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The Effect of Greater Auricular Nerve Block and Auriculotemporal Nerve Block on The Expression of Inflammatory Factors TNF-α and IL-6 in Mastoidectomy Surgery: A Randomized Controlled Trial

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ABSTRACT

Background: The immune system can be triggered to release different inflammatory mediators like TNF-α and IL-6 in response to trauma and surgical stress. These cytokines in the acute inflammatory reaction take 4 to 6 hours to elicit a response after the initial trigger and can last up to 24 hours. Greater auricular nerve (GAN) and auriculotemporal nerve (ATN) blocks with 0.5% ropivacaine local anaesthetic potentially suppress this inflammatory response. This study evaluates the effectiveness of these blocks on TNF-α and IL-6 expression in mastoidectomy, considering the crucial role of these cytokines in acute inflammatory responses. Methods: The study enrolled 36 patients scheduled for elective mastoidectomy between November 2024 and January 2025. General anesthesia was administered to all participants, while patients in the treatment arm also received greater auricular nerve (GAN) and auriculotemporal nerve (ATN) blocks. Inflammatory markers TNF-α and IL-6 were measured at two timepoints: after general anesthesia induction and following the surgical procedure. Statistical tests will use comparative tests. Results: The research indicated that GAN and ATN blocks utilizing 0.5% ropivacaine significantly mitigated the elevations of TNF-α and IL-6 after mastoidectomy. The block group exhibited no significant elevation in TNF-α ($P=0.595$) and IL-6 ($P=0.420$) postoperatively, while the control group demonstrated large elevations ($p<0.001$) in both markers. Postoperative levels of TNF-α ($P<0.001$) and IL-6 ($P<0.001$) exhibited substantial differences between groups, demonstrating the efficacy of GAN and ATN blocks in preventing and reducing the inflammatory response. Conclusion: GAN and ATN blocks with 0.5% ropivacaine in elective mastoidectomy significantly inhibit postoperative increases in TNF-α and IL-6 levels. The use of 0.5% ropivacaine demonstrates an anti-inflammatory effect in elective mastoidectomy surgery.

Keywords: *Mastoidectomy, GAN and ATN block, 0.5 % Ropivacaine, Inflammatory, TNF-α, IL-6.*

1. INTRODUCTION

Surgical trauma and stress can stimulate the immune system to generate diverse inflammatory mediators to fulfill the body's defensive function [1]. TNF-α, IL-1, and IL-6 are important cytokines involved in the initial inflammatory reaction, usually appearing 4 to 6 hours after the initial trigger and potentially lasting up to 24 hours [2]. The rise of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 will help to coordinate all of the responses and cause organ failure [3]. Local anaesthetics induce intracellular anti-inflammatory mechanisms mediated by the Gq protein complex, deactivate overly active granulocytes, inhibit NMDA (N-methyl D-aspartate) receptor signalling, induce vasodilation, demonstrate antimicrobial activity, produce sympatholytic effects, and modulate inflammatory responses by altering the production and secretion of various inflammatory mediators including eicosanoids, histamine, prostaglandins, and cytokines [4]. Local anesthetics have the ability to hinder the movement of axons and the release of different pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 [5].

Regional anaesthesia is often employed alongside general anaesthesia in certain surgical procedures [6]. Integrating peripheral nerve block methodologies General anesthesia has various advantages when utilized in conjunction with other modalities rather than in isolation [7]. The intention of the current research is to investigate the effects on inflammatory mediator TNF-α and IL-6 concentrations of utilizing GAN and ATN blocks with the local anaesthetic ropivacaine 0.5% during mastoidectomy surgery.

2. METHODS

A randomized controlled study (RCT) was performed including individuals undergoing elective mastoidectomy surgery at RSUD Dr Soetomo Surabaya from November 2024 to January 2025. In accordance with the code number 1152/KEPK/XI/2024, the study was carried out in a descriptive approach and was approved by the Ethics Committee of Doctor Soetomo General Hospital Surabaya. The study employed a cross-sectional design, involving 36 patients who underwent elective mastoidectomy surgery. The study comprised two groups, each containing 18 participants. Individuals between the ages of 18 and 60, categorized as American Society of Anaesthesiologists (ASA) I–II, met the requirements for inclusion, possessing a Glasgow Coma Scale (GCS) score of 15, and undergoing elective mastoidectomy surgery. Exclusion criteria encompassed patients with cardiovascular abnormalities, severe kidney and liver dysfunction, allergies to local anaesthetic drugs, individuals with a systemic infection, infections at the injection site, patients with autoimmune diseases, obese individuals, uncontrolled diabetes mellitus and other systemic diseases, uncontrolled hypertension, coagulation disorders, neuromuscular diseases, failed blocks, and peripheral neuropathy.

