Original Article

Evaluation of perioperative routine coagulation testing versus thromboelastography for major liver resection - A single-arm, prospective, interventional trial (PORTAL trial)

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Submitted: 18-Apr-2023
Revised: 27-Sep-2023
Accepted: 27-Oct-2023
Published: 13-Dec-2023

ABSTRACT

Background and Aims: The International Normalised Ratio (INR), which assesses the loss of procoagulant factors in the extrinsic pathway, fails to evaluate the coagulation abnormalities comprehensively after a major liver resection, which often leads to reduced synthesis of procoagulant and anticoagulant-factors. This study was conducted with an aim to study the trend and compare the results of routine coagulation tests and thromboelastography (TEG) during the perioperative period in patients undergoing major liver resections (≥3 segments). **Methods:** Twenty-five patients who underwent a major liver resection were enrolled. This prospective, single-arm, interventional study was performed with the primary objective of determining the serial changes in conventional coagulation tests and TEG during the perioperative period in patients undergoing major liver resections, at the preincision period, intraoperative period, postoperatively, at 48 h and on the fifth postoperative day. Transfusion requirements of blood components were also assessed with a TEG-guided replacement strategy. Spearman rank-order correlation was used to study the relationships of coagulation tests (both TEG and conventional tests) at each time point. **Results:** The prothrombin time (PT)-INR was elevated in 14 patients (56%) at the intraoperative, immediate postoperative and 48-h time points in contrast to the TEG parameters, which remained normal in all patients. Blood component transfusion was avoided in 4, 11 and 10 patients at the intraoperative, immediate postoperative and 48-h time points, respectively. **Conclusion:** International Normalised Ratio overestimates the coagulopathy in patients undergoing major liver resection, and a thromboelastography-guided transfusion strategy reduces overall transfusion requirements.

Key words: Blood transfusion, coagulation, hepatectomy, International Normalised Ratio, perioperative outcomes, prothrombin time, thromboelastography

Access this article online
Website: https://journals.lww.com/ijaweb
DOI: 10.4103/ija.ija_344_23
Quick response code

INTRODUCTION

Liver resections are complex surgical procedures and can result in derangement of a multitude of metabolic, excretory, secretory and synthetic functions performed by the liver.[1] Liver parenchymal cells produce both pro- and anticoagulants, and major liver resections result in a reduction of synthesis of both, which leads to changes in the balance between coagulation and thrombosis. In addition, in patients

How to cite this article: Ambulkar R, Baskar V, Patkar S, Kunte A, Agarwal V, Solanki SL, *et al*. Evaluation of perioperative routine coagulation testing versus thromboelastography for major liver resection – A single-arm, prospective, interventional trial (PORTAL trial). Indian J Anaesth 2023;67:1077-83.

with chronic liver disease, there is an increase in factor VIII and von Willebrand factor (vWF), which increases platelet adhesiveness. Elevation of the International Normalised Ratio (INR) only assesses the loss of procoagulant factors concerned with the extrinsic pathway and does not comprehensively assess the coagulation status.[2] Bleeding is a major postoperative concern following major liver resections due to loss of parenchyma, raw surface of the transacted liver and presence of coexisting liver disease, which is not uncommon. Recent retrospective studies report a perioperative bleeding incidence of approximately 6%, a postoperative transfusion rate of 0.8% and a delay in pharmacological prophylaxis for venous thromboembolism (VTE).[3-5] Delay in starting pharmacological prophylaxis can significantly increase the risks of VTE after major liver resections, with a reported overall incidence of 2.9% and a higher incidence for right (4.2%) and extended resections (5.8%).[6]

Another concern is requiring a near-normal INR <1.5 before removing the epidural catheter postoperatively.[7,8] The American Society of Regional Anesthesia (ASRA) has recommended removing epidural catheters when INR is less than 1.5.[9] Most centres monitor INR and correct the abnormal INR with fresh frozen plasma (FFP) before removal of the epidural catheter, which can be associated with the risks of anaphylaxis, transfusion-related acute lung injury (TRALI) and infections.[10-12]

Thromboelastography (TEG) is a sensitive test that uses shear elasticity performed on whole blood at the patient's body temperature to determine the speed and strength of clot formation, maximum clot stability and, eventually, clot lysis.[13] Limited studies have evaluated the use of TEG in liver resection surgeries compared to INR for perioperative transfusion requirement and epidural catheter removal. This study assessed the trends and the differences between the conventional coagulation tests (prothrombin time [PT], INR and activated partial thromboplastin time [aPTT]) and the TEG test during the perioperative period in patients undergoing major liver resection (≥3 segments).

