GLOBAL SCIENCE LIBRARY

Frontiers in Transplantation

RESEARCH ARTICLE

Thromboelastometry analysis of the heparin-like effect in the intra-operative period of orthotopic liver transplantation: An observational clinical trial

Camila de Souza Barros[1], Amanda Lopes de Castro[1], Rogean Rodrigues Nunes[1], Nathalia Krishna Pereira Fontenele[1], Juliane Sampaio do Vale[1], Nely Marjollie Guanabara Teixeira Reis[1], Germano Pinheiro Medeiros[1] and José Carlos Rodrigues Nascimento[1,2]*

[1]*Department of Anesthesia and Liver Transplantation, Fortaleza General Hospital, Brazil*

[2]*Institute of Health Sciences, Department of Medicine, University of International Integration of Afro-Brazilian Lusophony, Brazil*

Abstract

Introduction: Orthotopic liver transplant (OLT) can be followed by significant coagulopathy and the heparin-like effect (HLE). However, as the HLE may lead to important changes in blood coagulation, the objective of this study was to assess the prevalence of HLE in a cohort of patients undergoing liver transplantation.

Materials and methods: This was a observational study including 50 patients ≥ 18 years of age who were submitted to OLT and monitored using ROTEM® *delta*, including 36 patients with altered INTEM coagulation time (CT) and 14 patients with normal INTEM CT. Samples were collected during the procedure to analyse the HLE.

Results: Mild to moderate HLE was observed in 34% (17/50) of patients during surgery. Severe HLE was observed 10% (5/50) during surgery. Total 1-year survival was 80% (40/50) and mortality, 20% (10/50) (4% (2/5) with severe HLE in at NP; 5.9% (1/17) with mild/moderate HLE in OS and in at NP, respectively, and in 11.8% (2/17) at AP, died 1-month postoperative). The transfusion of patients with severe HLE was (median [IQR]: red blood cells 3 [0.5-9.2] units), and those with mild/moderate HLE was (median [IQR]: red blood cells 1 [0.0 -2.0] and cryoprecipitate 10 [9.0-15.0] units). In the INTEM CT analysis, the average neohepatic phase (327.9 ± 161.1 s) was significantly prolonged when compared to OS (266.5 ± 134.4 s) and AP (253.02 ± 75.4 s); P = 0.013, respectively.

Conclusion: The prevalence of HLE was considerable in neohepatic phase. In severe HLE, a high risk of mortality was identified in the neohepatic phase and a higher frequency of transfusion of red blood cells regardless of the surgical phase.

Keywords: *liver transplantation, tromboelastometry, heparin-Like effect, coagulation*

Abbreviations: *OLT: Orthotopic liver transplant, HLE: Heparin-like effect, CT: Coagulation time, FFP: Fresh Frozen Plasma, CLT: Conventional laboratory tests, TEG®: Thromboelastography, ROTEM®: Rotational thromboelastometry, ESA: European Society of Anaesthesia, REC: Research Ethics Committee, Hb: Hemoglobin*

Introduction

Orthotopic liver transplantation (OLT) remains the therapy of choice for patients with end-stage decompensated liver disease [1]. However, this procedure may be accompanied by severe bleeding, which occurs due to hyperfibrinolysis, collateral circulation resulting from portal hypertension, haemodilution, consumption of factors, and the heparin-like effect (HLE) [2-4]. OLT has been previously associated with massive transfusion of blood derivatives. In recent years, there has been a progressive reduction of perioperative blood loss due to advances in anaesthetic management and coagulation monitoring in general [5].

HLE has been described in different clinical settings, including transplantation, infection-associated liver disease and metastasis [6,7]. Additionally, HLE is generally attributed to natural circulating anticoagulants such as glycosaminoglycans (GAGs), primarily dermatan sulphate and heparan sulphate, which are normally bound to the endothelium and can be released by endothelial damage and result in coagulopathy during OLT, mainly in the post reperfusion phase. In addition, there may also be exogenous heparin, such as residual heparin from heparinisation of the donor graft, and/or endogenous heparin [6-9].

