Comparative study of impact of isoflurane and sevoflurane anaesthesia on the perioperative hemostatic response during open and laparoscopic surgeries

Mohamed Saeed Abd Elaziz, Ahmed Mohamed Khamis, Heba Foaad Abd Elaziz Toulan, Marco Noshy Younan

Anaesthesia, surgical ICU and Pain Management Department, Faculty of Medicine, Ain Shams University, Egypt
Email: nooooshy2009@yahoo.com

Abstract: **Introduction:** The hemostatic mechanisms have several important functions, which are maintaining blood in a fluid state while it remains circulating within the vascular system, arresting bleeding at the site of injury or blood loss by formation of hemostatic plug and ensuring the eventual removal of the plug when healing is complete. The normal hemostatic response to vascular damage depends on closely linked interaction between the blood vessel wall, circulating platelets and blood coagulation factors **Aim:** This prospective randomized study was designed to assess quantitatively the changes of coagulation proteins (namely fibrinogen and vWF), anticoagulants (namely Anti-Thrombin, protein C and protein S) and fibrinolysis proteins (namely plasminogen) in patients undergoing elective laparoscopic and open surgery under the effect of sevoflurane versus isoflurane inhalational agents. This might help us to know the best technique (open or laparoscopic surgeries) and the best drug (sevoflurane or isoflurane) with the least effect on hemostatic mechanism. **Patients and Methods:** Sixty adult patients of either sex scheduled for cholecystectomy were included in this study. They were subdivided into 2 main groups of 30 patients each: Group (I) received isoflurane while group (S) received sevoflurane anesthesia. Each group was further subdivided into two subgroups of 15 patients each according to the type of surgery: IO and SO subgroups performed open cholecystectomy while IL and SL subgroups performed laparoscopic cholecystectomy. **Results:** The results of our study showed that open surgery lead to activation of the clotting system of a higher degree than in the laparoscopic surgery group implying a greater thrombo-embolic risk for patients undergoing open surgery. Subclinical fibrinolysis was also more profound at the open surgery group. Although of a lower degree, hypercoagulability was still observed in patients undergoing laparoscopic surgery. The cytokine surge was correlated with the hypercoagulability. The correlation between cytokine levels and coagulation activation might be related to the type of surgery performed and the type of anesthesia used. **Conclusion**: Laparoscopic surgery under sevoflurane anesthesia was associated with less hypercoagulability and less inflammatory response than open surgery under isoflurane anesthesia. This can be referred to less activation of coagulation and platelets and lower level of inflammatory markers with higher level of anticoagulant and fibrinolytic factors in the former type of anesthesia and surgery.

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1. Introduction

The hemostatic mechanisms have several important functions, which are maintaining blood in a fluid state while it remains circulating within the vascular system, arresting bleeding at the site of injury or blood loss by formation of hemostatic plug and ensuring the eventual removal of the plug when healing is complete. The normal hemostatic response to vascular damage depends on closely linked interaction between the blood vessel wall, circulating platelets and blood coagulation factors ***(Hoffbrand et al., 2016).***

Coagulation begins almost instantly after an injury to the blood vessel has damaged the endothelium lining of the vessel. Platelets immediately form a plug at the site of injury; this is called primary hemostasis. Secondary hemostasis occurs simultaneously when proteins in the blood plasma, (coagulation factors or clotting factors) respond in a complex cascade to form fibrin strands, which strengthen the platelet plug ***(Furie and Furie, 2015).***

Platelet-selectin expressed on the surface of platelets seems to play an important role in mediating the platelet-endothelial cell and platelet-platelet interaction. Following platelet activation, platelet selectin is sheded in the blood in the form of soluble or s-platelet selectin so its level in the blood is an indicator of platelet activation ***(Wagner and Burge, 2013).***

Fibrinogen level is a reflection of clotting ability in the body. Reduction of its concentration may impair the body's ability to form a stable blood clot,

while its rising contributes to an increased risk for developing thrombosis ***(Wagner and Pincus, 2014).***

Von Willebrand factor (vWF) is a glycoprotein involved in platelet adhesion and carriage of coagulation factor VIII so it is essential for normal thrombus formation. High concentrations of (vWF) in plasma are associated with an increased risk of thrombosis ***(Budde et al., 2012).***

Disorders of coagulation can lead to an increased risk of bleeding (hemorrhage) and/or clotting (thrombosis). The hemostatic system represents a delicate balance between procoagulant and anticoagulant mechanisms allied to a process for fibrinolysis **(*O'Reilly and Pirie-Shepherd*, 2009).**

Protein C is a major physiological anticoagulant which is a vitamin K-dependent serine protease enzyme and is activated by thrombin into activated protein C. The activated form, with protein S as a cofactor, degrades activated Factor V and activated Factor VIII **(*Mosnier et al.*, 2009).**

Normally, the fibrinolytic system is activated simultaneously with the coagulation cascade and acts to maintain the fluidity of blood during coagulation. When a clot is formed, a large amount of plasminogen appears and changes into plasmin which in turn degrades cross-linked fibrin and fibrinogen to produce D-dimer and fibrin degradation products (FDPs) respectively. D-dimer is the final product of the simultaneous activation of blood coagulation and fibrinolysis **(*Rathbun et al., 2014).***

Acute-phase proteins are a class of proteins whose plasma concentrations increase (positive acute-phase proteins) or decrease (negative acute-phase proteins) in response to inflammation. This response is called the acute-phase reaction (also called acute-phase response). In response to injury, the liver responds by producing a large number of acute-phase reactants. Fibrinogen, vWF plasminogen and D-dimer are considered as positive acute-phase proteins **(*Ananian et al., 2012).***

Major surgery is followed by changes in the coagulation and fibrinolytic systems which may favour the development of postoperative thromboembolic complications. Laparoscopic cholecystectomy leads to no greater activation of plasma coagulation than open surgery. Thus laparoscopic surgery appears to be associated with a lower risk for thromboembolism than open surgery which may be due to limited tissue injury ***(Diamantis et al., 2017).***

General anesthesia causes activation of coagulation and fibrinolysis followed by depression of fibrinolysis. Isoflurane, enflurane, desflurane, barbiturates, etomidate, opioids and muscle relaxants seem to have negligible effects at therapeutic concentrations. Sevoflurane and halothane, at clinically relevant concentrations, suppresses secondary aggregation of human platelet in vitro ***(Mitra et al., 2010).***

In vivo, patients receiving nitrous oxide (3 L/ min) and isoflurane (1-2%) during anesthesia had significantly reduced platelet aggregation. In contrast, another study showed that there was no inhibition of intra- and postoperative platelet aggregation in isoflurane-anesthetised patients ***(Johannes et al., 2011).***

Anesthestists are involved in the peri-operative hemostatic management to reduce the incidence of arterial and venous thrombosis and therefore reducing morbidity from cerebrovascular, coronary artery disease or pulmonary embolism. Moreover, it is possible that some anesthetic agents may protect against intravascular thrombosis during surgery ***(Bolliger et al., 2010).***

Aim of the work:

This prospective randomized study was designed to assess quantitatively the changes of coagulation proteins (namely fibrinogen and vWF), anticoagulants (namely Anti-Thrombin, protein C and protein S) and fibrinolysis proteins (namely plasminogen) in patients undergoing elective laparoscopic and open surgery under the effect of sevoflurane versus isoflurane inhalational agents. This might help us to know the best technique (open or laparoscopic surgeries) and the best drug (sevoflurane or isoflurane) with the least effect on hemostatic mechanism.

