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Rotational thromboelastometry and standard coagulation tests for live liver donors

Mohammed M, Fayed N, Hassanen A, Ahmed F, Mourad W, El Sheikh M, Abofetouh F, Yassen K, Khalil M, Marwan I, Tanaka K. Rotational thromboelastometry and standard coagulation tests for live liver donors.

Abstract: Purpose: To study coagulation of live liver donors with standard coagulation tests (SCT) and rotational thromboelastometry (ROTEM) and investigate their relationship.
Methods: A descriptive prospective study involving 50 right hepatotomy donors with epidural catheters. ROTEM (EXTEM, INTEM, and FIBTEM represent extrinsic and intrinsic pathways of coagulation and fibrinogen activity, respectively) was measured perioperatively and on days 1, 3, 5, 10, and 30. SCTs include prothrombin time (PT), international normalized ratio (INR) of PT, activated partial thromboplastin time (aPPT), fibrinogen, and platelets.
Results: PT and INR reflect hypocoagulability reaching maximum on day one (16.9 $\pm$ 2.5 s, 1.4 $\pm$ 0.2, $p < 0.05$ compared with baseline). ROTEM was in normal ranges till day 30 with no hypercoagulability. Fibrinogen showed no correlation with maximum clot firmness (MCF) of FIBTEM ($r = 0.35$, $p > 0.05$). CFT of EXTEM was not in significant correlation with PT and INR ($r = 0.16$, 0.19, $p > 0.05$), respectively. Significant correlation between platelets and both MCF (EXTEM; $r = 0.59$, $p = 0.004$) and MCF (INTEM; $r = 0.48$, $p = 0.027$).
Conclusion: ROTEM disagreed with SCTs and did not show the temporary hypocoagulability suggested by SCTs. Both ROTEM and SCTs showed no signs of hypercoagulability. Future studies involving ROTEM could help develop new guidelines for coagulation monitoring.

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Living donor liver transplantation is currently an acceptable alternative offered to patients with end-stage liver disease, and it has been successfully performed in many centers around the world. However, despite improved techniques and results, donor safety still remains a major concern (1).

Removal of a considerable hepatic mass could reduce the hepatic synthesis of clotting factors resulting in a hypocoagulable state. Alternatively, a hypercoagulable profile can also result from diminished hepatic synthesis of anticoagulants (2). Both hypercoagulability and hypocoagulability could impose a risk for the volunteers during and after the process of donation with a particular concern when an epidural catheter is inserted for pain control. Postoperative coagulopathy is currently diagnosed by abnormalities in standard coagulation tests (SCTs) such as the prothrombin time (PT), partial thromboplastin time (PTT), and low platelet count (3). The rotational thromboelastometry (ROTEM) studies can evaluate the process of clot initiation, formation, and stability with whole blood or plasma, based on the viscoelastic properties of blood (4).

This study aims to investigate the coagulation profile during and after right hepatotomy for the purpose of adult living-related liver transplantation by the use of SCTs and ROTEM.

Patients and methods

Approval for this descriptive cross-sectional prospective study (2007–2011) was provided by the Research Ethic Board of the Liver Institute, Menoufiya University, Shebeen El Kom city, Egypt (Chairperson Prof. Magdy Kamal) on 5 November 2007 (Ethic committee No. MD12). Informed written consent was obtained from each donor. Fifty consecutive adult living liver donors undergoing right liver resection for living-related liver transplantation at the Liver Institute were included in this study. Donors aborted prior to schedule for surgery were excluded from the study and replaced by other volunteers. Reasons for exclusion are mentioned in the Results section.

Eligibility criteria for donors included in the study include age between 20 and 45 yr and relationship within the third degree of consanguinity with the recipient as well as ABO blood group compatibility. Negative serology for hepatic viruses is a must. Normal laboratory results for electrolytes, hepatic and renal functions are required. Routine coagulation studies in addition to protein C, protein S, antithrombin III, and factor V leiden mutation were performed. A graft weight with a ratio of more than 0.8% of the recipient's body weight (GRWR > 0.8) is necessary for a successful living donor liver transplantation (LDLT). A percutaneous ultrasound-guided liver biopsy was routinely performed to assess the status of the liver and the degree of steatosis.

