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PROTOCOL OF A THESIS FOR PARTIAL FULFILMENT OF MEDICAL DOCTORATE DEGREE IN ANESTHESIOLOGY, INTENSIVE CARE AND PAIN MANAGEMENT

Effect of Propofol and Dexmedetomidine-Based Total Intravenous Anesthesia Versus Sevoflurane-Based Inhalational Anesthesia on the Level of Inflammatory Markers in Patients Undergoing Inguinal Hernia Repair.

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What is already known on this subject? What does this study add?

Several studies showed that the anesthetic technique can affect several postoperative outcomes including the level of inflammatory markers such as Interleukins (ILs), C-reactive protein (CRP), ferritin, and neutrophil-to-lymphocyte ratio (NLR). This study will compare the effect of propofol and dexmedetomidine-based total intravenous anesthesia (TIVA) versus (vs) sevoflurane-based inhalational anesthesia (IA) on postoperative levels of inflammatory markers in patients undergoing inguinal hernia repair.

1. INTRODUCTION

A hernia is a condition in which part of the abdominal cavity contents bulges out through a weak part in the abdominal wall. Common types of hernias include inguinal, incisional, femoral, ventral, hiatal, umbilical, and epigastric. However, inguinal hernias are the most common type. Surgical intervention is usually needed to avoid complications which can range from mild discomfort or pain to intestinal strangulation. (Liu *et al.*, 2025; Costantini et al., 2025)

Surgical injury is followed by an initial systemic inflammatory response which is necessary for tissue repair. However, its effects on the body depends on the balance between pro-inflammatory and anti-inflammatory cytokine production. (Ostović *et al.*, 2025)

Disturbances in this balance can lead to a number of complications, such as delayed wound healing, an increased risk of infection, and multiple organs failure. (Yediyıldız *et al.*, 2025)

The stress response to surgery involves dynamic interactions between several different components of both the innate and adaptive immune systems throughout the inflammatory process. Cytokines are soluble proteins which are secreted from several immune cells, such as lymphocytes, macrophages, and natural killer (NK) cells. They modulate the immune response and act as important mediators in the inflammatory process. (Liu *et al*., 2021)

IL-6 is considered the most representative cytokine in the inflammatory response to tissue injury. It stimulates neutrophil production in the bone marrow, helps in the differentiation of T helper cells, which, in turn, produce other cytokines (Silva *et al*., 2024), and activates antigen-presenting cells, such as natural killer (NK) cells, which induce apoptosis in damaged cells. IL-6 also stimulates production of serum proteins known as acute phase reactants, such as CRP, ferritin, fibrinogen, and D-dimer. (Cusack and Buggy, 2020; Richardson, 2025)

Activation of the adaptive immune system requires interaction between T-lymphocytes and antigen-presenting cells. The immune response induced by surgery causes a relative increase in T-helper 2 (Th2) lymphocytes compared with T-helper 1 (Th1) lymphocytes. The imbalance in Th1:Th2 causes impaired adaptive immunity, leading to postoperative complications. (Cusack and Buggy, 2020)

The NLR is a ratio derived from a complete blood count and serves as an important hematological parameter reflecting systemic inflammation and immune response. It has gained attention as a potential biomarker for several conditions, including inflammation. (Zhang *et al*., 2024)

Several studies have shown that anesthetic management can influence the inflammatory response by modulating immune cell function. Thus, the choice of anesthetic technique affects the balance between pro- and anti-inflammatory responses, potentially altering postoperative outcomes. (Silva *et al*., 2024)

It has been standard practice worldwide to maintain general anesthesia with inhalational anesthetics due to their rapid onset, easy titration, and predictable recovery profiles. However, the use of TIVA has gained popularity over the last few decades. This can be attributed to its lower environmental impact compared with inhalational anesthetics which contribute considerably to greenhouse gas emissions. (Daccache *et al*., 2025)

Propofol is an intravenous (IV) anesthetic agent of rapid onset, short duration of action, and low incidence of side effects, all of which make propofol an ideal anesthetic agent (Kotani *et al*., 2023). Research has shown that propofol has an antioxidant effect as it induces the expression of oxidative stress biomarkers. It has been proven to help modulate the systemic inflammatory response by inhibiting the production of pro-inflammatory cytokines. (Jin *et al*., 2023)

