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Rotational thromboelastometry (ROTEM) 24 hours post liver transplantation predicts early allograft dysfunction

Dana Tomescu[1,2], Mihai Popescu[1,2], Simona Olimpia Dima[3]

[1] *Fundeni Clinical Institute, Department of Anaesthesia and Critical Care, Bucharest, Romania*
[2] *"Carol Davila" University of Medicine and Pharmacy, Department of Anaesthesia and Critical Care*
[3] *Fundeni Clinical Institute, "Dan Setlacec" Center for General Surgery and Liver Transplantation, Bucharest, Romania*

Abstract

Early allograft dysfunction (EAD) represents one of the most common and serious complications after liver transplantation (LT).

Methods. One hundred sixty-four patients who underwent LT were prospectively included in the present study. Patient demographics, intraoperative blood loss and transfusion were recorded at the time of LT. Lactate levels were recorded during surgery and daily for the first 3 postoperative days. Standard and derived rotational thromboelastometry (ROTEM) parameters were recorded 24 hours after LT. EAD was diagnosed according to Nanashima criteria and post anaesthesia care unit length of stay was recorded.

Results. Forty-seven patients (28.6%) developed EAD. Intraoperative blood loss ($p = 0.01$), packed red blood cells ($p = 0.04$) and fresh frozen plasma ($p = 0.01$) transfusion represented intraoperative risk factors for EAD. Lactate levels were significantly higher in patients with EAD at all time points. Patients with EAD demonstrated an increased clot formation time and decreased maximum clot firmness in both intrinsically ($p < 0.01$) and extrinsically ($p < 0.01$) activated assay, a decreased thrombin potential index ($p < 0.01$), area under the curve ($p < 0.01$) and clot elasticity ($p < 0.01$) on ROTEM assay.

Conclusion. Our results show that both standard and derived ROTEM parameters may indicate early signs of graft failure and can aid in the diagnosis of EAD.

Keywords: liver transplantation, coagulation, rotational thromboelastometry, early allograft dysfunction

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Introduction

Early allograft dysfunction (EAD) represents one of the most serious and frequent graft complications after liver transplantation (LT) [1]. Recent studies have focused mainly on finding different modifiable risk factors for EAD [2]. Unfortunately, most of these factors are not modifiable. Also, due to the worldwide decrease in organ donors and an increase in the number of patients awaiting LT, there is a significant need to use low quality grafts [3] that further increases the incidence of EAD. However, once diagnosed, EAD is associated with a poorer outcome in terms of both decreased graft and patient survival [4]. Thus, an early evaluation of graft function remains a crucial issue for the management of patients with EAD and identifying those that may potentially benefit from intensive care support therapies.

Different clinical and paraclinical parameters such as grade of hepatic encephalopathy, serum transaminases, bilirubin, standard coagulation tests have been proposed for the purpose of diagnosing EAD. Based on these parameters, current definitions vary widely [5, 6] and a clear diagnosis can be made with acceptable accuracy after a prolonged period of time. This time lag, that usually ranges between 48 and 72 hours, can lead to supplemental liver grafts losses. A new liver function test, LiMAx, has been proposed for

Address for correspondence: Mihai Popescu, MD, PhD
258 Fundeni street, 2nd District
022328 Bucharest, Romania
E-mail: mihai.popescu@umfcd.ro

the diagnosis of liver dysfunction [7]. Although published data show promising results, its availability remains low.

Coagulation disorders represent one of the most early and specific signs for initial graft poor function (IGPF) [8, 9]. Based on this assumption, the aim of our study was to evaluate if coagulation kinetics, as assessed by rotational thormoboelastometry (ROTEM) 24 hours after LT, can be used in the early diagnosis of EAD. Secondary endpoints were to assess if high intraoperative blood loss and transfusion are associated with an increased risk of developing EAD and whether EAD is associated with a low lactate clearance in the early postoperative period.

Methods

The ethical approval for the present study was provided by the Ethical Committee of Fundeni Clinical Institute, Bucharest, Romania. Informed consent was obtained from all patients before the study.