Preoperative investigations included full blood cell count, thyroid function tests, pregnancy tests, full virological tests and bacteriological cultures, chest radiograph, electrocardiogram plus Doppler cardiac ultrasound, respiratory spirometry, liver Doppler examination, magnetic resonance imaging (MRI), angiography, and cholangiography and a volumetric study of the whole liver and the right lobe. The volume and weight of the resected right lobe was calculated.

On admission to the operating room and after standard basic monitoring, a thoracic epidural catheter was placed between T6 and T11 preoperatively after patient consent. General anesthesia was induced with propofol (2 mg/kg), rocuronium (0.6 mg/kg), and fentanyl (2 μg/kg), followed by an endotracheal intubation. General anesthesia was maintained with a mixture of air/oxygen and sevoflurane with low flow at 2 L/min. An arterial line was routinely inserted into the left radial artery, and a central venous line was inserted into the right internal jugular vein with ultrasound guidance. During surgery, bupivacaine 0.125% + 2 μg/mL fentanyl was injected through the epidural catheter in 5 mL increments as required. Maximum dose according to weight was calculated to avoid over dosage.

The surgical technique was standardized; an ultrasonic dissector was used to divide the liver parenchyma. No Pringle maneuver was performed at any stage. The Pringle maneuver is a surgical technique used in abdominal operations, in which a vascular clamp is applied to the hepatoduodenal ligament interrupting the flow of blood through the hepatic artery and the portal vein to control blood flow to the liver or bleeding. It was developed by James Hogarth Pringle (5). The Pringle maneuver is often used during liver surgery to minimize blood loss; however, it can directly lead to reperfusion phenomenon in the liver.

In all donors, a right hepatectomy along the Cantlie line was performed, including segments 5–8, without involving the middle hepatic vein. Sodium heparin (15 IU/kg) was administered intravenously before vascular clamping, following the hypothesis that this could prevent intrahepatic thrombosis.

All living donors were extubated while still in the operating room. Postoperative analgesia was provided by patient-controlled epidural analgesia (PCEA), using 0.125% bupivacaine plus 2 μg fentanyl/mL. The PCEA pump was programmed for a basal infusion rate of 6 mL/h and 3 mL bolus every 15 min when needed. The aim was to achieve a visual analog pain score of 3 or less. Low-molecular-weight heparin (LMWH; 40 mg of enoxaparin) was given subcutaneously once daily for all donors from the second postoperative day until hospital discharge. Any blood products given were reported. The administration of non-steroidal anti-inflammatory drugs was avoided perioperatively. The epidural catheter was only removed when the international normalized ratio (INR) was <1.4 and the platelet count was $>100 \times 10^3$ cells/mm^3 and not before 12 h from the last dose of LMWH. The following dose of heparin was given 12 h after epidural catheter removal.

The ROTEM analysis was performed for each patient: before the skin incision baseline (Pre-Op), on postoperative day one (D1, 24 h after surgery), and on postoperative days 3, 5, 10, and 30 (D3, D5, D10, and D30). The SCTs (PT, PTT, INR, platelets) were also measured at the same time. The sampling was performed before the next LMWH dose in all donors. For ROTEM analysis, 4 mL of blood was drawn, and it was immediately mixed with 0.5 mL of a 3.2% citrate sodium solution followed by gentle mixing, and the blood samples were analyzed at 37°C.

The following ROTEM tests (Pentapharm, Munich, Germany) were performed for each sample: intrinsically activated thromboelastometry (INTEM), which evaluates the formerly known coagulation cascade intrinsic pathway; extrinsically activated thromboelastometry (EXTEM), evaluates the extrinsic pathway; and fibrinogen thromboelastometry (FIBTEM), which measures the fibrinogen activity. The following parameters were measured from the curves generated by INTEM and EXTEM assays: the coagulation time (CT), which is the time (seconds) that the blood takes to form the initial fibrin strands; the clot formation time (CFT), is the time (seconds) until a definite clot is formed (defined as an amplitude of 20 mm); the α-angle measured between the midline of the tracing and a straight line drawn from the 1-mm point tangential to the curve, indicates the rate of fibrin polymerization.

