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# The effects of Sevoflurane and Propofol on IFN-γ And IL-12 Study On Patients With Craniotomy Surgery

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***Abstract*— *Background: It has been documented that some anesthesia agents have effects on immune response, and may therefore, affect post-operative patients' condition. This research aimed to analyze the effects of sevoflurane and propofol on IFN-γ and IL-12 on patients with craniotomy surgery.*

*Methods: The study design is an observational study by using pre-and-post design. The subjects are patients aged 30-55 years old who were undergoing craniotomy surgery for tumor removal at Dr. Kariadi Hospital. The differences in the means before and after the same anesthesia agent were analyzed with paired T-test if the data distribution is normal, or with the Wilcoxon rank-sum test if the data distribution is not normal. The difference in the means between the two different anesthesia agents was analyzed using an independent T-test if the data distribution is normal, or with the Mann-Whitney test if the data distribution is not normal were applicable.*

*Results: The levels of IFN-γ before and after anesthesia with sevoflurane were 71.3 and 77.0 pg/ml respectively (p=0.2). Those for IL-12 were 2.3 and 3.4 pg/ml respectively (p=0.049). The levels of IFN-γ before and after anesthesia with propofol was 77.8 and 88.6 pg/ml respectively (p=0.006). Those for IL-12 were 3.2 and 4.2 pg/ml respectively (p=0.007). The increase of the IFN-γ level in the sevoflurane group was 0.57 pg/ml and in the propofol group was 0.83 pg/ml (p=0.19). The increase of IL-12 level in sevoflurane group was 0.98 pg/ml and in propofol group was 7.35 pg/ml (p0.26).*

*Conclusion: The level of IFN-γ increased significantly after anesthesia with propofol. The level of IL-12 increased after anesthesia with both sevoflurane and propofol. However, the increase difference between sevoflurane and propofol is not significantly different. Propofol and sevoflurane exerts comparables effect pro-inflammatory response in patients undergoing craniotomy surgery*

***Keywords*— *Sevoflurane, Propofol, IFN-γ, IL-12, Craniotomy Surgery.***

## I. INTRODUCTION

The immune system is important to live because there are a lot of hazardous pathogens in the environment. The immune system will protect us from those pathogens and diseases. The immune system identifies and eliminates pathogens by inducing innate immune responses and then adaptive response. Our immune system is influenced by internal factors such as HLA and external factors, such as medications. Some anaesthetic agents have been reported to influence the immune system, and thereby, influence patients condition after surgery, including the response to the overall management such as infection and malignancy.[1]

For the study of the effects of anesthetic drugs on the immune system, various for vitro studies with human immune cells, or animal models were used. Such studies have shown a range of effects, such as improvements in the number and role of immune cells, and effects on patterns of varying immune mediator secretions, Impact of the inflammatory response by releasing cytokines during the postoperative period. Such results can be clinically important as the balance between cytokine secretions pro and anti-inflammation also tissue injury.[2]

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Several studies have shown the effect of anesthetics on immune responses even in few days after administration.[3]

Impaired immunity in vivo is frequently found following major surgery and is multifactorial. Procopio et.al performed a randomized clinical trial to assess the independent impact on human immune function between general anesthesia (GA) and lumbar epidural anesthesia (LEA) in the absence of surgical trauma. To the pulmonary clinician, this heralds the dawn of innovative treatments in different fields such as diseases, allergies, and cancer.[4] The immune system mediates many adverse drug reactions. It may be because the drug's therapeutic role affects the immune system.[4] Mechanical ventilation can lead to ventilator-induced lung injury in animals and can contribute to acute lung injury or acute respiratory distress syndrome in humans, both high-strength mechanical ventilation and hyperoxia.[5] In the anesthesia community, the immunopathological effects of prolonged exposure to inhalation anesthesia have reduced neutrophils, leukocytes, B lymphocyte cells and natural killer cells (NK), which are the main features of the immune system.[6] A recent research examining the effects of immunity from first-inhalation anesthesia, halothane, showed that CD4, CD8 cells and B lymphocytes significantly decreased with repeated doses of halothane.[7]

