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The temporal pattern of postoperative coagulation status in patients undergoing major liver surgery

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Abstract

**Introduction:** After major liver surgery, there are risks of both postoperative bleeding and thrombosis. Routine coagulation monitoring is indicated, but may not provide adequate clinical guidance. Thus, we described the clotting status in a pilot study using broader coagulation testing. We analysed the temporal pattern of coagulation tests to assess whether thromboelastometry (ROTEM®) would improve the quality of the postoperative monitoring of the coagulation status in patients undergoing major hepatic resections.

**Material and methods:** Sixteen patients undergoing major liver resections were examined prior to surgery, on postoperative day 1, and subsequently, every three postoperative days during hospitalization. At the same time, the clinical signs of bleeding and thrombotic complications were monitored.

**Results:** On postoperative day 1, increases in bilirubin, PT-INR, APTT, and D-dimers were observed, together with concomitant decreases in fibrinogen, platelet count, antithrombin (AT), protein C and protein S compared to preoperative values. On postoperative days 4 and 7, all of the variables had returned to the normal range except for D-dimers, AT and protein C. The ROTEM® median values remained within the normal range. There were no significant episodes of postoperative bleeding. Two patients were diagnosed with a pulmonary embolism.

**Conclusion:** Despite the abnormalities observed in routine coagulation monitoring, thromboelastometry indicated a balanced coagulation status following major hepatic surgery. The levels of both pro- and anticoagulant proteins changed over time during this period. The exact clinical role for thromboelastometry in major hepatic surgery remains to be established.
Keywords: hemihepatectomy, thromboelastometry, ROTEM, blood coagulation, thromboembolism.
Introduction

In recent years, an increasing number of liver resections have been performed as a consequence of the improvement of surgical techniques, medical imaging, and chemotherapy as well as a consequence of changes in the selection criteria [1]. Major hepatic resections have been associated with a high risk of postoperative liver insufficiency, and this risk is directly proportional to the size of the resection. There is also a direct relationship between the degree of liver failure and mortality [2-4]. Postoperative liver insufficiency may involve coagulation aberrations, and a prolonged postoperative PT-INR is commonly observed following a major hepatectomy. This may be associated with an increased risk of bleeding. Recent retrospective studies report a perioperative bleeding incidence of approximately 6% [5, 6], and the overall rate of postoperative transfusion is 0.8% [7].

In addition, there have been reports of an increased risk of thrombotic complications following hepatic surgery, with an overall incidence of deep venous thrombosis between 0.8% and 3.6% and a pulmonary embolism incidence between 1.4% and 7.1% [7-9]. Concern about the risk of postoperative bleeding has led to a controversy as to whether routine postoperative thrombosis prophylaxis should be administered [8, 10]. After major hepatic surgery, venous thrombosis has been reported to occur mainly between postoperative days 5 and 7 [9, 11]. These data indicate that patients undergoing major hepatic resections may be affected by a postoperative hypercoagulable state despite the general perception of hypocoagulability indicated by usual coagulation tests, such as PT/INR. Currently, there are no conventional laboratory assays that can predict the occurrence of a venous thromboembolism.
There are a few prospective studies that focus on defining the coagulation status of patients undergoing major liver surgery. Hypercoagulation has been reported in studies on living liver donors [12] and in patients undergoing liver resections for primary and secondary malignancies [13].

Thromboelastography (TEG®) is a viscoelastic method for haemostatic testing in whole blood that provides a global assessment of coagulation function. It has long been used postoperatively following cardiac surgery, during liver transplantation, and in acute trauma patients to mainly detect hypocoagulation and to guide transfusion therapy [14-19]. Thromboelastography (TEG®) is reported to be able to detect hypercoagulation and predict thromboembolic events in surgical patients [20-22]. However, there are other reports that have showed that the predictive capacity may be highly variable [23].

Rotation thromboelastometry (ROTEM®) is based on the same principle as thromboelastography (TEG®). Depending on the method of initiating coagulation, different types of thromboelastometric curves result, which reflect the intrinsic pathway of coagulation (INTEM), the extrinsic pathway of coagulation (EXTEM), or the fibrinogen functionality (FIBTEM). Nevertheless, there are differences in the sensitivity between TEG® and ROTEM®, and thus, the results are not always comparable[14]. It has recently been found that the functional fibrinogen of TEG® may overestimate fibrinogen levels compared to the plasma fibrinogen concentration [24].

We prospectively examined consecutive patients scheduled for a major liver resection longitudinally during hospitalization in a descriptive pilot study. We used a battery of routine coagulation-related analyses and ROTEM® and simultaneously recorded the clinical signs of
bleeding and thromboembolism. The protocol extended from preoperative to every 3rd day, postoperatively.