2. Patients and Methods

Inclusion Criteria

1. Elective operation with duration ranging from 1.5- 2.5 hours.
2. Age: 25-55 years.
3. Gender: Both male and female.
4. BMI: < 30 kg/m^2 (Normal weight).
5. ASA Class: I & II.

Exclusion Criteria:

1. Ages less than 25 or more than 55 years old
2. Severe weight loss and obesity (BMI > 30).
3. Pregnancy and lactation.
4. Fever or sepsis.
5. Chronic liver disease.
6. Acute cholecystitis, cholangitis or other acute inflammation.
7. Patients suffering from severe renal, endocrine, rheumatic, cardiopulmonary disease or malignancy.
8. Patients with history of hemostatic abnormalities or who receives:

a. Medications with known effect on hemostasis. i.e. anticoagulations,

b. Antiplatelets or NSAIDS.

9. Patients who receive corticosteroids or other

drugs that affect their immunological responses.

Sample Size and grouping of patients:

All patients presented with symptomatic gallbladder stone disease. They were divided into 2 main groups (30 patients each): Group (I) received isoflurane anesthesia and group (S) received sevoflurane anesthesia. Each group was further subdivided into two subgroups of 15 patients each: IO and SO subgroups performed open cholecystectomy through a right subcostal incision while IL and SL subgroups performed laparoscopic cholecystectomy with four-trocar incision and 14 mmHg CO_2 pneumoperitoneum.

Evaluation:

Preoperative evaluation was carried out the day before surgery. During this evaluation, full medical history was taken in addition to full clinical examination and routine preoperative investigations. This was preceded by explanation of the study procedure, before an informed consent was obtained from the patient. Clinical examination included measuring body weight and height to calculate body mass index (BMI).

Anesthesia technique:

Premedication consisted of midazolam (0.05 mg/ kg) and ondansetron (4 mg) given intravenously half an hour before operation. Then the patients were transferred to the operating room. The following monitors were attached to the patients: 5 leads ECG, non-invasive arterial blood pressure, peripheral oxygen saturation, end-tidal carbon dioxide tension and inhaled anesthetic gas analysis. Anesthesia was induced with, fentanyl (2 µg/ kg), propofol (2.5 mg/ kg) and atracurium (0.5 mg/ kg) injected slowly in a peripheral intravenous line.

Anesthesia was maintained with 1 MAC sevoflurane (group I) or 1 MAC Isoflurane (group II) in 100% oxygen. Supplemental doses of fentanyl (1mic/kg) were given when MBP or HR increase more than 20% from base line reading. Atracurium (0.25 mg/kg) was given when TOF recovers to more than 25%. Mechanical ventilation was performed using a tidal volume of 6-8 ml/ kg with respiratory rate adjusted to maintain Pco_2 between 30 and 35 mm Hg and PEEP of 5 mmHg.

All the patients received crystalloids in the form of Ringer solution infused at a rate of 5-7 ml/kg/hr during surgery. No colloid or blood transfusion was allowed. During laparoscopic surgery, pneumoperitoneum at 14 mm Hg was performed through four-trocar ports and patients were placed at 30° reverse Trendelenburg position while open cholecystectomy was performed through a right subcostal incision. Residual neuromuscular blockade after surgery was antagonized by 0.05 mg/ kg neostigmine and 0.02 mg/ kg atropine. Postoperative analgesia was provided by intravenous infusion of 1 gm acetaminophen and IM mepridine 1 mg/ kg every 12 hours.

Blood Sampling:

Three blood samples were collected; before operation, immediate post-operative and 24 hours after the operation. Each sample consisted of 10 ml of venous blood and the following parameters were performed.

Routine laboratory tests:

1. Hemoglobin concentration.
2. Hematocrit.

Routine screening coagulation tests:

1. Prothrombin time (PT).
2. Prothrombin concentration (PC).
3. International normalized ratio (INR).
4. Partial thromboplastin time (PTT).
5. Platelets count.

Coagulation parameters:

1. Von Willebrand factor (vWF) level
2. Fibrinogen level
3. Thrombin-antithrombin (TAT) level

Anticoagulation parameters:

1. Antithrombin (AT) level
2. Protein C level
3. Protein S level

Fibrinolytic parameter:

Plasminogen level

Simultaneous coagulation and fibrinolytic parameter:

D-dimer level

Inflammatory markers:

1. High sensitivity C-reactive protein (hsCRP) level
2. IL- 1β level
3. IL-6 level

3. Results

Sixty adult patients of either sex scheduled for cholecystectomy were included in this study. They were subdivided into 2 main groups of 30 patients each: Group (I) received isoflurane while group (S) received sevoflurane anesthesia. Each group was further subdivided into two subgroups of 15 patients each according to the type of surgery: IO and SO subgroups performed open cholecystectomy while IL and SL subgroups performed laparoscopic cholecystectomy.

Data are expressed as median (minimum-maximum). I; patients anesthetized with isoflurane, S; patients anesthetized with sevoflurane, underwent O; open cholecystectomy or L; laparoscopic cholecystectomy. PO; postoperative.

$^{\#}p< 0.05$ relative to preoperative (baseline) within the same group.

Intra-group comparisons:

In all groups, there were statistical significant reductions ($p< 0.05$) of hemoglobulin level at different postoperative times i.e. immediate and 24 hrs posoperative when compared to the preoperative (baseline) level within each group (Fig.1).

Inter-group comparisons:

No statistical significant difference ($p > 0.05$) of hemoglobulin level was detected between different groups measured at preoperative, immediate or 24 hrs postoperative times (Fig.1).

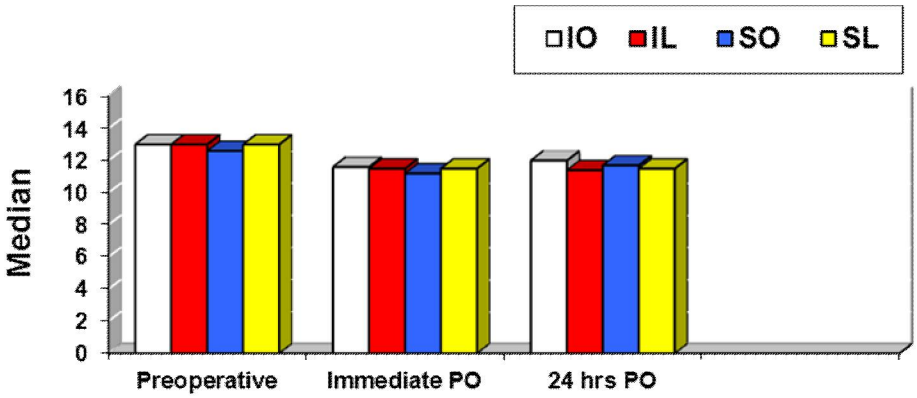

Fig.1: Level of hemoglobin (g dl^{-1}) (nomal Hb level: 12-16 g dl^{-1})

Intra-group comparisons:

In all groups, there were statistical significant reductions ($p < 0.05$) of hematocrit level at different postoperative times i.e. immediate and 24 hrs postoperative when compared to the preoperative (baseline) level within each group (Fig.2).

