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Research article

Rotational thormboelastolmetry guided transfusion practice in living donor liver transplantation, A retrospective comparative study

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ABSTRACT

Introduction: Living donor liver transplantation (LDLT) is a complex surgery with high risk for massive bleeding and blood component transfusion. This retrospective study investigated the effect of adopting ROTEM based transfusion algorithm on blood products transfusion practice among LDLT recipients and the effect of this change on patient outcome.

Material and methods: Data of 216 patients with predicted intraoperative massive bleeding (blood loss ≥70 ml blood/kg, or blood loss > 150 ml/min with hemodynamic affection with continuing need for transfusion) were collected from our database. Patients were divided into two groups according to transfusion protocol applied; Pre-ROTEM group (n = 95), ROTEM group (n = 121). Basal characteristics, blood component transfusion, graft outcome and patient outcome (28-day mortality and one-year mortality) were compared between the two groups.

Results: Transfused packed red blood cells (PRBCs) units, fresh frozen plasma (FFP) units, and application of massive transfusion protocol (MTP) were significantly lower in the ROTEM group compared to pre-ROTEM group [8(7) vs 4.5(5), $p < 0.01$, 12.5(4) vs 5.6(3), $p < 0.001$, 29% vs 20%, $p < 0.005$ respectively]. The survival distributions for the two studied groups showed no statistically significant difference, $p < 0.46$.

Conclusions: ROTEM based transfusion algorithms applied in LDLT decreased blood component transfusion and enhanced early graft function.

1. Introduction

Living donor liver transplantation (LDLT) is complex surgery with high risk for massive bleeding. Blood component transfusion has been associated with complications like infection, immunomodulation, volume overload and lung injury [1,2].

Standard laboratory tests like INR and platelet count have failed to predict or guide blood transfusion during orthotopic liver transplantation OLT [3]. Rotational thormboelastolmetry (ROTEM) has enhanced the understanding of coagulopathy changes during OLT thus improved transfusion practices, avoiding unnecessary transfusions and decreasing over all blood component transfusion [4].

In our center, ASA transfusion guidelines [5] were used for management of bleeding and blood component transfusion in the peri-transplant period. After 2012, ROTEM based algorithm was applied in patients with predictors of massive bleeding and in case of intraoperative massive transfusion.

This retrospective study investigated the effect of adopting ROTEM based transfusion algorithm on blood products transfusion practice during LDLT recipients and the effect of this change on patient outcome (early graft function - 28-day mortality).

2. Material and methods

After approval of institutional review board, Database of patients undergoing LDLT in our center, from 2008 to 2016 was screened for cases with pre-operative predictors of massive intraoperative bleeding (defined as bleeding ≥70 ml blood/kg) including the following parameters; (INR ≥ 2, platelet count $\leq 50 \cdot 10^9$/L, Hemoglobin level ≤8 gm/dl, Model for end stage liver disease (MELD) ≥30, Serum albumin ≤2.5 gm/dl) [1,6]. A patient was included in the analysis if one or more of the above mentioned predictors existed in the day before the operation. Included patients were divided into two groups; Pre-ROTEM group (n = 95), ROTEM group (n = 121), illustrated in Fig. 1.

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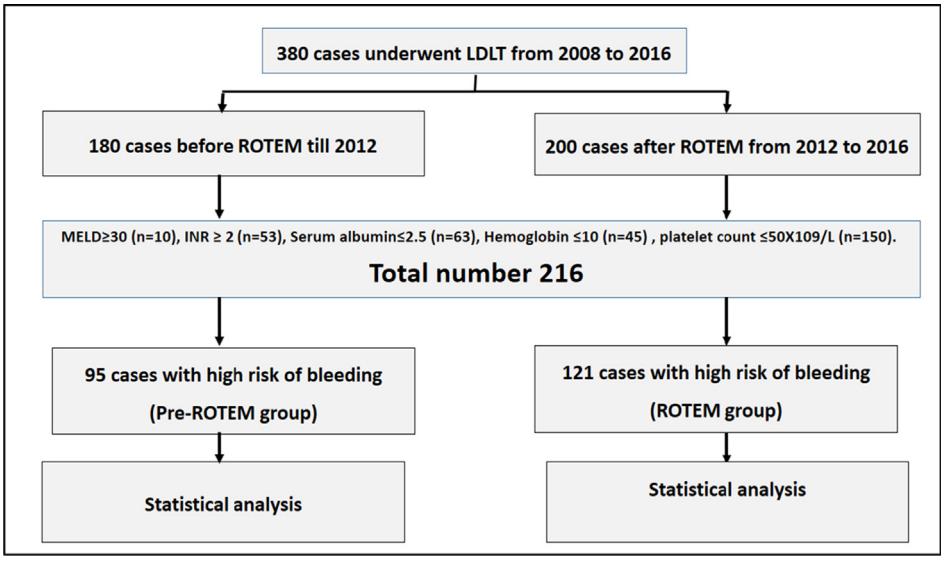