The maximum clot firmness (MCF, millimeters) measures the clot strength and depends primarily on platelet and fibrinogen function. The maximum lysis (ML) represents the maximum fibrinolysis detected during the analysis process. It is defined as the ratio of the lowest amplitude after MCF and the MCF itself. The MCF is the only parameter analyzed from the FIBTEM test. The FIBTEM reagent contains cytochalasin D, which is a substance that inhibits platelet function; the FIBTEM MCF roughly corresponds to the fibrinogen contribution to the coagulation process. The normal reference values for each parameter are depicted in Table 1 (4).

According to the SCTs, hypocoagulability was diagnosed whenever one of the following occurred: INR > 1.4, PTT > 1.5 times the laboratory control values, or the development of thrombocytopenia (platelet count $<100 \times 10^3$ cells/mm^3). Quantitative analysis of ROTEM tracings is commonly based on four main parameters: CT, CFT, α-angle, and MCF. Hypocoagulability or hypercoagulability was defined when at least two or more parameters were altered.

Table 1. ROTEM parameters of extrinsically activated thromboelastometry test (EXTEM), intrinsically activated thromboelastometry test (INTEM), and fibrinogen thromboelastometry test (FIBTEM) with normal reference range in a normal volunteer preoperatively (7)

Test name	CT (s)	CFT (s)	Angle α	MCF (mm)	ML (%)
EXTEM	38–79	34–159	63–83	50–72	<15
INTEM	100–240	30–110	70–83	50–72	<15
FIBTEM	MCF < 9 mm a sign of decreased fibrinogen level MCF > 25 mm is a sign of elevated fibrinogen level				

CT, clotting time; CFT, clot formation time; MCF, maximum clot formation; ML, maximum lysis.

Statistical analysis

All data were tested with Kolmogorov–Smirnov *Z*-test, and most of them were found normally distributed and so presented with mean ± SD in tables, power of the sample (83.0%) was calculated before initiation of the study by using power and sample software, and the study size detected was 50 cases. Both parametric and non-parametric tests were used for analyzing associations or correlations.

Data were statistically analyzed using Statistical Package for Social Science (SPSS) program version 13 for Windows, and for all the analyses, a p-value < 0.05 was considered statistically significant. Data are shown as mean and standard deviation. Repeated measures ANOVA test and Friedman tests were performed to differentiate changes in different follow-up results of normally and not normally distributed studied variables, respectively. Paired *t*-test and Wilcoxon test were performed to detect significant difference between the pre- and postoperative values of the same variable on the same group of patients. Paired *t*-test and Wilcoxon *t*-test were used for normally and not normally distributed data, respectively. Spearman's correlation tests were performed to study correlation between different quantitative variables.

Results

All donors were of American Society of Anesthesiology physical status grade I except one patient with mild controlled asthma. Mean age of donors was 26.2 ± 4.7 yr with a range of 19–38 and body mass index mean of 25.7 ± 3.1 kg m^2. Seven donors were excluded due to various reasons considered as a threat for survival: two donors due to the presence of homozygous factor V Leiden mutation, one donor due to a preoperative volumetric study showing a remnant liver tissue after resection (RLV) <30%, which is considered not sufficient for survival, and two due to a type four portal vein anomaly (multiple right portal vein branches), which is a challenge during the procedure of resection, and finally, two donors were aborted during surgery due to unsatisfactory gross appearance of the liver and abnormal anatomy. The procedure was not allowed to proceed for those two. A total of 50 donors were involved and completed the study (35 males and 15 females). They underwent right hepatectomy with a mean operative time of

8.1 ± 1.1 h (range 6–10 h) and mean stay in hospital of 13.04 ± 2.3 d (range 7–21 d). The median resident time for epidural catheters was 4 ± 1.5 d (range 3–5 d). No donors included in this study developed any clinically manifested thrombotic or hemorrhagic events during the hospital stay. No blood product transfusion was required in any case. All volunteers received crystalloids in the form of Ringer's acetate (4.6 ± 1.1 L) and colloids as hydroxyethyl starch (HES) 130/0.4 of 1 ± 0.2 L.

