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Fibrinolytic and coagulation pathways after laparoscopic and open surgery: a prospective randomized trial

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Abstract
Background Tissue injury poses increased risk for postoperative thromboembolic complications. Laparoscopic surgery, by causing limited tissue injury, is associated with lower risk for thromboembolism than is open surgery. We conducted a prospective randomized study in order to detect potentially existing differences in activation of coagulation and fibrinolytic pathways between open and laparoscopic surgery.
Methods Forty patients with chronic cholelithiasis were randomly assigned to undergo open (group A) or laparoscopic cholecystectomy (group B). Blood samples were taken preoperatively, at the end of the procedure, and at 24 and 72 h postoperatively. Prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), platelets (PLT), soluble fibrin monomer complexes (F.S. test), fibrin degradation products (FDP), D-dimers (D-D), and fibrinogen (FIB) were measured and compared within each group and between groups: Thrombin–antithrombin complexes (TAT) and prothrombin fragments (F1 + 2) were measured at 24 and 72 h postoperatively.
Results Demographics were comparable between groups. Immediately postoperatively, TAT and F1 + 2 were significantly higher in group A ($p < 0.05$). They also increased significantly postoperatively as compared with preoperative levels within each group ($p < 0.05$). D-dimers were significantly higher in group A ($p < 0.01$) immediately postoperatively. D-dimers also increased significantly postoperatively in group B as compared with preoperative levels ($p < 0.001$). FIB decreased slightly in both groups at 24 h postoperatively but there was a significant increase in group A ($p < 0.01$). Soluble fibrin monomer complexes (SFMC) were detected twice in group A and only once in group B. FDP levels over 5 μg/ml were detected more often in group A ($p < 0.05$). There was not any case of thromboembolism or abnormal bleeding.
Conclusions Open surgery leads to higher activation of the clotting system than do laparoscopic procedures. Although of a lower degree, hypercoagulability is still observed in patients undergoing laparoscopic surgery and therefore routine thromboembolic prophylaxis should be considered.

Keywords Hematology · Clinical trial

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Surgical trauma produces considerable alterations of the haemostatic system because of blood coagulation activation and therefore predisposes to a significant rate of

intraoperative or postoperative thromboembolic complications that can be as high as 40–80% [1].

Laparoscopic surgery has been widely accepted because of reduced tissue injury and therefore shorter convalescence [2, 3]. However its impact on haemostatic system has not been extensively studied on the basis of prospective randomized trials comparing it with open surgery.

We conducted a prospective randomized trial in order to study prevailing alterations of haemostasis over time after a specific type of surgery, assigning patients to either open or laparoscopic cholecystectomy. Nowadays, laparoscopic cholecystectomy has become the gold standard for treatment of uncomplicated cholelithiasis [4].

Patients and methods

Study population

In a prospective randomized trial that was conducted from 19 January to 26 September 2005, 40 patients with chronic cholelithiasis, American Society of Anesthesiologists (ASA) physical status classification grade I and II [5], were randomly assigned to undergo either open cholecystectomy (OC) (group A, 20 patients) or laparoscopic cholecystectomy (LC) (group B, 20 patients). All surgical operations were performed by the same surgical and anesthesiology team. In fact, this is an essential element of randomization, because the training and experience of an individual surgeon plays an important role in the outcome of surgery [6]. Patients and surgeons were aware of the result of randomization. Patients on medication affecting coagulation [anticoagulants, antiaggregants, nonsteroidal anti-inflammatory drugs (NSAIDs), steroids] as well as patients with known preexisting disorder that could affect the coagulation system (sepsis, cancer, history of thrombosis, recent surgery) were excluded from the study.

Informed consent was obtained by each patient and the study was approved by the ethics committee of the hospital.

Statistical hypothesis

The null hypothesis of the study (H_0) was that: (1) coagulation and fibrinolytic activity was not significantly different between the two groups of patients, and (2) plasma levels of coagulation and fibrinolysis markers did not change significantly from baseline values over time within each group.