Our hypothesis was that the combination of routine chemistry and ROTEM® may increase the quality of the surveillance of the coagulation status following liver surgery. The aim of our study was to assess whether ROTEM®, as a global test of coagulation would improve the predictability of postoperative bleeding or pulmonary embolism after hemihepatectomy and extended hemihepatectomy.

**Materials and Methods**

**Subjects**

Patients (n=16) scheduled for extensive liver surgery, namely, hemihepatectomy and extended hemihepatectomy, at Karolinska University Hospital Huddinge, were examined. The exclusion criteria were pre-existing coagulopathy and the use of anticoagulation drugs or platelet aggregation inhibitors. The patients’ characteristics are provided in Table 1. The patients provided written informed consent after having been informed about the study protocol, orally and in writing. The protocol was performed in accordance with the Helsinki Declaration and was approved by the Regional Ethics Committee in Stockholm, Sweden.
Table 1. Patients: characteristics, diagnoses, and surgical and transfusion aspects

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<td>Platelets (ml)</td>
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*Median (range)

** (chronic inflammation, IgG4+ sclerosing cholangitis)

PRC=packed red blood cells
Protocol

Blood samples for the coagulation status, as described below, were collected via a 12 F central venous catheter from all patients on the morning before surgery after the induction of anaesthesia, on postoperative day 1, and thereafter, every third postoperative day (0, 1, 4, 7, 10, 13, 16, 19 etc.) as long as the patient was hospitalised and the central venous catheter remained in place.

Intraoperative and postoperative bleeding were strictly monitored, and the clinical parameters indicative of thrombosis (deep vein thrombosis and thromboembolism) were recorded in conjunction with each blood sampling. These included the diameters of the legs, respiratory rate, oxygen administration, ECG, and body temperature.

All patients were treated according to the local protocol for liver resections at Karolinska University Hospital and this was not affected by the study. All patients received a thoracic epidural catheter before the induction of general anaesthesia. Ringer-Acetate and Volulyte® (6 % hydroxyethyl starch 130/0.4 in a balanced electrolyte solution) were used as intraoperative fluids. Central venous pressure was kept below 5 cm of water during the hepatic resection. Blood pressure was monitored via a 20G catheter in the left radial artery. All patients were extubated after the surgical procedure, Glucose 5% was administered during the initial 24 hours and as soon as the patients were circulatorily stable enteral nutrition was initiated. Analgesia was administered via an epidural catheter for 5-7 days postoperatively. All patients received thrombosis prophylaxis with Fragmin® (dalteparin) 5000 IE starting on the day before surgery and continuing regularly every day at 20:00 for as long as the patient was hospitalized.
Analyses

The following analyses were included at each blood sampling: total serum bilirubin (BIL-T, Roche Diagnostics on Modular P EVO, Roche Diagnostics, Mannheim, Germany), prothrombin time-international normalized ratio (PT-INR, Owren method Stago SPA, Diagnostica Stago, Asnières sur Seine, France on Sysmex CS 2100i, Sysmex Corporation, Kobe, Japan), activated partial thromboplastin time (aPTT) (Stago PTT automate, Diagnostica Stago, Asnières sur Seine, France, on Sysmex CS 2100i from Sysmex Corporation, Kobe, Japan), fibrinogen (Clauss method, Siemens Thrombin reagent on Sysmex CS 2100i from Sysmex Corporation, Kobe, Japan), platelet count (on Sysmex XE 5000, Sysmex Corporation, Kobe, Japan), antithrombin (AT) (anti-Xa based metod, Innovance Siemens on Sysmex CS 2100i Sysmex Corporation, Kobe, Japan), protein C (Berichrom PC, Siemens Healthcare Diagnostics Products GmbH on BCS® XP System, Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany), protein S (Coamatic PS-free, Chromogenix, Instrumentation Laboratory SpA Milano, Italy on BCS® XP System from Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany), D-dimers (Roche Tinaquant reagents from Roche Diagnostics Ltd. Rotkreuz, Switzerland on Sysmex CS 2100i from Sysmex Corporation, Kobe, Japan), and thromboelastometry, which was performed using a ROTEM® delta device (Pentapharm GmbH, Munich, Germany). Stimulating coagulation for each thromboelastometric assay was performed in the same manner as for routine clinical tests, according to the instructions of the manufacturer (ellagic acid for INTEM, tissue factor for EXTEM, and tissue factor and cytochalasin for FIBTEM).
The analysed thromboelastometric parameters for INTEM and EXTEM were: i) the clotting time, CT, which represented the time, in seconds, from the start of the analysis to the recognizable initiation of clotting; ii) clot formation time, CFT, which represented the time, in seconds, from the initiation of clotting until a clot firmness of 20 mm was established; and iii) maximum clot firmness (MCF), which represented the maximal amplitude (mm) of the graphical trace of the clot firmness. For FIBTEM, only the maximum clot firmness (MCF) was investigated. Briefly, disrupted activation of coagulation was indicated by a prolonged clotting time (CT), an abnormal clot formation was indicated by a prolonged clot formation time (CFT), and reduced clot strength was indicated by decreased maximum clot firmness (MCF). Conversely, the hypercoagulable state may be indicated by a shortening of the CT and CFT and an increase in MCF [25].

