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Coagulation activation after laparoscopic cholecystectomy in spite of thromboembolism prophylaxis

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Abstract.
Background: The aim of this study was to determine whether laparoscopic cholecystectomy (LC), in spite of its minimally invasive nature, causes coagulation activation.
Methods: Sixty-four patients undergoing LC were included prospectively. All received either dextran or low-molecular-weight heparin (LMWH). Blood samples taken the morning of the operation and the following morning were analyzed for TAT, FM, fragment 1+2, tPA, PAI-1, vWf, D-dimer, Hb, hematocrit, and APC resistance.
Results: Significant increases in TAT, FM, fragment 1+2, and D-dimer were seen, whereas APC resistance, Hb, and hematocrit decreased significantly. Dextran led to a decrease in vWf and no change in tPA, whereas LMWH led to an increase in both these parameters.
Conclusions: Laparoscopic cholecystectomy causes coagulation activation. There are differences in the response between patients receiving dextran and LMWH as thromboembolism prophylaxis. Since most patients are discharged the day after the operation, there could be practical as well as theoretical advantages to using dextran.

Key words: Laparoscopic cholecystectomy — Coagulation activation — Thromboembolism prophylaxis — Dextran — Low-molecular-weight heparin — Gallbladder

In less than a decade, laparoscopic cholecystectomy (LC) has replaced open cholecystectomy (OC) as the standard operation for symptomatic cholecystolithiasis. This new approach has led to a reduction in postoperative pain and recovery time after surgery [2], although similar results have been achieved by mini-laparotomy cholecystectomy [18]. Not all of the variables that have been studied, however, have been associated with a reduction in surgical trauma [20]. Furthermore, it has been suggested that LC may lead to a higher risk of postoperative thromboembolic complications than OC, since the longer operating time, the placement of the patient in the reverse Trendelenburg position during most of the procedure, and the increased intra-abdominal pressure cause venous pooling in the legs.

Only three studies have used objective methods for the surveillance of postoperative deep vein thrombosis (DVT) after laparoscopic cholecystectomy. The first [5] showed only one DVT in 100 patients screened by Doppler ultrasound on the 7th postoperative day; however, there was an increase in the thromboelastography index and activated partial thromboplastin time in plasma, suggesting activation of the coagulation postoperatively. The second study [16] showed DVT in 55% of the patients (11 of 19) studied by Doppler ultrasound on days 1, 7, and 30 after the operation in spite of both pharmacological and mechanical prophylaxis against thromboembolism. The third study [12], which used the ^{125}I fibrinogen uptake test, demonstrated postoperative DVT in 23.3% of patients undergoing LC and 62.5% in the OC group ($p > 0.05$). No prophylaxis against thromboembolism was given in this study.

The aim of the present study was to determine whether LC leads to a demonstrable activation of the coagulation system and if there is any difference between patients given prophylaxis against thromboembolism with low-molecular-weight heparin (LMWH) and those given dextran.

Patients and methods

Sixty-four patients (16 men and 48 women; mean age, 49.4 [±14.4] years)] undergoing LC at Skellefteå County Hospital, a rural hospital in northern Sweden, were included prospectively. Perioperative cholangiography was performed routinely. The standard prophylaxis against thromboembolism early in the study was 6% dextran 70 (Macrodex, Pharmalink, Spanga, Sweden) 500–1000 ml on the day of the operation), but approximately halfway through it was changed to LMWH (Fragmin, Pharmacia & Upjohn Sverige AB, Solna, Sweden) 2500 U subcutaneously once daily while

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Table 1. Comparison of preoperative values for subgroups receiving dextran and LMWH as prophylaxis against thromboembolism (values shown as mean (SD))