TNF-α and IL-6 were assessed in this work at two intervals: immediately following an anaesthetic induction and immediately following surgical completion. The levels of TNF-α and IL-6 were assessed through the use of ELISA kits, which utilize an enzyme-linked immunosorbent assay (ELISA) technique. Anesthesia was induced through the administration of fentanyl at a dosage of 1-2 mcg/kg, propofol at 1-2 mg/kg, and rocuronium at 0.6–1.0 mg/kg. Following induction, the initial blood sample was collected from both groups. In group A, a GAN and ATN block were administered with 0.5% ropivacaine. No block intervention was given to the control subjects (group B). An abrupt elevation in blood pressure or heart rate exceeding 20% above baseline during surgery was classified as unpleasant, leading to the administration of a 1 mcg/kg fentanyl bolus as rescue analgesia. Upon completion of the surgery, a second blood sample was collected (Figure 1).

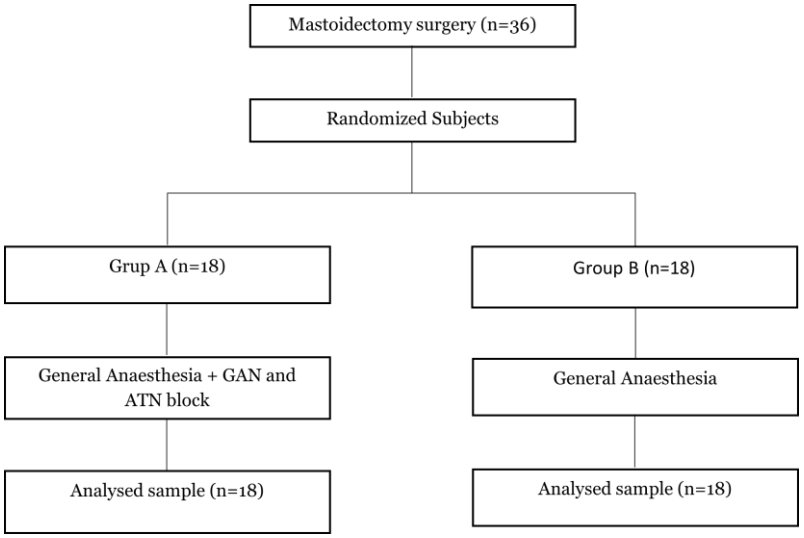

Figure 1 Flowchart of the research methodology

SPSS 26 software was used for a detailed analysis of data collected from different sources. Chi-Square analysis was employed to check for demographic similarity among participants. The Shapiro-Wilk test was utilized to assess the conformity of the data. Depending on the distribution of the data, either the Mann-Whitney test or a two-independent T-test was employed to compare the levels of TNF-α and IL-6 between the two groups.

3. RESULTS

The study covered a total of 36 patients. Chi-square analysis revealed that the two groups showed homogeneity about the homogeneity of variations, gender, age, weight, BMI, PS ASA, and surgical duration. Table 1 captures the demographic features of the subjects.

Table 1. Demographic characteristics of the subjects

Characteristics	Group		*p value*
	Group A (n=18)	Group B (n=18)	
Genre			
Male	9 (50%)	6 (33.3%)	0.499 [a]
Female	9 (50%)	12 (66.7%)	
Age			
Range (year)	18 - 60	18 - 60	0.950 [c]
Mean ± SD	37.39 ± 13.40	37.11 ± 13.10	
Weight			
Range (kg)	50 - 83	54 - 98	0.333 [c]
Mean ± SD	63.61 ± 8.08	65.89 ± 9.60	
BMI			
Range (kg/m^2)	20.10 - 29.70	21.00 - 29.10	0.107 [b]
Mean ± SD	23.77 ± 2.24	25.02 ± 2.42	
ASA			
1	8 (44.4%)	7 (38.9%)	
2	10 (56.6%)	11 (61.1%)	
Duration of Surgery			
Range (minutes)	180-300	190-340	0.962 [c]
Mean ± SD	255.56 ± 38.68	255.83 ± 41.80	