The alternative hypothesis (H_A) was that: (1) there was a significant difference concerning both coagulation and fibrinolysis between the two groups and (2) within each group, plasma levels of each coagulation or fibrinolysis marker changed significantly over time as compared with baseline values. Key parameters that were measured in order to determine coagulation and fibrinolytic activity were: prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), platelets (PLT), thrombin–antithrombin complexes (TAT), prothrombin fragment $1 + 2$ (F1 + 2), soluble fibrin monomer complexes (F.S. test), fibrin degradation products (FDP), D-dimer (D-D), and fibrinogen (FIB).

Procedures

The evening before surgery, all patients were put on low-molecular-weight heparin as antithrombotic prophylaxis, which was continued once daily postoperatively until discharge. A single dose of a second-generation cephalosporin was given as a prophylactic antibiotic at induction of anesthesia.

Open cholecystectomy was performed in patients of group A by means of a Kocher incision, whereas in patients of group B laparoscopic cholecystectomy was performed using four trocars (2 of 5 mm and 2 of 10 mm), inserting the umbilical trocar by the open technique. Postoperatively patients were maintained on intravenous fluids (Ringer's lactated and dextrose 5%) for 24 h and opioids were given parenterally as analgesics. Venous blood was drawn before surgery, immediately after surgery, at 1st postoperative day, and at 3rd postoperative day by venipuncture of a forearm vein not used for infusion of the i.v.'s with a 21-G needle. Immediately after collection, blood samples were mixed with trisodium citrate 3.2% (9:1 v/v) in test tubes (Vacuette, Greiner bio-one) and transferred to the laboratory, where they were centrifuged at 3000 rpm for 30 min at 4°C in order to obtain platelet-free plasma samples. Those plasma samples were stored at −70°C until the time of coagulation and fibrinolysis factors assay.

Assays of coagulation and fibrinolysis markers

All markers were measured before surgery, immediately after surgery, and at 1st and the 3rd postoperative day, except for TAT and F1 + 2, which were measured before surgery, immediately after surgery, and at 3rd postoperative day.

PT, APTT, and FIB coagulation assays were carried out with a STA Compact coagulometer (Diagnostica Stago, Asnieres, France). FDP and D-dimer in plasma were determined semiquantitatively by use of latex agglutination (FDP PLASMA KIT and D-DI TEST, respectively; Diagnostica Stago, Asnieres, France). SFMC marker was measured with commercially available kits using hemagglutination techniques (F.S. TEST, Diagnostica Stago, Asnieres, France). F1 + 2 and TAT markers were measured

with standard enzyme-linked immunosorbent assay (ELISA) kits (Enzygnost F1 + 2 micro and Enzygnost TAT micro, respectively; Dade Behring, Marburg, Germany).

Statistical analysis

Mann–Whitney *U*-test, a nonparametric statistical test for independent samples, was used for investigation of any statistical significance of the observed differences in the distribution of measurements of all the aforementioned markers (PLT, PT, APTT, FIB, D-dimer, TAT, INR, and F1 + 2) between the two groups (A and B). Data were not normally distributed between the two groups, so median values and ranges were used. The chi-square test was used to investigate any statistical significance of the differences in the distribution of cases with plasma concentration of FDP >5 μg/ml and also of cases with positive F.S. test (presence in plasma of SFMC) between the two groups.

In order to evaluate the statistical significance of the observed differences between the preoperative (baseline values) and postoperative mean values of coagulation and fibrinolysis markers, within each group, one-way analysis of variance (ANOVA) supplemented by Bonferroni post hoc multiple comparison test was used.

A difference was considered to be statistically significant when value of probability p (two-tailed p) was less than 0.05 ($p < 0.05$). SPSS software (SPSS, Chicago, IL) was used for statistical calculations.

Results

Demographic data (age, weight) of the two groups of patients were comparable. Operative time was shorter in the laparoscopic surgery group, but the difference was not statistically significant (Table 1).

Preoperatively, values of all hemostatic parameters were within normal limits in both groups A and B.