Parameter	Dextran group	LMWH group	*p* value
Number of patients	38	23	
Age (yr)	50.0 (13.4)	50.6 (16.8)	0.70
Duration of anesthesia (min)	122.1 (30.0)	120.0 (23.5)	0.77
Duration of operation (min)	86.7 (26.8)	82.2 (20.2)	0.46
Duration of pneumoperitoneum (min)	74.7 (23.1)	74.6 (19.8)	0.97
Hospital stay (days)	2.4 (1.4)	2.3 (1.2)	0.69
APC resistance (ratio)	2.52 (0.31)	2.57 (0.23)	0.52
D-dimer (μg/L)	22.3 (15.8)	26.2 (31.8)	0.57
Fibrin monomers (mg/L)	27.3 (7.9)	22.3 (6.5)	0.01
Fragment 1+2 (nmol/L)	0.87 (0.27)	1.01 (0.43)	0.16
TAT (μg/l)	4.6 (6.2)	3.5 (1.3)	0.31
VWf (%)	138.3 (8.3)	136.6 (11.9)	0.56
tPA (μg/L)	8.6 (3.8)	7.9 (4.2)	0.49
PAI-1 (IU/ml)	16.2 (13.7)	8.8 (7.0)	0.009
Hemoglobin value (g/L)	138.3 (8.3)	136.6 (11.9)	0.56
Hematocrit (%)	40.6 (2.5)	40.3 (3.0)	0.59

remaining in the hospital. Thirty-eight patients received dextran, 23 patients LMWH, and three patients both dextran and LMWH. The subgroups receiving dextran and LMWH were similar except for the preoperative values for FM and PAI-1 (Table 1).

All patients were negative for previous thromboembolic events or lower leg ulcers. None of them had undergone upper abdominal surgery, but 27 had had some sort of abdominal surgery, mainly appendectomies and gynecological procedures but also one operation for volvolus and one for perforation of the colon. Two patients had been operated on due to malignancies; one had breast cancer and the other had a carcinoid tumor of the lung, and neither had known metastases. One patient had undergone surgery for a fracture of the femoral neck.

The mean time of anaesthesia was 121 min (SD 27), the mean operating time was 84 min (SD 24), and the mean time of carbon dioxide pneumoperitoneum (upper limit, 12 mmHg) was 74 min (SD 21). There were four conversions to OC with pneumoperitoneum times ranging from 50 to 80 min in three patients due to difficulty in identifying the structures in Calot's triangle and in one patient due to slight but cumbersome bleeding with a drop in hemoglobin value (Hb) from 127 to 112 g/L.

Venous blood samples collected in the morning on the day of the operation and the following morning at approximately the same time amounted to 2 × 4.5 ml of blood in tubes containing 0.5 ml of citrate 0.129 M (Becton Dickinson Vacutainer Systems Eur. B.P. 37 38241, Myelan Cedex, France). The blood samples were centrifugated, and the plasma was frozen at–70°C within 30 min.

Thrombin-antithrombin complexes (TAT) and prothrombin fragment 1+2 (fragment 1+2) were analyzed using an ELISA kit (Behringwerke AG, marburg, Germany). Reference intervals were 1.2–5.0 μg/L and 0.4–1.5 nmol/L (2.5th to 97.5th percentile), with respective medians 2.3 βg/L and 0.8 nmol/L. The intraassay and interassay variations were between 5% and 9% for both analyses.

Using a spectrophotometric assay (Behrichrom; Behringwerke AG), fibrin monomers (FM) were measured. The reference interval was 2.8–17.3 mg/L, with a median value of 9.0 mg/L. Intraassay variation was between 3.3% and 7.4%, and interassay variation was between 2.3% and 10.4%.

von Willebrand factor (vWf) was analyzed using an ELISA kit (STA Liatest vWf; Diagnostica Stago S.A., Asnières, France), with a reference interval of 50–170%.

Activated protein C resistance (APC resistance) was assayed by conventional activated partial thromboplastin time (APTT) and expressed as a ratio between APTT in the presence of a normalized amount of APC and APTT in the absence of APC after dilution with factor V–deficient plasma (performed by the APC resistance test from Chromogenix, Mölndal, Sweden, and run on a Thrombolyzer from Behnk Elektronik, Frankfurt, Germany).

Enzyme immunoassay for quantitative determination of tissue plaminogen activator (tPA) was performed (Imulyse tPA; Biopool, Umeå, Sweden), with a reference interval of 3–10 μg/L, with intra- and interassay variations of 8% and 10%, respectively.