Sevoflurane is a modern form of inhalation anesthesia widely used in the practice of anesthesia today.[8] Sevoflurane is a highly fluorinated methyl-isopropyl ether typically used in the induction and maintenance of general anesthetics. In addition to the anesthetic function it was also proven to be involved in the protective cycle under hypoxia or endotoxemia conditions, often studied in neurons and myocardial tissue.[9] Research conducted by Kidani et al. examined the effect of sevoflurane pretreatment on mortality and inflammation during endotoxin-induced mice shock. Researchers reported that this pretreatment significantly increased the blood pressure, acid-base balance, and decreased the mortality and plasma rates of TNF-α and IL-6, suggesting a weakening of the inflammatory response. [10]

Sevoflurane induces postconditioning symptoms following exposure to hypoxia, or lipopolysaccharides (LPS). In this regard, the postconditioning of sevoflurane has been shown to reduce oxidative blood and brain damage and increase the immunity index in mice with ischemic reperfusion of the brain.[11] Importantly, data from Yue et al. evaluating sevoflurane postconditioning in an acute lung injury model in vitro showed that inflammatory mediators, chemotaxis and neutrophil adherence were significantly reduced.[12]

Propofol is an intravenous anesthetic and is used for surgical sedation. In vitro studies show that propofol does not impair immune function, and can improve NK cell activity.

IL-12 is also known as a stimulant factor for T-cells, since it contributes to the differentiation of CD4 T cells into TH1 cells. IL-12 family cytokines had important therapeutic targets or agents in a number of inflammatory diseases and induced surgical stress.[13] Surgical stress activates the aid's dominant T-cell type 2 (Th2) status and disturbs the cytokine balance between Th1 and Th2. Anesthesia can suppress the stress response to surgery, so it can reduce the imbalance in the Th1/Th2 ratio.[14]

IFN-γ, or type II interferon, is a cytokine that is very critical to innate immunity and immune to viral infections, multiple bacterial infections, and protozoa. IFN-γ is an essential macrophage activator that induces the expression of MHC class II (main histocompatibility complex) molecules.[15]

This study aimed to investigate the immune system effects of sevoflurane by measuring IFN-γ and IL-12 in patients underwent craniotomy surgery for tumour removal, which is considered as a major surgery that potentially affects immune system through stress that it may impact.

A craniotomy is a skull opening procedure (cranium) with the purpose of detecting and restoring damage to the brain. The aim of the surgery is to open the skull so it can locate and restore brain damage. Intracranial procedure or also called craniotomy is an intracranial problem-related intervention.

## II. METHODS

The population of this study is patients aged between 30-55 years old underwent craniotomy surgery at Dr. Kariadi Hospital for tumar removal who fulfill the inclusion and exclusion criteria as follows:

**Inclusion Criteria**

a) Female or Male b) 30–55 years old patient

b) Elective craniotomy surgery for tumor removal

c) More than 2 hours use of sevoflurane or propofol anesthesia e) ASA I/II

**Exclusion Criteria**

a) Tuberculosis b) Chronic Infection c) HIV

The minimum sample size estimated with $\alpha = 0.05$ and $\beta = 0.8$ was 14 for each group. IN this research will be used 16 patients for every group.

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Differences in the means levels of IFN-γ and IL-12 before and after anesthesia with the same agent were analyzed with paired T-test or with the Wilcoxon rank sum test where applicable. The difference in the means between the two different anesthesia agents were analyzed using the independent T-test or with the Mann-Whitney test where applicable.