Previous investigations have suggested some mechanisms that can lead to the appearance of HLE in the circulation, such as: lesions carried by neutrophils of the hepatocytes that can release heparan sulphate; reduced clearance of circulating GAGs during acute liver failure; and the direct release of GAGs from the endothelial surface and mast cells during the acute phase response. However, the best approach for therapeutic management in the context of bleeding-associated HLE is not yet clear [9].

Coagulation tests are designed to investigate specific steps in the coagulation cascade. However, conventional laboratory tests (CLT) examine only limited aspects of the cascade and are generally not available in a timely manner. Viscoelastic tests such as thromboelastography (TEG®) and rotational thromboelastometry (ROTEM® *delta*. Pentapharm GmbH, Munich, Germany) differ from CLT because they are point-of-care tests, which analyse the elastic variation of the blood clot during its formation and thus allow a wide evaluation of coagulation in real time [10,11]. The perioperative management of coagulation using TEG®/ROTEM® *delta* for targeted management of coagulopathy in OLT now forms part of the European Society of Anaesthesia (ESA) guidelines for the management of massive bleeding [12].

As HLE can lead to important changes in blood coagulation during OLT, and there are few studies addressing the prevalence of HLE in this population, we propose to carry out this research to determine the prevalence of HLE in 50 consecutive patients during the phases of OLT (pre-anhepatic, anhepatic and neohepatic), through the analysis of thromboelastometry (INTEM/HEPTEM), and also to investigate the frequency of transfusion of blood products among patients who did and did not develop HLE.

Materials and methods

Participation and study design

This prospective observational study is a follow-up of a study previously approved by the Research Ethics Committee (REC) of the General Hospital Fortaleza, in accordance with opinion number 794.061. Because this study did not involve new sample collection, costs, constraints or risks for the research subjects, no new submission

to the REC was required. Informed written consent was obtained from enrolled patients or their caregivers.

The study included 50 patients ≥ 18 years of age, of both genders, who were submitted to OLT under general anaesthesia using the *Piggyback* technique, which uses only partial or lateral clamping of the inferior vena cava, with preservation of blood flow in the vena cava, which results in less hemodynamic compromise [1], and monitored using ROTEM® *delta* between October 2014 and December 2017. Patients who died during the intraoperative period and those with incomplete data were excluded from the study.

Timepoints of blood collection

During the surgical procedure, blood samples were taken hourly for blood gas analysis and at three times for thromboelastometry: after arterial puncture and before skin incision at the onset of surgery (OS), at the beginning of the anastomosis of the vena cava in the anhepatic phase (AP), and at the beginning of the anastomosis of the bile ducts in the neohepatic phase (NP). When intervention was required, additional blood samples were collected 10 minutes after each intervention.

Blood collection technique

The blood collection for dosing of thromboelastometry samples and laboratory tests was performed by the investigator responsible through the arterial catheter (radial artery), using 10 mL disposable syringes, using the two-syringe method without heparin. In this method, the first sample of 10 mL of collected blood was discarded in order to avoid haemodilution, and the second sample after the procedure was used for analysis of thromboelastometry and or gasometry.

Thromboelastometry analysis and reagents used

Blood was collected for analysis of fibrinolysis and coagulation disorders using the thromboelastometry assays EXTEM and INTEM, with the following parameters: clotting time (CT), clot formation time (CFT), alpha angle (α), and maximum clot firmness (MCF); EXTEM and APTEM: maximal lysis in 60 minutes; FIBTEM: amplitude in 10 minutes (A10) and MCF; HEPTEM (CT) and the CT_{HEPTEM}/CT_{INTEM} ratio was also calculated.

HLE was detected when CT INTEM was > 240 sec and CT $_{HEPTEM}$/ CT $_{INTEM}$ ratio ≤ 0,8. For the analysis of the effects of heparin and/or heparinoids, patients were divided into three groups: INTEM CT normal group (CT_{HEPTEM}/CT_{INTEM} ratio > 0.8), mild/moderate (CT_{HEPTEM}/CT_{INTEM} ratio ≤ 0.8 > 0.5) and severe HLE (CT_{HEPTEM}/CT_{INTEM} ratio ≤ 0.5) [13].