The ROTEM® assay was performed at the Department of Transfusion Medicine, while the other analyses were performed at the Department of Clinical Chemistry.

**Statistics**

The GraphPad Prism 5® statistical software package was used (GraphPad Software, Inc., San Diego, CA) for calculations. Statistical comparisons for the coagulation parameters studied were performed for days 0-7 using Friedman’s ANOVA and Dunn’s post-hoc multiple comparison test.
Results

Patients scheduled for liver resection were studied longitudinally as long as they had a functional central venous catheter (range 4-19 days). If the postoperative course was uneventful, then they were discharged to a convalescent clinic on the 7th-10th postoperative day. Diagnoses, surgical procedures and intraoperative bleeding are shown in Table 1.

Results from the analyses made by the hospital’s Department of Clinical Chemistry are summarized in Figure 1 (panels 1A, 1B and 1C) and were normalized with preoperative values as 100%. In electronic supplementary material 2, the normal ranges of the analyses are indicated. On postoperative day 1, there were increases in bilirubin, PT-INR, APTT, and D-dimers, while fibrinogen, platelet count, AT, protein C and protein S all decreased compared with the preoperative values. On postoperative days 4 and 7, all of the variables tended towards a normal range, except for D-dimers, AT and protein C. The absolute values for these subjects are given in electronic supplementary material 2. Because the increase in D-dimers were derived and shown in the scales in Figure 1, these values are only provided in electronic supplementary material 2.

The results from the ROTEM® analyses are summarized in Figure 1 (panels 1D and 1E), and were normalized with preoperative values as 100%. Although there were temporal changes in ROTEM® parameters, the median values stayed within the normal range the entire study period. On postoperative day 1, there were increases in CFT-INTEM and CFT-EXTEM, while MCF-INTEM, MCF-EXTEM, and MCF-FIBTEM all decreased compared with the preoperative values. For CT-INTEM and CT-EXTEM, no significant changes were observed compared with the preoperative values. On postoperative days 4 and 7, all of the variables that demonstrated a change on postoperative day 1 tended towards the normal range. Importantly,
in CT-EXTEM and FIBTEM, individual subjects showed values that exceeded the normal range towards hypercoagulation on postoperative days 4 and 7. The absolute values for these subjects are provided in electronic supplementary material 2.

Figure 1(A-E). Perioperative changes in the coagulation parameters for patients undergoing liver surgery (n=16). Panels 1A, 1B and 1C depict the routine chemistry, while panels 1D and 1E depict the ROTEM® parameters. All of the values are expressed as the median and were normalized with preoperative values as 100%. The level of statistical significance for the ANOVAs calculated for the individual parameters are given in the parentheses in the figure panels. For panels 1D and 1E it should be emphasized that although the temporal changes in ROTEM® parameters attained statistical significance, the median values stayed within the normal range the entire study period. All of the numerical values, including sampling after postoperative day 7, are provided in Supporting Information 2 in the electronic supplement.
For the fibrinogen plasma concentration and MCF-FIBTEM, a post-hoc analysis dichotomizing the patients according to the size of the liver resection showed a significant difference. The decrease was more pronounced on postoperative day one and less of a catch-up towards the normal range in the group with extended hemihepatectomy compared with patients with a hemihepatectomy. This finding is illustrated in Figure 2(A, B). The absolute values for these subjects are provided in electronic supplementary material 3.

**Figure** 2(A, B). Perioperative plasma concentrations of fibrinogen (2A) and MCF-FIBTEM (2B) in patients undergoing liver surgery. Patients were grouped according to the size of the resection, and the results for the hemihepatectomy and extended hemihepatectomy (n=8+8) are shown in blue and red, respectively. Values are provided as the mean ± SD. The temporal pattern was significantly different between the 2 groups as tested using two-way ANOVA, (n=5+6).
Postoperatively, no patient was re-operated due to bleeding, but four patients were treated with packed red blood cell transfusion (for further details, see electronic supplementary material 1).