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## III. RESULTS AND DISCUSSION

**Characteristics of the Subjects**

*Table 1. Demographic Data*

| No | Descriptive | Propofol Group n (%) | Sevoflurane Group n (%) | p |
|---|---|---|---|---|
| 1 | Sex<br>- Male<br>- Female | <br>6 (37.5)<br>10 (62.5) | <br>3 (18.7)<br>13 (81.3) | 0.217 |
| 2 | Age,average (SD) | ± 45 (5.3) years | ± 44.4 (5.8) years | 0.7 |
| 3 | ASA<br>- I<br>- II | <br>12 (75)<br>4 (25) | <br>11 (68.7)<br>5 (32.3) | 0.361 |
| 4 | Kind of surgery | Intracerebral tumor | Intracerebral tumor | Not tested |

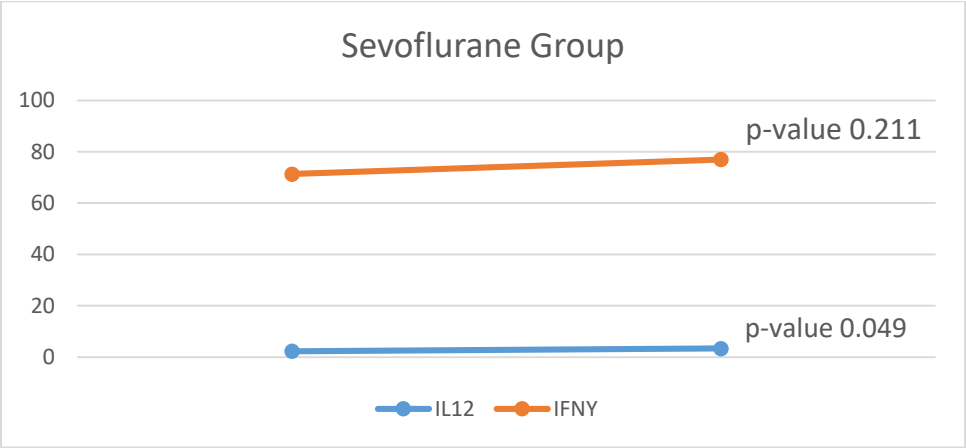
*Chi-square

** Independent t-test

*** Fischer's exact

The p-value showed that the subjects in the two groups were comparable with regards to gender, age, ASA, and type of surgery.

*The Effects of Sevoflurane on IFN-γ and IL-12 Levels*




*(*Wilcoxon rank sum test)*

*Graph 1. The Level of IFN-Y and IL-12 in Sevoflurane Group*

Graph 1 showed that the level of IFN-γ increased after anesthesia in sevoflurane group; however the difference was not statistically significant (p = 0.211). The level of IL-12 significantly increased after anaesthesia using sevoflurane (p = 0.049).

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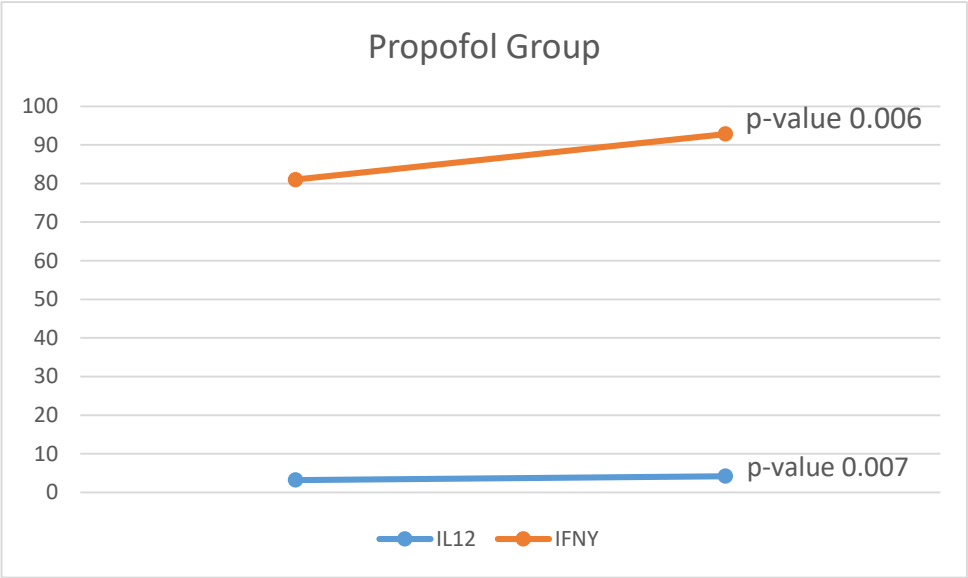
*The Effects of Sevoflurane on IFN-γ and IL-12 Level*




***(*Wilcoxon rank test)***

Graph 2. The Level of IFN-Y and IL-12 in Propofol Group

Graph 2. showed that the levels of both IFN-γ and IL-12 significantly increased after anesthesia using propofol.

