Original Article

Detection and quantification of perioperative heparin-like effects by rotational thromboelastometry in living-donor liver transplant recipients: A prospective observational study

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Abstract

Background and Aims: Heparin-like effects (HLEs) can affect hemostasis during liver transplantation. The aim of this study was to assess the perioperative incidence and severity of HLE with rotational thromboelastometry (ROTEM) and activated partial thromboplastin time (aPTT).

Material and Methods: ROTEM and aPTT were measured intraoperatively and on postoperative days (POD) 1, 3, and 7. HLE was identified if ROTEM INTEM/HEPTEM CT-ratio was >1.25 and severe forms of HLE when ratio was ≥2. Based on aPTT, HLE was defined when aPTT ratio was >1.25 (patient aPTT/control aPTT).

Results: Thirty-eight recipients were included. Variable degrees of HLE were detected by aPTT-ratio and INTEM/HEPTEM CT ratio. No significant correlation existed between both ratios. Based on INTEM/HEPTEM CT ratio, HLE was detected in 7/38 during anhepatic phase, 19/38 post-reperfusion, 10/38 on POD1, 4/38 on POD3, and 0/38 on POD7. Four cases of severe HLE were identified by INTEM/HEPTEM CT ratio only in the anhepatic phase. Postoperative infusion of unfractionated heparin led to mild-moderate HLE on POD1 and 3 as evident by both tests. Red blood cell and plasma transfusion were higher with severe HLE (1350 ± 191 ml and 3558 ± 1407 ml). Composite adverse outcome of any complication or death within 3 months for patients without HLE, mild-moderate HLE, and severe HLE as detected by ROTEM was 27.8%, 42.9%, and 66.7%, respectively.

Conclusion: INTEM/HEPTEM CT ratio was able to detect and quantify HLE as aPTT ratio. The ability of the INTEM/HEPTEM CT ratio to identify severe HLE earlier in the anhepatic phase needs to be studied in a larger population. HLE is self-limiting, but when identified in a severe form, it is associated with worse outcome.

Keywords: Blood coagulation, heparin-like effect, liver transplantation, thromboelastometry

Introduction

Heparin-like effects (HLEs) can affect hemostasis during and after living-donor liver transplantation (LDLT). Exogenous heparin effects can be based on systemic heparin administration to the liver donor prior to right lobe hepatectomy[1] or to the recipient prior to graft reperfusion or during postoperative anticoagulation. Endogenous HLE can be mediated by the release of heparinoids from the endothelial glycocalyx,

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activated macrophages, or mast cells in cirrhosis, infection, shock, and ischemia reperfusion injury.[2–6] Usually, HLE after reperfusion are self-limiting and disappear with hemodynamic stabilization. However, HLE can present in a severe form with persistent coagulopathy which can only be reversed by protamine.[7]

The primary goal of this trial was to monitor the incidence and severity of HLE among the recipients in our transplant center using two rotational thromboelastometry (ROTEM, Tem Innovations GmbH, Munich, Germany) parameters (INTEM and HEPTEM CT) and the corresponding INTEM/HEPTEM CT ratio as well as the activated partial thromboplastin time (aPTT) throughout the various stages of the transplant procedure and for 7 days postoperatively. The secondary aim was to assess the relationship between thromboelastometry results and aPTT, the effect of postoperative heparin infusion on thromboelastometry and aPTT, as well as the effect of HLE on patient outcomes such as reoperation, biliary leakage, cerebral complications, nosocomial infection, liver graft rejection or death within three months after liver transplantation.

Material and Methods

This prospective observational clinical trial in living-donor liver transplant recipients was approved by the local research and ethical committee of Menoufia University in Egypt (06092015) and registered at the Pan African Clinical Trial Registry (PACTR201712002839259). Adult recipients with end-stage liver disease (ESLD) as a result of hepatitis C and scheduled for LDLT were enrolled. No systemic heparin was given to the recipients prior to the surgery, but a dose of 1000 U unfractionated heparin (UFH) was routinely administered intravenously to all liver donors prior to right hepatectomy of the liver graft. All liver grafts were flushed with non-heparinized solutions (500 ml of 4.5% albumin) prior to completion of the venous anastomoses. Recipient's intravenous and arterial lines and flush bags were without heparin.