Inter-group comparisons:

No statistical significant difference ($p > 0.05$) was recorded in the hematocrit level between different groups measured at preoperative, immediate or 24 hrs postoperative times (Fig.2).

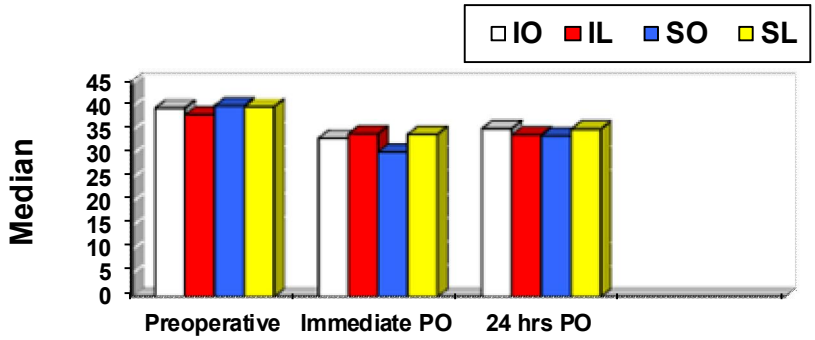

Fig.2: Level of the hematocrit (%) (Normal hematocrit 36-48%)

Intra-group comparisons:

In all groups, there were statistical significant prolongations ($p< 0.05$) in the prothrombin time at the different postoperative times of measurement i.e. immediate and 24 hrs postoperative when compared to preoperative baseline within each group (Fig.3).

Inter-group comparisons:

In IO group, there was a significant reduction in prothrombin time at immediate and 24 hours postoperative times when compared to IL and SL groups but when compared to SO group, the reduction was only significant at 24 hours postoperatively ($p< 0.05$) (Fig.3).

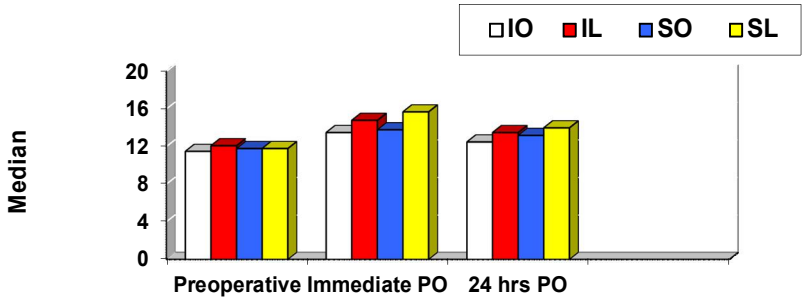

Fig.3: Level of prothrombin time (sec) (Normal prothrombin time 10-14 sec.)

Intra-group comparisons:

In all groups, there were statistical significant reductions ($p < 0.05$) in the prothrombin concentration at the different postoperative times of measurement i.e. immediate and 24 hrs postoperative when compared to preoperative baseline within each group (Fig.4).

Inter-group comparisons:

No statistical significant difference ($p > 0.05$) was recorded in prothrombin concentration between groups measured at different time of measurements i.e. preoperative, immediate or 24 hrs postoperative times (Fig. 4).

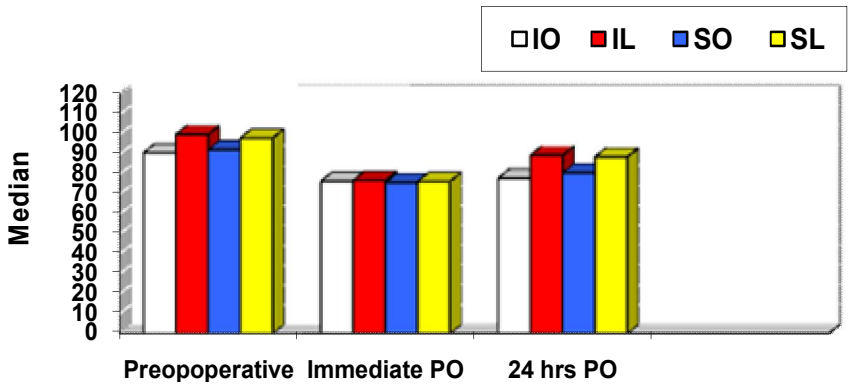

Fig.4: Level of prothrombin concentration (%) (Normal PC 90-100%)

Intra-group comparisons:

In all groups, there were statistical significant increase ($p < 0.05$) in the INR level at the different postoperative times of measurement i.e. immediate and 24 hrs postoperative when compared to preoperative baseline within each group (Fig.5).

Inter-group comparisons:

SL group showed statistically significant increase ($p < 0.05$) of INR level when compared to other groups at different postoperative time of measurements (Fig.5).

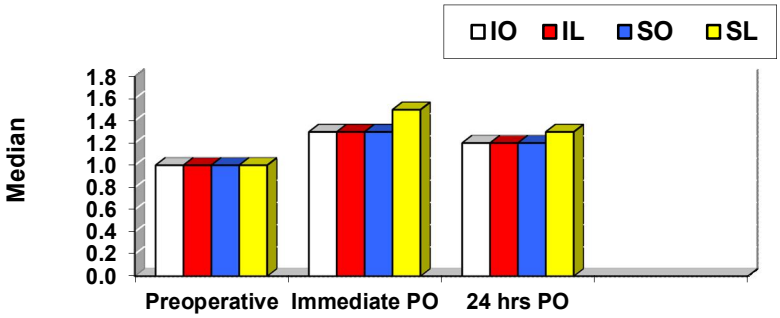

Fig.5: Level of INR (Normal INR is about 1.0)

Intra-group comparisons:

In IO group, there was a statistical significant prolongation ($p < 0.05$) in the PTT level at the different postoperative times of measurement i.e. immediate and 24 hrs postoperative when compared to preoperative baseline. The same results were also recorded in IL, SO and SL groups (Fig.6).

Inter-group comparisons:

There was no statistical significant difference in PTT level between different groups at all time of measurements ($p > 0.05$) (Fig.6).

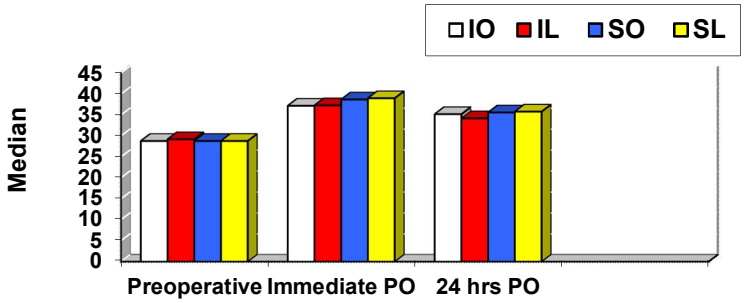

Fig.6: Level of PTT (sec) (Normal PTT 30-40 sec.)