The study protocol included clinical observations that are indicative of postoperative thromboembolic complications. No patients had local signs of swelling or discolouration of the legs, signs of right ventricular strain on the electrocardiography, or an elevation of body temperature > 38°C when investigated at the blood sampling times. In total, 11 patients were given extra oxygen at the blood sampling times (for further details, see electronic supplementary material 1).

Two patients who had a thoracic CT scan on postoperative days 5 and 8, respectively, due to increased oxygen administration, were confirmed with the diagnosis of pulmonary embolism. Both patients underwent right hemihepatectomies. In one of these patients, CT-EXTEM, CFT-EXTEM and MCF-FIBTEM revealed values indicating hypercoagulation prior to the occurrence of a pulmonary embolism. The other patient had a CT-EXTEM towards the hypercoagulation limit, but all of the other ROTEM parameters were within the normal range.

In both patients, there was a rapid rebound of fibrinogen, the values of which exceeded the upper limit of the plasma concentration in one patient on postoperative day 4; however, in the other patient, MCF-FIBTEM had values indicating hypercoagulation on postoperative day 4 and 7. Regarding the anticoagulant proteins in patients that developed a pulmonary embolism,
the levels of protein C and AT were lower than normal for both patients, while the levels of protein S were within the normal range. The absolute values for these subjects are provided in electronic supplementary material 4. These patients were given high-dose low-molecular heparin from the day of diagnosis and on subsequent days (one of the patients was still treated within the study protocol, which is indicated in electronic supplementary material 2 and 4).

Discussion

In this descriptive pilot study, the temporal pattern of the coagulation status of patients undergoing major liver resections was characterized. Both procoagulation and anticoagulation were reflected and compared in relationship to some of the aspects of the clinical course.

Clinically, there were no significant postoperative bleeding episodes. Nevertheless, the PT – INR value and the decreasing plasmatic fibrinogen indicated that patients may have a risk of bleeding on postoperative day 1. However, this finding was not supported by the ROTEM® parameters, which showed that most patients were within the normal range. Importantly, a discrepancy between the results of the conventional coagulation tests and ROTEM® on postoperative day 1 was observed. The decrease in the plasma concentration of fibrinogen and the pro-coagulant factors, was not reflected in the results of CT, CFT and MCF (INTEM and EXTEM), which demonstrated only slight variations in most of the subjects. However, not only the pro-coagulant factors were affected; the levels of the natural anticoagulant proteins (e.g. protein C, protein S and AT) were also reduced. The haemostatic balance may be maintained when the pro- and anticoagulant system are affected to the same extent [14]. This is probably
the most important mechanism behind the fact that the ROTEM® median values remained within the normal range on postoperative day 1. Another factor that affects the ROTEM® parameters, particularly MCF, is platelets. Although lower compared with preoperative values, platelet counts were sufficiently high enough to ensure the good strength of the clot on postoperative day 1 in most patients. ROTEM® evaluated the viscoelastic properties of non-centrifugal blood, resulting in a global viewpoint over the function of the coagulation system. All of the blood cells and the complete set of the coagulation components of the plasma were analysed within the same sample. Thus, it must be mentioned that erythrocytes can significantly affect the coagulation process [26, 27].

On postoperative day 4 and continuing to day 7, there were signs of an imbalance in favour of the procoagulant component in some subjects. This was a reflection of the rapid return to normal PT-INR, and plasma fibrinogen which was unaccompanied by an equally rapid normalization of the anticoagulant proteins, particularly protein C and AT, which continued to remain low. During this period, CT-EXTEM and MCF-FIBTEM exceeded the normal limits towards hypercoagulation for individual patients. Nevertheless, for the majority of patients, this potential hypercoagulation, from postoperative day 4 and onwards, was not highlighted by the ROTEM® parameters, which remained within the normal range.

According to local clinical routines at our hospital, thrombosis prophylaxis in a normal dosage was administered to all patients. However, two of the patients came under the suspicion of having developed a post-surgery pulmonary embolism, and a CT scan confirmed these suspicions. The ROTEM® values for these two particular cases were very close or exceeded the normal range towards hypercoagulation on postoperative day four and onwards. In one patient, CT-EXTEM, CFT-EXTEM and MCF-FIBTEM clearly indicated hypercoagulation within days prior to the occurrence of pulmonary embolism. This demonstrated that ROTEM®
is able to signal the risk of pulmonary embolism. Anyhow, other patients demonstrated the same coagulation pattern and had not been diagnosed with thrombosis complications. Clearly, the risk of thromboembolic events involves many aspects, not only concerning clotting but also the haemodynamics and blood flow in the venous system and, particularly in the case of liver surgery, the flow in the hepatic veins.