As a routine practice, UFH was infused (60–180 U/kg/day) postoperatively for two days to achieve an aPTT ratio of 1.5–2, and then was replaced by low molecular weight heparin (LMWH) (20 mg enoxaparin/12 h) until discharged from the intensive care unit (ICU) on day 5, in addition to thromboprophylaxis with elastic stockings and the use of a sequential compression device (SCD) for the lower limbs until early mobilization. Recipients on oral anticoagulants, procoagulant drugs, or with hereditary coagulopathies were excluded. Recipients with severe HLE during the postoperative period and those who developed severe forms of HLE with UFH were not infused with the UFH. The aPTT was determined through a Sysmex Automated Hematology Analyzer CA-1500 (SiemensHealthcare, Erlangen, Germany). The aPTT reagent was from Pathromtin SL Siemens Healthcare Diagnostics Products GmbH, Marburg/Germany.

The ROTEM delta assays were INTEM and HEPTEM. INTEM represents intrinsic coagulation pathways and HEPTEM represents the intrinsic coagulation pathway with the elimination of HLE by the addition of heparinase.[4] The following ROTEM parameters were recorded: coagulation time (CT) in seconds (time from start of measurement until the first 2 mm of clot firmness are reached); clot formation time (CFT) in seconds (time needed to increase clot firmness from 2 to 20 mm); maximum clot firmness (MCF) in mm; and the calculated index INTEM/HEPTEM CT ratio. ROTEM single use reagents in-tem S and hep-tem S were used for this trial. HEPTEM contains heparinase and neutralizes up to 10 IU UFH per ml whole blood. HLE was detected by the increase in INTEM/HEPTEM CT ratio to ≥1.25, as described by Mittermayr *et al*.[8] and Ichikawa *et al*.[9] On the other hand, HLE was identified by an aPTT prolongation (>56.3 s) with an increased aPTT ratio (patient aPTT/control aPTT >1.25 (control aPTT = 35 s)). Number and percentage of the recipients with HLE were reported in each phase of the liver transplant procedure. Severity of HLE was determined with INTEM/HEPTEM CT ratio as follows: no HLE (ratio <1.25), mild HLE (ratio, 1.25–1.49), moderate HLE (1.5–1.99), and severe HLE (ratio ≥2.0). Similarly with aPTT as follows: no HLE was defined with aPTT <56.3 s, mild HLE with aPTT 56.3–67.4, moderate HLE with aPTT 67.5–89.9 s, and severe HLE with aPTT ≥90 s.[10] Furthermore, the correlations between INTEM CT and aPTT, and between INTEM/HEPTEM CT ratio and aPTT as well as aPTT ratio were calculated.

Monitoring and general anesthesia was induced and maintained as per uniform standard general anesthesia care.[11] Packed red blood cells were transfused to keep hematocrit above 25%. ROTEM was utilized to guide intraoperative transfusion of blood products as described by Görlinger.[3] Perioperative fluid regimens consisted of Ringer's acetate solutions (6 ml/kg/h) and albumin 5% guided by corrected flow time of esophageal Doppler. Boluses of colloids (albumin 5%) were guided by an algorithm depending on the transesophageal Doppler (Cardio QP; Deltex Medical, Chichester, UK) stroke volume (SV) and corrected flow time (FTc) parameters.[12]

Intraoperative body temperature was maintained by forced warm air blankets and by warming of all infused fluids.

Same surgeons were present in all surgical procedures. The piggyback technique was adopted for all recipients. Portal vein anastomoses was performed first followed by hepatic artery anastomoses and bile duct reconstruction. No veno-venous bypass or temporary portocaval shunts were used. Postoperatively, recipients were admitted to the ICU for sedation and mechanical ventilation, with a plan to extubate when graft functions, systemic, and hepatic hemodynamics allows. ROTEM parameters and aPTT were assessed perioperatively at the following time points: preoperatively, intraoperative during the dissection phase, 10 minutes after the beginning of the anhepatic phase, 5 minutes after reperfusion, and postoperatively on days 1, 3, and 7 (POD1–3).

Patient demographic data such as age, sex, weight, and model for end-stage liver disease score (MELD score) were documented. Recipient complication, outcome, blood transfusion requirements, perioperative fluids, duration of operation, incidence of re-operation as well as three-month-mortality were documented. Composite adverse outcome was defined as number of recipients subjected to reoperation, evidence of biliary leakage in surgical drains, signs of cerebral encephalopathy, nosocomial infection as event from blood culture results, laboratory evidences for liver graft rejection or death within three months.