Fig. 1. Study flow chart. LDLDT: living donor liver transplantation, MELD: model for end-stage liver disease, INR: international normalized ratio.

In both groups, pH, electrolytes and body temperature are optimized based on the approved institutional protocol, target HB level was 8 gm/dl unless patient is known ischemic heart or developed new onset ischemic changes detected by transesophageal echocardiography or electrocardiographic trace, in this case target HB level was 10 gm/dl. In **Pre-ROTEM group,** ASA guidelines [5] was used to guide transfusion where FFP (15 ml/kg) was transfused if INR ≥ 2, Packed RBCs were transfused if hemoglobin became less than 8 gm/dl. In case of intraoperative massive bleeding; (blood loss ≥70 ml blood/kg or > 4 RBC units in 1 h, or blood loss > 150 ml/min with hemodynamic affection with continuing need for transfusion), FFP to RBCS to platelet 1:1:1 ratio protocol was applied. **In ROTEM group**, coagulation defects were screened by EXTEM and INTEM done before induction of anesthesia, according to the results of the two tests, further tests (FIBTEM, HEPTEM, APTEM) were done if indicated. Blood component transfusion was tailored according to the findings based on Essener-Runde algorithm [7]. A10 amplitude was used for earlier intervention. Low A10 amplitude in EXTEM while normal in FIBTEM indicates either platelet deficiency or dysfunction. A low A10 amplitude is low in both EXTEM and FIBTEM signifies fibrinogen deficiency. A prolonged CT in INTEM, that is corrected in HEPTEM demonstrates heparin or heparin-like effect. Fibrinolysis is diagnosed at a CLI < 85% within 60 min. APTEM test is used to assess antifibrinolytic drug effectiveness to stop lysis [8,9], Fig. 2.

3. Statistical analysis

Patients' data were extracted from our program database. Data were collected, tabulated, and statistically analyzed using IBM SPSS version 20. Continuous data were presented as mean ± SD or median [interquartile range] according to normality of distribution tested by Kolmogorov– Smirnov test. Nominal and categorical data were presented as number (percentage). Differences between the two groups were analyzed using two way independent samples T test, Mann-Whitney test or chi-square test as appropriate. A log rank test was run to determine if there were differences in the one-year survival between both groups.

4. Results

380 cases underwent LDLT surgery from January 2008 till December 2016, 216 patients showed at least one of the pre-operative predictors for intraoperative massive bleeding and was included in the study. Cases were divided into two groups according to availability of ROTEM device; Pre-ROTEM group (n = 95), ROTEM group (n = 121), Fig. 1. During assessment of graft function four cases (2 from each group) were excluded due to vascular occlusion with markedly elevated liver enzymes. As shown in Table 1, no statistical difference was found between the two groups regarding age, BMI, basal serum albumin, basal

