CHAPTER I

INTRODUCTION

1.1. Background

The immune system is important to life because there are a lot of hazardous pathogens in the environment. The immune system will protect us from that pathogens and diseases. The immune system identifies and eliminates pathogens by inducing innate immune responses and then adaptive response. Immunity innate, often known as normal or initial immunity, it is first line defense and refers to the system of protection that occurs long before infection. The epithelial membrane that prevents the entry of bacteria, phagocytic cells (neutrophils and macrophages), dendritic cells, natural killer cells (NK) and other plasma proteins is the main component of innate immunity, including the complementary network. Innate immunity's critical cellular reaction is inflammation, the mechanism by which the phagocytic cells are recruited and stimulated to remove microbes and viral removal, mediated by dendritic cells and NK. Adaptive immunity also known as acquired or specific immunity consists of a microbial mediated system, capable of identifying precisely called antigens microbial and non-microbial molecules.

Adaptive immune system such as lymphocytes comprising antibodies and cytokines and their constituents. The lymphocyte receptors in the innate immune system are far more complex and may identify large numbers of foreign substances. Adaptive immunity has 2 types that are humoral immunity, mediated by B-lymphocytes and secreted antibodies protecting against extracellular microbes and their toxins; and cellular or bacterial immunity mediated by T-lymphocytes protecting primarily against intracellular microbes. The two types of immunity obtained are related by the family of proteins known as cytokines, which play an important role in the activation, control and communication of immune cells.[1]

An inflammatory and immune molecules, including cytokines (TNF-α, IL-1β, and IL-6) and chemokines have been seen in different studies. (IL-8 and MCP-1), are released and secreted by airway epithelial cells. [2] TNF-α, IL-1β, and IL-6 serve as pro-inflammatory molecules while IL-8 and MCP-1 serve as chemo-attractants Its effector cells like neutrophils and monocytes responsible for this.[3] The primary role of innate immunity is to recruit immune cells at the infection site, and inflammation through cytokine development (small proteins involved in cell communication).[4] By the expression and processing of these molecules and the epithelium, initiation and inflammatory response of the exacerbations in the airways is of great importance.

Some data showed volatile anesthetics, such as sevoflurane and isoflurane to minimize heart damage caused by ischemia-reperfusion and to provide in vivo Anti-inflammatory activity in models of lung injury caused by endotoxin.[6] However, in vitro studies showed substantial anti-inflammatory and antinecrotic effects of sevoflurane on human renal cells developed following ischemic-reperfusion injury.[7]

In addition, to suppress the expression of MCP-1, inflammatory protein (MIP)-1β, MIP-2, and cytokine-1-triggered neutrophil chemoattractant and adhesion molecules ICAM-1, sevoflurane turned into additionally proven to minimize neutrophil. Adherence to weakened alveolar epithelial cells lipopolysaccharide in vitro.[8] In this context, one-lung ventilation (OLV) has been shown for growth in propofol and sevoflurane anesthetized patients with TNF-α, IL-1β, IL-6, IL-eight, and MCP-1 inflammatory molecules. However, the amount of inflammatory mediators after OLV, except for IL-1β, within the sevoflurane community was significantly lower compared to those within the propofol community. Thus, sevoflurane is in all likelihood to have an anti-inflammatory hobby in different cellular types. Specifically, it's been proposed that sevoflurane offers anti-inflammatory pastime via a method involving the discount of mRNA and protein levels from pro-inflammatory elements NF-ÿB and AP-1.[7]

For the study of the effects of anesthetic drugs on the immune system, different for human immune cell vitro studies,[10] or they used animal models. 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.[11] Such results can be clinically important as the balance between cytokine secretions pro- and anti-inflammation also tissue injury. Several studies have shown the effect of anesthetics on immune responses even in few days after administration.[12,13,14]

Impaired immunity in vivo is frequently found following major surgery and is multifactorial. Procopio et. al. performed a scientific randomized trial to assess the independent impact on human immune function between the absence of surgical trauma general anesthesia (GA) and lumbar epidural anesthesia (LEA). To the pulmonary clinician, this heralds the dawn of innovative treatments in different fields such as diseases, allergies, and cancer.[15,16] The immune system mediates many adverse drug reactions. It may be because the drug's therapeutic role affects the immune system.[17] Mechanical ventilation can lead to lung injury caused and contribute to acute lung injury or acute respiratory distress syndrome in humans, both high-strength mechanical ventilation and hyperoxia.[18,19] 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), the key characteristics of the immune system.[20] Recent research examining the effects of immunity from first-inhalation anesthesia, halothane, showed that CD4, CD8 cells, and B lymphocytes decreased significantly with repeated doses of halothane.[21]

