INTRODUCTION

In recent decades, the field of immunology has evolved rapidly, elucidating the cellular and molecular mechanisms underlying human immunity. Recent studies have shown that high levels of cytokines correlate with the degree of manipulation of brain tissue and lower levels of inflammation in brain tumor surgery are associated with higher safety rates. The use of scalp block in craniotomy surgery is associated with the modulating effect of both local and systemic inflammatory responses. This study aims to analyze the effect of scalp block with 0.5% ropivacaine on IL-6 and NLR in elective craniotomy surgery.

Method: A randomized controlled trial (RCT) was conducted at Dr. Soetomo General Hospital Surabaya with a total of 40 patients who underwent elective craniotomy from September to November 2023. Patients were divided into two groups: the scalp block (SB) group and the non-scalp block (non-SB) group. All patients were under general anesthesia and a scalp block was added to the SB group after general anesthesia. IL-6 concentration and NLR count were assessed after general anesthesia (T₀), 6 hours after incision (T₁), and 24 hours after surgery (T₂).

Results: IL-6 and NLR levels increased over time and reached their peak at 24 hours after surgery in both groups with IL-6 SB: 83.50 ± 2.289 pg/mL and IL-6 non-SB: 84,638 ± 2.25 pg/ml. NLR SB: 6.80 ± 1.17 and NLR non-SB: 7.33 (5.83-8.09). In the comparative test, there was a significant difference in IL-6 and NLR levels at 6 hours after incision (p:<0.001 and p=0.0015), and significant differences in changes IL-6 baseline and 6 hours after incision (ΔT₀-T₁) (P,<0.001). However, there was no significant difference in IL-6 and NLR levels at 24 hours after surgery and no significant difference in the changes between IL-6 baseline and 24 hours after surgery (ΔT₀-T₂), NLR baseline, and 6 hours after incision (ΔT₁-T₂), NLR baseline and 24 hours after surgery (ΔT₂-T₂) between two groups.

Conclusion: Scalp block suppresses pro-inflammatory mediators for only 6 hours after incision. It is most effectively used in short procedures, as an adjuvant for the head pinning procedure or incision.

Keywords: Scalp block, 0.5% ropivacaine, Craniotomy, IL-6, NLR.


Effect of scalp block with 0.5% ropivacaine on interleukin-6 and neutrophil lymphocyte ratio in elective craniotomy

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ABSTRACT

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Ropivacaine is the drug of choice for peripheral nerve block due to its longer duration of action compared to lidocaine, as well as its lower toxicity to the heart and central nervous system compared to bupivacaine. The concentration of ropivacaine that is often used in scalp blocks is 0.5 and 0.75%. In one study it was said that ropivacaine injection can significantly reduce IL-1, IL-6, and TNF-α levels in patients with severe trauma. In another study, ropivacaine also mentioned that it causes inhibition of inflammatory mediators NO, PGE2, and proinflammatory cytokines such as TNF-α, IL-6, and IL-1β. Preemptive analgesia, which reduces post-operative pain and minimizes an excessive surgical stress reaction, is achieved by administering ropivacaine-assisted scalp block prior to surgical incision. Therefore scalp block plays an important role in controlling hemodynamic changes that occur during craniotomy surgery while reducing the need for perioperative opioids.

The dosage and duration of the medication’s administration determine its immunosuppressive impact. Sophisticated perioperative care can be enhanced by a thorough assessment of the effects of anesthetic medications on the immune system.

Interleukin-6 is one of the cytokines that appears early and is an induction and control mediator in the synthesis of acute-phase proteins released by hepatocytes during pain stimuli such as trauma, surgical infections, and burns. Interleukin-6 is a pro-inflammatory cytokine secreted by T cells, macrophages, and other cells activating microglia which will then trigger the release of interleukin-6, interleukin-1β, TNF-α which will then go to systemic circulation through the damaged brain barrier. Interleukin-6 is produced transiently in response to infection and tissue damage, contributing to the body’s defense mechanisms and stimulation of acute phase responses, hematopoiesis, and immunological reactions. During sterile procedures on surgery, it is said that the increase in IL-6 released by damaged tissue precedes clinical signs of inflammation such as elevated body temperature and other proteins.