Intra-group comparisons:

In IO group, there was statistical significant decrease ($p < 0.05$) in platelet count in immediate postoperative time compared to the preoperative baseline. The same results were also recorded in SO and SL groups. In IL group, a significant decrease in both immediate and 24 hrs postoperative times of measurement ($p < 0.05$) when compared to their corresponding preoperative time (Fig.7).

Inter-group comparisons:

There was no statistical significant difference in platelet count between groups at different times of measurement ($p > 0.05$) (Fig.7).

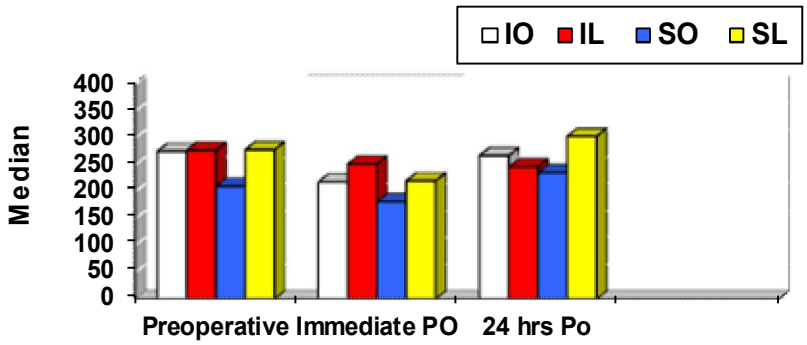

Fig.7: Platelet count (10^9 L^{-1}) (Normal platelet count 150,000-400,000 L^{-1})

Intra-group comparisons:

In all groups, there were statistically significant elevations ($p< 0.05$) in the vWF level at the different postoperative times of measurement i.e. immediate and 24 hrs postoperive when compared to preoperative baseline within each group (Fig.8).

Inter-group comparisons:

At immediate and 24 hrs postoperatively, there were statistical significant reductions in vWF level in IL, SO and SL groups when compared to IO group. At 24 hrs postoperatively, SL group recorded a significant decrease in vWF level ($p< 0.05$) when compared to IL group. SL group also recorded a significant postoperative decrease in vWF level when compared to SO group at each corresponding postoperative time ($p< 0.05$) (Fig.8).

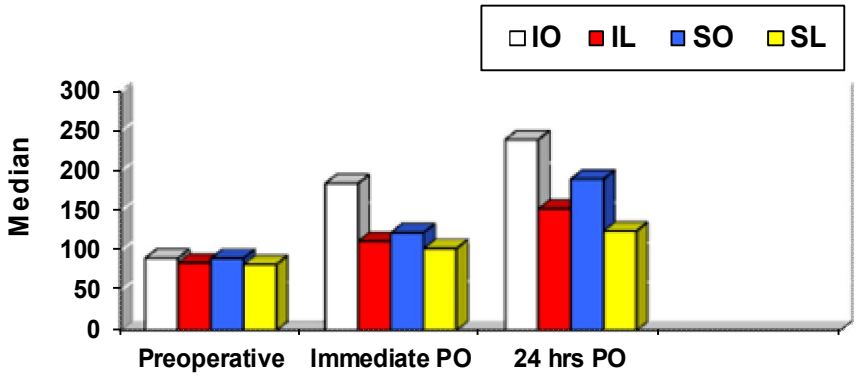

Fig.8: Level of vWF (%) (Expected value is 99.3%±39.0%.)

Intra-group comparisons:

In all groups, there were statistically significant decrease ($p< 0.05$) in the fibrinogen level between the preoperative baseline and the immediate PO reading followed by a statistically significant increase 24 hrs postoperative within each group (Fig.9).

Inter-group comparisons:

Compared with IO group, there were statistically significant reductions ($p< 0.05$) in fibrinogen level at immediate and 24 hrs postoperatively in IL group, at 24 hrs postoperatively in SO group as well as at different postoperative times in SL group. Compared with IL group, there were statistically significant differences ($p< 0.05$) in fibrinogen level at immediate and 24 hrs postoperatively in SO group. In SL group postoperative readings at immediate and 24 hrs showed statistically significant reduction ($p< 0.05$) in fibrinogen level when compared with their corresponding in SO group (Fig.9).

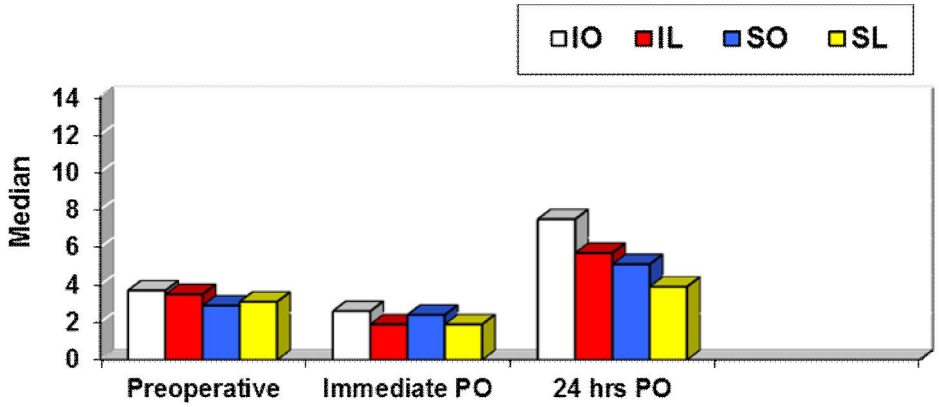

Fig.9: Level of fibrinogen (mg ml^{-1}). (Fibrinogen concentration in normal human plasma is in the range 1.5 to 5 mg/ml.)

Intra-group comparisons:

In all groups, there were statistically significant elevations ($p< 0.05$) in the TAT level at the different postoperative times of measurement i.e. immediate and 24 hrs postoperative when compared to preoperative baseline within each group (Fig.10).

Inter-group comparisons:

At different postoperative time of measurements i.e. immediate and 24 hrs, there were significant reductions ($p< 0.05$) in the TAT level in IL, SO and SL groups when compared to IO group as well as significant reductions ($p< 0.05$) in SL group than SO group at the same timings. At 24 hrs postoperatively, TAT level showed significant reduction ($p< 0.05$) in SL group than IL group (Fig.10).

