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The international normalized ratio overestimates coagulopathy in patients after major hepatectomy



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Abstract

BACKGROUND: The International Normalized Ratio (INR) is commonly used to guide therapy after hepatectomy. We hypothesized that the use of thrombelastography (TEG) would demonstrate a decreased incidence of hypocoagulability in this patient population.

METHODS: Seventy-eight patients were prospectively enrolled before undergoing hepatectomy. INR, TEG, and coagulation factors were drawn before incision, postoperatively, and on postoperative days 1, 3, and 5.

RESULTS: Patients demonstrated an elevated INR at all postoperative time points. However, TEG demonstrated a decreased R value postoperatively, with subsequent normalization. Other TEG measurements were equivalent to preoperative values. All procoagulant factors save factor VIII decreased postoperatively, with a simultaneous decrease in protein C.

CONCLUSIONS: TEG demonstrated a brief hypercoagulable state after major hepatectomy, with coagulation subsequently normalizing. The INR significantly overestimates hypocoagulability after hepatectomy and these data call into question current practices using the INR to guide therapy in this patient population.

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Partial hepatectomy remains the treatment of choice for a wide range of both benign and malignant diseases of the liver. Following major hepatectomy, derangement of hepatic synthetic function has been well characterized,

including impaired synthesis of serum clotting factors and regulatory proteins.¹

The International Normalized Ratio (INR) is a mathematical extrapolation of a patient's prothrombin time (PT). This test, originally devised to measure the adequacy of anticoagulation with warfarin, measures the extrinsic pathway of the coagulation cascade. Decreased serum levels of factors in this pathway, particularly factor VII, lead to a predictable increase in the PT-INR after hepatectomy.¹⁻⁴ Surgeons often treat patients an elevated INR with fresh frozen plasma (FFP) to normalize the INR and decrease a perceived risk of postoperative hemorrhage.⁵⁻⁷

Correction of an elevated PT-INR by the transfusion of FFP carries with it significant risk including fluid overload,

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anaphylaxis, transfusion-related acute lung injury, and infection.⁸⁻¹⁰ Additionally, elevation in the PT-INR often leads clinicians to delay chemical thromboprophylaxis by potentially increasing the risk of deep venous thrombosis (DVT) and pulmonary embolus (PE) in these patients and data suggest that the risk of thromboembolism outweighs bleeding risk in these patients.¹¹⁻¹³

Thrombelastography (TEG) is a sensitive, point-of-care test performed on whole blood at patient temperature which uses shear elasticity to determine the speed and strength of clot formation, maximum clot stability, and finally clot lysis.^{14,15} TEG is sensitive to changes both in cellular- and plasma-based clotting factors and has been validated in multiple patient populations to determine the functional coagulation status of a patient.¹⁶⁻¹⁹

Recent studies have called into question the use of an elevated PT-INR during and after hepatectomy to guide clinical decision making.^{5-7,20} Furthermore, in living donor liver transplantation patients, TEG has demonstrated a hypercoagulable state despite elevation in the PT-INR, further calling into question the validity of the test in patients after a dramatic change in hepatic function.¹⁷

The balance in decreases of both pro- and anticoagulant factors after hepatectomy is incompletely understood. Recent work by Barton et al²⁰ from our laboratory demonstrated normal thromboelastograms in patients after hepatectomy despite elevated INR. We sought to further elucidate mechanistic reasoning for this finding by analyzing plasma coagulation factors. The purpose of this study was to observe changes in patient's coagulation profiles after major hepatectomy by sequential analysis of conventional coagulation assays, TEG, and plasma levels of coagulation factors.

Methods

Patients

This study was approved by the Institutional Review Board at Oregon Health & Science University as a prospective, noninterventive study. This institution abides by the current federal Health Insurance Portability and Accountability Act guidelines. All patients scheduled to undergo elective, anatomic hepatic resection were screened for enrollment. Informed consent to participate was obtained from the patient or a legal representative. Demographics were collected from the patients including age, sex, diagnosis, presence of cirrhosis, American Society of Anesthesiologists Physical Status Classification, and body mass index.

Laboratories

Samples were obtained from patients before operation, 5 hours after completion of the operation (± 3 hours), and on postoperative days 1, 3, and 5. Citrated blood was centrifuged (3,750 rpm) at 4°C for 15 minutes. Plasma was collected and stored at -80°C until assayed.

PT-INR, activated partial thromboplastin time (aPTT), fibrinogen level, and coagulation factor analysis were determined using an STA Compact Hemostasis System (Diagnostica Stago, Inc, Parsippany, NJ). Thromboelastograms were performed on fresh whole blood with kaolin as an accelerant using a TEG 5000 machine (Hemoscope Corporation, Niles, IL) that was located at point of care. Practitioners were blinded to the results of the thromboelastograms and TEGs were not used to impact clinical decision making.

Procedure

Perioperative care and anesthetic administration were performed by an attending anesthesiologist. Patients were routinely offered epidural anesthesia if deemed appropriate candidates for such. Low central venous pressure (CVP) techniques were used throughout the course of the operation with a target CVP of ≤ 5 mmHg. An intermittent Pringle maneuver was performed at the discretion of the attending surgeon. Parenchymal transection was performed using either cavitron ultrasonic surgical aspirator (CUSA) or stapler transection at the discretion of the attending surgeon. Operation performed, procedure time, estimated blood loss (EBL), and Pringle time were recorded.

Postoperative care

Patients were routinely taken to the intensive care unit (ICU) for immediate postoperative care. Patients enrolled in the study were followed through the course of their hospitalization for blood product transfusion and the development of DVT or PE. As per institutional protocol, patients in the ICU underwent weekly bilateral whole leg duplex ultrasonography to screen for DVT. After the patient was transferred to the acute care unit, ultrasound was performed upon suspicion of DVT by the primary treatment team.

Statistical analysis

A database was maintained in Microsoft Excel (Microsoft Corporation, Redmond, WA). Statistical analyses were performed using SPSS version 19 (SPSS, Inc, Chicago, IL). Parametric, normally distributed data were compared using Student *t* test and values are presented as mean \pm standard error of the mean. Non-normally distributed data were compared using the Mann-Whitney *U* test and values are presented as median with interquartile range. Normally distributed data comparison within groups used a paired *t* test, whereas nonparametric data comparisons within groups were assessed using a Wilcoxon test.

Results

Ninety-one patients were enrolled in the study. Six patients had resection aborted because of metastatic disease discovered intraoperatively. Eighteen patients underwent a

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