GAN = greater auricular nerve, ATN = auriculotemporal nerve
a = Chi-Square
b = Independent T test
c = Mann-Whitney test

At baseline (T0), the groups did not show any notable variations in inflammatory markers according to statistical analysis. TNF-α levels measured 38.80 pg/mL (23.23-50.10) in the GAN and ATN blocks group compared to 41.01 pg/mL (20.53-50.50) in the control group (p=0.159). Similarly, IL-6 levels were 73.44 pg/mL (36.40-94.21) in the GAN and ATN blocks group versus 75.23 pg/mL (35.73-96.16) in the control group (p=0.476). As demonstrated in Table 2, the block group showed substantially lower TNF-α levels compared to the control group {69.43 (38.76-105.55) vs 92.62 (44.21-112.18) pg/mL; p=0.002}. Similarly, IL-6 concentrations were decreased in the block group when compared to the control group. Post-mastoidectomy inflammatory response was attenuated in the block group, evidenced by less pronounced elevations in both TNF-α and IL-6 markers relative to the control group. With p = 0.001, the GAN and ATN block groups showed values of 1.50 (-14.82 – 5.40) and 3.07 (-29.52 – 17.25) pg/mL, respectively, while the control group showed values of 8.04 (1.18 – 12.99) and 16.56 (5.64 – 25.9).

Table 2. TNF-α and IL-6 Concentration

Time	Group sample Median (min-max)		*p value**
	Group A (n=18)	Group B (n=18)	
TNF-α (pg/mL)			
T0	38.80 (23.23 – 50.10)	41.01 (20.53 – 50.50)	0.159
T1	34.51 (22.52 – 55.51)	50.27 (22.38 – 59.01)	0.002
ΔT	1.50 (-14.82 – 5.40)	8.04 (1.18 – 12.99)	<0.001
IL-6 (pg/mL)			
T0	73.44 (36.40 – 94.21)	75.23 (35.73 – 96.16)	0.476
T1	69.43 (38.76 – 105.55)	92.62 (44.21 – 112.18)	0.013

ΔT	3.07 (-29.52 – 17.25)	16.56 (5.64 – 25.94)	<0.001

GAN = greater auricular nerve, ATN = auriculotemporal nerve
T0 = after induction of anesthesia
T1 = after surgery
ΔT = delta, difference T0-T1
*Mann-Whitney test

An observation was made regarding the decrease in the average concentration of TNF-α in the block group according to the analysis of the data presented in Table 3 (36.09 ± 8.68 to 35.36 ± 8.69) pg/mL; p=0.595, whereas in the non-block group, a significant increase in TNF-α concentration was noted {41.01 (20.53 – 50.50) to 50.27 (22.38 – 59.01)} pg/mL; p<0.001 before and after surgery. There were no notable discrepancies in the levels of IL-6 in the block group when compared to the control group. However, in the control group, there was a significant increase in IL-6 levels {75.23 (35.73 – 96.6 – 112.18} p=0.420 vs p < 0.001. This study found an increase in the levels of TNF and IL-6 in the control group.

Table 3. Change TNF-α and IL-6 Concentration

Group	Sample Mean ± SD Median (min-max)		*p value*
	T0	**T1**	
TNF-α (pg/mL)			
GAN and ATN blocks	36.09 ± 8.68	35.36 ± 8.69	0.595 [a]
Control	41.01 (20.53 – 50.50)	50.27 (22.38 – 59.01)	< 0.001 [b]
IL-6 (pg/mL)			
GAN and ATN blocks	73.44 (36.40 – 94.21)	69.43 (38.76 – 105.55)	0.420 [b]
Control	75.23 (35.73 – 96.16)	92.62 (44.21 – 112.18)	< 0.001 [b]

GAN = greater auricular nerve, ATN = auriculotemporal nerve
T0 = after induction of anesthesia
T1 = after surgery
a = Paired T-test
b = Wilcoxon Sign Rank test

Discussion

The purpose of this study was to evaluate the influence of sympathetic blockade on inflammatory markers by measuring TNF-α and IL-6 concentrations before and after administering 0.5% ropivacaine for greater auricular nerve and auriculotemporal nerve blocks in mastoidectomy patients. The results showed that using the local anesthetic, 0.5% ropivacaine, the GAN and ATN blocks affected inflammatory variables. After the block, 0.5% ropivacaine lowered and Reduced levels of TNF-α and IL-6 were observed in comparison to the control group, according to the study findings.

