

Bloodless Liver Transplantation: ROTEM guided Rational Prophylactic use of Recombinant Activated Factor VII

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Abstract

Background: Improvement of surgical and anesthetic techniques, allowed total avoidance of blood transfusion during liver transplantation (LT) in some cases. The last years showed much debate about prophylactic administration of rFVIIa with no guide for its rational use. Giving that it is off label, preoperative ROTEM assessed coagulation reserve may help its judicious use.

Patients and methods: 3 groups retrospectively studied; (NRNB) n=38 not given rFVIIa and no blood transfusion (BT), (RNB) n=43 given rFVIIa and no BT and (RAB) n=35 given rFVIIa and BT. 40 ug/kg rFVIIa were given. Comparison NRNB vs. RNB group answers need or not need rFVIIa to achieve bloodless surgery (decision of admission), while RNB vs. RAB group determine which patients rFVIIa can help to achieve bloodless surgery (responders and non responders). Data collected: Preoperative Extem, Fibtem, hemoglobin (HB), INR, platelet, fibrinogen, blood loss, and blood transfused in RAB group.

Results: NRNB group had significantly higher HB, fibrinogen, platelets, and better ROTEM values vs. RNB. RAB had significantly lower HB, fibrinogen, platelets, and worse ROTEM values vs. RNB. Preoperative HB, fibrinogen level and ROTEM values are highly significant predictors to rFVIIa response. In RAB group, PRBCs transfusion correlated with preoperative HB and Ex MCF, platelet transfusion correlated with Ex MCF, angle α and CFT, cryoprecipitate transfusion correlated with fibrinogen and Fibtem MCF, plasma transfusion correlated with ExCT and ExCFT. Preoperative Rotem and HB cut values are sensitive and specific for admission and response to rFVIIa to achieve bloodless surgery.

Conclusion: ROTEM may help rational rFVIIa use, considering safety and cost, to achieve bloodless surgery. Non responders (RAB) may still require rFVIIa on risk benefit bases. Correction of HB and higher rFVIIa doses may improve their response.

Keywords: Bloodless surgery; ROTEM; Recombinant activated factor VII; Liver transplantation

Introduction

One of recipients' anesthetic management objectives during adult living donor liver transplantation (ALDLT) is to minimize blood transfusion as it is linked to increased morbidity and mortality [1]. With improvement of surgical and anaesthetic techniques, organ preservation and the successful experience in Jehovah's Witnesses management, [2-5] total avoidance of blood transfusion becomes possible. Different strategies, including use of pharmacological haemostatic support were implemented as prophylactic administration of recombinant activated factor VII (rFVIIa) (NovoSeven, Novo Nordisk, Denmark).

Recombinant activated coagulation factor VII (rFVIIa) (NovoSeven, Novo Nordisk, Denmark) is a coagulation protein that induces hemostasis through direct activation of factor X, starting the conversion of prothrombin to thrombin to form a hemostatic clot. At the site of vascular injury, rFVIIa binds to the surface of activated platelets, increasing localized thrombin generation [6]. It has been used during liver transplantation for different indication [7] but its prophylactic use has still much debate. Some studies found rFVIIa effective in reducing blood transfusion [8-10] others do not support its use even without considering its cost and potential thrombotic complications [11-13]. So, the blind prophylactic administration of rFVIIa to all patients may be questioned and the ability to predict patients whom the drug can help to achieve an important goal that is blood less surgery (no PRBCs, no plasma, no platelets and no cryoprecipitate), may help avoid the futile and unnecessary use of such off label expensive drug.

Recent evidence notes that conventional coagulation tests (CCT) have a poor correlation [14] and prediction [15,16] of bleeding or need for RBC transfusion in patients undergoing LT and are not useful in dosing rFVIIa [17] Rotation thromboelastometry (ROTEM®; Tem International GmbH, Munich, Germany) unlike CCT that are performed on platelet-poor plasma, is performed on whole blood and can provide rapid, comprehensive, global, clinical assessment of the patient's coagulation status, from initiation of coagulation to the formation, quality and potential breakdown of the clot [18-20].

It may also be beneficial in determining the optimal hemostatic therapy than CCT [21] and useful for predicting and monitoring the effects of rFVIIa [22-24].

The aim of this study is to use preoperative ROTEM parameters as a screening method to select patients who are most probably good candidate for prophylactic administration of rFVIIa, as an appropriate

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pharmacological haemostatic support, to maintain acceptable coagulability, permitting blood less surgery.