Statistical analysis

The minimal sample size was calculated based on a previous study aimed to investigate the presence and extent of HLE in patients with acute liver failure (ALF) undergoing liver transplant (LT) and to compare the extent of HLE in this group with a group of cirrhotic patients undergoing LT. Here, Senzolo *et al*.[13] in 2009 concluded that before transplantation, patients with ALF have a higher incidence of HLE than patients with liver cirrhosis. However, this did not affect the thrombin generation calculated by thromboelastography, and resolved after transplantation. Based on their data, a sample size of 38 patients is required to conduct this prospective observational study, based on a significance level of 95% ($\alpha = 0.05$), and a statistical power ($1 - \beta$) of 80%, with assumptions of the HLE discrimination of outcome of 75%. The sample size was calculated using MedCalc version 14.8.1. Data were tested for normal distribution by Kolmogorov–Smirnov test. Parametric tests with mean and standard deviation or non-parametric tests with median and interquartile range (IQR) or range were used as appropriate. Pair-wise comparison was done with Bonferroni correction. Pearson correlations were used. Chi-squared test was used to test the association between qualitative variables. Cohen's kappa coefficient (κ) was used for measuring inter-rater agreement for qualitative (categorical) items. A modification to Cohen's kappa called weighted Cohen's kappa was used too. Intra-class correlation (ICC) was used to assess agreements. For evaluation of ICC coefficient value, the Cicchetti guidelines were adopted. Cicchetti guidelines for interpretation of ICC <0.4, 0.4–0.59, 0.6–0.74, and 0.75–1.0 were considered as poor, fair, good, and excellent agreement, respectively.[14]

Results

Thirty-nine consecutive recipients with end-stage liver disease (hepatitis C only) scheduled for elective LDLT were enrolled. Thirty-eight recipients successfully completed the trial and were included in the study analysis. One patient was excluded since the transplant procedure was canceled due to living-donor gross anatomical concerns. Recipients demographic were age 50.0 [45.0–52.0] years, males 33/38 (86.8%), and females 5/38 (13.2%), graft weight 770.0 [760.0–840.0] g, operation time 11.0 [10.0–12.0] hours and MELD score 16 [15.0–17.0].

Prolonged INTEM CT (>240 s) was observed in 7/38 during anhepatic phase (range, 257–1523 sec), in 19/38 post reperfusion (range, 270–3312 sec) and in 10/38 on POD 1 with heparin infusion (range, 257û344 sec). INTEM, HEPTEM, and aPTT results during the perioperative period are presented in Table 1.

Severity of HLE based on ROTEM INTEM/HEPTEM CT ratio and aPTT ratio is presented as percentage in Figure 1. INTEM/HEPTEM CT ratio was only able to detect severe forms of HLE during the anhepatic or post-reperfusion phase, but variable degrees of HLE were detected by both aPTT ratio and INTEM/HEPTEM CT ratio. Figure 2 shows the individual course of the INTEM/HEPTEM CT ratio during the perioperative period in all 38 patients included in this study. There was no significant correlation between aPTT ratio and INTEM/HEPTEM CT ratio ($n = 266$), Pearson correlation $r = 0.048$, and $P = 0.440$. A weak correlation existed between aPTT and INTEM CT ($r = 0.16$, $P = 0.006$) and between aPTT and INTEM/HEPTEM CT ratio ($r = 0.15$, $P < 0.001$). A strong positive linear correlation existed between INTEM CT and HEPTEM CT ($r = 0.96$, $P < 0.001$). There was a fair aPTT and INTEM CT for overall agreement between diagnosis of HLE ($\kappa = 0.29$, $P < 0.001$) with a fair degree of reliability. The average measured intra-class correlation (ICC) coefficient was 0.455 with a 95% confidence interval (CI) from 0.306 to 0.572 ($P < 0.001$). Both aPTT and INTEM CT have negative agreement (89.4%) for HLE with an ICC of 0.45, 95% CI of 0.30–0.57 ($P < 0.01$). The impact of HLE on transfusion requirements and patient outcomes are displayed in