The Comparison of Sevoflurane and Propofol on the Difference in IFN-γ and IL-12 Level

*Table 2. Difference in Level IFN-γ and IL-12 between Groups*

| **Variables** | **Groups** | | **p*** |
|---|---|---|---|
| | **Sevoflurane Medianof Difference (IQR)** | **Propofol Median of Difference (IQR)** | |
| **IFN-**γ (pg/ml) | 0.57(-0.12- 1.03) | 0.83 (0.28 – 1.6) | 0.19 |
| **IL-12** (pg/ml) | 0.98 (-5.27 -14.7) | 7.35 (1.45-16.4) | 0.26 |

(* Mann-Whitney test)

Table 4.4. showed that the level of both IFN-γ and IL-12 were not significantly differences in propofol group and in sevoflurane group;

**Discussion**

In this study, the effects of general anesthesia on pro-inflammatory cytokines INF-γ and IL12 were assessed in pre-and post-anesthesia on patients with craniotomy surgery. This study result showed that the level of both IFN-γ and IL-12 were significantly higher in the propofol group rather than in the sevoflurane group. IFN-γ is known as a pro-inflammatory cytokine that plays a central role in infections and autoimmune diseases. It is synthesized by human macrophages in a single cell of human macrophages, in addition to lymphocytes that contribute to the IFN-γ response, and provide another correlation between the innate and acquired immune response. Interferon is also available as a drug. Interferon in the form of drugs works by increasing the body's immune response and inhibiting the growth of viruses, bacteria, or cancer, and also have a role in the immune system.

IL-12 and interferon-gamma, actually represent the inflammation conditions, not directly the immune condition, but they can be considered to represent immune condition because IL-12 and interferon-gamma are pro-inflammation. Inflammation is a response to various kinds of trauma. This matter is the most important part of innate

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immunity, too is an initiator and also a regulator important in adaptive immune responses. Inflammation involves tissue micro vascularization affected, especially the postcapillary venules. System Immune patients undergoing surgery influenced by anesthetic actions as well as the act of surgery itself. Hypothalamic-pituitary-adrenal axis the sympathetic nervous system will be active along with stress surgery, blood transfusion, hypothermia, hyperglycemia, and pain. Anesthetic action causing direct emphasis on activity cellular and neuro-hormonal immune system therefore it influences cell function immunocompetent and expression and secretion inflammatory mediator. Immunosuppression by anesthesia especially occurs in patients of intracerebral tumors, such as natural killer (NK) dysfunction and lymphocytes which accelerate growth and metastasis of malignant cells that may worsen the prognosis. Leukocytes are part of innate immunity. The cellular component of immunity innate consists of several types of cells and many found at the entry point of the pathogen. Examples of these cells are natural killer cells (NK), polymorphonuclear cells (PMN), macrophages, and dendritic cells Neutrophil/lymphocyte ratio (NLR) is a simple marker of the inflammatory response. NLR value peripheral blood is used as a parameter that provides information on the relationship between the inflammatory environment and stress physiology. Postoperative Value of NLR in surgery patients undergoing spinal anesthesia lower compared to patients who undergo general anesthesia. If IL12 level increase, mean inflammation increase, this is mean that immune become increase (good condition). It has been shown that IL-12 cytokine has an effect on both immune and hematological functions. It has been shown to be necessary for the independent induction of IFN-γ T cells. Therefore, IL-12 thus function to stimulates and binds innate and acquired immune responses. When the patients undergo the surgery, therefore the surgical trauma and anesthesia influence the immunological and inflammatory responses. Anesthetic agents like sevoflurane and propofol modulate the inflammatory reactions in this sense. The stress of surgery will result in an increase of level IFN-γ and IL-12 as a response to the inflammatory reaction.