The ROTEM parameters were within normal reference ranges without any signs of hypocoagulability or hypercoagulability as demonstrated in Table 2. In contrast, SCT results demonstrated a statistically significant increase in both PT and INR in comparison with the basal values with a peak on postoperative day one, decreasing later to normal value on postoperative day five. The preoperative value of PT was 12.3 ± 0.07 s and INR was 1 ± 0.01. The mean significant increase was on day one PT 16.9 ± 2.5 s and INR 1.49 ± 0.2 as shown in Table 3 and Fig. 1. Weak correlation was found between fibrinogen blood levels and MCF of FIBTEM ($r = 0.35$, $p > 0.05$).

The were also a weak correlation between PT and INR with CFT of EXTEM ($r = 0.16$, $r = 0.19$, $p > 0.05$; Fig. 2). The only significant correlation was between CT (EXTEM) and PT ($r = 0.44$, $p = 0.046$). This study demonstrates the disagreement between the SCTs and the ROTEM parameters. No coagulation abnormalities could be revealed with the later method during the 30-d study duration even when temporary hypocoagulability was diagnosed with SCTs.

Platelet counts showed a gradual decrease, 209.1 ± 47, 207.4 ± 40, and 160.5 ± 38/mm^3, intraoperatively and on days one and three, respectively, as given in Table 3. The decrease in platelet count was statistically significant, without any clinical implications. A significant correlation was observed between platelet count and the MCF (EXTEM; $r = 0.57$, $p = 0.004$) and MCF (INTEM; $r = 0.48$, $p = 0.027$).

The aPTT readings showed a significant increase intraoperatively and on day one in comparison with the basal values, but within normal range. The highest increase was in day one (34.1 ± 4.1 s; $p < 0.05$). No correlation between aPTT and CFT of INTEM ($r = 0.18$, $p = 0.42$). Tables 4 and 5 demonstrate the different correlations between ROTEM parameters and SCTs.

No epidural hematoma causing neurological signs or symptoms was detected. An injury to the left hepatic duct with intraoperative reconstruction and stent placement was reported in one volunteer. Bile leak was reported and treated with endoscopic retrograde cholangiopancreatography (ERCP) and

Table 2. Extrinsically (EXTEM), intrinsically (INTEM), and fibrinogen (FIBTEM)-activated thromboelastometry tests at different measuring points

Parameter	Pre-Op	Intra-Op	D1	D3	D5	D10	D30	p
CT (s)								
EXTEM	59 ± 12	65 ± 18	69 ± 12	65 ± 8	60.4 ± 12	63.8 ± 22	56.8 ± 10.0	<0.01
INTEM	150.4 ± 27.8	151.8 ± 27.8	146.6 ± 18.9	159 ± 25.8	153 ± 21.2	156.8 ± 24.8	151.5 ± 19.3	<0.01
CFT (s)								
EXTEM	108 ± 26	140 ± 36	135 ± 43	119 ± 34	116 ± 42	86 ± 16	101.4 ± 19	<0.01
INTEM	92.1 ± 20.1	102.6 ± 26.5	106.4 ± 30.6	95.1 ± 30.2	88.9 ± 25	79.4 ± 23.3	88.5 ± 25.8	<0.01
Angle α								
EXTEM	68.6 ± 14	67.3 ± 5.8	68.9 ± 6.5	70.2 ± 9	73 ± 5**	74 ± 2	72 ± 3.5	<0.01
INTEM	73 ± 3.2	71.9 ± 4.4	71.8 ± 4.2	74.2 ± 3.4	75 ± 3.3	75.2 ± 2.7	72.8 ± 3.2	<0.01
MCF (mm)								
EXTEM	61.6 ± 3.9	57.6 ± 5	56.5 ± 5	58 ± 5*	59.3 ± 6.1	63.8 ± 2.9	64.9 ± 4	<0.01
INTEM	61.8 ± 5.3	59.8 ± 5.1	58.1 ± 5.1	59.7 ± 5.6	60.3 ± 5.5	64.3 ± 3.7	64.4 ± 4.8	<0.01
FIBTEM	13 ± 3.2	12.3 ± 2.3	13.2 ± 4.6	17.4 ± 3**	17.9 ± 2**	19.6 ± 2**	15.1 ± 3.3	<0.01
A10 (mm)								
EXTEM	53.2 ± 4.1	48.4 ± 4.9	48.3 ± 5	53.4 ± 8	51.9 ± 5.9	53.1 ± 11.4	55.7 ± 4.2	<0.01
INTEM	54.1 ± 4.3	51.8 ± 5.9	50.9 ± 5.3	53.5 ± 5.6	53.6 ± 5.9	56.1 ± 4.3	55.8 ± 4.8	<0.01
FIBTEM	11.3 ± 2.8	11 ± 2.14	11.2 ± 3.6	15.1 ± 3**	16.1 ± 2**	17.8 ± 1**	13.4 ± 2.97	<0.01
ML %								
EXTEM	3.9 ± 5.1	4.4 ± 4.6	8.8 ± 11.2	4.9 ± 4	4.8 ± 4.9	3.7 ± 3.8	2.8 ± 3.1	>0.05
INTEM	4.3 ± 4.3	4.9 ± 4.2	5.8 ± 3.9	5.6 ± 4.3	4.5 ± 3.6	3.1 ± 5.6	3.2 ± 3.18	>0.05

