: Demographic characteristics of subjects

Demographic characteristics	Group		Total (n=40)	p value of homogeneity test
	SNB (n=20)	Non-SNB (n=20)		
Gender				
Male	9 (45.0%)	10 (50.0%)	19 (47.5%)	1.000a
Female	11 (55.0%)	10 (50.0%)	21 (52.5%)	
Age				
Range	38-61	41-60	38-61	0.302b
Mean $\pm$ SD	48.80 $\pm$ 5.83	50.80 $\pm$ 6.26	49.80 $\pm$ 6.06	
Body weight				
Range	47-72	44-72	44-72	0.665b
Mean $\pm$ SD	57.35 $\pm$ 7.18	58.45 $\pm$ 8.71	57.90 $\pm$ 7.90	
Height				
Range	154-171	153-172	153-172	0.333b
Mean $\pm$ SD	161.0 $\pm$ 5.34	162.65 $\pm$ 5.29	161.82 $\pm$ 5.31	
BMI				
Range	19.14-24.91	18.43-25.82	18.43-25.82	0.884b
Mean $\pm$ SD	22.07 $\pm$ 1.93	21.97 $\pm$ 2.09	22.02 $\pm$ 1.98	

a : Chi-Square test

b : Levene's test for equality of variances

Additionally, neither group's CPOT scores were normally distributed, so the data will be shown in median (min-max) form, and Mann-Whitney test was used as the statistical comparison between the two groups. Meanwhile, the correlation between PGE2 levels and CPOT scores was completed with Spearman test.

Findings and Discussion

Findings

In all, forty patients were included in the study. Levene's homogeneity test revealed that both groups had homogenous gender,

age, weight, height, and BMI. Table 1 provides a summary of the subjects' demographic features. Regarded as baseline levels, the two groups' initial PGE2 levels before surgical incision did not vary statistically [98.54 (63.48-411.38) pg/mL in the SNB group, 100.82 (21.35-427.38) pg/mL in the non-SNB group, $p=0.968$]. Six hours after incision, PGE2 levels were significantly lower in the SNB group than in the non-SNB group [100.82 (71.38-426.49) pg/mL vs 194.98 (72.38-542.49) pg/mL, $p=0.009$]. PGE2 levels measured 24 hours after completion of the surgery did not significantly differ between the two groups [214.43 (135.46-542.27) pg/mL vs 201.37 (78.67-556.83) pg/mL, $p=0.208$]. PGE2 levels are summarized in table 2.

Table 2: PGE2 levels

Sampling time	Groups		p value*
	SNB	Non-SNB	
Before surgical incision			
Median (min-max) (pg/mL)	98.54 (62.48-411.38)	100.82 (21.35-427.38)	0,968
6 hours after incision			
Median (min-max) (pg/mL)	100.82 (71.38-426.49)	194.98 (72.38-542.49)	0,009
24 hours after surgery			
Median (min-max) (pg/mL)	214.43 (135.46-542.27)	201.37 (78.67-556.83)	0,208

*Mann-Whitney test

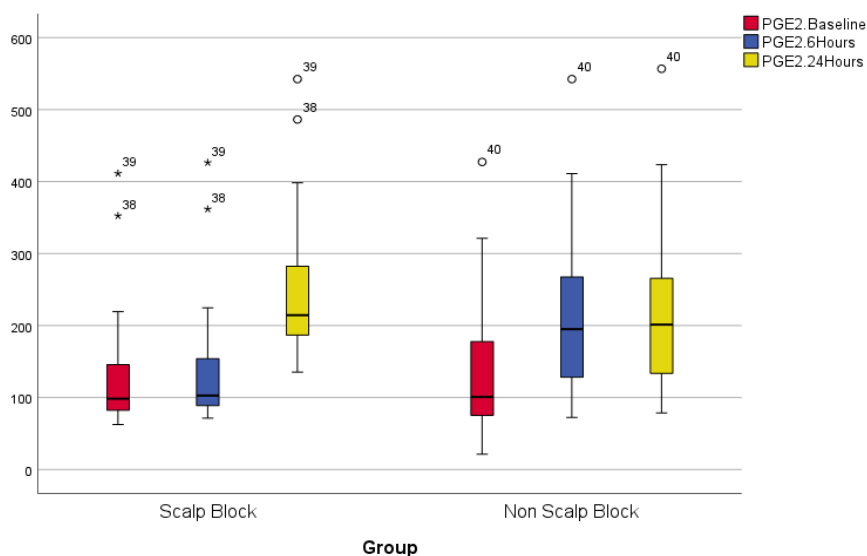
CPOT scores measured at 24 hours after surgical completion were significantly lower in the SNB group compared to the non-SNB group [1 (0-3) vs 2 (0-3), $p=0.017$]. Correlation test between PGE2 levels and CPOT score at 24 hours after surgery showed there was no significant correlation between those two variables ($p=0.404$; $r=0.136$). The data are summarized in table 3.