Table 1 Demographic data of patient groups

Demographic data	Group A (open cholecystectomy)	Group B (laparoscopic cholecystectomy)
Patient population	20	20
Age (years)	37–81 (65.7)	37–75 (60.4)
Sex (M/F)	8/12	10/10
Weight (kg)	67–90 (76.3)	55–92 (75.7)
Operative time (min)	40–120 (68)	45–135 (63)
ASA score		
1	12	14
2	8	6

Operative time OC versus operative time LC (not significant)

Immediately postoperatively, TAT levels (Fig. 1) increased significantly compared with preoperative (baseline) values within each group ($p < 0.05$) but this increase was more marked in the open surgery group (group A). At the same time, there was significant difference of TAT levels between the two groups, with higher levels measured in group A ($p < 0.05$).

F1 + 2 levels (Fig. 2) were found to be significantly increased compared with baseline values, immediately postoperatively in group A and 72 h postoperatively in group B, respectively ($p < 0.05$). Apart this, immediately after surgery, F1 + 2 levels were significantly higher in the open surgery group than in the laparoscopic surgery group ($p < 0.05$).

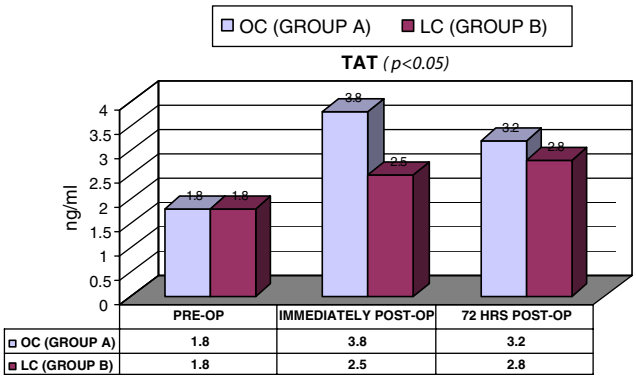

Fig. 1 Thrombin–antithrombin complex (TAT) plasma levels before and after open (OC) or laparoscopic (LC) cholecystectomy (median values). Baseline values versus postoperative values in OC, $p < 0.05$. Baseline values versus postoperative values in LC, $p < 0.05$. Values immediately after surgery in OC versus values immediately after surgery in LC, $p < 0.05$

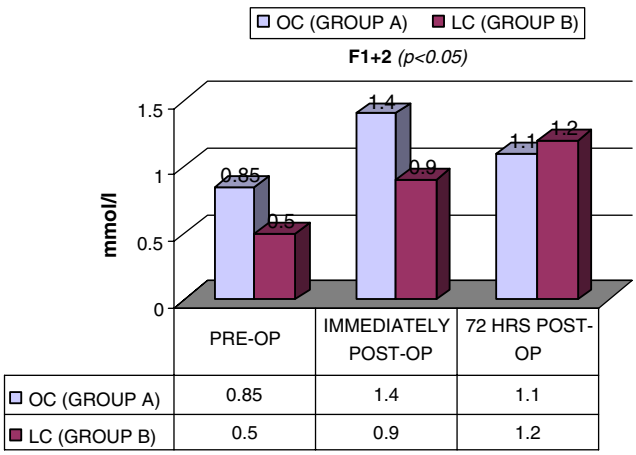

Fig. 2 Prothrombin fragment 1 + 2 (F1 + 2) plasma levels before and after open (OC) or laparoscopic (LC) cholecystectomy (median values). Baseline versus 24 h postoperative values in OC, $p < 0.05$. Baseline versus 72 h postoperative values in LC, $p < 0.05$. Values immediately after surgery in OC versus values immediately after surgery in LC, $p < 0.05$

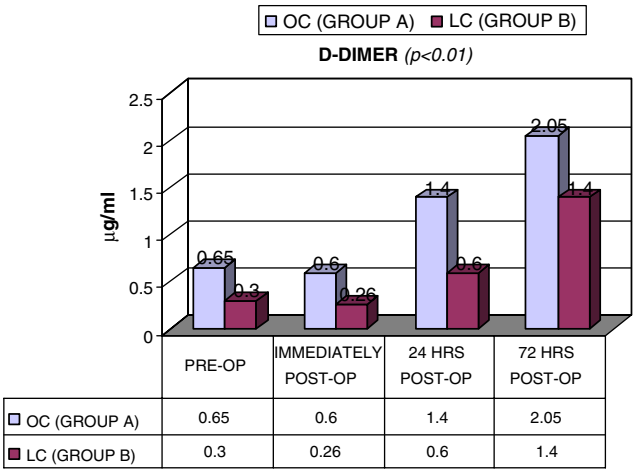

Fig. 3 D-Dimer plasma levels before and after open (OC) or laparoscopic (LC) cholecystectomy (median values). Baseline versus 72 h postoperative values in LC, $p < 0.001$. Postoperative values in OC versus postoperative values in LC, $p < 0.01$