Sevoflurane is a modern form of inhalation anesthesia widely used in the practice of anesthesia today.[22] Sevoflurane is usually highly fluorinated methyl-isopropyl ether used in the induction and maintenance of general anesthesia. Besides the anesthetic feature, it has also been shown to be involved in the protective process under conditions of hypoxia or endotoxemia, frequently studied in neurons and myocardial tissue.[23] Research conducted by Kidani et al. examined

the effect of pretreatment of sevoflurane on mortality and inflammation during a mice shock caused by endotoxin. Researchers reported that this pretreatment significantly improved blood pressure, acid-base balance and decreased TNF-α and IL-6 mortality and plasma levels, indicating a weakening of the inflammatory response.[24]

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 ischemical reperfusion of the brain.[25] 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.[26]

Propofol is the most widely used anesthetics for general anesthesia. It has been documented that propofol could help reduce the adverse immune response caused by surgical stress compared to sevoflurane, have more protective effects on circulating lymphocytes and have better short-term effects in patients undergoing surgery. Additionally, some research has shown that patients with general propofol radical surgery have a higher overall survival rate of one year than patients with sevoflurane.[12]

Interferon (IFN) is a type of protein integrated into a broad cytokine family. Interferon-is a result of a single gene derived from the 12th chromosome. Human IFN-α is a glycosylated protein with a length of 143 amino acids and has no sequence homology with class IFN-α and class IFN-β. While IFN- γ has a lot of the same biological activities as IFN-α and IFN-β, it also has a lot of other activities as well. This demonstrates the immune system's normal functions. IFN-γ is a cytokine with a significant role in macrophage activation and has a very important function in cell-mediated intracellular immunity to microbes. In non-activated (resting) T cells, genes IFN- γ is not expressed so that the protein could not be identified. However, after activation of T cells, the IFN- γ can be detected within 6-8 hours and the maximum level will be reached The IFN levels are higher in response to stimulation by a combination of IL-12 and IL-18 (also

referred to as the IFN inducing factor / IGIF) without the need for stimulation by TCR. IFN-π output that occurs as a response to cytokine stimulation has a longer duration than when it occurs due to stimulation of TCR.

IL-12 is also known as a stimulant factor for T-cells since it contributes to CD4 T cells division into TH1 cells. In a variety of inflammatory diseases, IL-12 family cytokines had significant therapeutic targets or agents and induced surgical stress.[13] Surgical stress activates the aid's dominant position of a T-cell type 2 (Th2) that disturbs the cytokine balance between Th1 and Th2. Anesthesia can suppress the stress response to the surgery, thereby reducing the imbalance in the procedure Th1/Th2 ratio.[28] In this study, the researcher will investigate the immune system effects of sevoflurane by measuring IFN- γ and IL-12.

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

1.2. Research Question

What are the effects of sevoflurance and propofol on IFN-γ and IL-12 study on patients with craniotomy surgery ?

1.3. Research Objectives

1.3.1. General Objective

To study the effects of sevoflurance and propofol on IFN-γ and IL-12 study on patients with craniotomy surgery.

1.3.2. Specific Objectives

1.3.2.1. To measure the level of IFN-γ and IL-12 before and after anaesthesia with sevoflurane

1.3.2.2. To compare the level of IFN-γ and IL-12 before and after anaesthesia with sevoflurane

1.3.2.3. To measure the level of IFN-γ and IL-12 before and after anaesthesia with propofol

1.3.2.4. To compare the level of IFN-γ and IL-12 before and after anaesthesia with propofol

1.3.2.5. To compare the level of IFN-γ and IL-12 after anaesthesia between group sevoflurane and propofol

1.4. Research Benefits

This study will provide information about the effects of sevoflurane on the immune system through IFN-γ and IL-12 measurements.

1. Clinical application field: This information will provide insight into the management after anesthesia using sevoflurane and propofol, in particular with regards to immune system.
2. Science: This study will add information to the explanation of the mechanism of the effects of anesthesia using sevoflurane and propofol on the immune system.
3. Research: The information will open future study, which confirms the findings and add detail mechanisms involved.

1.5. Research Originality

Table 1.1 Previous reports related to the study

No	Title publication and authors	Method	Results
1.	The Effect of Anesthesia on the Immune System in Colorectal Cancer Patients" (Dang et al., 2018)[29]	The methods of this study on the effect of anesthetics and associated pharmaceutical products on perioperative immune function and postoperative recurrence and metastasis in CRC patients. It is of utmost importance to assess the most effective medication for CRC	The factors including surgical trauma, unpredictable anesthetics, use of opioids, physiological stress, hyperglycemia, hypothermia, transfusion of blood products and mood may trigger a major TH1/TH2 imbalance in the human body between the antitumor and protumor environments. This may have a significant effect on the initiation and

		patients.	development of colon carcinogenesis, metastasis of the colon cancer, recurrence.
2	Effects of propofol anesthesia and sevoflurane anesthesia on the differentiation of human T-helper cells during surgery. (Ji et al., 2011)[30]	Twenty-eight patients with a clinical classification of the undergoing laparoscopic cholecystectomy in the American Society of Anesthesiologists (ASA) were chosen. They were divided at random into two classes of 14.	Propofol can better encourage Th cells to divide into Th1 cells compared to sevoflurane, and inhibit surgical stress. Consequently, Propofol can be immunoprotective to these patients.