Data are presented as mean ± SD. Repeated-measures ANOVA test and Friedman's test were used to test differences during follow-up period with p value presented at the end of each row. Each variable was also compared with the related Pre-Op value.
CT, clotting time; CFT, clot formation time; MCF, maximum clot formation; A10, clot formation at 10 min; ML, maximum lysis; Pre-Op, preoperative; Intra-Op, intraoperative; D, postoperative day.
*$p < 0.05$, significant; **$p < 0.01$, highly significant.

Table 3. Haemoglobin, hematocrit concentration, and other coagulation parameters at different measuring points

Parameters	Pre-Op	Intra-Op	D1	D3	D5	D10	D30	p
HB (g/dL)	13.8 ± 1.8	12.8 ± 1.4**	13.4 ± 1.0	11.5 ± 0.8**	11.4 ± 0.7**	12.05 ± 2.4**	12.5 ± 1.2	<0.01
Hct %	40.7 ± 4.9	37.9 ± 4.4**	35.04 ± 2.7**	35.0 ± 2.7**	33.4 ± 2.2**	34.9 ± 2.5**	37.3 ± 4.05	<0.01
Platelets (mm^3)	238.8 ± 46.4	209.1 ± 47.1**	207.4 ± 40.4**	160.5 ± 38.8**	187.6 ± 50.8**	232.8 ± 71.04	261.2 ± 45.8**	<0.01
INR	1.0 ± 0.01	1.19 ± 0.09**	1.49 ± 0.2**	1.48 ± 0.16**	1.12 ± 0.06**	1.03 ± 0.05*	1.01 ± 0.01	<0.01
PT (s)	12.3 ± 0.07	13.6 ± 1.2**	16.9 ± 2.5**	15.5 ± 2.2**	13.1 ± 33.6	12.7 ± 0.6**	12.3 ± 0.04	<0.01
aPTT (s)	28.6 ± 5.3	32.7 ± 7.6*	34.1 ± 4.1**	32.02 ± 6.01*	29.9 ± 4.7	27.3 ± 5.5	27.9 ± 4.9	<0.01
Fib (mg/dL)	331.9 ± 61.5	256.7 ± 54.1**	298.05 ± 96.6	371.1 ± 72.1**	384.3 ± 67.5**	383.5 ± 90.3*	325.9 ± 44.6	<0.01

Data are presented as mean ± SD. Repeated-measures ANOVA test and Friedman's test were used to test the differences during follow-up period with a p value presented at end of each row. Each variable was also compared with the related Pre-Op value.
HB, hemoglobin; Hct, hematocrit concentration; PT, prothrombin time; INR, international normalized ratio, aPTT, activated partial thromboplastin time; Fib, fibrinogen; FDPs, fibrinogen degradation products; Pre-Op, preoperative; Intra-Op, intraoperative; D, postoperative.
*p < 0.05, significant; **p < 0.01, highly significant.