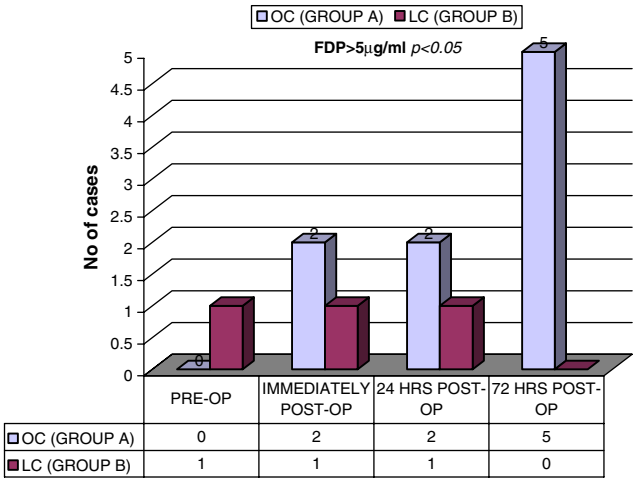

Fig. 5 Distribution of cases in which concentration of fibrin degradation products (FDP) > 5 µg/ml was detected before and after open (OC) or laparoscopic (LC) cholecystectomy. Number of cases with FDP > 5 µg/ml in OC versus number of cases with FDP > 5 µg/ml in LC, 72 h postoperatively, $p < 0.05$

In group B, D-dimer levels (Fig. 3) increased significantly 72 h postoperatively ($p < 0.001$) compared with preoperative values. In group A, D-dimer levels also increased postoperatively, but not significantly so. Immediately after operation, D-dimer levels were significantly higher in the open surgery group ($p < 0.01$) as compared with the laparoscopic surgery group and this continued at 24 h ($p < 0.01$) and at 72 h postoperatively ($p < 0.05$).

In group B, FIB levels (Fig. 4) decreased significantly immediately postoperatively ($p < 0.05$) as compared with baseline values. At 24 h after surgery, these levels increased insignificantly as compared with preoperative levels. At 72 h after surgery, there was a significant increase compared again with baseline levels ($p < 0.001$). In group A, FIB levels also decreased immediately after surgery but not to a significant level. At 24 and 72 h after surgery, respectively, a significant increase of FIB levels was noted when compared with preoperative levels ($p < 0.001$). Between the two groups, FIB levels were significantly higher at 24 and at 72 h after OC, than after LC ($p < 0.01$).

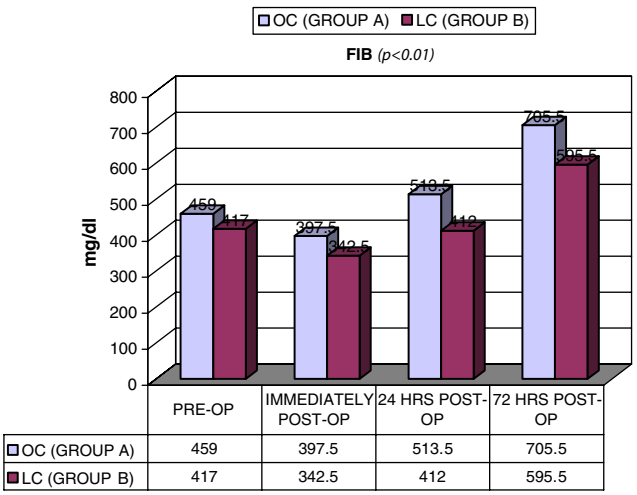

Fig. 4 Fibrinogen (FIB) plasma levels before and after open (OC) or laparoscopic (LC) cholecystectomy (median values). Baseline versus immediately postoperative values in LC, $p < 0.05$. Baseline versus 72 h postoperative values in LC, $p < 0.001$

In both groups FDP levels (Fig. 5) over 5 µg/ml were noted, starting immediately postoperatively, but there was not any statistical significance compared with preoperative levels. At 72 h after surgery FDP levels over 5 µg/ml occurred more often in the open surgery group (group A) than in the laparoscopic surgery group (group B), and this difference of occurrences between the two groups reached statistical significance ($p < 0.05$).