Other investigators have used thromboelastography (TEG®) to detect the potential hypercoagulant status [13, 28, 29]. However, associations with clinically relevant thromboembolic events was not reported, although special coagulation tests like prothrombin fragments 1 and 2, thrombin-antithrombin complexes and plasma von Willebrand Factor antigen performed at the same time, suggest activation of coagulation [13]. The potential hypercoagulation of these patients may be based on the accentuated decrease in anticoagulant proteins accompanied by the rapid resumption of specific procoagulant factors’ synthesis, including factor VIII or von Willebrand factor [12, 29], which are acute phase reactants. Unexpectedly, our study indicated that with regard to fibrinogen, which is also an acute phase reactant, this argument may be stronger following hemihepatectomy compared to extended hemihepatectomy. This may potentially be related to differences in the volume of the remaining liver tissue because fibrinogen is synthesized mainly by the liver. Thus, it may be speculated that the risk of fibrinogen concentrations reach supranormal values, thereby potentially contributing to hypercoagulation could be more pronounced following a hemihepatectomy. Further studies of this specific aspect are warranted.

A recent study reports brief hypercoagulability on postoperative day one after major hepatectomy with coagulation that was normalized during the following days [30]. We were unable to observe any signs of hypercoagulability on postoperative day one in our patients
using ROTEM®. In contrast, CT-INTEM and MCF-FIBTEM demonstrated hypercoagulation values on postoperative day four and afterwards in individual patients.

The use of ROTEM® (INTEM, EXTEM, and FIBTEM) generated relevant results regarding the postoperative coagulation balance after major liver surgery. Most of the subjects in our study were normocoagulable according to ROTEM® throughout the postoperative days, and this was consistent with the absence of significant postoperative bleeding. Individual patients presented ROTEM® signs that may indicate an imbalance towards hypercoagulation, and one of these patients was affected by a pulmonary embolism. Thus the results obtained from ROTEM® may signal an increased risk of venous thromboembolism. Future studies testing this hypothesis and the potential effect of enhanced prevention of thromboembolism are advocated.

The strengths of our study are (i) the selected patient group underwent major liver surgery, hemihepactomy or extended hemihepactomy, which is the group that is at risk to develop liver insufficiency, thromboembolism, and/or massive bleeding; (ii) all of the patients received thrombosis prophylaxis, regardless of the clotting test results; and (iii) both pro- and anticoagulant mechanisms were studied longitudinally and biochemically using the thromboelastometric method.

Our study also has several limitations: (i) the protocol did not allow for differentiation between the effects of coagulation by elective surgical trauma, in general, and the effect from the loss of liver tissue; (ii) clotting factors and biomarkers for thrombin generation and fibrinolysis were not analysed; (iii) pulmonary embolisms were not systematically diagnosed using computer tomography for patients who required O₂ administration after surgery; and (iv) echographic screening for deep vein thrombosis in the patients included in this study was not performed.
Furthermore, (v) we did not evaluate the effect of administered synthetic colloids that were routinely used at our hospital at the time of the study on the ROTEM® parameters.

**Conclusions**

Following major hepatic surgery, there were changes in the routine coagulation parameters. The addition of ROTEM® analyses indicated that nearly all of the patients had a balanced coagulation status. A potential tendency towards hypercoagulation for individual patients was observed and may be based on an accentuated decrease in anticoagulant proteins, which was accompanied by a rapid return of specific procoagulant factors towards normal levels. The combination of routine coagulation monitoring and ROTEM® analyses may provide a more complete picture of the coagulation status. Although this contributes to our understanding of the coagulation status after major liver surgery, this observational pilot study alone cannot provide support to the routine use of this type of enhanced monitoring in everyday clinical practice in these patients. Thus, studies that systematically combine postoperative thromboembolic related complications and enhanced monitoring will be necessary to support such a recommendation. It was also observed post-hoc that the size of liver resection may be a factor to consider and that postoperative fibrinogen trends are different between hemihepatectomy and extended hepatectomy.

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Conflicts of interest

The authors declare that there were no conflicts of interest.

References


Highlights

- Coagulation pattern was examined in patients undergoing major hepatic resections
- Most of the subjects were normocoagulable according to thromboelastometry (ROTEM®)
- Individual patients presented ROTEM® signs indicative of hypercoagulation
- Restoration of fibrinogen concentrations was slower in extended hemihepatectomy