Non-disposable reagents were used as a tissue factor activator for EXTEM; ellagic-acid/phospholipid activator for INTEM; heparinase in combination with INTEM for HEPTEM; cytochalasin D in combination with EXTEM for FIBTEM; and aprotinin, fibrinolysis inhibitor in combination with EXTEM for APTEM [14].

Protocol parameters and haemostasis support

The ROTEM results were compared with normal values and, if required corrections, along with the clinical diagnosis of hypocoagulation, fibrinolysis, presence of heparin and/or heparinoid action, and presence of microvascular bleeding, corrections were made from according to the haemostasis protocol (Table 1). During surgery, the objective was to maintain pH ≥ 7.3, temperature ≥ 35.5 °C, ionic calcium ≥ 1.1 mmol/L and haemoglobin (Hb) ≥ 8 g/dL. The stabilisation of these basic conditions is essential, as they have an important influence on haemostasis and can lead to clinically relevant dysfunctions of the coagulation system.

Statistical analysis

At the end of the study, the data were organised into a database and analysed. Normality was assessed using the D'Agostino & Pearson, Kolmogorov-Smirnov and Shapiro-Wilk tests. The mean ± standard deviation (SD) was calculated for the non-parametric data using the Mann-Whitney and Kruskall Wallis tests, in association with Dunn's test for multiple comparisons. Frequencies were compared using Cochran's test and Fisher's exact test was used for the categorical variables. The mean ± SD were calculated for the parametric data using the Friedman test for multiple comparisons. A value of $P < 0.05$ was considered significant. The analyses were carried out using R 3.3.1.

Results

During the study period, 72 patients undergoing OLT were monitored using ROTEM® delta during the intraoperative period, with 22 patients being excluded due to the following criteria: transoperative death or the absence of complete data. 50 patients included, of which 20/50 (40%) females and 30/50 (60%) males. Median [IQR]: (age 53.5 [45.5 – 59] years), (weight 68.5 [59.5 – 80] kg), [preoperative MELD score 22 (20 - 26.5)] and (operation duration 307.5 [300 – 360] min). As for the etiology: 26% of patients had hepatocarcinoma and/or hepatitis C, 24% had alcoholic cirrhosis, 18% had autoimmune cirrhosis, primary biliary cirrhosis or primary sclerosing cholangitis, 12% had cryptogenic cirrhosis, 12% had primary graft dysfunction retransplantation and hepatic artery thrombosis retransplantation, 8% had schistosomiasis, thrombosis of the portal vein and non-alcoholic steatohepatitis cirrhosis (Table 2).

Mild to moderate HLE was observed in 34% (17/50) of patients during surgery, with 8% (4/50) during OS, in 10% (5/50) at AP and in

Table 1: Protocol for treatment of coagulation disorders during orthotopic liver transplantation

• EXTEM CT > 80-100 s. • PT > 1.5 X normal; INR > 1.5.	↓ Coagulation Factors	**ROTEM®**	**Coagulopathy**	**Treatment Options**
• EXTEM A10 < 40 mm or MCF < 45 mm, FIBTEM normal. • Platelets < 50.000/mm³.	↓ Platelets	Platelets: 1unit for each 7 to 10 kg or 1 apheresis or 1 buffy coat.		
• EXTEM A10 < 40 mm or MCF < 45 mm, FIBTEM MCF < 9 mm. • Fibrinogen < 1.5-2.0 g/L.	↓ Fibrinogen	• FC: 25-60 mg/kg or 2-4 g; CRYO: 1 unit / 5-10 kg. • ROTEM®: Fibrinogen (g) = MCF ΔFIBTEM (mm) x weight (kg)/140 • Plasma concentration: Fibrinogen (g) = ΔFibrinogen (g/L) x weght (kg)/140.		
• INTEM CT > 240s and CT_{HEPTEM} / CT_{INTEM} ratio < 0.8.	Heparin	Protamine: 50-100mg		
• INTEM CT > 240s and CT_{HEPTEM} / CT_{INTEM} ratio ≥ 0.8. • aPTT > 1.5 X normal.	↓ Plasma factors	FFP: 15 a 20 ml/kg		
• EXTEM ML > 15% and APTEM ML < 15%.	Hyperfibrinolysis	EACA: 50 mg/kg		

OLT: Orthotopic Liver Transplantation, CT: Clotting Time, PT/INR: Prothrombin Time/International Normalized Ratio, A10: amplitude of clot firmness 10 min after clotting time, MCF: maximum clot firmness, aPTT: Activated Partial Thromboplastin Time, ML: Maximum Lysis in 60 minutes, PCC: Prothrombin Complex Concentrate, IU: International Unit, FFP: Fresh Frozen Plasma, FC: Fibrinogen Concentrate, CRYO: Cryoprecipitate, EACA: Epsilon Aminocaproic Acid.