Discussion

Gender, age and BMI are said to have an influence on PGE2 levels. A study stated that in peritonitis-induced mice, the production of PGE2 by the neutrophils of male mice was greater than that of female mice. Likewise with in-vitro experiments, in inflammation conditions, the production of PGE2 by male neutrophil cells is greater than that of women [11]. A study in mice reported that macrophages in old mice produced more PGE2 than young mice, and the higher the BMI, the higher the PGE2 levels [12]. The homogeneous distribution of gender, age and BMI characteristics in the subjects of this study brings the advantage of a lack of bias in the data that could occur. At 6 hours after incision, the PGE2 levels in the SNB group was significantly lower than those in the non-SNB group ($p=0.009$). On further observation, PGE2 levels 6 hours after incision in both groups increased significantly compared to baseline levels, but the increase in the SNB group was not as great as in the non-SNB group. This theoretically indicates the role of ropivacaine in scalp nerve block in inhibiting the increase of PGE2 due to surgical process. Similar conditions were seen in previous

studies regarding ropivacaine. An in vitro study mentioned that in macrophages stimulated with lipopolysaccharide, in the group that received ropivacaine and those that did not receive ropivacaine (control group), both PGE2 expression increased. However, the increase in the group that received ropivacaine was not as high as in the control group [13]. 24 hours after surgery, the PGE2 levels of the two groups were not significantly different ($p=0.208$). In the analysis of changes in PGE2 levels in the same group, there were different patterns of PGE2 level increase curves between the two groups, as shown in Figure 1. In the SNB group, PGE2 levels rose with a gentle curve at 6 hours after incision, and then rose again 24 hours after surgery with a sharp upward curve. Meanwhile in the non-SNB group, the rising curve at 6 hours after incision appeared sharp, then rose again 24 hours after surgery with a gentle curve.

This different pattern of increase in PGE2 levels theoretically indicates that scalp nerve block with ropivacaine appears to be able to suppress the high increase in PGE2 levels due to surgery, compared to subjects without scalp nerve block. However, this effect appears to be effective only up to 6 hours after the incision, and then then no longer has a significant effect 24 hours after surgery. There is no data from previous studies on how long ropivacaine for scalp nerve block can have an effect on PGE2 in surgery. In this study, the average incision time since the scalp nerve block was performed was 30-60 minutes, so the effect of ropivacaine in inhibiting the increase in PGE2 levels was still visible within 6.5-7 hours.

**FIGURE 1:** PGE2 levels over time

In this study, the pain intensity 24 hours after surgery was assessed by CPOT score. The CPOT score in the SNB group was significantly lower than that in the non-SNB group ($p=0.017$). Previous study mentioned that ropivacaine 0.5% for scalp nerve block in craniotomy can provide pain relief up to 4 hours after

surgery, with a mean surgery duration of 4.27 hours [14, 15] in their study stated that scalp nerve block with ropivacaine 0.5% can reduce pain up to 12 hours after craniotomy, with an average surgery time of 4.6 hours, which means that ropivacaine can reduce pain up to 16.6 hours after it is injected. The duration of

action of ropivacaine in reducing pain appears to vary because pain itself is multifactorial, not only related to pain mediators such as PGE2, but involves many other factors, including psychological factors such as previous pain experiences, beliefs about whether or not to feel pain, fear, or anxiety [16]. PGE2 itself is one of the factors that cause pain after craniotomy, which in this study appeared to be inhibited by ropivacaine via scalp nerve block, up to 6 hours after the incision. Considering the average incision time since the scalp nerve block was performed is 30-60 minutes, the effect of ropivacaine in inhibiting the production of PGE2 in this study still lasts for 6.5-7 hours, but its effect in reducing postoperative pain still persists even up to 24 hours after surgery, with the mean surgery time was 7.3 hours. There was no significant

correlation between PGE2 levels and CPOT scores, with a very weak correlation coefficient ($p=0.404$; $r=0.136$). Similar finding was obtained from a previous study, which stated that in subjects undergoing orthodontic treatment, PGE2 levels and pain intensity in the first 24 hours were very weakly correlated [17]. The very weak correlation of PGE2 levels with pain intensity is in accordance with the basic theory of pain, that the sensation of pain occurs based on the interaction between physiological sensory aspects, affective components, and cognitive responses of each individual. The severity of pain perception is not always directly proportional to the severity of tissue damage that occurs, or the amount of pain stimuli experienced [18]. Psychological factors also play a role in pain perception.

Table 3: CPOT scores and its correlation with PGE2 levels

Variable	Groups		p value
	SNB	Non-SNB	
CPOT Score			
Median (Min-Max)	1 (0-3)	2 (0-3)	0.017 ^a
PGE2 Levels			
Median (Min-Max)	214.43 (135.46-542.27)	201.37 (78.67-556.83)	0.208 ^a
Correlation of PGE2-CPOT			0.404 ^b

a : Mann-Whitney test

b : Spearman test

The long duration of analgesia effect of ropivacaine, which outlasts its inhibitory effect on elevated PGE2 levels, could also be due to its administration being carried out before incision, thus causing a pre-emptive analgesia effect that prevents central sensitization. Postoperative pain is caused by peripheral and central sensitization process.

Peripheral sensitization occurs due to inflammatory mediators that reduce the nociceptor threshold. Central sensitization occurs due to hyperexcitability of neurons in the dorsal horn of the spinal cord, causing postoperative hyperalgesia. Providing pre-emptive analgesia before surgery suppresses central sensitization so that postoperative hyperalgesia can be minimized [10]. Thus, even

though PGE2 levels are still at high levels, they are not always manifested as severe pain intensity.

Conclusion and Discussion

Prior to craniotomy, ropivacaine scalp nerve block administration is useful in reducing the rise in PGE2 levels for a period of up to 6.5-7 hours after administration; however, this effect does not last until 24 hours following surgery. On the other hand, its impact on pain control seems to last for up to 24 hours following surgery. At 24 hours after surgery, there was no significant correlation between PGE2 levels and CPOT score.

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