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Coagulation status and the presence of postoperative deep vein thrombosis in patients undergoing laparoscopic cholecystectomy

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Abstract
Background: Venous thromboembolism is a relevant social and health care problem because of its high incidence among patients who undergo surgery (20–30% after general surgical operations and 50–75% after orthopedic procedures), its pulmonary embolism-related mortality rate, and its long-term sequelae (postthrombotic syndrome and ulceration), which may be disabling. This study aimed to determine the coagulation status and the presence of postoperative deep vein thrombosis (DVT) in patients undergoing laparoscopic (LC) and open cholecystectomy (OC).
Methods: Prospectively, 114 patients were randomized into two groups. group 1 (58 patients undergoing LC) and group 2 (56 patients who are undergoing OC). The coagulation parameters (prothrombin time [PT], partial thromboplastin time [PTT], D-dimer, prothrombin F1 + 2, antithrombin III, and factor VII) were monitored preoperatively and during the operation, then 24 and 72 h after the operation. The patients in both groups underwent color duplex scan examination preoperatively, then 3 and 7 days after surgery to establish the presence of DVT. None of the patients in either group received thrombosis prophylaxis.
Results: In the LC group, postoperative DVT developed in four patients (6.9%; in the calf veins of 3 patients and in the popliteal vein of 1 patient). In the OC group, nine patients (16.07%) had postoperative DVT (in the calf veins of 7 patients and in the popliteal and femoral veins of 2 patients). The plasma levels of monitored parameters in the patients of both groups were altered, but the difference between the groups was not statistically significant. For the patients in both groups who experienced DVT, only the decrease of factor VII had statistical significance ($p < 0.05$).
Conclusions: The incidence of postoperative DVT among the patients who underwent OC was higher than among the patients who underwent LC ($p < 0.05$). The decrease in factor VII among the patients who underwent surgery could be a potentially useful parameter indicating the patients at high risk for developing DVT.

Key words: Cholecystectomy — Coagulation status — Deep vein thrombosis

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Venous thromboembolism is a relevant social and health care problem because of its high incidence among patients who undergo surgery (20–30% after general surgical operations, 10–35% after gynecologic operations, and 50–75% after orthopedic procedures), its pulmonary embolism–related mortality rate, and its long-term sequelae (postthrombotic syndrome and ulceration), which may be disabling.

The exact incidence of deep vein thrombosis (DVT) among patients undergoing laparoscopic cholecystectomy (LC) is unknown because most studies are limited by the inherent inaccuracy of the clinical diagnosis. More importantly, most DVTs are occult and usually resolve spontaneously without complication. The reported studies on postoperative coagulation and fibrinolytic activation are inconclusive and sometimes show contradictory results [1–3]. In the past few years, however, several authors have reported thromboembolic complications after laparoscopy [1, 4–7].

This prospective, randomized study aimed to investigate hemostatic system alterations and the presence of DVT among patients who have undergone open cholecystectomy (OC) and LC.

Materials and methods

For a power of 80% ($\beta = 20\%$) and a significance level of $\alpha = 5\%$, if the difference between the examined groups is 0.400 times the within-group standard deviation, a total of 100 patients is needed for the

study. Because the patient population included in this study could differ to some extent, and allowing for a dropout rate of 10% to 20%, a sample size of 120 patients was calculated to be required for the study. Of the 130 patients considered for the study, 120 were randomized into the two study groups: 60 into the LC group and 60 into the OC group. The randomization was computer generated.

After randomization, four protocol violations occurred: one conversion to OC in the LC group, two inadequate blood sample tests in the OC group, a color duplex scan not performed according to the protocol for one patient in the LC group, and withdrawal of consent to participate in the study by two patients in the OC group.

Only patients for whom a full set of data was available were used for the analysis. Both groups were well matched for age and sex. Overall, 114 patients (64 women and 50 men; mean age, 52.9 years) were included in the study from June 2005 to April 2006. All these patients presented with symptomatic gallbladder stone disease.