Table 1: INTEM, HEPTEM, and aPTT results (mean±SD and reference ranges (RR)) during the perioperative period

Mean±SD (Reference range)	Preoperative	Dissection phase	Anhepatic phase	Postreperfusion	POD1	POD3	POD7
INTEM CT in s (RR, 110-240 s)	171.3±32.3	169.1±35.1	292.5±327.4	487.9±710.5	248.8#±54.3	195.7±50.2	174.5±32.0
INTEM CFT in s (RR, 30-110 s)	246.9±137.6	255.5±96.0	318.8±137.9	245.1±145.8	255.4±130.8	266.3±143.8	223.3±169.6
INTEM MCF in mm (RR, 50-72 mm)	39.8±7.4	38.7±7.5	35.9±6.4#	37.6±6.0	38.8±8.6	43.7±9.2	43.6±11.9
HEPTEM CT in s (RR, 100-240 s)	186.2±88.8	155.8±31.6	178.9±48.1	212.8±57.4	212.0±41.0	174.1±31.7	152.1±25.6
HEPTEM CFT in s (RR, 30-110 s)	214.7±153.1	207.5±69.9	238.2±97.7	234.9±146.8	231.6±105.3	226.4±124.4	199.8±133.9
HEPTEM MCF in mm (RR, 50-72 mm)	40.1±12.6	43.3±7.5	39.9±6.9	39.1±7.1	38.8±9.4	47.3±11.6	49.1#±9.0
INTEM/HEPTEM CT ratio	1.00±0.18	1.09±0.14	1.57±1.52	2.17±3.02	1.18±0.21	1.13±0.24	1.15±0.12
aPTT in s (RR, 30-45 s)	37.6±6.7	36.5±2.6	39.3±5.6	51.0±13.6	52.3±16.6	48.1±17.3	41.3±9.0
aPTT ratio	1.08±0.19	1.04±0.07	1.12±0.16	1.46±0.39	1.50±0.47	1.37±0.49	1.18±0.26

aPTT: activated partial thromboplastin time; CFT: clot formation time; CT: coagulation time; MCF: maximum clot firmness; #: Pairwise comparison (significance compared with preoperative values)