Protocol for coagulation management in liver transplantation of the General Hospital of Fortaleza, Brazil. Adapted from Kozek-Langenecker et al. [15], Carvalho et al. [16] and Görlinger et al. [17].

Table 2: Demographic and surgical profile of the patients studied

Variables	Patients (n=50)
Age (year), median (p25-p75)	53.5 (45.5 - 59)
Gender, n (%)	
Female	20 (40%)
Male	30 (60%)
Weight (kg), median (p25-p75)	68.5 (59.5 - 80)
MELD score, median (p25-p75)	22 (20 - 26.5)
Surgical time (min), median (p25-p75)	307.5 (300 - 360)
Causes, n (%)	
Alcoholic cirrhosis	12 (24%)
Cryptogenic cirrhosis	6 (12%)
Schistosomiasis	2 (4%)
HCV and / or HCC	13 (26%)
Autoimmune cirrhosis or PBC or PSC	9 (18%)
Cirrhosis by NASH	1 (2%)
Retransplantation due to primary graft dysfunction	3 (6%)
Portal vein thrombosis	1 (2%)
Retransplantation for hepatic artery thrombosis	3 (6%)
Blood Group, n (%)	
A	17 (34%)
B	8 (16%)
O	25 (50%)

MELD: Model For End-Stage Liver Disease, HCV, Hepatitis C Virus, HCC: Hepatocellular Carcinoma, PBC: Primary Biliary Cirrhosis, PSC: Primary Sclerosing Cholangitis, NASH: Nonalcoholic Steatohepatitis

Table 3: Analysis of the parameters of the INTEM and HEPTEM in the orthotopic liver transplantation phases

ROTEM®	**Onset of surgery mean ± SD**	**Anhepatic phase mean ± SD**	**Neohepatic phase mean ± SD**	***P* Value**
INTEM CT (100-240 s)	266.5 ± 134.4	253.02 ± 75.4[a]	327.9 ± 161.1[a]	**0.013***
HEPTEM CT (100-240 s)	256.5 ± 60.1	237.6 ± 49.9	274.9 ± 92.1	0.429

[a]Anhepatic phase vs. neohepatic phase, *P*=0.017
CT: Coagulation Time

Table 4: Frequency of use of protamine in the orthotopic liver transplantation phases

Use of Protamine	n (%)	*P* Value
Onset of Surgery	4 (6.2)	0.348
Anahepatic Phase	6 (9.2)	
Neohepatic Phase	9 (13.8)	

Cochran's q test, $P < 0.05$.