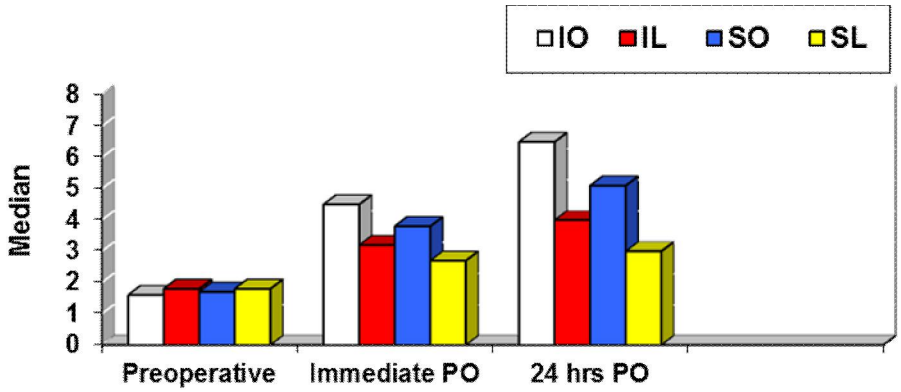

Fig.10: Level of TAT (ng mL^{-1})

Intra-group comparisons:

In all groups, there were statistically significant reductions ($p< 0.05$) in the antithrombin level at the different postoperative times of measurement i.e. immediate and 24 hrs when compared to preoperative baseline within each group (Fig.11).

Inter-group comparisons:

At immediate and 24 hrs postoperatively, there were significant elevations ($p< 0.05$) in antithrombin level in SL group when compared to their corresponding in SO group. Also there was significant increase ($p< 0.05$) 24 hrs postoperatively in SL group when compared to IO group (Fig. 11).

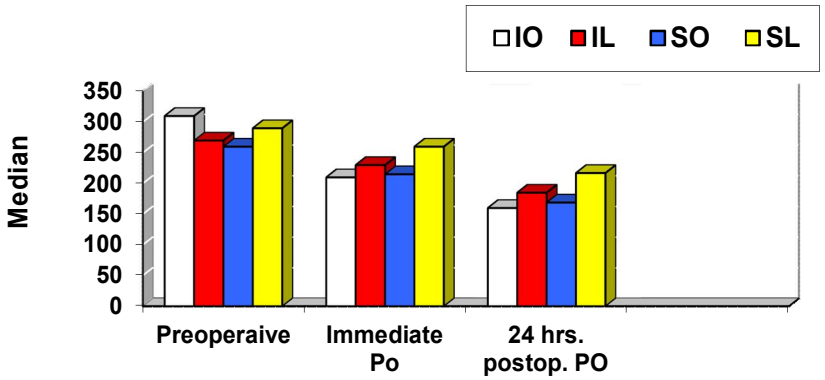

Fig.11: Level of Antithrombin (µg mL^{-1}) (The normal blood level of AT III is averaged 290 µg/ml.)

Intra-group comparisons:

In all groups, there were statistically significant reductions ($p< 0.05$) in the protein C level at the different postoperative times of measurement i.e. immediate and 24 hrs when compared to preoperative baseline within each group (Fig.12).

Inter-group comparisons:

At immediate and 24 hrs postoperatively, there were significant elevations ($p< 0.05$) of protein C level in IL group when compared to their corresponding in IO and SO groups as well as significant elevations ($p< 0.05$) in SL group when compared to SO group at the same timings. At 24 hrs postoperatively, SL group showed significant elevation ($p< 0.05$) in protein C level when compared with IO group (Fig.12).

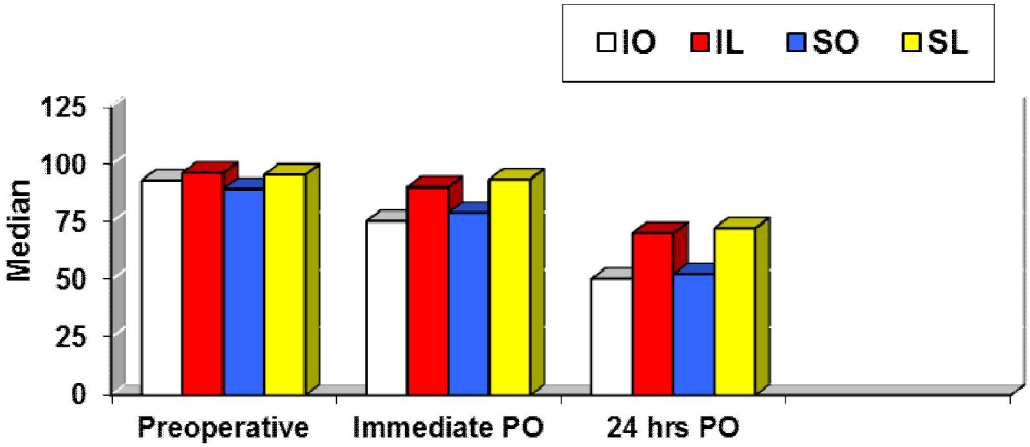

Fig.12: Level of protein C (%) (The normal range of protein C antigen in this assay is 72-160%)

Intra-group comparisons:

In all groups, there were statistically significant reductions ($p< 0.05$) in the protein S level at the different postoperative times of measurement i.e. immediate and 24 hrs when compared to preoperative baseline within each group (Fig.13).

Inter-group comparisons:

At 24 hrs postoperatively, there were significant increases in protein S level in IL, SO and SL groups when compared to IO group (Fig. 13).

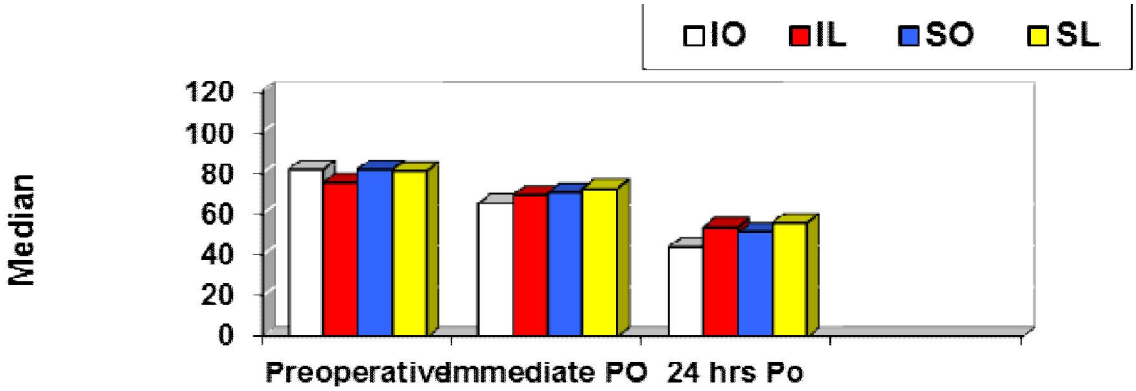

Fig.13: Level of protein S (%) (The normal range of protein S for this assay is 60-150%.)

Intra-group comparisons:

In all groups, there were statistically significant reductions ($p< 0.05$) in the plasminogen level at the different postoperative times of measurement i.e. immediate and 24 hrs postoperative when compared to preoperative baseline within each group except at immediate postoperative time in SL group (Fig.14).

Inter-group comparisons:

At immediate and 24 hrs postoperatively, there were significant elevations ($p< 0.05$) in plasminogen level in IL, SO and SL groups when compared to their corresponding in IO group as well as significant elevations ($p< 0.05$) in SL group when compared to SO group at the same timings. Significant elevation ($p< 0.05$) was also observed in SL group than IO group at 24 hrs postoperatively (Fig.14).