The neutrophil lymphocytes ratio and C-reactive protein itself are immunosuppressive and inflammatory biomarkers and all these inflammatory and immunosuppressive mediators are involved both in cellular immune responses in trauma and in the acute phase. Neutrophils are granulocyte cells that play an important role in the body’s defense and inflammatory cells are the earliest to infiltrate traumatized or damaged tissue with a half-life of 4-10 hours. The neutrophil lymphocytes ratio is widely studied because of its easy measurement and not only for indicators of infection, but recent studies have shown the use of neutrophil-lymphocyte ratio as a predictor in cancer patients.

Most studies in glioma patients suggest that higher NLR is associated with poorer patient outcomes, but research by Mason et al suggests that NLR cannot be used as a single biomarker.

This study aims to analyze the impact of scalp block with 0.5% ropivacaine on the surgical stress response, represented by IL-6 and NLR among elective craniotomy patients.

METHODS

Study Design and Sample Collection
A randomized controlled trial (RCT) was conducted among patients undergoing elective craniotomy under general anesthesia at Dr. Soetomo General Academic Hospital Surabaya from September to November 2023. Patients between the ages of 18 and 64, Physical Status with American Society of Anesthesiologists (ASA) classification I–III, Glasgow Coma Scale (GCS) score > 13, and elective craniotomy were the inclusion criteria used to choose the subjects. Exclusion criteria were patients with impaired renal and hepatic function, diabetes mellitus, systemic and/or local infections of the scalp, and a history of current dexamethasone treatment. Forty subjects in total were split into two groups at random: the non-scalp block (non-SB) group and the scalp lock (SB) group.

Study Variables and Procedures
In this study, IL-6 and NLR were assessed three times in a row: immediately following anesthesia induction, six hours following incision, and twenty-four hours following surgery. The Human IL-6 ELISA kit (BT Lab Bioassay Technology Laboratory, Zhejiang, China) was used to determine the quantity of IL-6 using the enzyme-linked immunosorbent assay (ELISA). NLR was calculated by dividing the absolute count of neutrophils and lymphocytes from the complete blood count.

General anesthesia is achieved by administering fentanyl 1-2 mcg/kg, propofol 1-2 mg/kg, and rocuronium 0.6 mg/kg. Following induction, the first blood sample was obtained. In the SB group, a scalp block using 0.5% ropivacaine was then administered. Target-controlled infusion (TCI) of propofol and a continuous rocuronium pump dose of 0.15 mg/kg/hour were used to maintain anesthesia. The non-SB group was continuously given fentanyl at a rate of 1 mcg/kg/hour to maintain analgesia. 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. Following surgery, 1g of intravenous paracetamol was given to each individual every 8 hours as a pain reliever. The third blood sample was taken 24 hours following surgery.

Statistical Analysis
Statistical analysis was performed on all collected data using SPSS 26 (SPSS Inc,. Chicago, USA). The individuals’ demographic homogeneity was assessed using Fisher’s exact test and Chi-Square. The Shapiro-Wilk test was used to determine the data normalcy. At the first, second, and third samplings, IL-6 and NLR were compared between the two groups using a Mann-Whitney test if the data was not normally distributed, or a two-independent T-test if the data was.