Presence of SFMC (F.S. test positive) (Fig. 6) was detected twice in the open surgery group (group A), immediately postoperatively and 72 h postoperatively, respectively. In the laparoscopy group (group B), it was detected only once, at 72 h postoperatively. The difference in the distribution of cases with a positive F.S. test between the two groups was not statistically significant.

A fall of PLT counts (Fig. 7) was noted in group B in relation to preoperative counts. This is noted immediately after surgery and persists until the 3rd day. This fall was very significant ($p < 0.001$). A nonsignificant fall of PLT counts took place later in group A, from the 1st until the 3rd day. When the two groups were compared, PLT counts did not differ significantly.

APTT values (Fig. 8) did not change significantly over time in both groups. Similarly, there was no statistically

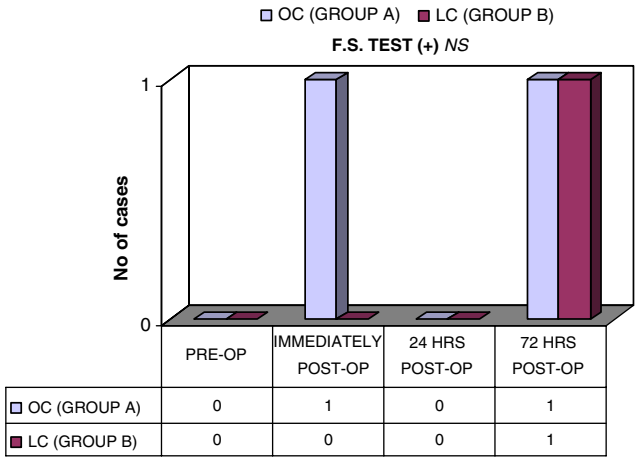

Fig. 6 Distribution of cases in which presence of soluble fibrin monomer complexes (SFMC) was detected (F.S. test positive), before and after open (OC) or laparoscopic (LC) cholecystectomy. Number of cases with F.S. test (+) in OC versus number of cases with F.S. test (+) in LC, not significant (NS)

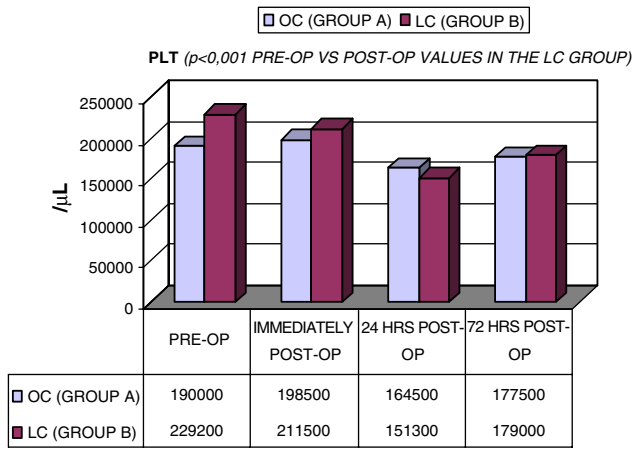

Fig. 7 Platelet (PLT) counts before and after open (OC) or laparoscopic (LC) cholecystectomy (median values). Baseline counts versus 24 h postoperative counts in OC and baseline counts versus 72 h postoperative counts in LC, $p < 0.001$. PLT counts in OC versus PLT counts in LC, not significant (NS)

significant difference of measured values of APTT between the two groups.

Levels of INR (Fig. 9) increased significantly ($p < 0.05$) 72 h after both laparoscopic and open cholecystectomy in relation to preoperative levels. However when the two groups were compared, levels of INR were not significantly different between group A and group B.

When PT (Fig. 10) was measured, a very significant increase within each group was noted when levels immediately after surgery and 24 h after surgery were compared with preoperative levels ($p < 0.001$). PT levels were not significantly different when group A (OC) was compared with group B.