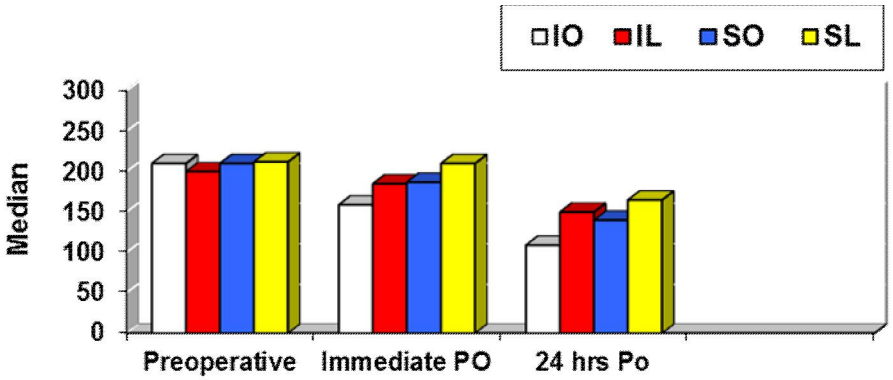

Fig.14: Level of plasminogen (µg mL^{-1})

Intra-group comparisons:

In all groups, there were statistically significant elevations ($p< 0.05$) in the D dimer level at the different postoperative times of measurement i.e. immediate and 24 hrs postoperative when compared to preoperative baseline within each group (Fig.15).

Inter-group comparisons:

At different postoperative time of measurements i.e. immediate and 24 hrs, there were significant reductions ($p< 0.05$) in the D dimer level in IL and SL groups when compared to IO group as well as significant reductions ($p< 0.05$) in SL group than SO group at the same timings (Fig. 15).

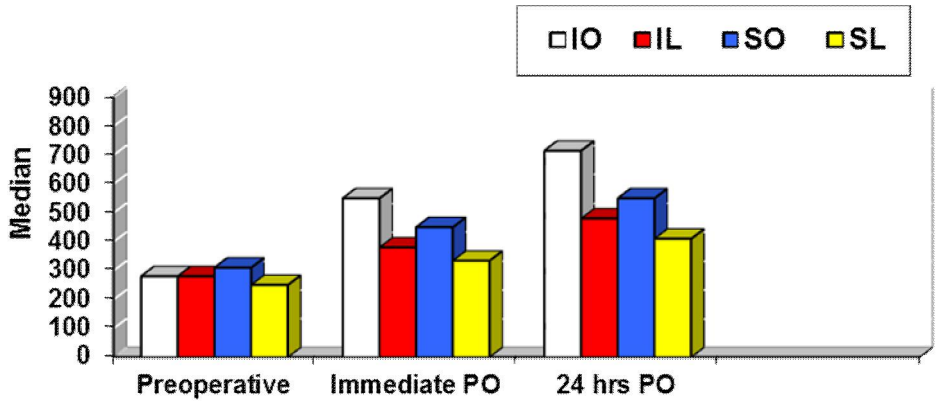

Fig.15: Level of D dimer (ng mL^{-1}) (Expected values are < 400 ng/ml.)

Intra-group comparisons:

In all groups, there were statistically significant elevations ($p< 0.05$) in the hs CRP level at the different postoperative times of measurement i.e. immediate and 24 hrs postoperative when compared to preoperative baseline within each group (Fig.16).

Inter-group comparisons:

At different postoperative time of measurements i.e. immediate and 24 hrs, there were significant elevations ($p< 0.05$) in the hs CRP level in IO group when compared to other groups as well as significant elevations ($p< 0.05$) were observed in SO group than SL group at the same timings (Fig.16).

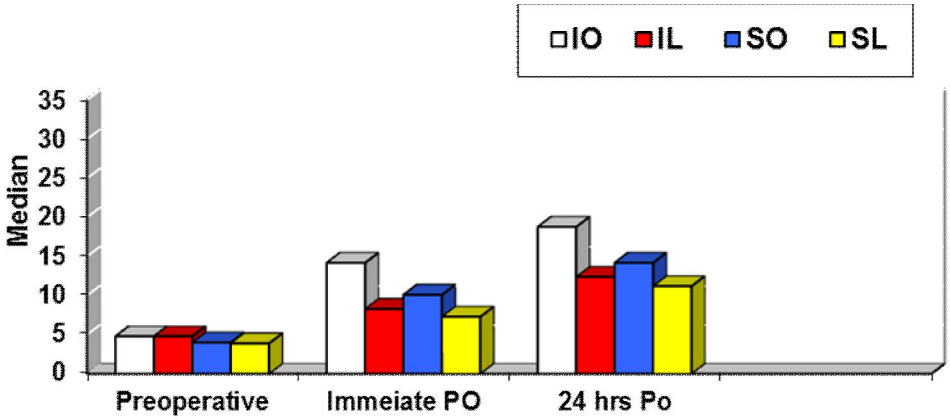

Fig.16: Level of hs CRP (mg L^{-1}) (Normal value: 0.068 to 8.2 mg/L.)

Intra-group comparisons:

In all groups, there were statistically significant elevations ($p< 0.05$) in the IL-1β level at the different postoperative times of measurement i.e. immediate and 24 hrs postoperative when compared to preoperative baseline within each group (Fig.17).

Inter-group comparisons:

At different postoperative time of measurements i.e. immediate and 24 hrs, there were significant elevations ($p< 0.05$) in the IL-1β level in IO group when compared to other groups and significant reduction ($p< 0.05$) were observed in SL group than other groups at the same timings (Fig.17).

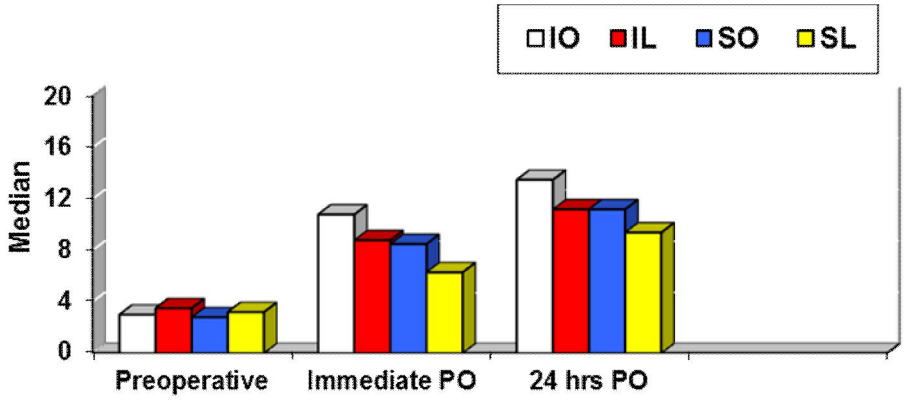

Fig.17: Level of IL-1β (pg mL^{-1})

Intra-group comparisons:

In all groups, there were statistically significant elevations ($p< 0.05$) in the IL-6 level at the different postoperative times of measurement i.e. immediate and 24 hrs postoperative when compared to preoperative baseline within each group (Fig.18).