RESULTS

The study included 40 patients in total. Both groups were homogenous in terms of equality of variances, gender, age, weight, height, BMI, PS ASA, and length of operation, according to Chi-Square and Fisher’s Exact test. The demographic characteristics of the subjects are summarized in Table 1.
Table 1. Demographic characteristics of subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group</th>
<th>Value</th>
<th>p value of homogeneity test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>1.000^a</td>
</tr>
<tr>
<td>Male</td>
<td>SB (n=20)</td>
<td>9 (45.0%)</td>
<td>9 (45.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>Non-SB (n=20)</td>
<td>11 (55.0%)</td>
<td>10 (50.0%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>0.302^b</td>
</tr>
<tr>
<td>Range</td>
<td>SB (n=20)</td>
<td>38 - 61</td>
<td>41 - 60</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>Non-SB (n=20)</td>
<td>48.80 ± 5.83</td>
<td>50.80 ± 6.26</td>
</tr>
<tr>
<td>Body Weight</td>
<td></td>
<td></td>
<td>0.665^b</td>
</tr>
<tr>
<td>Range</td>
<td>SB (n=20)</td>
<td>47 - 72</td>
<td>44 - 72</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>Non-SB (n=20)</td>
<td>57.35 ± 7.18</td>
<td>58.45 ± 8.71</td>
</tr>
<tr>
<td>Height</td>
<td></td>
<td></td>
<td>0.333^b</td>
</tr>
<tr>
<td>Range</td>
<td>SB (n=20)</td>
<td>154 - 171</td>
<td>153 - 172</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>Non-SB (n=20)</td>
<td>161.0 ± 5.34</td>
<td>162.65 ± 5.29</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td>0.884^b</td>
</tr>
<tr>
<td>Range</td>
<td>SB (n=20)</td>
<td>19.14 - 24.91</td>
<td>18.43 – 25.82</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>Non-SB (n=20)</td>
<td>22.07 ± 1.93</td>
<td>21.97 ± 2.09</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
<td>0.695^c</td>
</tr>
<tr>
<td>2</td>
<td>SB (n=20)</td>
<td>8 (20%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>3</td>
<td>Non-SB (n=20)</td>
<td>32 (80%)</td>
<td>17 (85%)</td>
</tr>
<tr>
<td>Duration of surgery</td>
<td></td>
<td></td>
<td>0.518^b</td>
</tr>
<tr>
<td>Range (minutes)</td>
<td>SB (n=20)</td>
<td>540-550</td>
<td>230-735</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>Non-SB (n=20)</td>
<td>385.25 ± 136.471</td>
<td>417.60 ± 124.28</td>
</tr>
</tbody>
</table>

SB: Scalp Block; Non SB : Non Scalp Block
a: Chi-square homogeneity test
b: 2 Independent T-test
c: Fisher exact test

Table 2. IL-6 concentration

<table>
<thead>
<tr>
<th>Time</th>
<th>Scalp Block (Mean ± SD)^a</th>
<th>Non scalp block (Mean ± SD)^a</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;0&lt;/sub&gt;</td>
<td>74,769 ± 2,909</td>
<td>76,314 (70.04 – 79.98)</td>
<td>0.314^a</td>
</tr>
<tr>
<td>T&lt;sub&gt;1&lt;/sub&gt;</td>
<td>75,606 ± 2,815</td>
<td>83,974 (80-89.18)</td>
<td>&lt;0.001^a</td>
</tr>
<tr>
<td>T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>83.50 ± 2,289</td>
<td>84,638 ± 2.25</td>
<td>0.121^d</td>
</tr>
</tbody>
</table>

T<sub>0</sub>: After induction of anesthesia
T<sub>1</sub>: 6 hours after incision
T<sub>2</sub>: 24 hours after surgery
a: data is normally distributed;
b: data is not normally distributed;
c: Mann-Whitney U
d: Independent T-test

Table 3. Changes in IL-6 concentration

<table>
<thead>
<tr>
<th></th>
<th>Scalp Block (Mean ± SD)^a</th>
<th>Non scalp block (Mean ± SD)^a</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆ T&lt;sub&gt;0&lt;/sub&gt; – T&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.836 ± 4,042</td>
<td>8,756 ± 3,865</td>
<td>&lt;0.001^b</td>
</tr>
<tr>
<td>∆ T&lt;sub&gt;1&lt;/sub&gt; – T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>8,817 ± 3,247</td>
<td>8,809 ± 3,812</td>
<td>0.994^b</td>
</tr>
</tbody>
</table>

Δ: delta (difference)
a: data is normally distributed; b: Independent T-test

At 24 hours after completion of surgery, there were no significant differences in IL-6 concentration between both groups (83.50±2,289 vs 84,638±2.25 pg/mL; p=0.121) (Table 2).