Moreover, it has been reported to enhance infiltration of NK cells, T cells, and Th cells into tissues without affecting total T cell counts or leukocyte apoptosis.(Yediyıldız *et al*., 2025)

Dexmedetomidine is a selective alpha-2 (α2)-adrenergic receptor agonist which has gained wide use in anesthesia and critical care due to its ability to induce sedation, analgesia, and anxiolytic effect without causing respiratory depression (Liu *et al.,* 2024; Kocaoğlu *et al.*, 2025). Moreover, it has been reported to have protective and healing effects, as well as antioxidant, anti-inflammatory and anti-apoptotic effects on various tissues and organs. (Kocaoğlu *et al*., 2025).
On the other hand, inhalational anesthetic agents have been proven to have pro-inflammatory effects. For instance, sevoflurane has been associated with apoptosis in T and B lymphocytes, altered Th1/Th2 ratios, reduced lymphocyte and NK cell counts, and elevated neutrophil levels. (Yediyıldız *et al*., 2025)

2. AIM

This study aims to compare the postoperative levels and trends of change of inflammatory markers, namely IL-6, CRP, ferritin, and NLR in patients undergoing inguinal hernia repair using propofol and dexmedetomidine-based total intravenous anesthesia (TIVA) vs sevoflurane-based inhalational anesthesia (IA).

3. METHODOLOGY:

Type of Study: Prospective, randomized, double-blind, comparative clinical study.
Study Setting: Ain Shams University hospitals, Cairo, Egypt.
Study Period: 6-12 months.
Study Population: Adult patients scheduled for elective inguinal hernia repair.

Inclusion Criteria:

1. Adult patients between 18 and 50 years of age undergoing elective inguinal hernia repair.
2. American Society of Anesthesiologists physical status classification (ASA) I and II.

Exclusion Criteria:

1. Patient's refusal.
2. ASA > II
3. Complicated hernia.
4. Previous hernia repair with mesh.
5. History of allergy to any of the study drugs.
6. History of any heart disease affecting cardiac function or rhythm or receiving medications that decrease the heart rate (HR).
7. Baseline HR≤60 beat/min.
8. Baseline mean arterial pressure (MAP)≤70 mmHg.
9. Psychiatric illness.
10. Patients with chronic kidney or liver disease. (Creatinine clearance<50 mL/min or serum albumin level<2g/dL.)
11. Patients with immunological disorders or receiving immunosuppressive treatment or anti-inflammatory drugs.
12. Patients with neoplasms, chronic inflammatory states, or active infections.
13. Patients with any type of anemia or those who received iron therapy or blood transfusion within 4 weeks.

Sampling Method: Random sampling
Sample Size: Using the PASS 15 program from sample size calculation, reviewing results from the previous study (Yediyıldız *et al*., 2025) showed that postoperative IL-6 levels were significantly lower in the TIVA group than in the sevoflurane group 20,1±23,5 versus 54,8±45,4, based on these findings a sample size of at least 20 patients per group achieve 80% power to reject the null hypothesis of equal means when the population mean difference is μ1-μ2 = 54.8-20.1 = 34.7 with standard deviations of 45.0 for group 1 and 23.5 for group 2, and with a significance level (alpha) of 0.050 using a two-sided two-sample unequal-variance t-test.

Ethical Considerations: The study protocol will receive ethical approval from the Research Ethical Committee, Faculty of Medicine Ain Shams University. Informed consent will be obtained from all participants before starting study.

Randomization and blinding: Group allocation will be contained in sequentially numbered, sealed opaque envelopes, which will be opened by the primary investigator. The collector of blood samples and the data analyzer will be blinded about the study group.

Study Procedures:

All patients will be assessed preoperatively by careful history taking and airway examination. Complete blood count (CBC), coagulation profile, liver and kidney function tests for all patients and electrocardiogram (ECG) for patients older than 40 years of age will be reviewed from patients medical records. A written informed consent will be signed by all patients before the surgery. All patients will be admitted after completing fasting hours for both solid food and clear fluids. Upon arrival to the operating room (OR), IV access of the size 20 gauge (G) will be inserted. Venous blood samples for baseline levels of IL-6, ferritin, and CRP and CBC (for baseline NLR) will be collected (sample 0). All patients will be monitored with a five-lead ECG, non-invasive blood pressure (NIBP) measurement and finger pulse oximetry. Baseline vital data (MAP, HR, and oxygen saturation (SO_2)) will be recorded. HR and SO_2 will be monitored continuously and BP will be measured every 5 minutes (min) till the end of the surgery.