In LC group, 58 randomized patients (34 women and 24 men; mean age, 50.1 years) underwent LC using the standard technique with a four-trocar incision and a 14-mmHg carbon dioxide (CO_2) pneumoperitoneum. The remaining 56 patients (30 women and 26 men; mean age, 53.6 years), in the OC group, underwent OC using a right subcostal incision. All the patients in both groups had surgery performed by the same surgical team, and all the patients gave written consent. The diagnosis was confirmed by ultrasound examination.

None of the patients had a history of thromboembolic events or lower leg ulcers. None of them had undergone abdominal surgery, and none had been treated for malignancy or inflammatory disease of the bowel. Serologic test results (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin, serum protein) were in the normal range.

The exclusion criteria specified age exceeding 75 years; the presence of congenital coagulopathy, trombophilia, malignancy, renal, or liver diseases; recent surgical procedures (within the preceding 12 months); cardiologic or neurologic disease; heart arrhythmias; pregnancy; use of estrogens; acute cholecystitis; cholangitis; other acute inflammation; current or recent (within 12 months) acute pancreatitis; hematologic disorders; anticoagulant treatment; thromboembolic disorders; rheumatic or vascular disease; and body mass index exceeding 32. Patients with preexisting coagulation disorder as shown by abnormalities in the preoperative history and physical examination or in the preoperative platelet count, prothrombin time (PT), or activated PTT (aPTT) were excluded as well. We also excluded patients taking corticosteroids or other drugs that could affect their immunologic responses.

During hospitalization, the patients were not given antispastic drugs, steroids, or nonsteroidal antiinflammatory drugs (NSAIDs). They received no thrombosis prophylaxis. The patients were classified as grade 1 or 2 according to the American Society of Anesthesiologists (ASA) grading system. Ages, sex, ASA grades, and times of anesthesia, were comparable between the two groups, but hospitalization was significantly shorter for the LC group.

Anesthesia was achieved for both groups using the same procedure. Preanesthesia was accomplished using atropine (0.01 mg/kg) plus promethazine (0.5 mg/kg), and anesthesia was induced using sodium thiopental (5 mg/kg) and atracurium (0.5 mg/kg), as well as tracheal intubation and assisted ventilation using nitrogen dioxide (NO_2)/oxygen 2:1. The mean operating time was 44 $\pm$ 16.1 min (range, 28–60 min) for the OC group and 51.2 $\pm$ 11.3 min (range, 40–60 min) for the LC group. There were no conversions to OC. The pneumoperitoneum time ranged from 30 to 45 min.

The coagulation parameters (PT, PTT, D-dimer, prothrombin F1 + 2, antithrombin III, and factor VII) were monitored preoperatively during the operation (at skin closure), then 24 and 72 h after the operation. The patients in both groups underwent color duplex scan examination preoperatively, then 3 and 7 days after the operation to establish the presence of DVT. The color duplex scan examinations were performed using the Siemens Sonoline Sienna ultrasonography device (Erlangen, Germany) with a 7-MHz probe.

The blood samples were taken using the vacutaner system with 3.8% Na citrate, after which centrifugation was performed for 15 min at 1,000 g. The plasma was divided and used for the examination. Using standard methods with the ACL 2000 coagulometer (Instrumentation Laboratory, Milano, Italy) and commercial kits for these tests (Instrumentation Laboratory), we analyzed PT, PTT, and factor VII. The concentrations of antithrombin III were analyzed using standard colorimetric methods (CL 2000 coagulometer and commercial kits with chromogenic substrate; Instrumentation Laboratory). Additionally, D-dimer was analyzed with the commercial kit Simpli-RED, Brisbane, Australia. Analyzed parameters were expressed as follows: PT, factor VII, and antithrombin III in percentages; PTT in seconds; and D-dimer in milligrams per liter. Complete testing of coagulation parameters was performed in the Laboratory for Haemostasis, Institute for Blood Transfusion Nis.