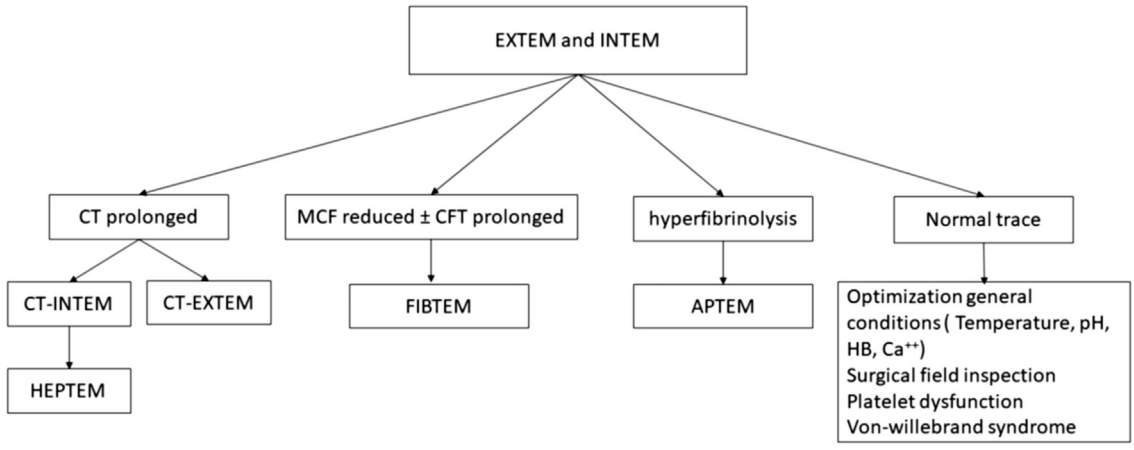

Fig. 2. ROTEM based transfusion algorithm. Hb: Hemoglobin level, CT: Clotting time, MCF: maximum clot firmness, CFT: clot formation time.

Table 1
Perioperative characteristics in the studied groups. Pre-ROTEM (n = 95), ROTEM group (n = 121). Data is presented as mean ± SD or median(IQR), or n (%).

	Pre-ROTEM group (n = 95)	ROTEM group (n = 121)	*P*
Age (years)	50 ± 10	49 ± 7	0.79
BMI (kg/m^2)	27 ± 4	27 ± 7	0.31
Gender (M/F)	86/9	108/13	0.46
Preoperative INR	1.7(0.6)	1.60.4)	0.265
Preoperative MELD	15(10)	16(7)	0.94
Preoperative Platelet count (10^9 per liter)	46(33)	46(34)	0.34
Basal Hemoglobin level (gm/dl)	10.7 ± 1.7	10.9 ± 1.2	0.47
Basal Serum Albumin (gm/dl)	2.8(1)	2.8(2.7)	0.48
HCC (%)	35%	31%	0.26

BMI: body mass index, M: male. F: Female, INR: International normalized ratio, MELD: Model for end-stage liver disease, HCC: hepatocellular carcinoma.
*P is significant if less than 0.05.

platelet count, basal hemoglobin, presence of hepatocellular carcinoma (HCC), or preoperative MELD score.

Fig. 3 demonstrates blood components transfusion in the two groups. Transfused RBCs units, FFP units, and application of massive transfusion protocol (MTP) were significantly lower in the ROTEM group compared to pre-ROTEM group [8(7) vs 4.5(5), $p < 0.01$, 12.5(4) vs 5.6(3), $p < 0.001$, 29% vs 20%, $p < 0.005$ respectively. Otherwise no differences were detected between the two groups regarding intraoperative blood loss, platelet transfusion requirement, processed cell saver volume, incidence of packing to control bleeding.

Regarding outcome variables, the only graft functions which were significantly improved in the ROTEM group compared to pre-ROTEM group was in the form lower SGPT day 7 and lower total bilirubin level in day 7 and day 28. No statistical difference was detected between the two studied groups regarding post-transplant mortality (28 day-1-year), Table 2.

In Fig. 4, a log rank test was run to determine if there were differences in the survival distribution for both studied groups. The survival distributions for the two studied groups showed not statistically significant difference, $p < 0.46$.

Table 2
Postoperative patient outcome in the two studied groups, Pre-ROTEM group (n = 95), ROTEM group (n = 121). Data are presented as median (IQR), % [n].