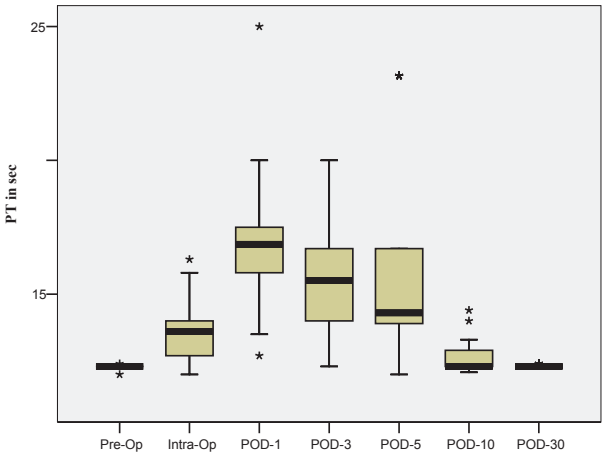

Fig. 1. Box and whisker plot of PT during and after liver resection. Results are expressed as maximum, minimum, and median (line within the box), and 25–75th percentiles (error bars) are shown at selected time points. Repeated-measures ANOVA was used, and changes were highly significant throughout the measuring points (p < 0.01). PT, prothrombin time; Pre-Op, preoperative; Intra-Op, intraoperative; POD, postoperative day.

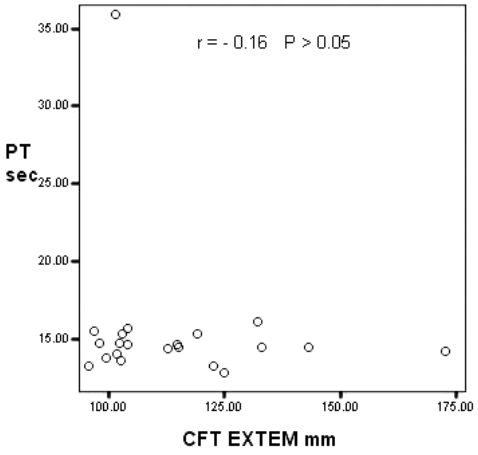

Fig. 2. Spearman correlation coefficient between prothrombin time (PT) and coagulation formation time (CFT) of the rotational thromboelastography (ROTEM). p < 0.05 is considered significant.

stent insertion in two volunteers. Two patients complained of postoperative lower limb paresthesia, which was relieved when epidural analgesia was ceased. Finally, a volunteer suffered a vasovagal syncope during the epidural catheter placement and recovered spontaneously when allowed to lie down and lift both lower limbs.

The preoperative radiological studies showed the mean total estimated right lobe weight to be 927.29 ± 119.11 g. The mean actual weight of the resected right lobe liver was 861.39 ± 150.9 g, when compared statistically with the preoperative estimated right lobe (p value < 0.01).The mean remnant liver volume percentage (%) was 37 ± 4.6, with minimum to maximum range 43.2–28.6. The mean graft weight/recipient weight ratio was 1.08 ± 2, with most donor right hepatectomies performed with preservation of the middle hepatic vein and with no intermittent vascular occlusion, except for three donors' right hepatectomies in which the middle hepatic vein was not preserved.

Discussion

The coagulation changes associated with liver resection in live liver donors were the primary focus for our study. Donors in this study had a normal coagulation profile during the perioperative period and up to 30 d postoperatively as indicated by a series of ROTEM analysis tests with no reported hypercoagulation or thrombotic incidence. This is different from several related studies on live donors reporting tendency to hypercoagulate as in Cerutti et al.'s (2) study, which concluded that the live liver donors were either

Table 4. Spearman correlation coefficients (*r*) and p values between rotational thromboelastometry (ROTEM) parameters of extrinsically activated thromboelastometry (CT, CFT, MCF) and standard coagulation tests (SCTs)

ROTEM Parameters	PT (s)	INR	aPTT (s)	Platelet (mm^3)	Fibrinogen (mg/dL)
CT (s)					
r	0.441	0.379	0.148	−0.507	−0.061
p-Value	0.046*	0.090	0.522	0.019*	0.793
CFT (s)					
r	0.108	0.203	0.009	−0.385	0.126
p-Value	0.642	0.378	0.969	0.085	0.586
MCF (mm)					
r	−0.093	−0.161	−0.449	0.595	−0.090
p-Value	0.687	0.485	0.041*	0.004*	0.699

PT, prothrombin time; INR, international normalization ratio of prothrombin; aPTT, activated partial thromboplastin time; CT, clotting time; CFT, clot formation time; MCF, maximum clot formation.
*$p < 0.05$ is considered significant.