Statistical analysis was performed using Student's two-sided *t*-test for paired values. Subgroup analysis between the LC and OC groups compared the changes in the studied parameters for the respective groups using Student's two-sided *t*-test, not assuming equal variances. Differences were considered statistically significant at *p* values less than 0.05. Analysis of coagulation parameters between the subgroups of patients who did and did not experience postoperative DVT, regardless of the operation procedure (LC or OC) was performed as well.

Results

Activation of the coagulation process was registered for the patients in both groups. The incidence of postoperative DVT was higher among the patients who underwent OC than among those who underwent LC ($p < 0.05$). In the LC group, DVT developed in four patients (6.9%) (3 patients had DVT of the calf veins and 1 patient had DVT of the popliteal vein), whereas in the OC group, nine patients (16.07%) had postoperative DVT (7 patients had DVT of the calf veins and two patients had DVT of the popliteal and femoral veins). In the LC group, DVT was established for three patients 3 days after the operation and for one patient 7 days after surgery. In the OC group, DVT was established for six patients 3 days after the operation and for 3 patients 7 days after surgery.

The plasma levels of the monitored parameters for the patients in both groups were altered, but the difference between the groups was not statistically significant (Table 1). Elevation of D-dimer was detected 24 and 72 h after OC and LC, but there was no difference in the degree of elevation between the two groups (Fig. 1).

However, for the subgroup of patients who experienced DVT (4 patients in LC group and 9 patients in OC group), the median value of factor VII at 24 and 72 h postoperatively was significantly lower than for the patients who did not experience DVT (Table 2), indicating that factor VII could be a potentially useful parameter for establishing patients at high risk for DVT. No statistically significant difference between the plasma levels of any other monitored parameters, including D-dimer, was shown ($p > 0.05$).

Discussion

In less than a decade, LC has replaced OC as the standard operation for symptomatic cholecystolithiasis. This new approach has led to a reduction in postoperative pain and recovery time after surgery. It is suggested that LC may lead to a higher risk of postoperative thromboembolic complications than OC because of the longer operating time, the placement of the patient in the reverse Trendelenburg position during most of the procedure, and the increased intraabdominal pressure, which causes venous pooling in the legs.

Table 1. Plasma levels of monitored coagulation parameters in examined groups of patients

Coagulation parameter	Sample	LC (x + SD)	OC (x + SD)	T	p Value
D-dimer	Preop	340.3655 + 219.6704	311.6275 + 139.9182	0.777	0.439
	Periop	441.0615 + 349.6985	475.0027 + 366.5191	−0.439	0.662
	24 h postop	525.0075 + 394.4014	556.6297 + 383.2706	−0.381	0.705
	72 h postop	499.4737 + 250.7928	555.1563 + 267.1670	−0.893	0.375
F1 + 2	Preop	404.4444 + 79.5740	390.0000 + 93.7263	0.462	0.648
	Periop	363.8000 + 156.5322	353.7000 + 177.7802	0.146	0.886
	24 h postop	381.1333 + 164.9566	387.7000 + 199.1025	−0.086	0.932
	72h postop	417.1429 + 75.2140	400.0000 + 65.7267	0.439	0.670
Factor VII	Preop	119.3846 + 22.8689	116.7500 + 25.5571	0.513	0.609
	Periop	102.0943 + 33.0869	97.0541 + 35.7258	0.679	0.499
	24 h postop	103.6038 + 26.5376	99.7778 + 27.6272	0.651	0.517
	72h postop	102.7368 + 22.1941	99.9375 + 23.4685	0.510	0.612
APTT	Preop	26.8276 + 2.2876	26.9767 + 2.3953	−0.315	0.753
	Periop	29.4615 + 14.1109	33.9189 + 22.5418	−1.064	0.292
	24 h postop	25.8704 + 1.7809	26.1053 + 2.0506	−0.571	0.570
	72h postop	28.9737 + 12.2992	32.0313 + 18.2518	−0.806	0.424
ATIII	Preop	100.7800 + 0.0000	100.3400 + 0.0000	0.521	0.604
	Periop	101.4231 + 7.3601	101.8108 + 11.2196	0.765	0.448
	24 h postop	103.7120 + 0.0000	104.8340 + 0.0000	0.832	0.078
	72h postop	102.6500 + 0.0000	103.5680 + 0.0000	0.788	0.13
PT	Preop	94.2222 + 10.7570	92.1429 + 8.0561	0.625	0.537
	Periop	88.2667 + 22.4864	84.6000 + 25.1758	0.372	0.714
	24 h postop	94.5333 + 14.7835	95.6000 + 14.1358	−0.181	0.858
	72h postop	94.0000 + 14.0475	92.3333 + 14.6105	0.209	0.839