In the comparison test for the changes in IL-6 concentration (∆T<sub>0</sub>–T<sub>1</sub>), the SB group was 0.836 ± 4,042 pg / mL, and the non-SB group was 8,756 ± 3,865 pg / mL (p-value <0.001). This means the increase in IL-6 concentration in the SB group was lower than in the non-SB group in 6 hours after incision. In the comparison test for the changes in IL-6 concentration (∆T<sub>1</sub>–T<sub>2</sub>), the SB group was 8,817 ± 3,247 pg / mL, and the non-SB group was 8,809 ± 3,812 pg / mL (p=0.994). This means, there were no differences in the increase in IL-6 concentration between 2 groups 24 hours after surgery (Table 3).

When comparing the two groups, there was no discernible difference in the baseline concentration—the first NLR count obtained following induction (5.54 (4.30-8.04 in SB group, and 7.1 (4.25-7.98) in the non-SB group; p=0.102). Six hours after the incision, the SB group's NLR...
count was notably lower than the non-SB group's (6.40±1.17 vs 7.20±0.79; p<0.015). Between the two groups, there were no appreciable variations in NLR count 24 hours following surgery (6.80±1.17 vs 7.33 (5.83-8.09); p=0.083) (Table 4).

In the comparison test for the changes in NLR count (∆T

1

–T

0

), the SB group was 0.44 ± 1.69, the non-SB group was 0.52 ± 1.16 (p=0.850). This means, there were no differences in the changes NLR count between 2 groups in 6 hours after surgery (Table 5).

The results of this study are in line with research by Yang et al. who found that IL-6 concentrations were significantly lower in the scalp block group 6 hours after incision in elective craniotomy patients due to cerebral aneurysms. These results also support the administration of promising local anesthetics associated with anti-inflammatory effects in elective craniotomy patients. In the event of tissue damage, the substance released by sensory nerve endings produces inflammation of the target tissue, which will then become a neurogenic inflammatory response. The main key to neurogenic inflammation is that the use of 0.5% ropivacaine is able to provide an anti-inflammatory effect on elective craniotomy by suppressing the increase in IL-6 concentrations. The termination of IL-6 production. Although when exposed to environmental stresses such as tissue injury, IL-6 is expressed both immediately and momentarily. Eliminating the source of stress will also be followed by a decrease in IL-6 levels with a cascade of degradation and termination of IL-6 production. Although the cause is still unknown, it does not rule out the possibility of dysregulation and IL-6 production that continues to occur even though the source of stress

**Figure 1.** The trend of change in IL-6 concentrations in the SB group.

**Figure 3.** Increased concentrations of IL-6 during surgery indicate that IL-6 has a strong relationship with the degree of surgical trauma up to 24 hours after surgery. When exposed to environmental stresses such as tissue injury, IL-6 is expressed both immediately and momentarily. Eliminating the source of stress will also be followed by a decrease in IL-6 levels with a cascade of degradation and termination of IL-6 production. Although the cause is still unknown, it does not rule out the possibility of dysregulation and IL-6 production that continues to occur even though the source of stress.