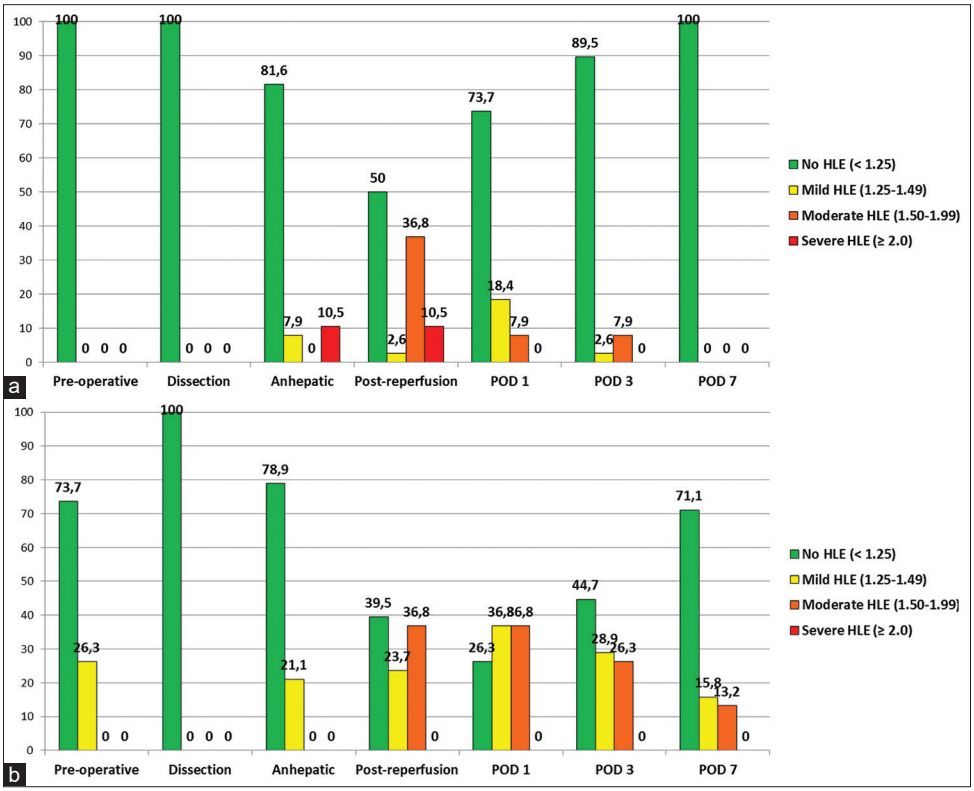

Figure 1: a) Incidence (%) and severity of HLE as detected by INTEM/HEPTEM CT ratio during and after liver transplantation. b) Incidence (%) and severity of HLE as detected by aPTT ratio during and after liver transplantation. aPTT = activated partial thromboplastin time; CT = coagulation time; HLE = heparin-like effect

Table 2. Ten out of 38 recipients (26.3%) required no packed red blood cells (RBCs). Plasma transfusion was required in 17/38 patients (4.35 ± 1.58 units) and cryoprecipitate was administered to 9/38 recipients (11.22 ± 6.16 units). None of the 38 patients required platelet transfusion. Severe HLE ($n = 6$) was associated with increased transfusion requirements for RBCs and plasma. Overall complication rates for reoperation, biliary leakage, cerebral encephalopathy, nosocomial infections, liver graft rejection, and any other complication was 6/38 (15.8%), 3/38 (7.9%), 2/38 (5.3%), 2/38 (5.3%), 1/38 (2.6%), and 13/38 (34.2%), respectively. Overall three-month mortality was 8/38 (21.1%), and three-month mortality for no HLE, mild-to-moderate HLE, and severe HLE was 3/18 (16.7%), 3/14 (21.4%), and 2/6 (33.3%), respectively. Accordingly, overall composite adverse outcome of any complication or death within three months after liver transplantation was 15/38 (39.5%), and composite adverse outcome for no HLE, mild-to-moderate HLE, and severe HLE was 5/18 (27.8%), 6/14 (42.9%). and 4/6 (66.7%), respectively.

Discussion

HLEs during liver transplantation were first reported by Kang *et al.* in 1985.[15] Later in 1998, Kettner *et al.*[16] demonstrated

Table 2: Impact of HLE (as assessed by INTEM/HEPTEM CT ratio) at any time during the perioperative period (from preoperative until POD7) on transfusion requirements and patient outcomes

Mean±SD (Reference range)	Pre-operative	Dissection phase	Anhepatic phase	Postreperfusion	POD1	POD3	POD7
INTEM CT in s (RR, 11-240 s)	171.3±32.3	169.1±35.1	292.5±327.4	487.9±710.5	248.8#±54.3	195.7±50.2	174.5±32.0
INTEM CFT in s (RR, 30-110 s)	246.9±137.6	255.5±96.0	318.8±137.9	245.1±145.8	255.4±130.8	266.3±143.8	223.3±169.6
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HEPTEM CFT in s (RR, 30-110 s)	214.7±153.1	207.5±69.9	238.2±97.7	234.9±146.8	231.6±105.3	226.4±124.4	199.8±133.9
HEPTEM MCF in mm (RR, 50-72 mm)	40.1±12.6	43.3±7.5	39.9±6.9	39.1±7.1	38.8±9.4	47.3±11.6	49.1#±9.0
INTEM/HEPTEM CT ratio	1.00±0.18	1.09±0.14	1.57±1.52	2.17±3.02	1.18±0.21	1.13±0.24	1.15±0.12
aPTT in s (RR, 30-45 s)	37.6±6.7	36.5±2.6	39.3±5.6	51.0±13.6	52.3±16.6	48.1±17.3	41.3±9.0
aPTT ratio	1.08±0.19	1.04±0.07	1.12±0.16	1.46±0.39	1.50±0.47	1.37±0.49	1.18±0.26

*CT: coagulation time; HLE: heparin-like effect; IQR: interquartile range; POD: postoperative day; RBC: red blood cells; F: Repeated measure analysis; W Welch correction; *: significance level P<0.05*