LC, laparoscopic cholecystectomy; OC, open cholecystectomy; SD, standard deviation; preop, preoperative; periop, perioperative; postop, postoperative; F1 + 2, prothrombin F1 + 2; aPTT, activated partial thromboplastin time; ATIII, antithrombin III; PT, prothrombin time

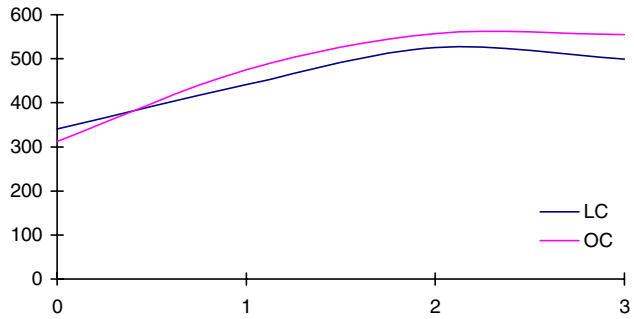

Fig. 1. The values of D-dimer in the study groups of patients.

Only three studies have used objective methods for surveillance of postoperative DVT after LC. The first study [8] showed only one DVT case in 100 patients screened by Doppler ultrasound on postoperative day 7. However, there was an increase in the thromboelastography index and activated PTT in plasma, suggesting activation of coagulation postoperatively. The second study [9] showed DVT in 55% of the patients (11 of 19) studied by Doppler ultrasound on days 1, 7, and 30 after the operation despite both pharmacologic and mechanical prophylaxis against thromboembolism. The sample sizes were small in both investigations. Moreover, the sensitivity of ultrasonography for the surveillance of asymptomatic patients in the postoperative situation has been questioned [10]. The third study [11], which used the 125I fibrinogen uptake test, demonstrated postoperative DVT in 23.3% of the LC patients and 62.5% of the OC patients. No prophylaxis against thromboembolism was given in this study.

Although LC is considered to be a minimally invasive procedure, its greatest difference from OC is the degree of trauma to the abdominal wall. Important to the patient and affecting postoperative mobilization, however, trauma to the intraabdominal organs is just as great because the gallbladder is dissected from the gallbladder bed and the cystic duct and artery are divided just as in OC. Animal studies [12] have suggested that pneumoperitoneum may damage the vessel wall, causing exposure of the subendothelium, coagulation, and platelet activation. In addition, intraabdominal pressure may temporarily affect the hepatic function and biliary excretion and may produce a diminished synthesis of vitamin K–dependent factors of coagulation [13].

The routine diagnosis of coagulation abnormalities implies examination of PT, PTT, and D-dimer. The most sensitive marker of intravascular coagulation, D-dimer is a reliable indicator of the degree of coagulation system activation [14]. Increases in D-dimer indicate increased formation and breakdown of fibrin. Several studies have shown a correlation between increased D dimer and venous thromboembolism, although the specificity is too low to be of diagnostic value for individual patients. A negative test result, on the other hand, may rule out thromboembolism [15].