Inter-group comparisons:

At different postoperative time of measurements i.e. immediate and 24 hrs, there were significant reductions ($p< 0.05$) in the IL-6 level in IL, SO and SL groups when compared to IO group as well as significant reductions ($p< 0.05$) were observed in SL group than SO group at the same timings (Fig.18).

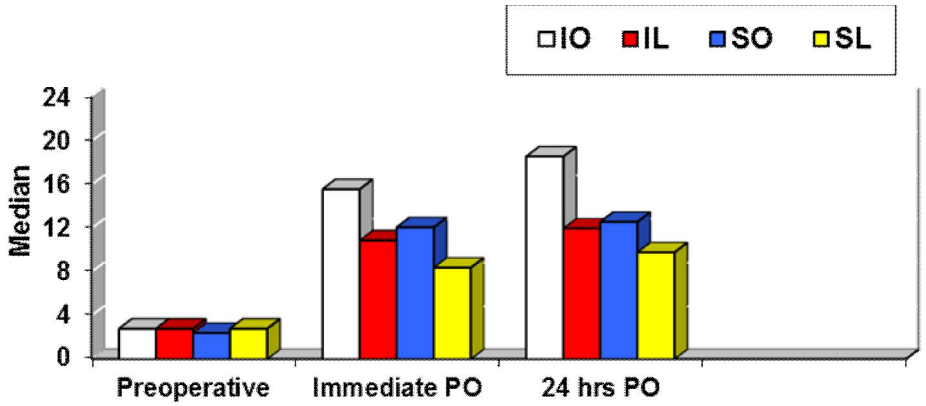

Fig.18: Level of IL-6 (pg mL^{-1}).

4. Discussion

Many factors can alter postoperative hemostatic and inflammatory status of the patient as the type and duration of the procedure, anesthetic technique or agent, and the use of autologous or allogenic transfusion. All patients were anesthetized by the same anesthesiology team also; they were operated upon by the same surgical team ***(Hoffbrand et al., 2016).***

In general, there are two potentially important alterations in hemostasis after surgery predisposing to thrombo-embolic complications. The first alteration is a tendency towards hypercoagulability. Plasma fibrinogen concentrations and platelet counts are increased in the first 24 hours postoperatively in addition to increased platelet aggregation in response to the release of a variety of aggregation-promoting agonists. The second alteration is an initial enhancement of fibrinolysis which followed by a decrease of its activity **(Milic et al., 2009).**

Most studies evaluating the perioperative alterations of hemostasis concern open surgery. The risk of developing deep venous thrombosis after open surgery can be high. Laparoscopic surgery may be associated with a lesser degree of thrombo-embolic complications despite pneumoperitoneum which, by reducing venous inflow towards the heart, promotes venous stasis of the legs and predisposes to deep venous thrombosis **(Milic et al., 2009).**

In this study, postoperative decrease of Hb and Hct levelswere observed in all groups when compared to the preoperative values. This can be explained by intraoperative hemodilution and minimal blood loss; however, these changes were within the clinically acceptable range **(McPherson and Pincus, 2014).**

PT, PC, PTT, INR, and Platelet count are part of a broader testing of coagulation. There was significant reduction in postoperative PC level and significant increase in PT, INR and PTT at different postoperative times in all groups when compared to the baseline value. There was no marked difference between groups except significant INR increase in sevoflurane_ laparoscopic group immediate and 24 hours postoperatively and significant PT reduction in isoflurane_open group immediate and 24 hours postoperatively when compared to other groups **(Brueckner et al., 2013).**

Another study conducted to compare open and laparoscopic cholecystectomy and their influence on hemostatic markers. They found that PTT values did not change significantly over time in either group nor between both groups. INR levels increased significantly 24 hours after both laparoscopic and open cholecystectomy in relation to preoperative levels without significant differences between groups. Level of PT was significantly increased within each group immediately and 24 hours after surgery when compared to the preoperative levels without significant differences between groups **(Diamantis et al., 2017).**

In the present study, significant reduction in platelet count was observed at immediate postoperative time and significant elevation 24 hours postoperatively when compared to preoperative level in isoflurane_open, sevoflurane_open and sevoflurane_ laparoscopic groups while in isoflurane_ laparoscopic group the reduction was significant in both immediate and 24 hours after surgery **(Brueckner et al., 2013).**

We noted that the level of vWF was elevated postoperatively in all groups but with higher level in the open cholecystectomy groups than the laparoscopic cholecystectomy groups in both types of anesthesia which means that platelet activation and endothelial activation are higher in the open groups. The highest level of vWF factor was observed in the isoflurane_ open group and the lowest level was in the sevoflurane_ laparoscopic group **(Budde et al., 2012).**

In this study, vWF was significantly higher in patients anesthetized by isoflurane than those

anesthetized by sevoflurane. This indicates that sevoflurane anesthesia was associated with less hypercoagulability due to inhibition of platelet activationand less stimulation of endothelial activation **(Michelson and Furman, 2015).**

Sevoflurane has a significant inhibitory effect on intraoperative platelet aggregation, while isoflurane has no effect. Therefore, at increased risk of intraoperative and postoperative bleeding, isoflurane may be preferred as a general anesthetic ***(Dogan et al., 2012).***

In a randomized study, general anesthesia using isoflurane has resulted in a significant elevation of specific hemostatic parameters (vWF) whether the liver condition was normal or compromised **(Khafagy et al., 2010).**

Fibrinogen is an acute phase protein synthesized by the liver and plays a key role in the blood clotting. During clot formation, it is converted to fibrin via thrombin. Increased levels are noted after inflammation and demonstrate the close association between the stress and coagulation activation (**Shietroma et al., 2014).**

In our study, there was significant reduction of fibrinogen level at the end of surgery, followed by significant elevation on the first postoperative day when compared to preoperative baseline in all groups. Morever, significant elevation of fibrinogen plasma levels was noted in the open groups when compared to the laparoscopic groups in both types of anesthesia immediately and 24 hours postoperatively. The highest levels were observed in the isoflurane_open group and the lowest levels were in the sevoflurane_ laparoscopic group (**Diamantis et al., 2017).**

Similar results were given which compared open and laparoscopic cholecystectomy. In the laparoscopic group, fibrinogen levels decreased significantly immediately postoperatively then non-significantly increased at 24 hours postoperatively when compared to the baseline values. On the other hand, in the open group, fibrinogen levels showed non-significant decrease immediately after surgery then significantly increased at 24 hours when compared to preoperative levels. Between the two groups, fibrinogen levels were significantly higher at 24 hours after open cholecystectomy rather than after laparoscopic one (**Diamantis et al., 2017).**

According to our study, in isoflurane open group, there was a significant prolongation in the PTT level at the different postoperative times of measurement i.e. immediate and 24 hours postoperative when compared to preoperative baseline. The same results were also recorded in the other groups **(Horn et al., 2015).**

An experimental study on pigs has found that when isoflurane was introduced, the PTT showed a significant increase while fibrinogen concentration decreased. The introduction of sevoflurane led also to a decrease in fibrinogen concentration, while the PTT was unchanged. These decreases in fibrinogen concentration were not accompanied by reduced maximal clot strength or elevated fibrinolysis **(Horn et al., 2015).**