Table 2. Mean values for 64 patients before and after laparoscopic cholecystectomy

Parameter	Preoperative mean	Postoperative mean	*p* value
APC resistance (ratio)	2.55	2.50	0.012
D-dimer (μg/l)	23.67	72.40	<0.0001
Fibrin monomers (mg/L)	25.23	27.23	0.013
Fragment 1+2 (nmol/L)	0.92	1.29	<0.0001
TAT (μg/L)	4.10	7.40	0.0012
VWf (%)	116.3	124.6	0.14
tPA (μg/L)	8.18	8.85	0.11
PAI-1 (IU/ml)	13.18	13.04	0.93
Hb (g/L)	137.7	121.0	<<0.0001
Hematocrit (%)	40.5	35.7	<<0.0001

Quantitative determination of plasminogen activator inhibitor I (PAI-1) was performed by a bioimmunoassay (Biopool Chromolize; Biopool, Umeå, Sweden). The reference interval was 12.8 ± 12.1 (SD) IU/ml (median, 9.6 U/ml). The intra- and interassay variation was 2.6–3.7% and 3.6–16.9%, respectively.

Human cross-linked fibrin degradation product (D-dimer) was determined quantitatively by using a sandwich enzyme immunoassay (Enzygnost D-dimer micro; Behring Diagnostics GmbH, Marburg, Germany), with a reference interval of 4–78 μg/L and intra- and interassay variations of 2.4–4.4% and 12.3–15.4%, respectively.

Operating times (to the nearest 5 min) and pre- and postoperative Hb and hematocrit values were obtained from the operative charts. Evidence of clinically manifest postoperative thromboembolic complications were searched for in the patients' records at the Departments of Surgery and Radiology ≥1 month after the operation.

Values are generally presented as mean (SD). Statistical analysis was done with Student's two-sided *t*-test for paired values. Subgroup analysis between the LMWH and dextran groups was done comparing the changes in the studied parameters in the respective groups by Student's two-sided *t*-test not assuming equal variances. Differences were considered statistically significant at $p < 0.05$.

The study was approved by the ethics committees at Uppsala and Umeå universities.

Results

Significant increases were seen postoperatively in TAT, FM, fragment 1+2, and D-dimer, whereas Hb, hematocrit, and APC resistance decreased significantly. Nonsignificant increases were seen in vWf and tPA. No significant change in PAI-1 was seen (Table 2).

When the dextran and LMWH subgroups were compared, their responses differed significantly in vWf, Hb, hematocrit, and tPA. The dextran patients showed a significant decrease in mean vWf(111.9–97.2%; $p < 0.01$), whereas the LMWH patients showed a significant increase (126.1–164.2%; $p < 0.001$). The dextran patients had an average decrease in Hb of 20.8 g/L (95% CI 18.1, 23.6), whereas the LMWH patients only showed a decrease of 9.7 g/L (95% CI 5.9, 13.6). The dextran group showed no change in tPA (an increase by 0.044 μg/L (95% CI [–1.10], 1.01), whereas the LMWH group showed a significant increase by 1.69 μg/L (95% CI 0.37, 3.01) (Table 3).

Three patients had an increased APC resistance, one of whom was a homozygote, which is the expected rate in Sweden. No patients developed clinically manifest thromboembolic complications, nor were they subjected to diagnostic measures due to suspicion of such complications.