Patient inclusion. We prospectively included patients undergoing deceased donor LT between January 2013 and May 2016. Exclusion criteria were: patients undergoing emergency LT or living-donor LT, patients younger than 18 years, need of pro-coagulant interventions (blood compounds or fibrinogen concentrate transfusion, prothrombin complex, antifibrinolytic therapy) within the first 24 hours after LT, need for anticoagulant therapy other than standard prophylaxis, need for surgical re-intervention for bleeding or other immediate surgical complications and severe complications such as sepsis, ARDS and primary graft non-function.

Anaesthetic and perioperative management. All patients underwent LT under general anaesthesia. Intraoperative management, transfusion and pro-coagulant interventions, were performed in accordance with the institutional protocols of Fundeni Clinical Institute. At the end of surgery, patients were transferred to the Post Anaesthesia Care Unit (PACU). Immunosuppression therapy during the study period consisted of methylprednisolone 15 mg/kg during the neohepatic phase, basiliximab 20 mg before end of surgery and mycophenolate mofetil 750 mg twice daily. Postoperative therapeutic pro- or anti-coagulant interventions were performed at the attending anaesthesiologists' discretion if there were overt signs of bleeding and these patients were subsequently excluded. Thromboprophylaxis was performed using low-molecular weight heparin once daily, started six hours after the end of surgery.

Collected data. Patient demographic data, etiology and severity of liver disease (MELD-sodium score) were collected before surgery. Intraoperative data consisted of blood loss and transfusion (Packed Red Blood cells – PRBc and Fresh Frozen Plasma - FFP), lactate levels before clamping the inferior vena cava, 15 minutes into the neohepatic phase and at the end of surgery. Postoperative data consisted of lactate levels during the first three postoperative days, liver functional tests (standard coagulation tests, alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin) and platelet count for the first 3 days. Postanaesthesia Care Unit (PACU) length of stay was recorded.

ROTEM data. ROTEM assay was performed 24 hours after LT and consisted of four tests: ExTEM, InTEM, FibTEM and ApTEM. For ROTEM analysis venous blood was collected from the central venous line and the sample was immediately processed. Thromboelastometric parameters included in the final analysis were: ExTEM and InTEM clotting time (CT), ExTEM and InTEM clot formation time (CFT), ExTEM and ApTEM maximum lysis (ML), ExTEM, InTEM and FibTEM maximum clot firmness (MCF), ExTEM, InTEM and FibTEM maximum clot firmness at 10 minutes (A10), ExTEM alpha angle, ExTEM and InTEM thrombin potential index (TPI), ExTEM maximum velocity of clot formation (MaxV), ExTEM time to MaxV (MaxVt) and ExTEM area under the curve (AUC). A graphic representation of the results was printed for further interpretation. If the assay was deemed inappropriate due to machine malfunction or other external factors, the test was repeated using another sample.

Data analysis. The patients were included in one of two groups: patients who developed EAD (EAD group) and patients who did not develop EAD (non-IGPF). The diagnosis of EAD was made with the aid of criteria developed by Nanashima et al. [10]. Statistical analysis was performed using SPSS 19.0 (IBM, Armonk, NY). Data distribution was examined in order to insure the proper statistical examination. Data is presented as mean ± standard deviation, median (min, max) or percentage. Categorical variables were analyzed with Chi-square test and quantitative data were analyzed with independent samples t-test. Data that were not normally distributed were analyzed using the Mann-Whitney test. Statistical significance was considered at a p value < 0.05.

Results

After applying the exclusion criteria, 164 patients were included in the final analysis. Of those, 47 (28.6%) patients developed EAD. Demographic and intraoperative data are presented in Table 1. Univariate analysis demonstrated that intraoperative blood loss ($p = 0.01$), PRBc ($p = 0.04$) and FFP ($p = 0.01$) transfusion were associated with a greater incidence of EAD.

