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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,

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 al[20] 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, noninterventional 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 ± 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

Table 1   Patient demographics

Age	56.5 ± 13.5
Male (n)	40
Diagnosis	
Met CRC	27
HCC	16
Cholangiocarcinoma	4
Gallbladder	3
Other	17
Cirrhosis	8
ASA	
2	14
3	50
4	3

ASA = American Society of Anesthesiologists; CRC = colorectal cancer; HCC = hepatocellular carcinoma.

Table 2   Procedures

R Hepatectomy	30	
Extended R hepatectomy	4	
L hepatectomy	15	
L lateral segmentectomy	7	
Two or fewer segments	11	
Estimated blood loss (mL)	314 (130, 760)	
Operative time (min)	195 (130, 265)	
Pringle (no. of patients)	40	
Pringle time (min)	19.2	

Transfusions	Intra op	Post op
Packed red blood cells (U)	1 (.8)	0 (.7)
Fresh frozen plasma	0 (.3)	0 (.2)
Platelets	0 (.2)	0 (.1)

Data are expressed as median (IQR).

nonanatomic liver resection. The remaining 67 patients underwent anatomic hepatectomy and had a mean age of 57.5 years (Table 1).

As demonstrated in Table 2, the most common indication of resection was metastatic colorectal adenocarcinoma. Primary hepatocellular carcinoma was the 2nd most common indication, followed by cholangiocarcinoma. The most common procedure performed was a right hepatectomy. The median EBL was 315 mL and the median operative time was 195 minutes. Forty of the 67 patients underwent Pringle maneuver and the median Pringle time was 19.2 minutes.

Conventional coagulation assays

As expected, patients had a rise in the PT-INR at all time points as demonstrated in Table 3. The peak mean INR was 1.42 on postoperative day 2. Patients had an initial decrease in the aPTT immediately postoperatively, followed by a return to the preoperative value at postoperative day 1. There was a significant increase in the aPTT at postoperative days 3 and 5. Fibrinogen levels decreased initially at postoperative day 1, followed by an increase at postoperative days 3 and 5.

Thrombelastography

When thromboelastograms were analyzed, a decrease in the R time (time to clot formation) was found immediately

postoperatively and at postoperative day 1. This difference ceased to exist at postoperative days 3 and 5. No other TEG values were found to be significantly different from baseline at any of the time points. As summarized in Table 4, this led to a significantly increased coagulation index postoperatively and at post-operative day #1, but similar values to baseline at post-operative day #3 and 5.

Coagulation factor analysis

As demonstrated in Table 5, there was a decrease in the majority of plasma procoagulant factors at all time points. Factors II, V, VII, X, XI, and XII all decreased postoperatively and the majority of these remained decreased at all time points. Factor IX did not significantly change at any measured time point. Coagulation factor VIII was significantly elevated at every measured postoperative time point. Protein C was dramatically decreased at all measured postoperative time points.

Comments

Analysis of the coagulation status of a patient after a major hepatectomy remains challenging and recent studies have questioned the value of the PT-INR as a diagnostic tool in these patients. This study used conventional coagulation assays, TEG, and coagulation factor analysis

Table 3   Conventional coagulation assays

	Preoperative	Postoperative	Postop day 1	Postop day 3	Postop day 5
PT-INR	1.05	1.32*	1.38*	1.42*	1.31*
aPTT	30.1	28.3[†]	29.9	34.5*	35.9*
Fibrinogen	397.5	306.5*	319.8*	438.9[†]	439.4[†]

aPTT = activated partial thromboplastin time; PT-INR = prothrombin time-international normalized ratio.

*P < .01.

[†]P < .05.

Table 4   Thrombelastography

	Preoperative	Postoperative	Postop day 1	Postop day 3	Postop day 5
R time	6.88 ± 2.93	5.54 ± 1.62*	5.65 ± 1.97*	7.11 ± 3.60	6.14 ± 3.15
K time	1.92 ± .69	1.73 ± .59	1.75 ± .56	2.01 ± .95	1.85 ± .95
α Angle	63.6 ± 8.5	65.1 ± 7.8	64.4 ± 9.7	61.2 ± 11 .7	64.5 ± 10.3
MA	69.5 ± 5.3	69.0 ± 6.7	68.3 ± 9.9	67.8 ± 6.3	69.9 ± 7.4
LY-30	.96 ± 1.67	.53 ± 1.24	2.21 ± 6.19	2.92 ± 3.96	3.27 ± 11.73
CI	.34 ± 2.86	1.33 ± 2.05†	1.20 ± 2.43†	−.24 ± 3.81	.97 ± 3.41

CI = coagulation index; K time = speed of clot; LY-30 = LY30: percent lysis at 30 minutes; MA = maximum amplitude; R time = time to clot formation.
*$P < .01$.
†$P < .05$.

in an attempt to further elucidate the global coagulation status of patients after anatomic hepatectomy.

A prolonged PT-INR has long been characterized after hepatectomy and holds many therapeutic implications. This laboratory value has long been used to guide transfusion of FFP postoperatively. In addition, many clinicians will withhold standard postoperative chemoprophylaxis from DVT in patients with a prolonged PT-INR under the assumption that the prolongation of this laboratory value leaves these patients "auto-prophylaxed" from DVT. Furthermore, emerging treatment patterns include preoperative pharmacologic DVT prophylaxis and hepatectomy patients are largely excluded from these treatment protocols because of the thought that these patients are hypocoagulable.