All patients will be premedicated with 0.03 mg/kg IV midazolam. Preoxygenation will be performed using 100% oxygen at a fresh gas flow (FGF) of 10 L/min via face mask for 3 minutes, followed by induction of general anesthesia.

- Group A (TIVA group): will receive 1 µg/kg IV dexmedetomidine over 10 min, 1 µg/kg IV fentanyl, 2 mg/kg IV propofol, and 0.5 mg/kg IV atracurium. Maintenance of anesthesia will be achieved by 0.5 µg/kg/h dexmedetomidine IV infusion and 6-12 mg/kg/h propofol IV infusion titrated according to bispectral index value (BIS) with target BIS 40–60.
- Group B (Sevoflurane group): will receive 1 µg/kg IV fentanyl, 8% sevoflurane via face mask and 0.5 mg/kg IV atracurium. Maintenance of anesthesia will be achieved with 2%-4% sevoflurane titrated according to BIS with target BIS 40–60.

After induction, intubation will be done for all patients using suitable size endotracheal tube (ETT). Both groups will be mechanically ventilated using volume control mode with tidal volume 7-10 ml/kg/min, positive end-expiratory pressure (PEEP) 5 cmH_2O and oxygen-air mixture with fraction of inspired oxygen (FiO_2) 50% and FGF of 3 L/min, and respiratory rate adjusted with target end-tidal carbon dioxide (ET CO_2) 30-40 mmHg. 0.1 mg/kg IV atracurium will be given as needed to maintain muscle relaxation. 0.5 mcg/kg fentanyl will be given if HR or MAP increase ≥20% from their basal value. HR and MAP ≤20% of the basal value will be treated with needed doses of atropine and ephedrine, respectively. All patients will be extubated in the operating room and transferred to postanesthesia care unit (PACU).

Sample Collection and Laboratory Analysis:

Venous blood samples will be collected from each patient at three time points: preoperative (baseline, sample 0), 6 hours postoperative (sample 1), and 24 hours postoperative (sample 2). At each time point, 5 mL of venous blood will be aseptically withdrawn into a sterile plain tube. The blood will be allowed to clot at room temperature, followed by centrifugation at 2000–3000 rpm for 20 minutes. The resulting serum will be carefully separated and stored at −80°C for subsequent analysis.

Serum interleukin-6 (IL-6) levels will be measured using the enzyme-linked immunosorbent assay (ELISA) method. Ferritin and C-reactive protein (CRP) concentrations will be analyzed using a COBAS automated analyzer.

Additionally, a 2 mL blood sample will be collected in an EDTA tube for complete blood count (CBC) analysis, which will be performed using the Sysmex Coulter hematology analyzer.

All laboratory analysis will be conducted at the main laboratories of Ain Shams University Hospital.

Primary outcome:

IL-6 level 24 h postoperatively compared to baseline value.

Secondary outcomes:

1. Trend of change of IL-6 level within the postoperative 24 h.
2. Trends of change and levels of CRP, NLR, and ferritin 24 h postoperatively.
3. Time to discharge.

4. Incidence of PONV.

Both time to discharge and incidence of PONV will be reviewed from patients medical records.

- The main researcher of the study will be the principal investigator responsible for the preparation and conduct of the study under supervision of the director and co-directors. Each member of the team will ensure that the study is conducted according to the protocol approved in their meetings that will be arranged on regular basis. Results of the study and any complications that might occur during the study will be recorded and reported by the principal investigator and revised by the director and co-directors.

Statistical Analysis

The collected data will be revised, coded and introduced to a PC using statistical package for social science (SPSS 23). Data will be presented as mean and standard deviation (+/-SD) for quantitative parametric data, median and range for quantitative non-parametric data and as numbers and percentage for qualitative data. Suitable analysis will be done according to the type of data obtained. P< 0.05 will be considered significant.

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