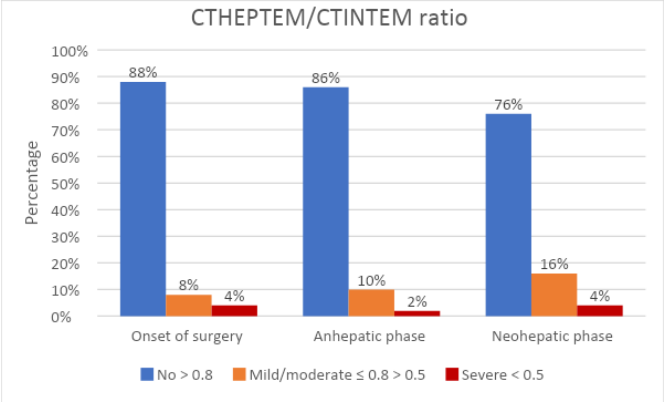

Figure 1: Grades and percentages of heparin-like effect

16% (8/50) at NP, one patient with mild/moderate HLE observed during OS and another during AP continued to demonstrate HLE during NP. Severe HLE was observed 10% (5/50) during surgery, with 2% (1/50) during AP, in 4% (2/50) at OS and in at NP, respectively. One patient with severe HLE observed during OS continued to demonstrate HLE during AP, although it disappeared in NP. Grades and percentages of HLE are presented in the (Figure 1). Total 1-year survival was 80% (40/50) and mortality, 20% (10/50) (4% (2/5) with severe HLE in at NP, died 1-month postoperative by septic shock; 5.9% (1/17) with mild/moderate HLE in OS and in at NP, respectively, and in 11.8% (2/17) at AP, died 1-month postoperative). No blood was transfused in 12% (6/50) during surgery. The transfusion of patients with severe HLE was (median [IQR]: red blood cells 3 [0.5-9.2] units), and those with mild/moderate HLE was (median [IQR]: red blood cells 1 [0.0 -2.0] and cryoprecipitate 10 [9.0-15.0] units).

In the INTEM CT analysis, the average neohepatic phase (327.9 ± 161.1 s) was significantly prolonged when compared to OS (266.5 ± 134.4 s) and AP (253.02 ± 75.4 s); $P = 0.013$, respectively (Table 3). There was protamine administration in 6.2% of the patients at the OS, 9.2% of the patients in the AP and 13.8% of the patients in the NP. The comparative analysis of the frequency at the three timepoints showed no significant difference (Table 4).

Discussion

Severe coagulopathy, especially after graft reperfusion, is frequent in OLT. The causes associated with the change in coagulation that accompanies reperfusion are marked by disseminated intravascular coagulation, platelet activation, hyperfibrinolysis, presence of HLE, platelet entrapment in the graft, and reduction of coagulation factors by bleeding and hemodilution [18].

ROTEM® *delta* has been shown to be a useful monitoring method for assessing coagulation abnormalities during OLT. The addition of heparinase I, an enzyme that cleaves heparin and compounds similar to heparin, using in vitro whole blood samples in the HEPTEM assay, is able to identify the presence of HLE during OLT. This provides important information about coagulopathy arising from the presence of heparin or substances similar to heparin [8,9,19]. A previous study has shown that modified thromboelastography with heparinase-I is capable of diagnosing anticoagulant activity of glycosaminoglycans (heparan sulphate and dermatan sulphate), which could be responsible for the HLE present in cirrhotic patients with sepsis [20].

We found HLE in 44% of patients during OLT, with 4 % severe HLE being present in the NP. In contrast, Agarwal et al [21]. identified HLE in 75%, which was severe in 39% of subjects after reperfusion. Other authors also identified higher HLE after in-OLT reperfusion, which regressed at the end of the surgery [22]. Previous reports have shown that the prevalence of HLE after reperfusion ranged from 75% to 93% of patients [19,23]. Total 3-month survival (80%) and mortality (20%), as well as mortality from severe HLE in NP were similar to the findings of Yassen et al. [13].

Differing from our findings, Senzolo et al [7]. identified a significantly higher presence of HLE in patients with acute liver failure at the beginning of liver transplantation when compared to those with liver cirrhosis. However, this effect was similar in both groups after reperfusion.

In OLT, the origin of the HLE is multifactorial, and infected patients may present greater release of HLE substances into the systemic circulation due to neutrophil-mediated inflammatory injury of the hepatocytes and endothelial cells [18,24]. There are also exogenous sources of heparin from the infusion of 400 IU/kg of intravenous heparin before cannulation of the arterial and venous vessels of the donor [25], exogenous heparin present in the graft preservation fluid, and irrigation of the surgical site with heparinised solutions during vascular anastomoses by the surgical team. Associated therewith, the resulting endogenous heparin of the donor ischemic endothelium may also be released into the recipient's bloodstream during the reperfusion phase [18,25]. Thus, although in our service the graft is irrigated with 1500–2000 mL of 2% albuminated lactated ringer serum prior to portal vein anastomosis, some patients had a residual effect of heparin on ROTEM® *delta*, mainly after reperfusion in the neohepatic phase.

According to our findings, Gouvêa et al. [26] identified the frequency of protamine administration as being higher in the post-reperfusion phase of the liver graft, but without significant difference.

Also, similar to our findings, previous studies have documented reverse HLE in patients with liver cirrhosis OLT after administration of protamine in vivo [19,27].