	Pre-ROTEM group (n = 95)	ROTEM group (n = 121)	p
Early mortality% (n)	15% [14]	11% [13]	0.9
1-year mortality% (n)	21% [20]	17% [20]	0.46
Graft function			
● 7th day SGPT	67(63)	44(51)	0.002*
● 28th day SGPT	20(13.5)	21(21)	0.107
● 7th day Total bilirubin	5.5(7.2)	4.2(4.5)	0.004*
● 28th day Total Bilirubin	1.6(2.2)	1.3(1.1)	0.008*
● 7th day INR	1.3(0.3)	1.3(0.3)	0.18
● 28th day INR	1.2(0.4)	1.1(0.3)	0.074

SGPT: Serum glutamic pyruvic transaminase, INR: international normalized ratio.
* P value is significant if less than 0.05.

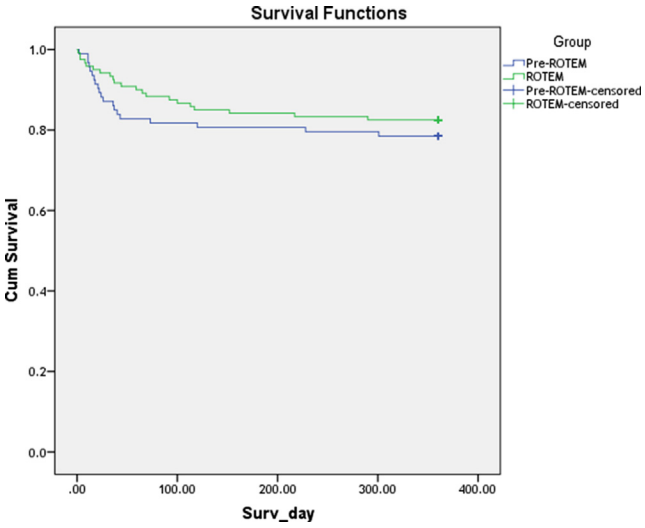

Fig. 4. One-year survival curve in the two studied groups, Pre-ROTEM group (n = 95), ROTEM group (n = 121).

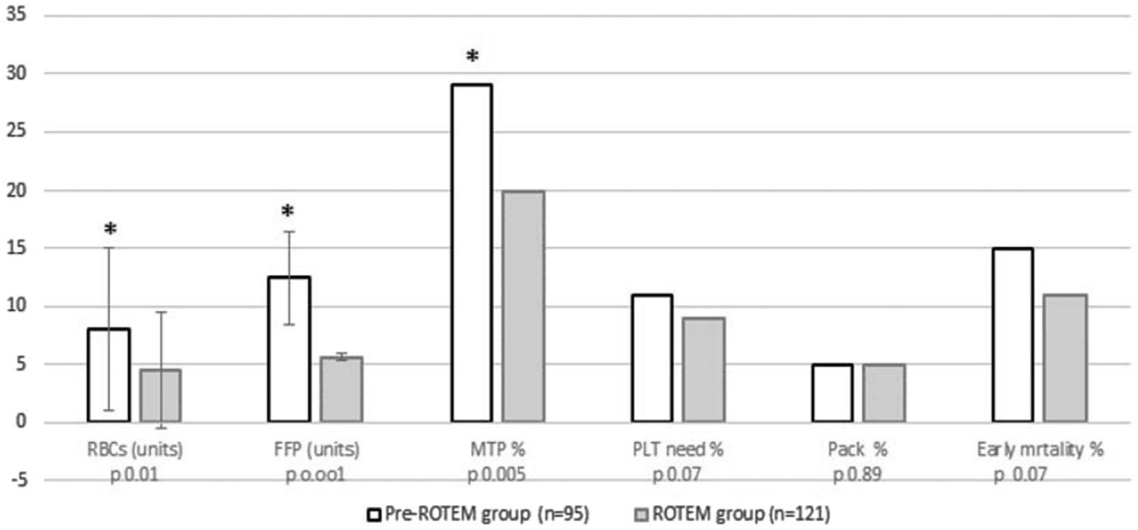

Fig. 3. Blood transfusion practice and patient outcome in the two groups, Pre-ROTEM (n = 95), ROTEM group (n = 121). RBCs, red blood cells, FFP: fresh frozen plasma, MTP: massive transfusion protocol, PLT: platelet, Pack: surgical packing for control of bleeding. *p value is significant if less than 0.05.