After surgery and give anesthesia, the result showed that the level of IFN-γ increased after anesthesia with sevoflurane; however, the difference was not statistically significant. Meanwhile, the level of IL-12 increased after anesthesia using sevoflurane; however, the increase was significant. Therefeore. This is because the patients' age also gives an effect on the increase of level IFN-γ and IL-12. Sevoflurane not give too significant effect to the patients between before and after surgery and given anesthesia. This indicates that sevoflurane can reduce patients' stress and good pro-inflammatory.

Another result of this study showed that the level of IFN-γ increased after anesthesia with propofol; however the difference was statistically significant, therefore hypothesis number 2 is accepted. The level of IL-12 increased after anesthesia using propofol, however, the increase was significant. In addition, the increase of IFN- γ and IL-12 were not significantly higher in propofol group indicating that propofol exerts not stronger proinflammatory response that sevoflurane. This finding were supported also by previous research done by Deegan et al. (2010) that reported there were not significantly different in cytokine levels between propofol and sevoflurane based anesthesia during breast cancer surgery.[15] Most inhaled anesthetics, opioids, local anesthetics, and other intravenous anesthetics can reduce immunity to a certain extent, which sometimes leads to an increased recurrence of malignant tumors. However, tramadol, selective nonsteroidal anti-inflammatory analgesics, and propofol have protective effects on the immune function of the body and can reduce the recurrence and metastasis of the tumor. Therefore, it is important to make a careful anesthesia plan and to select appropriate narcotic drugs for patients with malignant tumors, since these decisions will have a crucial impact on the therapeutic effect and prognosis.[16]

Also supported the result of a previous study done by Ji et al. (2011) that stated immune response in the process of tumor development is not just a single factor, but it plays a multifaceted role affecting tumor initiation, growth, progression, and other processes. The immune system regulates and promotes cancer programs, a process known as immunoediting. There are three phases to this process: elimination, balance, and escape. Although experimental evidence shows that inflammation can also promote the occurrence and development of tumors, the immune inflammatory response in colon carcinogenesis requires further study and is still under debate. Some clinical data show that the immune response inhibits the tumor. However, other investigators have concluded that the opposite is true. IL-12 is an early promoter of T-cell-induced inflammatory responses and can amplify the inflammatory response by promoting the release of proinflammatory cytokines. Intravenous anesthesia can maintain a safe, constant concentration of drug treatment during surgery and can reduce the stimulation of surgical trauma. Intravenous anesthesia can also reduce the intraoperative inflammatory response albeit affecting the patient's immune system function.

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Immune system disorders or inhibition during the perioperative period can cause postoperative complications, especially in cancer patients. Immunosuppression after surgery can accelerate the spread of residual cancer cells and promote a new transfer.[17]

The advantage of this study testing the different effects between anesthetic agents of propofol and sevoflurane in clinical setting, thus it describes what happens in the real patientas. However, this leads to the weakness of this study, i.e., could not eliminate bias from the surgical stress it self. The observation of the BIS (Bispectral Index) which indicate the depth of anaesthesia, as a confounding variable in the next study might be done to reduce such bias. A longer duration of observation period would still be necessary to clarify the possible effects of anesthetics on pro-inflammation cytokines after tumor craniotomy.

Although the strong proinflammatory property of propofol and sevoflurane is beneficial in preventing immunosuppression in cancer patients, the anaesthesiologists and surgeons must be more careful during and after the surgery, particularly on the manifestations of inflammatory reactions, such as fever, hemodynamic and respiratory instability. Sevoflurane may probably also exert proinflammatory reaction but to a smaller extend. Our findings should incite future studies to prove a potential medically important anesthesia agent's role with pro-inflammatory on other cytokines.

## IV. CONCLUSION

When sevoflurane was used as anesthesia agent, the level of IFN-γ dose not significantly increase while the level of IL-12 signifcantly increase.When propofol was used as anesthesia agent, the level of both IFN-γ and IL-12 increase significantly. The increase of both IFN-γ and IL-12 levels after anasthesia with sevoflurane and with propofol is not significantly different. Sevoflurane and propofol exert similar pro-inflammatory response in patients undergoing craniotomy surgery.

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