In this study, a higher percentage of patients received blood when compared with the results of Yassen et al. [13]. during surgery. On the other hand, corroborating with these authors, those with severe HLE received more red blood cells. Furthermore, our worst mortality outcome in severe HLE was within the 1-month period in NP.

Limitations of the present study include the observational nature of the research and the small sample, which imposes limitations on the results. Thus, it is of fundamental importance to carry out future prospective and randomised studies with a larger sample in order to verify the real impact of the HLE on haemostatic disorder during OLT.

Conclusion

We conclude that the prevalence of HLE was considerable in neohepatic phase. In severe HLE, a high risk of mortality was identified in the neohepatic phase and a higher frequency of transfusion of red blood cells regardless of the surgical phase. Thus, it is of fundamental importance to carry out future prospective and randomised studies with a larger sample in order to verify the real impact of the HLE on haemostatic disorder during OLT.

Contribution of authors: J.C.R.N. contributed to the study design, data collection and supervised the study; J.C.R.N. and C.S.B. data analysis and interpretation of data; J.C.R.N., C.S.B., G.P.M., A.L.C., N.K.P.F., J.S.V., R.R.N., and N.M.G.T.R., contributed in writing of the manuscript and revision of the manuscript for important intellectual content.

Acknowledgements: This work was supported by Ceara School of Public Health.