METHODS

This prospective single-arm, interventional trial was conducted after obtaining approval from the Institutional Ethics Committee (IEC/0220/3433/002, dated 27 February 2020) and registration with the Clinical Trials Registry-India (CTRI/2020/04/024419, www.ctri.nic.in). All patients planned for a liver resection were screened for inclusion in the study. The inclusion criteria for the study were patients 18 years of age or older who underwent major hepatic resection ≥3 segments. Patients with known coagulation disorders, on therapeutic doses of anticoagulants, or with abnormal coagulation or platelets (platelets below 1,00,000/mm^3 or INR >1.5) preoperatively were excluded. A day before the surgery, written informed consent was taken from all the patients in Hindi, English or Marathi as per the patient's preferred language for participation in the study and use of patient data for research and educational purposes. This study was conducted per the Declaration of Helsinki 2013 and Good clinical practice.

As per our institutional practice, an epidural catheter was inserted in all patients before induction of anaesthesia (unless contraindicated). Thereafter, central or peripheral blood was collected to evaluate the coagulation parameter (INR) and TEG at five time points – preincision (time point 1), intraoperative (time point 2) (anaesthesiologists' discretion), postoperative within 6 h of shifting to intensive care unit (ICU) (time point 3), at 48 h (time point 4) and on the fifth postoperative day (POD) (time point 5). TEG was performed per the manufacturer's instructions (TEG 5000 analyzer; Haemonetics, Braintree, MA, USA). The primary outcome of this study was to determine the serial changes of conventional coagulation tests (PT, INR and aPTT) and TEG during the perioperative period in patients undergoing major liver resection (≥3 segments). The secondary outcomes were to estimate the reduction in transfusion requirements of blood components (FFP, cryoprecipitate and platelets) with a TEG-guided transfusion strategy as opposed to an INR-guided transfusion strategy and to assess for complications like epidural haematoma and deep venous thrombosis (DVT).

After securing the arterial line, the first blood samples were collected for complete blood count (CBC), coagulation profile (PT, INR and aPTT) and TEG before incision. These investigations were repeated intraoperatively at the discretion of the anaesthesiologist. Subsequent blood samples were collected at time points 3–5. Prophylactic pharmacological thromboprophylaxis was followed according to our standard institutional protocol (enoxaparin 1 mg/kg subcutaneously once a day) 1 day before surgery and restarted within 24 h postoperatively.

In addition to pharmacological thromboprophylaxis, all patients were prescribed compression stockings. Any delay in starting thromboprophylaxis in the postoperative period was recorded with the reason for the deviation from our standard institutional protocol. Samples were taken at least 12 h after administration of routine thromboprophylaxis to minimise any anticoagulant effects on the laboratory assays.

In addition to the above baseline demographics, the American Society of Anesthesiologists (ASA) physical status, surgery, intraoperative fluids, blood loss and replacement blood and blood components, if any, and haemodynamic instability requiring vasopressors were recorded. Institutional protocol for transfusion of blood products was followed with TEG-guided correction with an INR value of >1.5 and an abnormal TEG assay. Institutional protocol for epidural catheter removal was followed with a requirement of an INR <1.5 or normal TEG and platelet count >75,000/mm³ (as per ASRA guidelines). DVT was evaluated if clinical signs or symptoms suggested the same.

Without related literature, a purposive and convenient sample of 25 patients was chosen for this study. Categorical data like gender, ASA physical status, diagnosis and surgical procedure were reported as frequency, and continuous data like age, weight, height, body mass index (BMI) and amount of fluid administered were reported as median with interquartile range (IQR) depending on the distribution. Spearman rank-order correlation was used to study the relationships of coagulation tests (both TEG and conventional tests) at each time point. The data was analysed by IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). The correlation was termed significant at a *P*- value of ≤0.01 (two-tailed).

RESULTS

A total of 40 patients were screened for inclusion (from 18 August 2020 to 31 December 2020), of which 33 patients consented and were enrolled in the study. From them eight more patients were excluded from the analysis [Figure 1]. The demography, diagnosis and surgical procedure are summarised in Table 1.

Arterial cannulation was done in all 25 patients, and central venous access was secured in 19 patients.