Table 1. Demographic and intraoperatory data

	All patients (n = 164)	EAD group (n = 47)	Non-EAD group (n = 117)	p value
Age (years)	50.5 ± 12.5	51.1 ± 12.0	50.0 ± 12.5	0.33
Sex (male)	59.1% (n = 97)	55.3% (n = 26)	60.6% (n = 71)	0.36
MELD-sodium score	21.2 ± 6.3	21.7 ± 5.7	20.4 ± 6.2	0.43
Blood loss (L)	3 [0.1,35]	4.5 [0.1, 35]	2.5 [0.1,23]	0.01
PRBc transfusion (U)	4 [0,30]	5 [0.30]	4 [0,24]	0.04
FFP transfusion (U)	8 [0,45]	10 [0,45]	6 [0,37]	0.01

Variables are presented as mean ± standard deviation, median [min, max] or percentage
EAD – early allograft dysfunction; MELD – Model for End-Stage Liver Disease; PRBc – Packed Red Blood Cells; FFP – Fresh Frozen Plasma

There was a statistically significant difference in both extrinsically ($p < 0.01$) and intrinsically ($p < 0.01$) activated clot formation time, extrinsically ($p < 0.01$) and intrinsically ($p < 0.01$) activated maximum clot firmness, ExTEM alpha angle ($p = 0.03$), extrinsically ($p < 0.01$) and intrinsically activated ($p < 0.01$) thrombin potential index, area under the curve ($p < 0.01$) and maximum clot elasticity ($p < 0.01$) between the two groups. Statistical data are presented in Table 2. There was no significant statistical difference between the two groups in the fibrinogen concentration (184 ± 57 mg/dL in the EAD group and 202 ± 78 mg/dL in the Non-EAD group, $p = 0.07$) and platelet count (46000 [17000, 303000] /mm^3 in the EAD group and 50500 [15000, 194000] / mm^3 in the Non-EAD group).

There was no difference in the lactate levels before clamping of the inferior vena cava but the univariate analysis demonstrated a significant difference in lactate levels at all measurements: after reperfusion of the liver graft ($p = 0.01$), at the end of surgery ($p < 0.01$) and the first three postoperative days ($p < 0.01$). Statistical data are presented in Table 3.

Table 2. A comparison of ROTEM parameters between patients with EAD and those without EAD

	All patients (n = 164)	EAD group (n = 47)	Non-EAD group (n = 117)	p value
ExTEM CT	70 [33, 1075]	73 [47, 1075]	63 [33, 209]	0.57
InTEM CT	188 [83, 3515]	184 [87, 3515]	196.5 [83, 360]	0.72
ExTEM CFT	296 [105, 4000]	399 [115, 4000]	222 [105, 3000]	< 0.01
InTEM CFT	237 [79, 3000]	353 [96, 3000]	190 [79, 2000]	< 0.01
ExTEM MCF	40 [7, 59]	36 [7, 59]	44 [19, 58]	< 0.01
InTEM MCF	41 [10, 60]	36 [13, 59]	44 [10, 60]	0.01
FibTEM MCF	10 [2, 25]	9 [3, 25]	10 [2, 23]	0.21
Alpha angle	57 [3, 81]	49 [3, 72]	58 [27, 81]	0.03
ExTEM TPI	8 [1, 46]	4,5 [1, 38]	14 [4, 42]	< 0.01
InTEM TPI	7 [1, 42]	5 [1, 42]	17 [4, 37]	< 0.01
ExTEM MaxV	10 [1, 31]	9,5 [1, 23]	11 [3, 31]	0.07
ExTEM MaxVt	75 [21, 1690]	78.5 [21, 1690]	72 [52, 291]	0.51
ExTEM AUC	3798 [273, 5922]	3471 [273, 5922]	4444.5 [3227, 5710]	< 0.01
ExTEM MCE	62 [15, 146]	55.5 [15, 146]	81.5 [48, 138]	< 0.01

Data are presented as median [min, max]
ROTEM – rotational thromboelastometry EAD – early allograft dysfunction

Table 3. Comparison of lactate levels between patients with EAD and those without EAD

	All patients (n = 164)	EAD group (n = 47)	Non-EAD group (n = 117)	p value
Preanhepatic	1.4 [0.6, 6.0]	1.5 [0.7, 6.0]	1.4 [0.6, 5.9]	0.20
15 min into neohepatic phase	4.0 [1.1, 10,4]	4.5 [2.3, 10.4]	3.9 [1.1, 8.9]	0.01
End of surgery	2.6 [0.6, 9.0]	3.6 [1.0, 9.0]	2.3 [0.6, 8.9]	< 0.01
Postoperative day 1	1.3 [0.3, 5.5]	1.6 [0.6, 5.5]	1.2 [0.3, 5.1]	< 0.01
Postoperative day 2	1.0 [0.4, 12.3]	1.2 [0.5, 12.3]	1.0 [0.4, 2.4]	< 0.01
Postoperative day 3	0.9 [0.3, 4.3]	1.0 [0.5, 4.3]	0.9 [0.3, 1.9]	< 0.01