References

1. Hall TH, Dhir A. Anesthesia for liver transplantation. *Semin Cardiothorac Vasc Anesth*. 2013; 17: 180-194.
2. Junior RFM, Salvalaggio P, Rezende MB. Transplante de fígado: história, resultados e perspectivas. *Einstein.* 2015; 13: 149-152.
3. Saner FH, Gieseler RK, Akız H, Canbay A, Görlinger K. Delicate Balance of Bleeding and Thrombosis in End-Stage Liver Disease and Liver Transplantation. *Digestion*. 2013; 88: 135-144.
4. Port RJ, Molenaar IQ, Begliomini B, Groenland TH, Januszkiewicz A, et al. Aprotinin and transfusion requirements in orthotopic liver transplantation: a multicentre randomised double-blind study. *Lancet*. 2000; 355: 1303-1309.
5. Nascimento JCR, Neto EBL, da Silva EL, Nunes RR, Marinho DS, et al. Analysis of the hemostatic therapy in liver transplantation guided by rotational thromboelastometry or conventional laboratory tests. *Eur J Gastroenterol Hepatol*. 2020; 32: 1452-1457.
6. Premkumar M, Bihari C, Saxena P, Devurgowda DR, Vyas T, et al. Heparin-like effect associated with risk of bleeding, sepsis, and death in patients with severe alcohol-associated hepatitis. *Clin Gastroenterol Hepatol*. 2020; 18: 486-495.
7. Senzolo M, Agarwal S, Zappoli P, Vibhakorn S, Mallett S. Heparin-like effect contributes to the coagulopathy in patients with acute liver failure undergoing liver transplantation. *Liver Int*. 2009; 29: 754-759.
8. Agarwal A, Sharma N, Vij V. Point-of-care coagulation monitoring during liver transplantation. *Trends in Anaesthesia and Critical Care.* 2013; 3: 42.
9. Yu Y, Bruzdoski K, Kostousov V, Hensch L, Hui SK, et al. Structural characterization of a clinically described heparin-like substance in plasma causing bleeding. *Carbohydr Polym*. 2020; 244: 116443.
10. Song AT, Avelino-Silva VI, Pecora RA, Pugliese V, D'Albuquerque LA, et al. Liver transplantation: fifty years of experience. *World J Gastroenterol.* 2014; 20: 5363-5374.
11. Kamel Y, Hassanin A, Ahmed AR, Gad E, Afifi M, et al. Perioperative Thromboelastometry for Adult Living Donor Liver Transplant Recipients with a Tendency to Hypercoagulability: A Prospective Observational Cohort Study. *Transfus Med Hemother*. 2018; 45: 404-412.
12. Clevenger B, Mallett SV. Transfusion and coagulation management in liver transplantation. *World J Gastroenterol*. 2014; 20: 6146-6158.
13. Yassen K, Refaat E, Helal S, et al. Perioperative heparinase rotational thromboelastometry monitoring during and after adult living related liver transplantation. *Eur J Anaesthesiol*. 2018; 35: 286.
14. Gorlinger K, Bhardwaj V, Kapoor PM. Simulation in coagulation testing using rotational thromboelastometry: A fast emerging, reliable point of care technique. *Ann Card Anaesth*. 2016; 19: 516-520.
15. Kozek-Langenecker SA, Ahmed AB, Afshari A, Albaladejo P, Aldecoa C, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: first update 2016. *Eur J Anaesthesiol*. 2017; 34: 332-395.
16. Carvalho M, Rodrigues A, Gomes M, Carrilho A, Nunes AR, et al. Interventional algorithms for the control of coagulopathic bleeding in surgical, trauma, and postpartum settings: recommenda-tions from the share network group. *Clin Appl Thromb Hemost*. 2016; 22: 121-137.
17. Görlinger K, Pérez-Ferrer A, Dirkmann D, Saner F, Maegele M, et al. The role of evidence-based algorithms for rotational thromboelastometry-guided bleeding management. *Korean J Anesthesiol*. 2019; 72: 297-322.
18. Senzolo M, Cholongitas E, Thalheimer U, Riddell A, Agarwal S, et al. Heparin-like effect in liver disease and liver transplantation. *Clin Liver Dis*. 2009; 13: 43-53.
19. Pivalizza EG, Abramson DC, King FS Jr. Thromboelastography with heparinase in orthotopic liver transplantation. *J Cardiothorac Vasc Anesth*. 1998; 12: 305-308.
20. Senzolo M, Coppell J, Cholongitas E, Riddell A, Triantos CK, et al. The effects of glycosaminoglycans on coagulation: a thromboelastographic study. *Blood Coagul Fibrinolysis*. 2007; 18: 227-236.
21. Agarwal S, Senzolo M, Melikian C, Burroughs A, Mallett SV. The prevalence of a heparin-like effect shown on the thromboelastograph in patients undergoing liver transplantation. *Liver Transpl*. 2008; 14: 855-860.
22. Harding SA, Mallett SV, Peachey TD, Cox DJ. Use of heparinase modified thrombelastography in liver transplantation. *Br J Anaesth.* 1997; 78: 175-179.
23. Kettner SC, Gonano C, Seebach F, Sitzwohl C, Acimovic S, et al. Endogenous heparin-like substances significantly impair coagulation in patients undergoing orthotopic liver transplantation. *Anesth Analg*. 1998; 86: 691-695.
24. Dhainaut JF, Marin N, Mignon A, Vinsonneau C. Hepatic response to sepsis: interaction between coagulation and inflammatory processes. *Crit Care Med*. 2001; 29: S42-S47.
25. Pereira WA, Fernandes RC. Diretrizes básicas para captação e retirada de múltiplos órgãos e tecidos da Associação Brasileira de Transplante de Órgãos. São Paulo: ABTO; 2009.
26. Gouvêa G, Toledo R, Diaz R, Auler L, Enne M, et al. Protamine sulphate for treatment of severe post-reperfusion coagulopathy in pediatric liver transplantation. *Pediatr Transplant.* 2009; 13: 1053-1057.
27. Bayly PJ, Thick M. Reversal of post-reperfusion coagulopathy by protamine sulphate in orthotopic liver transplantation. *Br J Anaesth*. 1994; 73: 840-842.

[*] ***Correspondence:*** José Carlos Rodrigues Nascimento, PhD, Institute of Health Sciences, University of International Integration of Afro-Brazilian Lusophony, Rua José Franco de Oliveira, s/n – center, 62790970 - Redenção, CE, Brazil, Tel: +55 85 99668-8500 / +55 (85) 33326116, E-mail: jcr.nascimento@hotmail.com / jcarlos@unilab.edu.br

Received: September 29, 2022; **Accepted:** October 30, 2022; **Published:** November 04, 2022

Citation: de Souza Barros C, Lopes de Castro A, Nunes RR, Pereira Fontenele NK, Sampaio do Vale J, et al. Thromboelastometry analysis of the heparin-like effect in the intra-operative period of orthotopic liver transplantation: An observational clinical trial. *Front Transplant*. 2022; 1: 101.