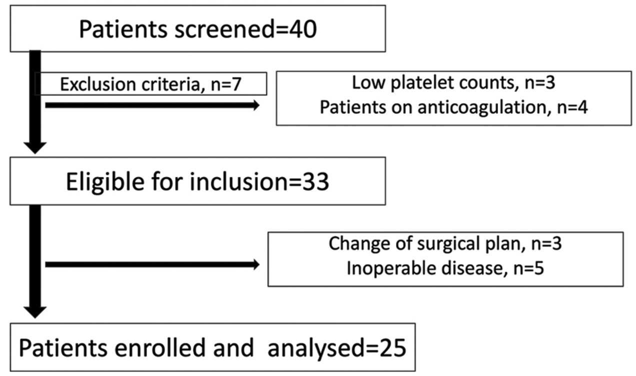

Figure 1: Flow diagram of the study

Table 1: Patient demographics and intraoperative variables

Variable	Value
Age (years), median (IQR)	55 (44–65)
Gender, male/female (*n*)	14/11
Weight (kg), mean (SD)	62 (12.8)
Height (cm), mean (SD)	163.3 (11.0)
Body mass index (kg/m²), mean (SD)	23.2 (3.9)
ASA, I/II (*n*)	15/10
Diagnosis (HCC/CRLM/NET liver/ cholangiocarcinoma)	13/6/3/3
Surgery (right hepatectomy/left hepatectomy/central hepatectomy)	17/6/2
Surgery duration (min), median (IQR)	360 (240–480)
Total blood loss (ml), mean (SD)	2980 (1632)
Crystalloids (ml), mean (SD)	2264 (768)
Colloids (ml), mean (SD)	1530 (685.9)
Total fluids administered (ml), mean (SD)	3974 (726)
Blood transfusion (ml), mean (SD)	622.8 (488.2) (88% patients intraoperatively)

ASA=American Society of Anesthesiology, CRLM=colorectal liver metastasis, HCC=hepatocellular carcinoma, IQR=interquartile range, NET=neuroendocrine tumour, SD=standard deviation

Intraoperative vasopressor (norepinephrine) support was initiated in 10 patients according to the anaesthesiologists' discretion.

Baseline preoperative haemoglobin and coagulation testing showed all patients' normal platelet, PT-INR and TEG values. In the perioperative period, PT-INR was elevated in 16 patients. In 14 patients, PT-INR was elevated at time points 2, 3 and 4, which normalised on the fifth POD [Figure 2a]. The aPTT remained within the normal range throughout the study period. In two of these patients, FFP was given during the intraoperative period. Of the remaining two patients, one had abnormal PT-INR and TEG at time point 3, and the other had abnormal PT-INR and TEG at time points 3, 4 and 5, for which FFP was given. Haemogram showed six patients had a platelet value less than normal (<1,00,000/mm³) on POD 2. In contrast to the routine coagulation tests, TEG parameters remained normal throughout the various study points in the intraoperative and immediate perioperative periods [Figure 2b]. No correlation existed between the R-time on TEG and INR or between the maximum amplitude (MA) and platelet count [Table 2].

Five patients were electively ventilated postoperatively and required an ICU stay of 2 days. All patients received postoperative thromboprophylaxis from POD 1 as per the institutional protocol. Thromboprophylaxis was stopped in two patients on POD 2 due to raised INR and abnormal TEG. It was restarted on POD 3 after TEG became normal in both patients, although one of the patients continued to have an INR >1.5. Ten patients received packed red blood cell transfusion, and four patients received FFP transfusion in the perioperative period with INR >1.5 and deranged TEG. Transfusion of blood components (FFP, cryoprecipitate) was avoided in 14 patients [Table 3]. Among the 14 patients, three patients avoided transfusion on three occasions (time points 2, 3, 4), five patients on two occasions (time points 3, 4) and six patients on one occasion (one at time point 2, three at time point 3 and two at time point 4) as TEG was normal despite INR being >1.5.

Table 2: Correlation between INR and thromboelastography parameters at all time points

		Correlations			
Test	**Timing of test**	**R**	**K**	**Alpha**	**MA**
INR	Preincision	−0.373	0.060	0.068	0.210
		0.066	0.777	0.748	0.314
	Intraoperative period	0.397	0.449	−0.479	−0.433
		0.143	0.093	0.071	0.107
	Postoperative period	0.095	0.244	−0.195	−0.013
		0.653	0.239	0.350	0.952
	48 h postoperatively	0.032	0.169	−0.162	−0.033
		0.883	0.429	0.449	0.879
	Postoperative day 5	0.009	0.420*	−0.311	−0.459*
		0.965	0.041	0.139	0.024

INR=International Normalised Ratio, K=K (kinetic) time, MA=maximum amplitude, R=R (reaction) time. *Correlation at *P*<0.05 level