TNF-α is a pro-inflammatory cytokine that serves as an important marker for the occurrence of inflammatory activity. It is mainly generated by activated macrophages, monocytes, T cells, and natural killer cell, although it is also synthesised in smaller amounts by various other cells, including fibroblasts, smooth muscle cells, nerve cells, and tumour cells. TNF-α initiates the inflammatory process by stimulating cytokines and growth factors, while also enlisting specific immune cells. Increased vascular permeability brought about by elevated TNF-α helps macrophages and neutrophils migrate to the damaged tissue area. In contrast, decreased TNF-α levels have been proven to support the restructuring or substitution of damaged tissue by boosting the growth of fibroblasts. Trauma, sepsis, infections, and rheumatoid arthritis are among the acute and chronic inflammatory diseases whose TNF-α concentrations are noted to be higher. TNF-α is produced more rapidly than other pro-inflammatory cytokines. Generally, an increase in TNF-α levels after trauma is detrimental to the body and can trigger central sensitisation and hyperalgesia by enhancing the transmission of excitatory synapses. TNF-α levels were found to increase in trauma patients right after the trauma and stayed high for a maximum of three days. After five days post-trauma, the levels of plasma TNF-α slowly went back to baseline [8].

At this study, at baseline (T0), TNF-α concentrations in the block group ranged from 23.23 to 50.10 pg/mL with a median of 38.80 pg/mL, while the unblocked group showed levels between 20.53 and 50.50 pg/mL with a median of 41.01 pg/mL. TNF-α concentration increased with age and in obesity [9]. Furthermore, TNF-α and IL-6 exhibited a favorable correlation with BMI, WC, and CRP, consistent with prior results [10], [11]. A research was conducted to investigate the TNF-α levels in individuals suffering from chronic suppurative otitis media, revealing a range of 13.62-35.70 pg/mL in the blood serum [12]. In comparison to healthy individuals, subjects with chronic suppurative otitis media and active mucosa had significantly

higher average serum TNF-α levels (46.373±41.76 pg/mL versus 15.021±7.16 pg/mL; p=0.004) [13]. Another study conducted by Edward Y et al. showed that TNF-α levels in patients with cholesteatoma were higher compared to normal patients [14].

During the second sampling period (T1), the levels of TNF-α were noticeably elevated in the control group compared to the group that was blocked (p=0.002). Further analysis revealed that the control group experienced a substantial increase in TNF-α levels after surgery compared to baseline measurements (p<0.001). In contrast, the blocked group showed no significant elevation in TNF-α levels between the initial and postoperative measurements (p=0.595). Previous studies on ropivacaine reported a similar condition. In individuals with severe trauma, ropivacaine injection for stellate ganglion block can markedly diminish the levels of IL-1, IL-6, and TNF-α [15]. An in vitro study pointed out that ropivacaine caused a decrease in TNF-α expression by macrophages stimulated with lipopolysaccharide [16]. Elderly patients with pelvic fractures can reduce their average levels of TNF-α by undergoing a femoral nerve block with ropivacaine [17]. Studies show that administering ropivacaine for infraclavicular blocks during arteriovenous fistula repair surgery can lead to a reduction in TNF-α levels within one hour after the block [18]. In a study on lipopolysaccharide-stimulated leucocyte production in human blood samples, Weinschenk et al. discovered that there was no noteworthy difference in the levels of TNF-α between the control and treatment groups when local anesthetics were administered [19]. With an average incision time of 30 to 60 minutes in the study using a scalp nerve block, the effect of ropivacaine in inhibiting TNF-α production in craniotomy surgery studies was examined [20].

In this study, the post-surgery IL-6 levels in the group that received the block were notably lower compared to the control group. Furthermore, a study revealed that there was a noticeable variance in IL-6 levels pre and post-operation among the two sets, with a p-value below 0.001. The findings suggest that, unlike the control group, the block group showed a notably smaller alteration in IL-6 levels from the initial to the subsequent samples (T0-T1). The use of 0.5% ropivacaine is believed to decrease the rise in IL-6 levels, potentially exhibiting anti-inflammatory properties following elective mastoidectomy. What this study found is same with Yang et al., indicating that patients undergoing elective craniotomy for cerebral aneurysms had significantly lower IL-6 levels six hours after the incision [21]. These findings further back up the application of prospective local anesthetics with anti-inflammatory properties for patients undergoing elective craniotomy [22]. Local anesthesia drugs decrease the body's inflammatory reaction by inhibiting the production of substance P, which then hinders nerve function in injured areas [23], [24], [25].