**Table 4.** NLR count

<table>
<thead>
<tr>
<th></th>
<th>Scalp Block (Mean ± SD)</th>
<th>Non Scalp Block (Mean ± SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₀</td>
<td>5.54 (4.30 – 8.04)</td>
<td>7.1 (4.25 – 7.98)</td>
<td>0.102</td>
</tr>
<tr>
<td>T₁</td>
<td>6.40 ± 1.17</td>
<td>7.20 ± 0.79</td>
<td>0.015</td>
</tr>
<tr>
<td>T₂</td>
<td>6.80 ± 1.17</td>
<td>7.33 (5.83 – 8.09)</td>
<td>0.083</td>
</tr>
</tbody>
</table>

a: data is normally distributed; b: data is not normally distributed.

c: Mann-Whitney U d: Independent T-test

**Table 5.** Changes in the NLR count

<table>
<thead>
<tr>
<th></th>
<th>Scalp Block (Mean ± SD)</th>
<th>Non Scalp Block (Mean ± SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆T₀ – T₁</td>
<td>0.44 ± 1.69</td>
<td>0.52 ± 1.16</td>
<td>0.850</td>
</tr>
<tr>
<td>∆T₁ – T₂</td>
<td>1.21 (-3.37 – 2.55)</td>
<td>0.577 ± 1.27</td>
<td>0.242</td>
</tr>
</tbody>
</table>

a: data is normally distributed; b: data is not normally distributed.

c: Mann-Whitney U d: Independent T-test

**DISCUSSION**

In this study IL-6 concentrations at six hours after incision in the SB group were lower than in the non-SB group (p<0.001). Furthermore, when a comparison test was carried out to see whether the change in baseline IL-6 concentrations and 6 hours after incision in the two groups was significantly different, it was found p=<0.001 which means that the change in IL-6 concentrations from baseline and 6 hours after incision (ΔT₀–T₁) in the SB group was significantly lower than the non-SB group (Table 3). IL-6 concentrations at 24 hours after surgery did not differ significantly in the two groups (p=1.21). The difference between IL-6 baseline concentration and at 24 hours after surgery (ΔT₀–T₂) also showed no significant differences (p=0.994). It can be assumed that the use of 0.5% ropivacaine is able to provide an anti-inflammatory effect on elective craniotomy by suppressing the increase in IL-6 concentrations.
is not in line with research by I Gusti Agung et al., which showed that after surgery, the NLR value was significantly different in the scalp block group. The NLR value was lower than that of the group without the scalp block. However, if we take a look at the study, we obtained a median duration of surgery of 155 minutes in the scalp block group and 180 minutes in the non-scalp block group. This means that after surgery, sampling in the study ranged from 3-6 hours, the same as the second sampling in this study, which was 6 hours after incision. The NLR values of both groups 24 hours after surgery showed insignificant results with a p=0.083. Furthermore, the comparison test of the difference between baseline NLR count and 24 hours after surgery (∆T₀-T₂) also showed the same results p=0.242.

The use of regional anesthesia decreases the inflammatory response and is associated with the modulating effect of local and systemic inflammatory responses. The neutrophil-lymphocyte ratio is one of the immunosuppressive biomarkers where scalp block can lower NLR. These results are in line with research conducted by Lan Zheng et al. in patients with glioblastoma who found no significant difference in NLR values 24 hours after surgery. These results may be due in addition to the neutrophilia and lymphopenia effects of tumors as well after surgery steroid use that can interfere with the immune response where Fuca et al. get absolute neutrophil values and NLR values higher in patients receiving steroid therapy.

In this study, we can see that the addition of a scalp block to craniotomy surgery can suppress the increase in perioperative NLR, especially at 6 hours after incision. This significant effect that occurs 6 hours after incision may be related to neutrophil activity, which is the first acute phase response that infiltrates tissue with a half-life of 4-10 hours. Neutrophils will increase to their peak <6 hours after physiological stress occurs. However, in this study, the use of a scalp block cannot suppress pro-inflammatory mediators for up to 24 hours after surgery. This is possible first because the effect of scalp block in general can reduce pain values up to 8 hours after surgery if done before incision.
and only up to 12 hours after surgery if done during skin closure after surgery.\textsuperscript{17} In this study, we can see that the addition of a scalp block to craniotomy surgery can suppress the increase in perioperative NLR, especially at 6 hours after incision. This significant effect that occurs at 6 hours after incision may be related to neutrophil activity which is the first acute phase response that infiltrates tissue with a half-life of 4-10 hours.\textsuperscript{3} Ropivacaine is not able to suppress NLR that has increased 3-5 times due to chronic inflammatory processes in patients with tumors.