Data are presented as median [min, max]
EAD – early allograft dysfunction

Median PACU length of stay was 6 [2, 30] days. The presence of EAD was associated with a more prolonged PACU length of stay: a median of 5 [3, 30] days compared to 7 [2, 25] days ($p < 0.01$) – Figure 1.

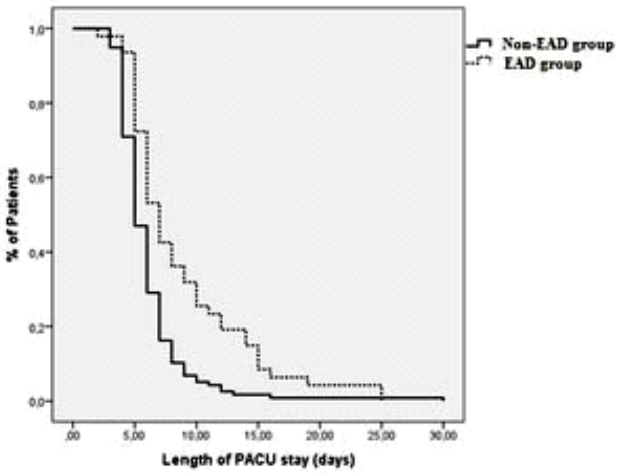

Fig. 1. Postanaesthesia Care Unit (PACU) length of stay (Los) comparison between patients with and without early allograft dysfunction (EAD)

Discussion

EAD is associated with early haemostatic disorders that can be objectified by standard ROTEM assay: increased clot formation time and decreased maximum clot firmness in both intrinsically and extrinsically activated coagulation pathways. Also, the derived ROTEM parameters showed decreased thrombin potential index, area under the curve and clot elasticity. With no significant difference in fibrinogen concentration and platelet count in our study this may be attributed to reduced clotting factors synthesis by the liver graft other than fibrinogen and decreased functional platelet levels.

Viscoelastic tests have been extensively used recently in guiding transfusion in the perioperative period of liver transplantation. This practice has been shown by many studies to be associated with decreased transfusion requirements and improved patient outcome [11, 12]. Outside their initial use as point-of-care tools for the management of bleeding disorders, recent studies have focused on finding prediction models for intraoperative [13] or postoperative [14] increased blood loss with promising results. Our study aims for a new utility of viscoelastic tests: early prediction and diagnosis of EAD.

EAD represents one of the most common and serious complications after LT. The incidence observed in our study (28.6%) is similar to that reported by other authors [2]. Our data suggests that blood loss and transfusion of both PRBc and FFP represent significant risk factors for the development of EAD. This is in accordance with the study published by Cywinski et al. [15]. These factors are probably modifiable and further research should be performed in order to minimize both intraoperative blood loss and transfusion in order to improve patient outcome. Pre-transplant severity of liver disease did not significantly influence the incidence of IGPF.

In a recent study published by Akamatsu et al. [9], platelet count and prothrombin time represented a significant risk factor for severe complications after living-donor LT. This was stated in another study by Lesurtel et al. [16]. This may be attributed to the fact that outside their role in thrombosis and haemostasis, platelets may have a significant role in liver regeneration [17]. Although the exact effects of thrombocytopenia in patients with liver dysfunction is not fully understood, low platelet count has been associated with EAD [18]. Because platelet count was not significantly different in patients who developed EAD, our proposal of using extrinsically activated ROTEM assay to test platelet function (ExTEM CFT, TPI and MCE) may prove superior to the proposed platelet count monitoring.