Contemporary diagnosis of coagulation abnormalities uses some other tests also. These tests determine antithrombin III, alfa-2 antiplasmin, sensitive markers of thrombotic activity (fibrinopeptid A and B, thrombin–antithrombin III [TAT] complex, prothrombin fragment F1 + 2) and markers of fibrinolytic activity (plasmin-alfa-2 antiplasmin [PAP] complex). Lower values of alfa-2 antiplasmin and antithrombin III [16]

Table 2. The values of factor VII in subgroups of patients with and without postoperative deep vein thrombosis (DVT)

Factor VII	DVT group (x + SD)	Non-DVT group (x + SD)	t	p Value
24 h postop	86.0769 + 3.7072	102.3766 + 36.3296	−3.821	0.001
72 h postop	94.6154 + 9.2154	103.3289 + 28.7023	−2.091	0.041

with increased values of fibrinopeptid A and B [17] are found in patients with DVT of the leg. Higher values of TAT complex [18] and prothrombin fragment F1 + 2 [19] also are a reliable marker of thrombotic activity.

The results obtained in our study show the presence of coagulation activation among most of the patients undergoing OC and LC. The level and extent of these abnormalities could vary among patients. During the examination in our laboratory, we observed the decrease of factor VII 24 and 72 h after surgery in patients with postoperative DVT, suggesting that factor VII could be the parameter for marking patients at high risk for DVT.

The changes in coagulation status are manifested through activation of coagulation with an increase in fibrinopeptid A, TAT complex, and D-dimer, and a decrease in antithrombin III [20]. Some other authors note the importance of hypercoagulability in patients undergoing surgery and the correlation between coagulation disorders and vasospasm, concluding that hypercoagulability directly causes vasospasm. The injury of blood vessels endothelium, apart from activating coagulation, also releases endothelin, which causes vasospasm, further complicating DVT [21].

Regardless of the cause, locally originated activation of coagulation elevates the values of coagulation and fibrinolysis markers in blood. The most precise diagnosis of coagulation disorders would include determination of these sensitive coagulation and fibrinolysis markers. The most important parameters are tissue factor, prothrombin F1 + 2, and TAT complex as markers of thrombotic activity, and PAP complex as a marker of fibrinolysis.

In this study, D-dimer was the only true sensitive marker of coagulation and fibrinolysis, whereas the other examined parameters (PT, PTT, thromboplastin time, factor VII, antithrombin III) represented indirect indicators of coagulation and fibrinolysis. The results obtained in this study show that coagulation activation is present in early postoperative stages.

For the patients who experienced postoperative DVT, the observed decrease in PT probably resulted from decreased concentration of factor VII after its binding to tissue factor. The largest decrease in factor VII was observed in the group of patients with DVT of the femoral and popliteal veins.

Laparoscopic cholecystectomy leads to postoperative activation of the coagulation system, which is a prerequisite for thromboembolic complications. Still, the rate of clinically evident DVT is very low. One possible explanation is that there is in fact a development of DVT in the calf postoperatively, but that the early ambulation activates the fibrinolytic system, preventing the thrombi from increasing in size and propagating proximally. Perhaps small clots in the veins of the lower extremities are common but not particularly important clinically in freely ambulating persons with normal fibrinolytic systems.

Only a few studies have addressed the perioperative changes in hemostatic parameters after laparoscopic surgery. Dexter et al. [1], comparing OC and LC, found similar changes in coagulation and fibrinolysis, except for a longer euglobin clot lysis time and a higher plasminogen activator inhibitor-1 level observed in the OC group 6 h after surgery. According to their results, LC does not increase the risk of thromboembolic complications as compared with open surgery. Martinez-Ramos et al. [22] indicated that laparoscopy induced activation of plasma coagulation to a lesser degree than open surgery. Fibrinolytic activity, however, was increased, and according to the authors, these changes may possibly reduce the thromboembolic risk in laparoscopic surgery. Prisco et al. [2] also demonstrated activation of the coagulation pathway, which was less marked in the laparoscopic group than in the open group, and observed similar fibrinolytic changes in the open and laparoscopic surgeries.

Conclusion

Only a mild hypercoagulability state was observed in the patients who had undergone LC. Nevertheless, laparoscopy must be considered for postsurgical thromboembolism. It therefore should be recommended that routine thromboembolic prophylaxis be used for patients undergoing LC, especially high-risk patients. A marked decrease in factor VII 24 and 72 h after surgery could be a potentially useful parameter indicating patients at high risk for DVT.

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