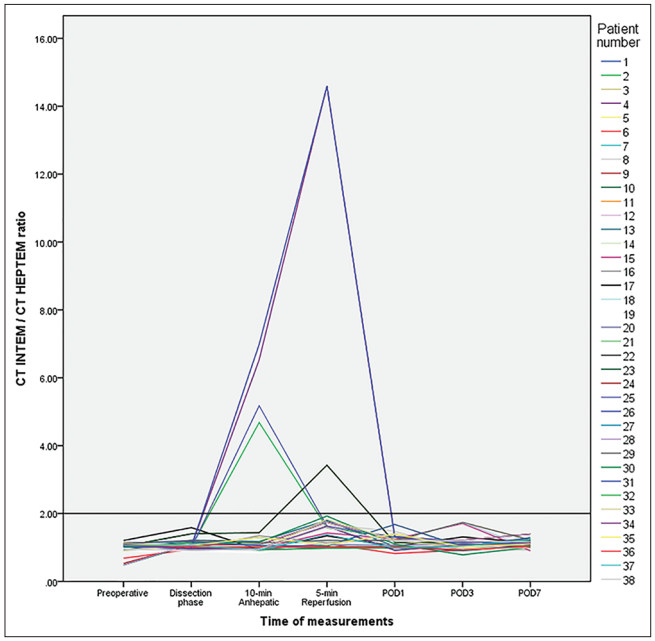

Figure 2: Individual course of the INTEM/HEPTEM CT ratio during the perioperative period in all 38 patients included in the study. Notably, there is a misleading visual impression that the number of cases with severe HLE is only five instead of effectively six since the values for case number 9 and 23 are very similar. CT = coagulation time; HLE = heparin-like effect

that HLEs were present among patients suffering from fulminate hepatic failure to a variable extent already prior to liver graft reperfusion when comparing thromboelastography (TEG) results from celite-activated and celite-activated plus heparinase tests. Here, they observed that HLEs prior to reperfusion were less frequent than after reperfusion. Only 12% of their patients had severe HLE prior to reperfusion similar to our results (10.5%), whereas severe HLEs were observed in 39% of their recipients after reperfusion in contrast to only 10.5% in our population. This may be based on the high incidence of fulminant liver failure in their study population.

Definitions of HLE vary from study to study. Kettner *et al.* described the HLE as the difference between *r*-values with and without heparinase on TEG. In our study, HLE was defined as an INTEM/HEPTEM CT ratio of ≥1.25. This definition is in line with the definition used by Mittermayr *et al.*[8] and Ichikawa *et al.*[9] Notably, Ichikawa *et al.* demonstrated that INTEM/HEPTEM CT ratio provided a much better correlation to the heparin concentration as assessed by anti-Xa activity ($r = 0.72$) compared to aPTT ($r = 0.36$) or ACT ($r = 0.12$).

The results of this trial demonstrate the ability of the INTEM/HEPTEM CT ratio to detect and to quantify HLE during and after liver transplantation. Here, the HLE cannot be mediated by reperfusion of the liver graft only, since a severe HLE was already evident in 10.5% of the recipients during the anhepatic phase. Therefore, other mechanisms have to be considered, too. On the one hand, HLE could be derived from an exogenous source; for example, as a result of the routine administration of 1000 IU UFH intravenously immediately prior to clamping of the donor hepatic vessels, as practiced in our transplant center. On the other hand, endogenous heparinoids could be released from activated mast cells and macrophages as well as from the endothelial glycocalyx due to systemic shock or visceral ischemia during the anhepatic phase.[5] In order to avoid a washout of heparinoids from the liver graft during reperfusion, the liver graft was flushed with 500 ml of 4.5% albumin prior to completion of the venous anastomoses. This was adopted in the current trial and was routinely practiced for every donor liver graft by our team.

The HLE detected on POD1 and 3 by INTEM/HEPTEM CT ratio as well as aPTT-ratio can be considered as a result of the postoperative intravenous infusion of UFH (60–180 U/kg/day), as routinely practiced in our ICU. Accordingly, INTEM CT and INTEM/HEPTEM CT ratio can be used to monitor the effect of UFH in critically ill patients.[9,17] In contrast, no HLE could be detected by INTEM/HEPTEM CT ratio with subcutaneously administered LMWH (20 mg/12 h)

on POD3.[18,19] However, recognition of patients with severe HLE helped to identify recipients with a high complication rate and mortality.[20,21]