Patients and Methods

After approval of the local Ethical comity, three groups of recipients of ALDLT were retrospectively studied in the period between January 2009 and March 2012. These patients were operated by the same operative team with the same surgical techniques. Exclusion criteria; history of portal vein thrombosis or thrombosis elsewhere, sever portal hypertension and cases with surgical mishaps as accidental vascular injury with massive bleeding.

The 1st group (38 patients) included patients who did not receive rFVIIa and did not need any blood products transfusion (NRNB) this group of patients were done before starting the protocol of rFVIIa administration at our institute, the 2nd group (43 patients) received rFVIIa and did not need any blood products (RNB) and the 3rd group (35 patients) received rFVIIa and required blood products (RAB).

RFVIIa was given in a dose of 20 µg kg⁻¹ infused over 20 min, just before inducing anesthesia followed after one hour by a similar dose given as an infusion over another one hour. The precondition criteria of rFVII administration were ensured in all patients received the drug including: Fibrinogen levels of ≥50 mg dL⁻¹, Platelet levels of ≥50,000 × 10⁹ L⁻¹, pH to ≥ 7.2 and normal body temperature.

Rotem based transfusion triggers were followed in all patients according to this protocol [25].

Check surgical field if there is:

Diffuse surgical bleeding

Then if:

Extem MCF<25 mm give platelets, cryoprecipitate, FFPs

Extem MCF<45 mm and fibtem MCF<8 mm give cryoprecipitate

Extem MCF<45 mm and fibtem>8 mm give platelets

No diffuse clinical bleeding

Then if:

Extem MCF>35 mm no haemostatic therapy is indicated

Extem MCF MM<35 mm and fibtem MCF<8 mm give cryoprecipitate

Extem MCF<35 mm and fibtem MCF>8 mm give platelets

If Extem CT>80 s give FFPs

Tranexamic acid was given if there is evidence of hyperfibrinolysis as indicated by ROTEM in a dose of 20 mg/kg. Hematocrit kept above 24% in all cases.

Anesthesia

Patients did not receive premedication. After standard monitoring was in place, anaesthesia was induced with propofol 2 mg kg⁻¹ and rocuronium 0.9 mg kg⁻¹ was given to facilitate rapid sequence orotracheal intubation with a cuffed tube followed by fentanyl 2 µg kg⁻¹. Anesthesia was maintained with sevoflurane (1.5-2.0% end tidal in O₂:air mixture (FiO₂=0.4), fentanyl, and rocuronium, keeping spectral entropy (GE Healthcare, Helsinki, Finland) between 40% and 60%. Normothermia was achieved with forced-air warming device and mechanical ventilation adjusted to keep normooxia and normocarbida. Transesophageal Doppler

was used in all cases for hemodynamic monitoring and fluid adjustment to ensure normovolaemia.

The following data were collected: Preoperative Rotem Extem CT, CFT, angle apha and MCF and Fibtem MCF, INR, fibrinogen level, platelet count, HB, MELD score, intraoperative blood loss, fluid infused and perioperative blood products transfused till postoperative day3 and vascular thrombotic complications within the 1st month. Intraoperative blood loss (BL) in NRNB group and RNB group was calculated from a modification of the Gross formula [26] given below. While in RAB group blood loss was estimated by previous method in addition to the quantity of transfused red blood cells.

$BL = BV [Hct (i) - Hct (f)] / Hct (m)$ Where BV was the blood volume calculated from the Body Weight (Blood Volume=Body Weight in Kgs × 70 mlkg⁻¹) [27] Hct (i), Hct (f) and Hct (m) were the initial, final and mean (of the initial and final) Hematocrits respectively.

Statistical analysis

Data was statistically analyzed using SPSS (statistical package for social science) program version 13 for windows and for all the analysis a p value < 0.05 was considered statistically significant: Student t- test was done for normally distributed quantitative variables to measure mean and standard deviation and p-value < 0.05 was considered significant. Mann-Whitney test was done for quantitative variables, which are not normally distributed and p-value < 0.05 was considered significant. Sensitivity: true positive cases divided by all positive cases. Specificity: True negative cases divided by all negative cases. Accuracy: all true positive plus true negative cases divided by all cases (either true positive or true negative or false positive or false negative). Roc curve (Receiver operating characteristic curve): was done to detect cut level of any tested variable where at this level, there is the best sensitivity and specificity cut off values of the variables. The validity of the model was measured by means of the concordance[®] statistic (equivalent to the area under the Roc curve). A model with a c value above 0.7 is considered useful while a c value between 0.8 and 0.9 indicated excellent diagnostic accuracy. Spearman's correlation test was done to study the correlation between blood products transfused and different studied variables in RAB group and p value less than 0.05 was considered significant. All data are tested with kolmogorov-Smirnov Z test and most normally distributed were presented with mean ± SD and using parametric testes on doing association or correlation.

