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Full Length Article

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.

1. 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.

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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.

2. Materials and Methods

2.1. 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.

2.2. 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.

Table 1
Patients: characteristics, diagnoses, and surgical and transfusion aspects.

Patients	
Sex	
Male	6
Female	10
Age*(years)	66 (46–80)
Body mass index*(kg/m^2)	25 (18.5-32.7)
Diagnosis	
Metastatic cancer	10
Hepatocellular carcinoma	1
Cholangiocarcinoma	3
Benign conditions**	2
Type of surgery	
Hemihepatectomy	8
Extended hemihepatectomy	8
Intraoperative bleeding*(ml)	600 (100–4500)
Intraoperative transfusion	
PRC*(ml) (n = 2)	1250 (1000–1500)
Plasma*(ml) (n = 2)	875 (750–1000)
Platelets (ml)	0
Postoperative transfusion	
PRC*(ml) (n = 4)	500 (500–500)
Plasma (ml)	0
Platelets (ml)	0

PRC = packed red blood cells.
* Median (range).
** (chronic inflammation, IgG4+ sclerosing cholangitis).

2.3. 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).