Low coagulation factor synthesis and coagulopathy represent the earliest signs of liver dysfunction. Low levels of factor V seem to be early predictors (day 2) of allograft failure [8]. ROTEM assay, as a viscoelastic test, may represent a superior method of detection decreased coagulation kinetics. Both standard and derived ROTEM parameters may offer significant information about decreasing coagulation factors levels. Because fibrinogen also represents an acute phase reactant and inflammation is common after major surgery, fibrinogen levels may increase more quickly after LT [19] then other coagulation factors. In our study we did not observe a statistically significant difference in fibrinogen levels between the two groups. Consequentially, we can assume that the significant differences in clot kinetics observed can be attributed to the decreased levels of coagulation factors synthesized in the insufficient liver.

EAD remains one of the most significant factors for increased PACU length of stay as recently demonstrated by Hudcova et al. [20]. This was also observed in our study.

Low lactate clearance after LT represents an early indicator of allograft dysfunction [21] and is associated with a worse outcome [22]. As increased lactate levels may be attributed to other factors other than graft failure that are frequently encountered in the early postoperative period of LT, we consider that the combined use of low lactate clearance and decreased clot kinetics could theoretically improve the diagnostic accuracy.

The main limitation of our study was that the timeframe for ROTEM assay was randomly chosen

and further studies using different time points may be required in order for an accurate algorithm to be established. Also, a larger number of patients must be included in order to accomplish the statistical power necessary to develop a cut-off value and a predictive model for ROTEM parameters. Another point that we want to stress is that ROTEM represents an ex-vivo coagulation assay. One of the most important factors involved in coagulation and possible in the etiology of graft dysfunction, the vascular endothelium, cannot be assessed alongside pro-inflammatory mechanisms that may represent the trigger for graft failure.

Conclusions

Our results show that standard and derived ROTEM parameters may represent early signs of graft failure and may aid in the diagnosis of EAD. Patients who show decreased clot kinetics after the first 24 hours of LT may benefit from extended observation and possibly therapeutic interventions in order to support liver function. Further studies are needed in order to assess optimal time points for assessment as well as cut-off values for improving diagnostic accuracy.