In our study, TAT complex was measured as a sensitive marker of activation of coagulation. The TAT levels increased significantly at the end of the operation in the four groups and continued till 24 hours postoperatively showing that thrombin generation and hypercoagulability started immediately after surgery and continued after that. TAT levels were higher in the open surgery groups than laparoscopic groups. Also TAT complex level were lower in sevoflurane groups when compared to isoflurane groups in both types of surgery **(Diamantis et al., 2017).**

Similarly, another sudy found significant immediate postoperative elevation of TAT complexes when compared to preoperative baseline in both open and laparoscopic cholecystectomy groups but this increase was more marked in the open surgery groups **(Diamantis et al., 2017).**

TAT level between patients was randomly assigned to open or laparoscopic gastric by-pass (GBP) and they found a significant increase of TAT level after surgery in both groups over baseline levels without significant differences between groups at any time. They suggest that laparoscopic GBP induced a degree of hypercoagulability similar to that of open GBP. The discrepancy in results could be attributed to the chosen model of operation of their study because GBP is a major procedure with more surgical stress. Therefore, a degree of hypercoagulablilty was induced **(Nguyen et al., 2011).**

The primary down-regulators of the coagulation cascade are antithrombin (AT), protein C and protein S. Antithrombin has its down-regulatory effect through the inactivation of several activated factors, including factors IX, X, XII, and thrombin. The binding of thrombin with AT blocks thrombin's interaction with fibrinogen and TAT complex is formed. Protein C and its cofactor protein S reduces thrombin generation by inactivation of activated factor V and VIII **(Schietroma et al., 2014).**

In our study we found a significant postoperative reduction of AT, protein C and S in all groups when compared to the preoperative levels. These antithrombotics were higher in the laparoscopic and the sevoflurane groups, a finding which might favor doing this procedure laparoscopically under sevoflurane anesthesia. Another study showed significant higher AT in the laparoscopic cholecystectomy group at 24 hours postoperatively

when compared to open surgery group **(Papaziogas et al., 2016).**

Plasminogen is the precursor of plasmin which, in turn, is the primary molecule responsible for fibrin degradation. In our study, there was significant postoperative reduction of plasminogen level in all group. The increase in fibrinogen with a concomitant decrease in plasminogen may favor increased fibrin formation and hypercoagulability. These changes were observed in this study and they were more pronounced in the open surgery groups when compared to the laparoscopic groups in both types of anesthesia. Also this state of hypercoagulability was detected with a greater degree in isoflurane groups than sevoflurane groups in both types of surgery **(Papaziogas et al., 2016).**

Plasmin splits the cross-linked fibrin to produce D-dimer. Thus, D-dimer is a marker of simultaneous activation of blood coagulation and fibrinolysis and its elevation indicates recent or ongoing fibrinolysis. In our study, D-dimer level was significantly higher in the open cholecystectomy groups than in the laparoscopic cholecystectomy groups in both types of anesthesia. This indicates activation of both coagulation and fibrinolysis is more enhanced in the open surgical groups than that in the laparoscopic groups. The highest levels of D-dimer were in the isoflurane_open group and the lowest levels were in sevoflurane laparoscopic group **(Diamantis et al., 2017).**

The same results concerning D-dimer plasma levels are found when compared open with laparoscopic cholecystectomy operations. There was significant postoperative increase of plasma levels of D-dimer in open cholecystectomy when compared to preoperative values which was not the case in the laparoscopic cholecystectomy group **(Schietroma et al., 2014).**

To evaluate the role of inflammatory response, the inflammatory markers hs CRP, IL-1β and IL-6 were measured and they showed significant postoperative elevation in all groups which are more marked in patients undergoing open surgery compared to laparoscopic procedure. This may be explained by greater tissue damage inflicted by the open technique **(Jones, 2015).**

CRP is a widely used acute phase protein whose levels after operations are roughly proportional to the magnitude of the trauma. IL-6 induces hepatic synthesis of CRP and may be a faster reacting and more accurate indicator of tissue damage than CRP **(Jones, 2015).**

In agreement with our results, another study showed the postoperative inflammatory response in patients undergoing recurrent inguinal hernia repair who were randomized to open surgery under local anesthesia or laparoscopic surgery with total intravenous anesthesia. They reported a significant postoperative increase of CRP levels when compared to preoperative baseline. The level of CRP did not differ between groupsfour hours after incision, but they were significantly higher in the open surgical group 24 hours postoperatively **(Rahr et al., 2014).**

We found that sevoflurane anesthesia was associated with lower levels of IL- 6 and IL-1β than isoflurane anesthesia and so less inflammatory response and less hypercoagulability. IL-6 and IL-1β have been shown to be associated with hypercoagulability state due to increased fibrinogen synthesis, increased TAT, reduced AT and platelets activation. The highest levels of IL-6 and IL-1β were observed in the isoflurane_ open group and the lowest levels were observed in sevoflurane laparoscopic group that showed better hemostatic stability with lowest level of inflammatory markers. This confirms the strong relationship between hemostatic markers and inflammatory response **(Rahr et al., 2014).**

Conclusion:

- The results of our study showed that open surgery lead to activation of the clotting system of a higher degree than in the laparoscopic surgery group implying a greater thrombo-embolic risk for patients undergoing open surgery. Subclinical fibrinolysis was also more profound at the open surgery group. Although of a lower degree, hypercoagulability was still observed in patients undergoing laparoscopic surgery. The cytokine surge was correlated with the hypercoagulability. The correlation between cytokine levels and coagulation activation might be related to the type of surgery performed and the type of anesthesia used.
- Inflammation and coagulation play vital roles in host defense. There is extensive cross-talk between inflammation and coagulation in enabling an adequate immune response against potentially injurious stimuli. Immune cells are important in the initiation of coagulation pathways, while various inflammatory mediators are capable of altering hemostasis.
- Laparoscopic surgery under sevoflurane anesthesia was associated with less hypercoagulability and less inflammatory response than open surgery under isoflurane anesthesia. This can be referred to less activation of coagulation and platelets and lower level of inflammatory markers with higher level of anticoagulant and fibrinolytic factors in the former type of anesthesia and surgery.

Recommendations:

- For high risk patients of thromboembolic complications as ischemic heart disease, performing laparoscopic surgery under sevoflurane anesthesia is better than open surgery under isoflurane anesthesia.

- Routine thromboembolic prophylaxis (low molecular weight subcutaneous heparin, elastic compression stockings, intraoperative pneumatic stockings, and early postoperative patients mobilization) should be considered not only for patients undergoing open surgery but also for laparoscopic surgery due tolow hypercoagulability state presentin the laparoscopic type.
- We recommend new studies to understand the mechanisms involved in the crosstalk between inflammation and coagulation as this may yield new therapeutic strategies for human diseases. Also proinflammatory cytokines seem to be a fairly reliable indicator for the amount of tissue damage, but it remains to be determined whether this laboratory finding may translate into differences in clinical outcome.

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