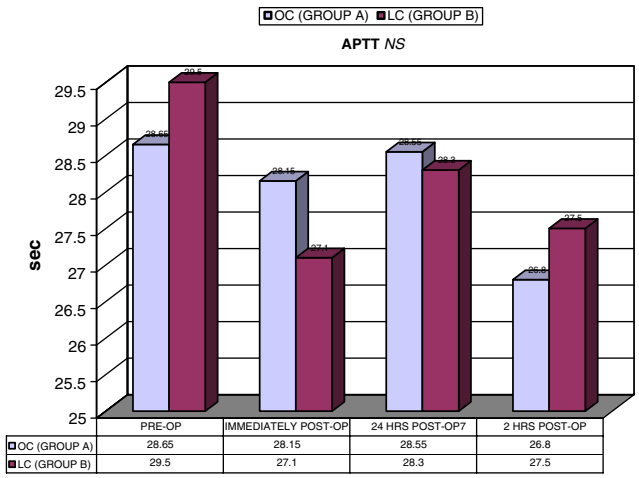

Fig. 8 Activated partial thromboplastin time (APTT) before and after open (OC) or laparoscopic (LC) cholecystectomy. Baseline values versus postoperative values in OC and baseline values versus postoperative values in LC, not significant (NS). APTT levels in OC versus APTT levels in LC, NS

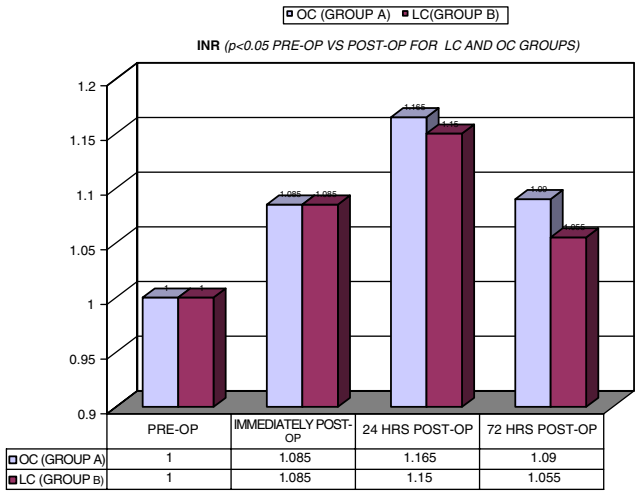

Fig. 9 International normalized ratio (INR) levels before and after open (OC) or laparoscopic (LC) cholecystectomy. Baseline levels versus 72 h postoperative levels in OC, $p < 0.05$. Baseline levels versus 72 h postoperative levels in LC, $p < 0.05$. INR levels in OC versus INR levels in LC, not significant (NS)

No patient from either group presented with a thromboembolic incident or abnormal bleeding as postoperative complication.

Discussion

Two potentially important alterations of hemostasis, predisposing to thromboembolic complications, occur in patients after surgery. The first alteration is a tendency

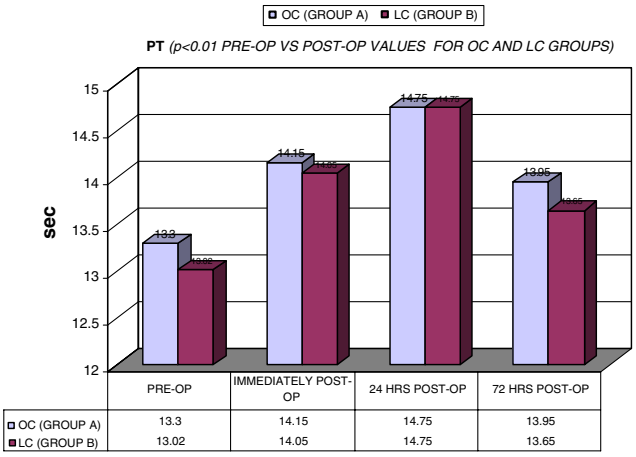

Fig. 10 Prothrombin time (PT) levels before and after open (OC) or laparoscopic (LC) cholecystectomy. Baseline levels versus immediate postoperative levels and baseline levels versus 24 h postoperative levels in OC, $p < 0.01$

towards hypercoagulability [7]. Plasma fibrinogen concentrations and platelet counts are increased in the first 24 h postoperatively [8]. There is increased platelet aggregation, presumably in response to release of a variety of aggregation-promoting agonists [9]. The second alteration, an initial enhancement of fibrinolysis, is followed by a decrease of its activity [10].