Data not-normally distributed were presented with range (median, inter quartilerange) using non-parametric tests.

Results

The study was conducted on 116 recipients of ALDLT. The underlying liver disease indicating liver transplantation was as follow: in NRNB group 23 patients had hepatitis C virus (HCV) versus 15 patients with HCV and hepatocellular carcinoma (HCC), in RNB group there were 26 patients had HCV versus 17 patients had HCV and HCC on the other hand 25 patients had HCV and 10 patients had HCV and HCC. Regarding MELD score patients in the RAB group tended to have the highest values. But the comparison between RAB group with RNB group was insignificant similarly the comparison between NRNB group and RNB group was insignificant. Also there were no significant difference between NRNB group versus RNB group and RAB group versus RNB groups regarding preoperative liver enzymes AST and ALT and serum bilirubin. Patients' preoperative characteristics were shown in table 1. The preoperative comparison between NRNB group versus RNB group aimed to answer which patient can have bloodless surgery

Variable	NRNB	RNB	RAB
Number	38	43	35
Age /Y Mean (SD)	47.3 (6.68)	48.47(5.24)	45.6(4.69)
Gender M/F	30/8	40/3	29/6
AETIOLOGY HCV/HCC+HCV	23/15	26/17	25/10
MELD Mean (SD)	15.50(4.4)	15.47(3.3)	15.95(4.9)
AST IU/L Mean (SD)	55.32(17.8)	58.5(16.1)	61(19.3)
ALT IU/L Mean (SD)	63.6(19.08)	67.6(23.2)	71(22.3)
Bilirubin mg/dl Mean (SD)	3.86 (1.83)	3.98(1.92)	4.2(1.99)

NRNB : not given rFVIIa nor any blood products, RNB: given rFVIIa and no blood products, RAB :given rFVIIa and blood products.HCV=hepatitis C virus, HCC=hepatocellular carcinoma

No statistical significant difference when comparing NRNB group with RNB and when comparing RAB group with RNB group regarding MELD score, AST, ALT, and bilirubin

Table 1: Patient's characteristics.

Variable	NRNB	RNB	P1	RAB	P2
HB (gm/dl) Mean (SD)	12.27(0.56)	11.43(0.38)	< 0.01	9.83(1.29)	< 0.01
INR Mean (SD)	1.67(0.22)	1.76(0.22)	> 0.05	1.92 (0.30)	< 0.01
Platelet (10 ⁹ /L) Mean (SD)	84.25±21	73.86(18.9)	< 0.05	62.15(11.48)	< 0.01
Fibrin. mg/dl Mean (SD)	168.95(33.13)	153.67(31.29)	< 0.05	86.95(34.29)	< 0.01
EX MCFmm Mean (SD)	56.45(3.15)	46.67(3.6)	< 0.05	39.25(4.86)	< 0.01
EX α (deg) Mean (SD)	68.51(5.11)	54.06 (4.3)	< 0.01	45.95 (6.4)	< 0.01
EX CFTsec Mean (SD)	155.8(27.4)	197.81(33.9)	< 0.01	251.35(31.3)	< 0.01
Ex CTsec Mean (SD)	77.8(9)	88.1(11)	< 0.01	107 ± 14	< 0.01
FIB MCFmm Mean (SD)	11.7(1.17)	10.05(1.72)	< 0.01	7.50(2.09)	< 0.01

NRNB : not given rFVIIa nor any blood, RNB: given rFVIIa and no blood, RAB :given rFVIIa and blood

Data represented as mean and SD P1 < 0.05 denotes statistically difference between NRNB group and RNB group

P2 < 0.05 denotes statistically difference between RNB group and RAB group

Table 2: Initial coagulation parameters.