Twenty-four patients received continuous epidural infusion of 0.1% levobupivacaine and 2 μg/ml fentanyl. One patient had a rectus sheath catheter inserted as the epidural was not inserted due to chronic back pain with disc prolapse, and the patient received 20 ml of 0.25% levobupivacaine at eight-hourly intervals. Epidural was removed on POD 4 for 17 patients as per the institutional protocol. There was a delay in removing the epidural catheter in five patients beyond POD 4 as INR was >1.5 on POD 4. The epidural catheter came out accidentally before POD 4 in the remaining two patients. Four of the five patients with delayed epidural removal had normal TEG and INR on POD 5 (time point 5); epidural catheters were removed from them. One patient had deranged INR (2.3) and TEG values and received an FFP transfusion before removing the epidural catheter on POD 6. No patients had clinical evidence of VTE.

DISCUSSION

The present study demonstrated that the use of TEG in patients undergoing a major oncologic liver resection

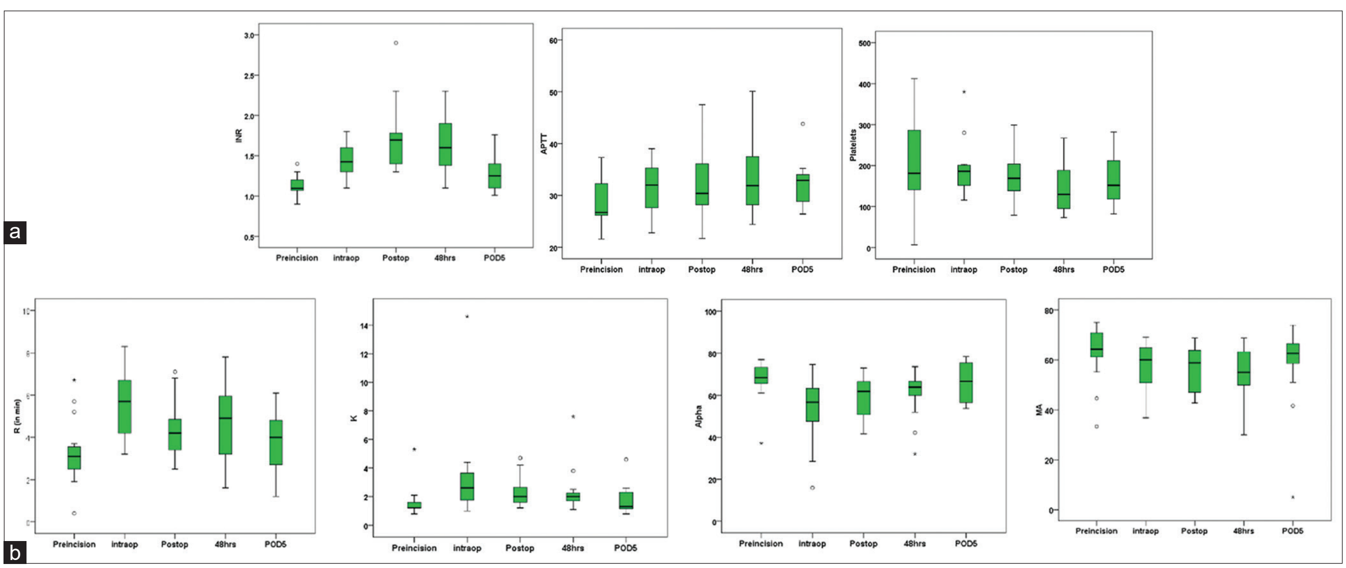

Figure 2: Serial changes in coagulation parameters over time: (a) serial changes in INR (reference range <1.5), aPTT (reference range 26–36 s) and platelets (reference range 150,000–400,000); (b) serial changes in R (reference range 2–8 min), K (reference range 1–3 min), alpha angle (reference range 55–78) and MA values (reference range 51–69). aPTT = activated partial thromboplastin time, INR = International Normalised Ratio, intraop = intraoperative period, K = K (kinetic) time, MA = maximum amplitude, POD5 = postoperative day 5, Postop = postoperative period, R = R (reaction) time