Most studies evaluating the perioperative alterations of hemostasis concern open surgery [7–11]. The risk of developing deep venous thrombosis after open surgery can be as high as 40–80%, while the incidence of fatal pulmonary embolism is 1–5% [1, 12]. Laparoscopic surgery is associated with a lesser degree of thromboembolic complications despite pneumoperitoneum which, by reducing venous inflow towards the heart, promotes venous stasis of the legs and predisposes to deep venous thrombosis [4, 13].

In the literature, only few randomized studies [14–17] have addressed the issue of comparing the alterations of hemostasis after laparoscopic and open surgery.

TAT complexes form when antithrombin III binds to thrombin, a product of prothrombin [18, 19]. F1 + 2 reflects in vivo thrombin generation [20]. Thus, these coagulation markers are direct indices of thrombin production and activation of the coagulation pathway which leads to hypercoagulability. In our study, TAT and F1 + 2 plasma levels increased significantly at the end of the operation in both groups when compared with preoperative values, showing thus thrombin generation and hypercoagulability immediately after surgery in both groups. Plasma levels of both these coagulation markers were significantly higher in group A. Additionally, increase of F1 + 2 levels in group A was higher and happened earlier when compared with group B. Therefore hypercoagulability, which is of a higher degree and happens earlier in the open surgery group than in the laparoscopic surgery group, is detected.

Fibrinogen is an acute-phase protein synthesized by the liver and plays a key role in blood clotting. During clot formation, it is converted to fibrin via the enzymatic action of thrombin [21]. Low levels may indicate increased consumption (fibrinolysis), and increased levels, which are often noted after inflammation, reflect the close association between stress and coagulation activation [11]. In our study, the significant decrease of FIB plasma levels noted in the laparoscopy group immediately after surgery as compared with the minor insignificant decrease noted at the same time in the open surgery group is attributed to early activation of fibrinolysis in the laparoscopy group. However, the earlier and higher increase of postoperative FIB plasma levels in group A indicates increased, earlier, and prolonged activation of coagulation in the open surgery group.

SFMC, a 1:2 complex of fibrin-monomer and fibrinogen, is present in circulating blood under conditions in which blood coagulation is activated [22]. It plays a role as a modulator of the thrombogenic process in vivo and may serve as an independent molecular marker for the detection of thrombin generation and the diagnosis of thrombosis [22]. Presence of SFMC in plasma can be quickly visualized with F.S. test. The early detection, and increased frequency, of a positive F.S. test indicates early activation of blood coagulation in the open surgery group as compared with the laparoscopic surgery group.

During fibrinolysis, fibrin and fibrinogen split to various fibrin/fibrinogen degradation products and finally to the terminal product D-dimer, in a process mediated by plasmin [23]. Normal plasma levels of FDP are under 5 μg/ml [24]. Constantly elevated FDP plasma levels are indicative of an important fibrinolytic activity [25]. Elevated D-dimer plasma levels are also indicative of recent or ongoing fibrinolysis [26]. However a constant elevation of D-dimer plasma levels raises suspicion of deep vein thrombosis [27]. The newer, sensitive D-dimer tests have negative predictive value for presence of deep venous thrombosis in patients with low prior probability [26]. In our study, postoperative increase of D-dimer and FDP plasma levels in both groups A and B indicates that activation of fibrinolysis takes place after both kinds of surgery. However, fibrinolytic activity is higher after open surgery, as D-dimer and FDP plasma levels are significantly higher in group A than in group B.

The significant postoperative increase of PT and INR levels in both groups implies an activation of coagulation after both kinds of surgery. An interesting finding in our study was the marked fall of PLT counts noted immediately postoperatively in the laparoscopic surgery group. It is not clear if this might account for platelet activation and

therefore greater risk for thrombi formation. Vecchio et al. [28] determined perioperative plasma beta thromboglobulin levels, as an index of platelet activation, in patients undergoing laparoscopic cholecystectomy and found it to be significantly increased 24 h after surgery.