Table 5. Spearman correlation coefficients (*r*) and p values between rotational thromboelastometry (ROTEM) parameters of intrinsically activated thromboelastometry (CT, CFT, MCF) and standard coagulation tests (SCTs)

ROTEM Parameters	PT (s)	INR	aPTT (s)	Platelets (mm^3)	Fibrinogen (mg/dL)
CT (s)					
r	−0.032	−0.211	0.186	−0.004	0.101
p-Value	0.889	0.360	0.420	0.987	0.662
CFT(s)					
r	−0.032	−0.211	0.186	−0.004	0.101
p-Value	0.889	0.360	0.420	0.987	0.662
MCF (mm)					
r	−0.111	−0.111	−0.062	0.483	−0.140
p-Value	0.633	0.632	0.788	0.027*	0.546

PT, prothrombin time; INR, international normalization ratio of prothrombin; aPTT, activated partial thromboplastin time; CT, clotting time; CFT, clot formation time; MCF, maximum clot formation.
*$p < 0.05$ is considered significant.

normal or hypercoagulable using repeated TEG analysis, and both Sterneck et al. and Emre studies (6, 7), in which a case of fatal pulmonary embolism was reported by the first study and a donor mortality due to pulmonary embolism in the second, were attributed to the existence of an increased thrombotic risk in the setting of living donor liver resections.

This study results also demonstrated that the ROTEM data obtained from the involved donors highlight a clear disagreement perioperatively between the blood clot viscoelastic monitoring device (ROTEM), which monitors blood clot formation, and the SCTs, which looks at the coagulation cascade from different views without being able to provide enough information about the interaction between various blood components as platelets, hemoglobin, and other coagulation factors. Similar results demonstrating these disagreements between ROTEM parameters and SCTs were also reported by Gouvêa et al. among the live liver donors when ROTEM was used to monitor coagulation profile for 16 of them (8), but some limitations were mentioned by Gouvêa et al., as performing the measurements only during the first three postoperative days and the limited number of the donors involved in their study, these were avoided in our study which extended to day 30 postoperatively and with more donors involved.

In response to the query raised by the Gouvêa et al.'s study concerning the hypothesis that hypercoagulation could exist beyond the third day, this was denied clearly in the results section of our study in which ROTEM demonstrated no evidence for hypercagulability, even when the follow-up period was extended to day 30 postoperatively.

As for the correlation between ROTEM and SCTs, studies not involving liver resection presented different results such as the study by Stancheva et al. (9), which looked into the correlation between ROTEM and SCTs during and after orthotopic liver transplantation and found a significant correlation between PT (INR) and EXTEM CFT and also between aPTT and INTEM CFT in the preoperative period only, but later this correlation was reduced to insignificant during the intraoperative periods and two h postoperatively.

Another study by Hass et al. (10) among pediatrics undergoing elective surgeries found no correlation between PT and aPTT with ROTEM CT, but demonstrated a significant correlation with other ROTEM parameters.

Tripodi et al.'s study (11) defined the role of PT and INR as *in vitro* tests that measure the activity of procoagulants, but not the anticoagulants that could be reduced in any liver disease or dysfunction. ROTEM tests involve whole blood with procoagulants and anticoagulants involved and interacting with one another to present a sum up end result for the whole coagulation process.