The effects of local anesthesia on NLR are still not fully understood, but on this basis, ropivacaine is a local anesthetic drug that works by inhibiting nerve conduction. Elimination of local anesthesia is followed by the return of nerve conduction mechanisms. In regional anesthesia, there will be an anti-inflammatory effect due to the block in the C nerve fiber, thereby decreasing cytokine production and decreasing sympathetic nerve activity. Afteroperative pain is caused mainly by local inflammation and activation of the C nerve fiber, which can be inhibited by decreasing cytokine production so as to limit the inflammatory response after tissue trauma.\textsuperscript{3}

Another study said that ropivacaine 0.5% for scalp nerve block in craniotomy could provide analgetic effects up to 4 hours after surgery, with an average length of surgery of 4.27 hours.\textsuperscript{18} Assuming that the analgetic effect describes the length of action of ropivacaine on peripheral nerve blocks, the pattern of increasing IL-6 and NLR concentrations in this study is in line with the assumption of the length of action of ropivacaine. However, there are also other studies that say that scalp block with 0.5% ropivacaine can reduce pain up to 12 hours after craniotomy, with the average length of surgery being 4.6 hours.\textsuperscript{19} From that study, it means that ropivacaine can reduce pain up to 16.6 hours after being injected. IL-6 and NLR themselves are some of the factors that cause pain after craniotomy, which, in this study, appeared to inhibit production by ropivacaine through scalp block up to 6 hours (360 minutes) after incision. With regard to immunomodulatory properties, local anesthesia has been shown to directly affect PMNs, as well as the function of macrophages and monocytes. Ropivacaine and lidocaine decrease TNF-α upregulation induced CD11b/CD18 surface expression on PMN in vitro. In healthy patients sedated for brief procedures, where the inflammatory response is typically balanced, well-controlled, and limited in duration, anesthesia may not have a clinically significant effect on immune function because the effects of anesthesia on the immune system are generally too small when compared to effects caused by major surgery or trauma.\textsuperscript{20}

Some of the weaknesses of this study include: first, this study did not take into account the relationship of neutrophils and lymphocytes as stand-alone factors for biomarkers, so it cannot be evaluated which factor is dominant in changes in the ratio of neutrophil lymphocytes. Second, the study did not assess the association between patients’ diagnoses and IL-6 and NLR levels. Third, the study did not link the length of surgery with IL-6 and NLR levels.

**CONCLUSION**

Regional anesthesia has been shown to modulate inflammatory and immunosuppressive responses in surgery. This study showed a significant effect at 6 hours after incision on IL-6 and NLR. In the scalp block group, the IL-6 concentration and NLR value at 6 hours after incision were significantly lower than the non-scalp block group. In this study, scalp block suppresses pro-inflammatory mediators for only 6 hours after incision. It is most effectively used as an adjuvant for the head pinning procedure or incision. The use beyond 6 hours as intraoperative pain control, pain management in the ICU, or chronic pain prevention may not be enough and may require additional opioids in this study. The immunomodulating effect of scalp block with 0.5% ropivacaine in elective craniotomy surgery may need further evaluation.

**ETHICAL CLEARANCE**

The research was approved by the Ethical Committee (0769/KEPK/IX/2023) of Dr. Soetomo Hospital Surabaya, Indonesia.

**CONFLICT OF INTEREST**

The authors declared no conflict of interest.

**FUNDING**

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**AUTHOR’S CONTRIBUTION**

All authors significantly contributed to conceiving and designing the study.
collecting and analyzing data, drafting the article, critically revising it for important intellectual content, and approving the final version for publication.

REFERENCES