Conflict of interest

Nothing to declare

References

1. Olthoff KM, Kulik L, Samstein B, Kaminski M, Abecassis M, Emond J, et al. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. Liver Transpl 2010; 16: 943-949. doi: 10.1002/lt.22091
2. Hoyer DP, Paul A, Gallinat A, Molmenti EP, Reinhardt R, Minor T, et al. Donor information based prediction of early allograft dysfunction and outcome in liver transplantation. Liver Int 2015; 35: 156-163. doi: 10.1111/liv.12443
3. Orman ES, Mayorga ME, Wheeler SB, Townsley RM, Toro-Diaz HH, Hayashi PH, et al. Declining liver graft quality threatens the future of liver transplantation in the United States. Liver Transpl 2015; 21: 1040-1050. doi: 10.1002/lt.24160
4. Lee DD, Croome KP, Shalev JA, Musto KR, Sharma M, Keaveny AP, et al. Early allograft dysfunction after liver transplantation: an intermediate outcome measure for targeted improvements. Ann Hepatol 2016; 15: 53-60. doi: 10.5604/16652681.1184212
5. Cieślak B, Lewandowski Z, Urban M, Ziarkiewicz-Wróblewska B, Krawczyk M. Microvesicular liver graft steatosis as a risk factor of initial poor function in relation to suboptimal donor parameters. Transplant Proc 2009; 41(8): 2985-2988. doi: 10.1016/j.transproceed.2009.08.019
6. Nemes B, Gelley F, Zádori G, Piros L, Perneczky J, Kóbori L, et al. Outcome of liver transplantation based on donor graft quality and recipient status. Transplant Proc 2010; 42: 2327-2330. doi: 10.1016/j.transproceed.2010.05.018
7. Stockmann M, Lock JF, Malinowski M, Seehofer D, Puhl G, Pratschke J, et al. How to define initial poor graft function after liver transplantation? – a new functional definition by the LiMAx test. Transpl Int 2010; 23: 1023-1032. doi: 10.1111/j.1432-2277.2010.01089.x
8. Zulian MC, Chedid MF, Chedid AD, Grezzana Filho TJ, Leipnitz I, de Araujo A, et al. Low serum factor V level: early predictor of allograft failure and death following liver transplantation. Langenbecks Arch Surg 2015; 400: 589-597. doi: 10.1007/s00423-015-1290-2
9. Akamatsu N, Sugawara Y, Kanako J, Arita J, Sakamoto Y, Hasegawa K, et al. Low Platelet Counts and Prolonged Prothrombin Time Early After Operation Predict the 90 Days Morbidity and Mortality in Living-donor Liver Transplantation. Ann Surg 2017; 265: 166-172. doi: 10.1097/SLA.0000000000001634
10. Nanashima A, Pillay P, Verran DJ, Painter D, Nakasuji M, Crawford M, et al. Analysis of initial poor graft function after orthotopic liver transplantation: experience of an australian single liver transplantation center. Transplant Proc 2002; 34: 1231-1235. doi: 10.1016/S0041-1345(02)02639-8
11. Leon-Justel A, Noval-Padillo JA, Alvarez-Rios AI, Mellado P, Gomez-Bravo MA, Álamo JM, et al. Point-of-care haemostasis monitoring during liver transplantation reduces transfusion requirements and improves patient outcome. Clin Chim Acta 2015; 446: 277-283. doi: 10.1016/j.cca.2015.04.022
12. Mallett SV. Clinical Utility of Viscoelastic Tests of Coagulation (TEG/ROTEM) in Patients with Liver Disease and during Liver Transplantation. Semin Thromb Hemost 2015; 41: 527-537. doi: 10.1055/s-0035-1550434
13. Fayed N, Mourad W, Yassen K, Görlinger K. Preoperative Thromboelastometry as a Predictor of Transfusion Requirements during Adult Living Donor Liver Transplantation. Transfus Med Hemother 2015; 42: 99-108. doi: 10.1159/000381733
14. Dötsch TM, Dirkmann D, Bezinover D, Hartmann M, Treckmann JW, Paul A, et al. Assessment of standard laboratory tests and rotational thromboelastometry for the prediction of postoperative bleeding in liver transplantation. Br J Anaesth 2017; 119: 402-410. doi: 10.1093/bja/aex122
15. Cywinski JB, You J, Argalious M, Irefin S, Parker BM, Fung JJ, et al. Transfusion of older red blood cells is associated with decreased graft survival after orthotopic liver transplantation. Liver Transpl 2013; 19: 1181-1188. doi: 10.1002/lt.23695
16. Lesurtel M, Raptis DA, Melloul E, Schlegel A, Oberkofler C, El-Badry AM, et al. Low platelet counts after liver transplantation predict early posttransplant survival: the 60-5 criterion. Liver Transpl 2014; 20: 147-155. doi: 10.1002/lt.23759
17. Lisman T, Porte RJ. Mechanisms of platelet-mediated liver regeneration. Blood 2016; 128: 625-629. doi: 10.1182/blood-2016-04-692665
18. Li L, Wang H, Yang J, Jiang L, Yang J, Wang W, et al. Immediate Postoperative Low Platelet Counts After Living Donor Liver Transplantation Predict Early Allograft Dysfunction. Medicine (Baltimore) 2015; 94: e1373. doi: 10.1097/MD.0000000000001373
19. Stine JG, Northup PG. Coagulopathy Before and After Liver Transplantation: From the Hepatic to the Systemic Circulatory Systems. Clin Liver Dis 2017; 21: 253-274. doi: 10.1016/j.cld.2016.12.003

20. Hudcova J, Scopa C, Rashid J, Waqas A, Ruthazer R, Schumann R. Effect of early allograft dysfunction on outcomes following liver transplantation. Clin Transplant 2017; 31: e12887. doi: 10.1111/ctr.12887
21. Wu JF, Wu RY, Chen J, Ou-Yang B, Chen MY, Guan XD. Early lactate clearance as a reliable predictor of initial poor graft function after orthotopic liver transplantation. Hepatobiliary Pancreat Dis Int 2011; 10: 587-592
22. Basile-Filho A, Nicolini EA, Auxiliadora-Martins M, Silva Ode C Jr. The use of perioperative serial blood lactate levels, the APACHE II and the postoperative MELD as predictors of early mortality after liver transplantation. Acta Cir Bras 2011; 26: 535-540. doi: 10.1590/S0102-86502011000600021