Table 3: Coagulation trends over time

Patient no.	T1- INR	T1- TEG	T2- INR	T2- TEG	T3- INR	T3- TEG	T4- INR	T4- TEG	T5- INR	T5- TEG
1	N	N	1.8	N	2.9	N	1.9	N	1.4	N
2	N	N	1.7	N	1.3	N	1.2	N	1.01	N
3	N	N	1.8	N	1.7	N	1.8	N	1.2	N
4	N	N	1.3	N	1.4	N	1.78	N	1.4	N
5	N	N	1.6	ABN/FFP	1.6	N	1.4	N	1.2	N
6	N	N	1.6	ABN/FFP	1.9	N	1.4	N	1.4	N
7	N	N	1.58	N	1.6	N	2.2	N	1.3	N
8	N	N	1.3	N	1.69	N	1.96	N	1.4	N
9	N	N	1.2	N	1.9	N	2.3	N	1.3	N
10	N	N	1.3	N	1.7	N	1.5	N	1.3	N
11	N	N	1.3	N	1.7	N	1.3	N	1.1	N
12	N	N	1.3	N	1.8	N	2.76	N	1.1	N
13	N	N	1.45	N	2.3	ABN/FFP	1.3	N	1.3	N
14	N	N	ND	ND	3	*Hep inf/ABN	3.2	ABN/FFP	2.3	ABN/FFP
15	N	N	ND	ND	1.4	N	1.8	N	1.4	N
16	N	N	ND	ND	1.5	N	1.6	N	1.2	N

ABN=abnormal, FFP=fresh frozen plasma, INR=International Normalised Ratio, N=normal, ND=not done, T=time point, TEG=thromboelastography.
T1: preincision, T2: intraoperative at anaesthesiologists' discretion, T3: postoperative within 6 h of shifting to the intensive care unit, T4: at 48 h postoperatively, T5: fifth postoperative day. *Patient had a vascular injury and received heparin- No FFP given

avoided transfusion of FFP in 14 patients (56%). Assessment of TEG despite deranged INR allowed to continue thromboprophylaxis and assist in removing the epidural catheter without blood product transfusion. TEG is a dynamic point-of-care test, and it has been demonstrated that there is a hypercoagulable state in some patients after liver resection, as demonstrated by TEG but not by routine coagulation tests.[14] This is likely due to the loss of anticoagulants like proteins C and S in combination with the loss of coagulation factors, which complicates the understanding of alterations in coagulation after major hepatectomy or liver transplant. Hence, TEG allows for better evaluation of coagulation and gives more valuable information about the overall haemostatic status than INR in liver surgery patients.[15-17]

Most literature evaluates TEG's application in trauma and liver transplant settings. Ågren *et al*.[18] demonstrated a poor correlation between TEG values and conventional coagulation tests in their study of 60 surgical patients. Barton *et al*.[19] demonstrated liver resections to be associated with a brief but significant hypercoagulability despite elevated INR, thus calling into question the practice of using PT-INR to guide plasma transfusions in liver resections. Wang *et al*. published a randomised trial of 28 patients that compared TEG-guided monitoring and routine coagulation tests in patients undergoing a liver transplant and found that using TEG significantly reduced FFP transfusion requirements.[20]

Studies have shown that pulmonary embolism (PE) and VTE incidence after liver resection ranges from 4.2% to 6%.[21] Postoperative thromboprophylaxis in major hepatectomy should be started despite deranged INR to avoid DVT and PE. However, it is resisted by clinicians due to the fear of bleeding.[14,22-24] TEG-guided transfusion algorithms also decreased the blood component transfusion requirements.[25] TEG can impact the rate of blood component transfusion and its associated complications.[11,12]

Continuous epidural analgesia is currently considered the standard of pain relief for patients undergoing liver surgery with a low risk of spinal haematoma.[26] Deranged clotting parameters can delay catheter removal and warrant blood component transfusion before catheter removal, as seen in a recent study wherein 32% of patients required vitamin K or plasma transfusion before epidural removal.[8] Normal TEG parameters suggest a rebalance of coagulation factors in patients following liver resection. Decisions regarding blood component therapy must be based on TEG parameters and the presence of clinical evidence of bleeding rather than PT/INR.

While this study demonstrates the effectiveness of TEG in evaluating perioperative coagulation following liver resection, it does have some limitations. Due to its small sample size, this study was not powered to identify the difference between TEG and routine coagulation tests. In addition, as our study period extended only up to POD 5, complications, including DVT beyond POD 5, were not recorded. The incidence of epidural haematoma is extremely low. Hence, no conclusion on the safety of epidural catheter removal using a TEG-based strategy can be drawn from our study.

CONCLUSION

Patients undergoing elective liver resection showed normal functional coagulation as demonstrated by TEG in contrast to elevated INR. Elevated INR significantly overestimated hypocoagulability following liver resections.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' institution policy.

Financial support and sponsorship

We acknowledge TMC Research Administration Council (TRAC) for intramural funding to conduct the study.

Conflicts of interest

There are no conflicts of interest.

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