In a randomized trial, Prisco et al. [14] compared laparoscopic with open cholecystectomy, by studying perioperative changes of fibrinogen, prothrombin fragment F1 + 2, D-dimer, and plasminogen activator inhibitor type 1 (PAI-1). They found a postoperative significant increase of fibrinogen in the open surgery group and a postoperative significant increase of F1 + 2 in both groups. They concluded that laparoscopic cholecystectomy induces activation of the clotting system, even if it is of low degree and short duration.

In another randomized trial, Milic et al. [17] compared only perioperative plasma levels of F1 + 2, D-dimer, antithrombin III (AT), PT, and thromboplastin time (PTT) and the incidence of postoperative deep vein thrombosis between open and laparoscopic cholecystectomy. They failed to show a significant difference of plasma levels of the aforementioned markers between the two groups of patients. On the contrary, incidence of postoperative deep vein thrombosis was significantly higher in the open cholecystectomy group than in the laparoscopic cholecystectomy group.

Comparative studies of hemostasis after laparoscopic and open surgery have been carried out using several other operations as a model of study, apart from laparoscopic and open cholecystectomy [15, 16].

Neudecker et al. [15] studied fibrinolysis after laparoscopic and open colorectal resection by measuring perioperative concentrations of tissue plasminogen activator (TPA), PAI-1, tPA/PAI-1 complex, fibrinogen, and D-dimer in patients randomly assigned to either type of surgery. No significant differences existed between the two groups as far as postoperative fibrinolysis was concerned.

Nguyen et al. [16] compared plasminogen, TAT, F1 + 2, FIB, D-dimer, AT III, and protein C levels between patients randomly assigned to open or laparoscopic gastric bypass (GBP). They found an insignificant increase of TAT and F1 + 2 levels and an insignificant decrease of plasminogen levels after surgery in both groups. Differences in plasma levels of these markers were insignificant between the two groups. On the other hand, D-dimer plasma levels were significantly higher after open GBP than after laparoscopic GBP. This could be attributed to the chosen model of operation for the study of perioperative alterations of coagulation, because gastric bypass is a major procedure adding increased surgical stress, and therefore coagulation activation of a high degree is induced, regardless of the surgical technique (open or laparoscopic) chosen.

In a nonrandomized trial Shietroma et al. [29] compared TAT, F1 + 2, FIB, soluble fibrin, and D-dimer plasma levels until 72 h after surgery between patients assigned to open or laparoscopic cholecystectomy and found that levels of the aforementioned markers were significantly higher in the open surgery group than in the laparoscopic surgery group, implying significantly higher activation of coagulation and fibrinolysis in the open surgery group.

Martinez-Ramos et al. [30], in another nonrandomized comparative study between laparoscopic cholecystectomy ($n = 20$) and low-risk open surgery (Bassini herniorrhaphy, $n = 12$) reported that FIB levels were significantly higher than the preoperative ones 24 h after surgery in both groups

Three other nonrandomized studies [31–33] compared fibrinolytic activity between open and laparoscopic cholecystectomy and found insignificant differences between the two groups of patients.

Conclusions

Results of our study showed that open surgery, as compared with laparoscopic procedures, leads to activation of the clotting system of a higher degree than in the laparoscopic surgery group, implying thus greater thromboembolic risk for patients undergoing open surgery. Subclinical fibrinolysis was also more profound in the open surgery group. Although of a lower degree, hypercoagulability is still observed in patients undergoing laparoscopic surgery. This fact, combined with the pneumoperitoneum-induced venous stasis of the legs, explains the reduced, but not negligible, rate of thromboembolic complications after laparoscopic surgery. Therefore, routine thromboembolic prophylaxis (low-molecular-weight subcutaneous heparin, elastic compression stockings, intraoperative pneumatic stockings, and early postoperative patient mobilization) should be considered for patients undergoing laparoscopic surgery.

Until recently, this was a recommendation that was based on findings of studies dealing only with open surgery. Several comparative randomized studies between open and laparoscopic surgery, including our study, by confirming the existence of hypercoagulability after laparoscopic surgery, seem to further reinforce this recommendation.

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