The clinical relevance of HLEs and its association with increased blood loss during transplantation is still on debate. Our study showed that patients with severe HLE based on INTEM/HEPTEM CT ratio had significantly higher RBC and plasma transfusion requirements. However, it is still unclear whether the severe HLE during the anhepatic phase is caused by severe blood loss and hemorrhagic shock with subsequent damage of the endothelial glycocalyx or vice versa. Since HLEs have not been treated with protamine in our study, it is still unclear whether this is beneficial, but may be considered in severe HLE since severe HLE was also associated with an increased incidence of adverse events as well as increased three-month mortality.[7] Accordingly, some authors reported the use of protamine to reverse the HLE during liver transplantation.[3,6,10,15,22,23] On the other hand, mild-to-moderate HLEs after liver graft reperfusion have been reported to be self-limiting and not requiring specific treatment.[3,4]

Two authors even report the presence of HLE before surgical incision in recipients with acute liver failure and urgently listed patients with primary non-functioning grafts.[6,19] However, none of our 38 patients demonstrated any HLE prior to surgery, may be due to the elective nature of the LDLT procedure and due to the sample size of our study. Accordingly, a baseline ROTEM analysis might be advisable in patients with acute or acute-on-chronic liver failure or urgent liver transplantation.

Despite improvements in liver transplant surgery as well as coagulation monitoring and management, thromboembolic complications are still contributing to morbidity and mortality.[24] De Pietri *et al*.[25] reported recently that the bleeding tendency in cirrhotic patients is not only an expression of an acquired bleeding disorder, but could also be based on other factors such as portal hypertension, hypervolemia, and infections. Bacterial infections have been postulated as a trigger for variceal bleeding in cirrhotic patients, and for the impairment in coagulation as evaluated by viscoelastic testing. Accordingly, endogenous heparinoids have been detected in cirrhotic patients with infection and variceal bleeding. Montalto *et al*.[26] demonstrated significant HLEs by TEG only in infected cirrhotics (28/30) but not in non-infected (28/30 vs 0/30; $P = 0.0003$). Accordingly, Zambruni *et al*.[27] detected anti-Xa activity in 9/15 (60%) infected cirrhotics and only in 1/15 (6.7%) non-infected cirrhotic. In between, HLEs could be verified in other clinical settings such as trauma and postpartum hemorrhage too.[28,29] Notably, Shimauchi *et al*.[30] reported that fibrinolysis developed during the dissection phase was associated with increased 30-day and 6-month mortality but fibrinolysis in the post-reperfusion phase was not. Portal vein and hepatic artery thrombosis was also more common in patients with fibrinolysis and tranexamic acid treatment in the post-reperfusion phase. Since severe HLEs in the anhepatic and post-reperfusion phase were associated with an increased incidence of adverse events and increased three-month mortality, HLEs and hyperfibrinolysis should be assessed by viscoelastic testing during and after liver transplantation.

It is important to understand that the balance of hemostasis can shift quickly between hypo- and hypercoagulability in any recipient, particularly in the postoperative period, as demonstrated by Kamel *et al*.[19] This encourages considering the need for anticoagulants or antiplatelet drugs in the postoperative period of liver transplantation. A multimodal monitoring approach depending on clinical judgement, standard coagulation tests, and thromboelastometry is essential for monitoring and guiding coagulation management.

This study has several limitations. It focused on the ROTEM assays INTEM and HEPTEM only, and did not include any clot firmness and fibrinolysis parameters. Second, anti-Xa activity was not included in the study to assess HLEs. However, the authors think that this study provides important information on the incidence and severity grades of HLEs during and after liver transplantation and its effect on patient outcomes.

In conclusion HLEs during and after liver transplantation can be detected and quantified reliably by INTEM/HEPTEM CT ratio as aPTT ratio despite lack of correlation. The ability of the INTEM/HEPTEM CT ratio to identify severe HLE earlier in the anhepatic phase needs to be studied in a larger population. HLEs are often self-limiting during liver transplantation, but when identified in a severe form as by the INTEM/HEPTEM CT ratio, it is associated with increased transfusion requirements, worse patient outcomes, and high three-month mortality.

IRB number

Local ethics committee approval of Faculty of Medicine, Menoufia University, Egypt dated 6 September 2015.

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Conflicts of interest

KG works as the Medical Director of Tem Innovations GmbH, Munich, Germany since July 2012. All other authors reported no potential conflict of interest relevant to this article.

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