As would be expected from previous studies, we found an increase in the PT-INR after hepatectomy. This effect persisted for up to 5 days postoperatively. Fibrinogen levels initially decreased postoperatively and at postoperative day 1, yet subsequently increased at postoperative days 3 and 5. Patients initially had a shortening of the aPTT postoperatively, but this too was prolonged at postoperative days 3 and 5.

In contrast, TEG data remained largely stable after hepatectomy. Patients demonstrated a brief hypercoagulable state as evidenced by a shortened R time immediately postoperatively and on postoperative day 1. This effect ceased to exist on postoperative days 3 and 5. There were no other significant aberrations from baseline in any other measured TEG parameters. The difference in R time lead to

a significant increase in the coagulation index at the postoperative time point as well as postoperative day 1, demonstrating a hypercoagulable state.

Coagulation factor analysis revealed an expected decrease in factors II, V, VII, X, XI, and XII. Simultaneously, there was a significant decrease in serum protein C. Additionally, there was a rise in factor VIII, which is a known acute phase reactant.[21] As would be expected from the decrease in the factors in the external coagulation pathway, we saw an increase in the PT-INR. However, there was no evidence of hypocoagulability seen in TEG. Rather the contrary, as patients were briefly hypercoagulable. This is at least partially explained by the concurrent decrease in plasma anticoagulant factors, as well as the increase in factor VIII.

The cell-based model of coagulation includes both plasma proteins and cellular components to analyze the coagulation dynamics of a particular patient. Traditional assays such as the aPTT and PT-INR solely analyze particular parts of the coagulation cascade and do not incorporate cellular components of coagulation.

This study incorporated TEG to demonstrate that patients after partial hepatectomy were briefly hypercoagulable and then returned to normal coagulation dynamics. Although decreases in procoagulant factors were seen, simultaneous decreases in anticoagulant factors may explain the maintenance of homeostasis postoperatively. Treatment algorithms involving TEG are gaining widespread use and would readily incorporate patients after hepatectomy. This is being

Table 5   Plasma coagulation factors

	Preoperative	Postoperative	Postop day 1	Postop day 3	Postop day 5
Factor II	98.9 ± 20.9	72.1 ± 18.7*	67.0 ± 18.9*	63.4 ± 16.3*	66.7 ± 20.1*
Factor V	83.7 ± 32.6	54.1 ± 25.5*	52.2 ± 24.3*	61.9 ± 25.2*	78.9 ± 41.2*
Factor VII	114.2 ± 30.5	77.3 ± 25.9*	55.6 ± 26.3*	60.8 ± 25.2*	63.5 ± 24.7*
Factor VIII	126.1 ± 73.5	220.5 ± 119.5*	188.1 ± 101.1*	197.6 ± 104.3*	225.8 ± 119.7*
Factor IX	112.9 ± 35.6	109.72 ± 37.6	106.3 ± 39.5	113.8 ± 49.1	118.5 ± 50.1
Factor X	98.9 ± 22.2	91.5 ± 19.8*	64.4 ± 17.6*	63.5 ± 18.3*	73.7 ± 19.7*
Factor XI	142.2 ± 98.1	121.8 ± 82.9†	119.8 ± 108.1†	125.5 ± 106.5	134.7 ± 113.9
Factor XII	112.5 ± 41.4	98.3 ± 44.3*	97.9 ± 45.8*	88.2 ± 48.0*	78.9 ± 42.5*
Protein C	121.1 ± 30.0	73.0 ± 26.5*	63.6 ± 27.0*	52.2 ± 28.2*	53.7 ± 28.4*

*$P < .01$.
†$P < .05$.

actively investigated at our institution. Although the PT-INR remains a useful test to predict postoperative liver failure and mortality, it is rapidly falling out of favor to guide transfusion and prophylaxis decisions.[22–24] These data suggest that the PT-INR, in isolation, should no longer be used to guide plasma transfusion or delay thromboprophylaxis in the postoperative period after hepatectomy.

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Discussion

Chad Ball, M.D.: Dr. Lewis and colleagues have presented their evaluation of The International Normalized Ratio (INR) as an estimate of coagulopathy following scheduled hepatectomy in a concise, thorough and thought provoking manner. More specifically, this team has evaluated 91 patients who underwent variable hepatectomies for a standard distribution of pathological indications. By using thromboelastography (TEG), they observed that patients appear briefly hypercoagulable following resection over the first 1 to 2 days. More impressive however is the apparent rapid return to normal TEG coagulation status despite a prolonged increase in INR. This detailed update supports preceding observations that chemical DVT prophylaxis is still required in patients with elevated INR following major hepatectomy. Despite a well presented manuscript, I have a few short questions for the authors:

1. TEG is already rapidly advancing the care and resuscitation of patients within our trauma and critical care units on a global basis. How do the authors expect to utilize this data to alter and/or improve the care of hepatectomy patients?
2. Do the authors recommend preoperative thromboprophylaxis immediately prior to beginning a hepatectomy (similar to a Whipple procedure for example) based on this data?
3. The operative duration, blood loss and percentage of patients requiring inflow occlusion (Pringle) is significantly higher in the author's experience when compared to most modern series. Do you think these technical issues have any impact on the post-operative coagulation status of the patient? What instrumentation do the liver surgeons utilize to divide hepatic parenchyma?
4. Are there any variables that the authors believe may alter TEG results in certain cases (technical, physiologic, or patient)? Should TEG be routinely employed in our algorithmic care of hepatectomy patients?