The SCT readings in our study, as PT and INR, demonstrated a transient post-resection hypocoagulopathy, but this was demonstrated to a lesser extent among ROTEM parameters in which there was some delay in clot formation among the traces in comparison with the preoperative values, but without any clinical effects and within normal ranges. Cammu et al.'s study (12) demonstrated similar changes in SCT results, and also De Pietri et al.'s study (13) observed that the TEG traces showed a normocoagulability in patients undergoing liver resections for hepatic tumors. They also

reported a discrepancy between laboratory values and thromboelastographic variables. The attempted correlation between the ROTEM and SCTs reached frequently to statistical insignificance at several occasions in our study; this could be due to the difference in the techniques and constituents of the blood samples used to perform the study, as ROTEM always includes the cellular elements of blood while SCTs do not. This could raise the issue to argue that the correlation between the SCTs and ROTEM should not be studied or looked in as both techniques differ basically in their components and methodology.

Fibrinogen, an acute-phase reactant, is expected to increase during the postoperative period of any major surgery (14), but these study results demonstrated an increase in fibrinogen blood levels but not beyond the normal ranges and, again, with no significant correlation between fibrinogen blood levels and MCF FIBTEM of ROTEM. These finding from our study were also supported by Karakoc et al.'s study (15), in which fibrinogen blood level was not in correlation with the ROTEM parameters.

Major liver resections may result in transient metabolic impairment (15) and temporary disturbances in hemostasis (8). The use of an indwelling epidural catheter and the timing of its removal in patients undergoing liver resection for LDLT remain controversial and would require a reliable method to monitor coagulation changes (16).

In this study, the epidural catheter insertion in donors for living donor liver transplantation faces several problems that recommend meticulous attention: first is the introduction of intraoperative heparin (15 IU/kg) before graft removal, second is the postoperative coagulation derangement, which could associate liver resection, and third is the administration of postoperative LMWH for prophylaxis of DVT.

During this study, all donors received around 15 IU/kg of heparin at the end of liver parenchyma dissection to prevent blood clotting in the graft following interruptions of the hepatic artery, hepatic vein, and portal vein. Cammu et al. administered 50 IU/kg of heparin intravenously at the end of hepatic dissection, which is greater than this study dose. The usual timing of intraoperative heparin injection in this study was more than four h after the epidural catheter insertion to help minimize the risk of hematoma formation (11).

Intraoperative coagulation monitoring after the administered heparin in this study showed a slight increase in aPTT, which was statistically significant but still within normal range without any clinical implications. On the other hand, CT INTEM, which indicates heparin effect on ROTEM study, nearly showed no abnormal change out of the normal reference range after injection. Therefore, this dose of heparin administered does not seem to increase the risk from what is available from ROTEM monitoring, and the epidural catheters were removed in all donors by day four without the need for fresh frozen plasma, with no clinical evidence for epidural hematoma formation and in accordance with the indications of the European Society of Regional Anesthesia (platelets >100 000/mm^3) (17).

SCTs reflect coagulation factor activity at a particular part of the coagulation cascade, while the ROTEM reflects the end product of coagulation balance between both coagulants and anticoagulants. During the study period, all parameters in ROTEM were normal without hypo- or hypercoagulability coinciding with the actual clinical hemostatic state of the 50 studied donors.

Regarding postoperative LMWH administration, epidural catheters in this study group were removed only 10–12 h after the last dose of LMWH as a precaution, while subsequent doses were only given after two h at least from catheter removal.

Limitations in this study is that epidural hematoma formation was only observed clinically with no radiological investigations used to follow-up any possible hematoma subclinical formation in the epidural space, such as the use of thoraco-lumbar MRI. Another limitation to the ROTEM is the inability of both EXTEM and INTEM parameters to detect the coagulation effect of LMWH used in the study for the donors.

In summary, the coagulation profile for the live liver donors involved in this study showed no hypocoagulability with ROTEM during and after the liver surgery, despite the temporary hypocoagulability observed with PT and INR on days one and two post-resection. No hypercoagulation was observed during the immediate postoperative period after liver resection and for 30 d after. The ROTEM parameters were generally not in agreement with the SCTs. Further studies on a larger scale are needed to decide which test is more reliable as a perioperative coagulation monitor, and this could help develop new protocols and guidelines for this specific group of donors. This will have important clinical implications in increasing preoperative live liver donor safety.

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