For up to 24 hours following surgery, elevated levels of IL-6 point to a clear correlation between IL-6 and the degree of surgical trauma. Environmental stressors, such as tissue injury, induce the immediate and transitory expression of IL-6. Eliminating the root cause of anxiety can lead to a decrease in IL-6 levels, triggering a chain reaction that results in the breakdown and halt of IL-6 production. The origin remains unidentified; nevertheless, this does not preclude the potential for dysregulation and persistent IL-6 production subsequent to the removal of the stressor [26]. During elective surgeries, there is an increase in serum IL-6 levels, reaching different peak values. The precise mechanism accountable for the synthesis and secretion of IL-6 remains unidentified [27]. Szabo et al. discovered that immunosuppressive patients exhibited elevated levels of IL-6 compared to normal patients. The patient's prognosis could depend on finding a balance between immunosuppressed and inflammatory states; The duration of IL-6 following trauma may be critical for achieving homeostasis and averting adverse outcomes such as multiple organ failure and infection [28]. The levels of IL-6 are directly correlated with the extent of this altered immune reaction [29].

Serban's et al. study found that patients with simple chronic suppurative otitis media had the highest average serum IL-6 levels, which ranged from 57.23 pg/mL to 193.33 pg/mL [30]. The presence of cholesteatoma in patients suffering from chronic suppurative otitis media, whose IL-6 levels ranged from 240.62 to 519.63 pg/mL, followed this trend. Meanwhile, the group with recurrent chronic suppurative otitis media recorded IL-6 levels of 87.71 pg/mL and 147.38 pg/mL. These values are higher compared to the control subjects (healthy individuals), in whom the IL-6 levels range from 3.09 pg/mL to 8.06 pg/mL [30]. In the Video-Assisted Thoracoscopy Surgery procedure, the addition of dexmedetomidine to the serratus anterior plane block with ropivacaine demonstrated that the use of dexmedetomidine as an adjuvant can reduce the increase in IL-6 at 6 hours post-incision, as well as decrease the need for opioids during and after the surgery. However, the difference was not significant at 24 hours post-incision [31]. Examinations performed by Desiree et al. indicated that the use of a scalp block with 0.5% ropivacaine significantly ($p < 0.001$) inhibited the increase in IL-6 levels 6 hours post-craniotomy surgery between the group that received the scalp block (75.60 ± 2.81 pg/mL) and the group that did not receive the scalp block (83.974 [80–89.18] pg/mL). Observations of IL-6 levels 24 hours post-craniotomy surgery revealed no considerable difference (p=0.121) in the increase of IL-6 levels between the scalp block group (83.50 ± 2.28 pg/mL) and the non-scalp block group (84.63 ± 2.25 pg/mL) [32].

Under normal conditions, IL-6 secretion occurs as a response to tissue damage, such as during sterile surgery, viral stimuli, and cytokine secretion released by various cells, including macrophages, monocytes, muscle cells, and other epithelial cells. This conclusion is consistent with other studies indicating that IL-6 levels in cholesteatoma are four times higher compared

to IL-6 levels in normal patients. The elevated levels of IL-6 can be attributed to the secretion of osteoclastogenic cytokines, such as TNF-α and IL-1, by macrophages during inflammatory processes, thereby playing a role in the development of bone resorption associated with cholesteatoma. Interleukin-1 stimulates fibroblasts and macrophages, prompting the synthesis of collagen and prostaglandin (PGE2), which ultimately contributes to bone degradation. Macrophages also produce TNF-α and IL-1 as a physiological response to antigens originating from bacteria [33].

4. CONCLUSION

GAN and ATN nerve blocks with 0.5% ropivacaine during mastoidectomy surgery effectively suppress the inflammatory response. Pro-inflammatory markers TNF-α and IL-6 remained relatively stable in the block group but showed significant elevation in the non-block group. These findings demonstrate that peripheral nerve blockade using 0.5% ropivacaine exhibits anti-inflammatory properties through its inhibitory effect on pro-inflammatory mediator release.

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