Discussion

The increases in fragment 1+2 and TAT indicate increased formation of thrombin, whereas the increases in FM and

Table 3. Changes in coagulation parameters after laparoscopic cholecystectomy in the dextran ($n = 38$) and LMWH ($n = 23$) groups (negative values indicate decreases) and subgroup analysis comparing the two groups

Parameter	Mean change in dextran group	Mean change in LMWH group	*p* value
APC resistance (ratio)	−0.069	−0.025	0.31
D-dimer (μg/L)	47.47	48.42	0.95
Fibrin monomers (mg/L)	2.11	1.57	0.73
Fragment 1+2 (nmol/L)	0.36	0.38	0.80
TAT (μg/L)	3.09	3.56	0.78
VWf (%)	−14.75	38.09	<0.0001
tPA (μg/L)	−0.04	1.69	0.049
PAI-1 (IU/ml)	−0.64	1.06	0.59
Hb (g/L)	−20.83	−9.73	<0.0001
Hematocrit (%)	−5.88	−2.87	0.00015

D-dimer indicate increased formation and breakdown of fibrin. There is, thus, at least indirect evidence of activation of the coagulation system in patients undergoing LC, which is considered a minor surgical procedure. Furthermore, several studies have shown a correlation between increased D-dimer and venous thromboembolism, although the specificity is too low to be of diagnostic value in individual patients. A negative test, on the other hand, may rule out thromboembolism under certain circumstances [19].

The greater decrease in Hb and hematocrit after receiving dextran rather than LMWH is what could be expected due to the hemodilution effect. Our finding that dextran lowers the vWf concentration has been reported previously [1], although the mechanism is unclear. This effect could be beneficial, since vWf has been shown to correlate to an increased risk of venous thromboembolism [4]. Likewise, the finding that LMWH (and unfractioned heparin) increases tPA levels is not new [7]. This effect could also be of benefit, since an increase in fibrinolysis could counteract the development of manifest thrombosis.

Though LC is considered to be a minimally invasive procedure, its greatest difference from OC is the degree of trauma to the abdominal wall. Though it is important to the patient and affects postoperative mobilization, the trauma to the intraabdominal organs is as great, since the gallbladder is dissected from the gallbladder bed and the cystic duct and artery are divided just as in OC. The dissection is commonly performed with a dissection hook using bipolar diathermy, which could cause more injury to the hepatocytes than the scissors used during OC. Furthermore, it has been shown that pneumoperitoneum reduces the splanchnic blood flow [6, 9, 17]. Thus it seems possible that the intraabdominal trauma is in fact greater after LC.

Indeed, other investigators have speculated that LC may lead to a higher risk of postoperative thromboembolism than OC. However, we were unable to substantiate this notion in a previous literature review, which found that the rate of clinically evident thromboembolic complications was very low after LC [13]. When surveillance has been done systematically, the variation was huge, ranging from 1%[5] to 55% [16] in two studies using Doppler ultrasonography. 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 [15]. Obviously, it would have been of value to have performed bilateral venography in our study, but we did not consider it ethical at the present stage.

As shown by this study and an earlier one by Caprini et al. [5], LC leads to postoperative activation of the coagulation system, which is a prerequisite for thromboembolic complications. Prophylaxis against thromboembolism cannot counteract this effect, at least not completely. Still, the rate of clinically evident deep vein thrombosis is very low. One possible explanation is that there is in fact a development of deep vein thrombosis in the calf postoperatively, but the early ambulation activates the fibrinolytic system, which prevents the thrombi from increasing in size and propagating proximally. This would explain the 55% rate of DVT demonstrated early postoperatively by Patel et al. [16] and the 1% rate found by Caprini et al. [5] at 7 days postoperatively. Perhaps small clots in the veins of the lower extremities are common but clinically not particularly important in freely ambulating persons with normal fibrinolytic systems. When movement is impaired by a plaster, by postoperative pain, or by lack of space (for example, during long air trips), however, the fibrinolytic system may prove inadequate and clinically manifest deep vein thrombosis may develop.

Prophylaxis against thromboembolism should probably be given to patients who undergo LC. Both dextran and LMWH have been shown to be effective in preventing thromboembolic complications in postoperative situations [3, 10] and will most likely work also after LC. When deciding which prophylaxis to use, the time factor is also important, since most LC patients are discharged on the 1st postoperative day. LMWH should be continued for at least 5–7 days [8]. Dextran, on the other hand, has been shown to be effective in preventing fatal pulmonary embolism after a single dose of 500–1000 ml intravenously [11, 14] and therefore appears to be a more appealing alternative in many patients, especially those undergoing short-stay or day-care surgery.

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