5. Discussion

LDLT is a complex surgery that is commonly associated with intraoperative massive bleeding that may require blood component transfusion. Added to economic burden and exhausting the limited resources of blood banks; blood component transfusion is associated with various complications like transfusion related acute lung injury (TRALI), immunomodulation, transfusion associated circulatory overload (TACO), infections, poor graft function and worse patient outcome [1,6,10,11]. Multiple efforts aimed to define timing and trigger for blood component transfusion during LDLT. Depending on standard laboratory tests e.g. INR, APTT, fibrinogen level and platelet count fails to predict or guide transfusion in LDLT [3,4,6,12–14].

Recently, coagulation monitoring in LDLT using point-of-care (POC) devises (ROTEM-TEG) has been offered as a more efficient guide for hemostatic therapy. ROTEM assess whole blood coagulation based on the cell based model rather than the conventional cascade model utilized by standard laboratory tests (SLTs) like; INR, APTT [4,7,15]. An important advantage of using ROTEM is the earlier diagnosis of coagulation defects allowing prompt goal directed therapy with specific hemostatic drugs, coagulation factor concentrates, and blood products [4,16,17]. While SLTs need a turnaround time of at least 45 min, A10 amplitude in ROTEM have been proved in many studies to be correlated to MCF and have been applied in many algorithms for rapid correction of coagulation defects [9,18–20]. The theranostic approach offered by ROTEM based algorithm allows early prediction and diagnosis of coagulation abnormalities with concurrent goal guided therapy.

The use of ROTEM based algorithms reduced blood component transfusion in situations frequently associated with coagulopathy and bleeding like trauma, cardiac and liver transplantation surgery. Grlinger et al. [21] studied effect of ROTEM on blood component transfusion in 3 different hospitals in Germany and Australia. They found a significant reduction in RBCs, FFP in transplant cases with significantly lower massive transfusion episodes. Also in a Cochrane review, the application of ROTEM decreased the bleeding episodes but was not associated with improvement in patients outcome [22].

In our study, FFP was significantly lower when ROTEM based algorithm was applied. This is concordant with results of many studies [17,23]. FFP transfusion is associated with increased complications like transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), and allergic transfusion reactions (ATR) [10,11]. The results of this study are consistent with the growing evidence that increased blood product transfusion is associated with worse patient outcome [24–27]. This negative impact of intraoperative blood transfusion was explained by its multiple complications including immunologic adverse effects, metabolic disorders, increased infection rates, and acute lung injury. Large volumes of allogenic blood transfusion with large amounts of foreign antigens result in impaired cell-mediated and natural killer cell activity, and deterioration in liver regeneration [28].

Platelet transfusion did not show statistical difference between pre-ROTEM and ROTEM group. Although results from EXTEM and FIBTEM can identify platelet deficiency, it is still documented that ROTEM is not sensitive detection of platelet dysfunction [3,29], its use is not expected to decrease platelet transfusion needs. This may be improved by the use of platelet function analyzer which still not available in our center.

In our results, Although the difference in one-year survival could not reach statistical significance, survival was higher in the ROTEM group (17% vs. 21%). This is matching the results of several studies that links blood component transfusion to poorer graft and patient outcome [24–28,30]. Due to our awareness of the fact that advancement in transplant science and buildup in local experience may play a role in overall reduction improvement in patient outcome, we explicitly excluded cases performed from 2004 to 2008 to avoid the confounding effect of surgical learning curve. This was reflected as statistically non-significant difference in intraoperative blood loss in the two groups.

The retrospective nature of our study is attributed to the fact that rising evidence for the value of point-of-care coagulation monitoring made a prospectively designed study ethically questionable. The non-availability of fibrinogen concentrates and prothrombin complex concentrate (PCC) and FVIIa in our center would increases the rate of FFP usage and minimize the efficacy of ROTEM based therapeutic measures.

6. Conclusions

ROTEM based algorithms applied in LDLT decreases blood component transfusion, and can positively affect both graft and patient outcome. Further prospective studies are encouraged to assess its impact on graft and patient outcome.

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Conflict of interest

The authors declared that there is no conflict of interest

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