(meaning no transfusion of packed red blood cells, fresh frozen plasma, platelets, and cryoprecipitate) without the need to rFVIIa, while that of RNB with RAB aimed to answer which patient would benefit from rFVIIa to have blood less surgery and which patients would be rFVIIa non responders (meaning in spite of giving rFVIIa they needed blood products to maintain adequate haemostatic condition).

The comparison of the preoperative coagulation data (Table 2) has shown that NRNB group had significantly higher HB, platelets and fibrinogen levels compared to RNB group while the comparison of preoperative INR was statistically insignificant. Regarding ROTEM; all parameters were of statistical significant better values in NRNB group compared to RAB group. Also the comparison of RNB group and RAB group showed that RNB group had statistically significant higher HB, platelets, fibrinogen and significantly lower INR compared to RAB group. Regarding ROTEM all parameters were of statistical significant better value in RNB group compared to RAB group.

Regarding post operative values the comparison between NRNB group and RNB group was insignificant regarding HB, INR and platelet count and fibrinogen level. Also the comparison between RNB group and RAB group was insignificant regarding the same parameters. The comparison between NRNB group and RNB group regarding blood loss and colloid transfusion was in significant while, the RAB group had significantly higher blood loss and higher colloid replacement than RNB group and the cost of haemostatic support was significantly higher in RAB group versus RNB group while it was zero in the NRNB group. Post operative data was shown in table 3.

Also these results found all selected ROTEM parameters; Extem

Variable	NRNB	RNB	P1	RAB	P2
HB(gm/dl) Mean (SD)	8.87 (0.45)	8.6 (0.36)	>0.05	8.83(0.74)	>0.05
INR mean (SD)	2.85(0.22)	2.72(0.29)	>0.05	2.63(0.35)	>0.05
Platelets (109/L)	58.7 (24.43)	54.67(25.63)	> 0.05	51.9(19.89)	>0.05
Mean (SD) Fibrinogen(mg/dl)	57.15(38.89)	49.81(22.34)	> 0.05	60.95(31.04)	>0.05
Mean (SD) PRBCs (units/ range) Median (IQR)	0	0	—	0 – 18 5 (6)	<0.01
Plasma(unit/ range) Median (IQR)	0	0	—	4 – 20 5 (6.5)	<0.01
Platelets (unit/range) Median (IQR)	0	0	—	0 – 18 0 (9)	<0.05
Cryoprecipit (unit/range) Median (IQR)	0	0	—	0 – 25 0 (10)	<0.01
RA (L) Mean (SD)	4.91(0.54)	5.11(0.34)	> 0.05	6.03(0.89)	>0.05
HES 130/4 (L) Mean (SD)	2.03(0.44)	1.9(0.49)	> 0.05	3.16(1.14)	< 0.01
Blood loss (ml/ range) Median (IQR)	1750-2500 2000(400)	1500-3000 2000(500)	> 0.05	2500-7000 3250(3500)	< 0.01
Surgical time(h) Mean (SD)	8.55(2.19)	8.85(2.570)	> 0.05	9.08(2.31)	> 0.05
Cost (\$) Mean (SD)	0	2330.86(403.66)	< 0.01	2934.5(543.58)	< 0.01

NRNB: not given rFVIIa nor any blood products , RNB: given rFVIIa and no blood transfusion, RAB: given rFVIIa and blood. RA: Ringer acetate.

P1 < 0.05 denotes statistically difference between NRNB group and RNB group P2 < 0.05 denotes statistically difference between RNB group and RAB group

Table 3: postoperative clinical data.

Studied variables	Mean (S)	p- value
Age /Y	48.48(5.24)	> 0.05
MELD	15.48(3.33)	> 0.05
HB (gm/dl)	11.43(0.38)	< 0.01
Platelets (109/L)	73.86(18.92)	> 0.05
Fibrinogen (mg/dl)	153.67(31.29)	< 0.01
INR	1.76(0.22)	< 0.05
Ex MCF(mm)	46.67(3.65)	< 0.01
Ex α (deg)	54.06 (4.32)	< 0.01
Ex CFT(sec)	197.81(33.93)	< 0.01
Ex CT(sec)	88.1(11)	< 0.01
Fib MCF(mm)	10.05(1.72)	< 0.01

P < 0.05 denotes statistically significant values

Table 4: Predictors of response to rFVIIa.

Variable		EXMCF	FIBMCF	CFT	CT	α (deg)	MELD	HB	INR	Platel.	Fibrin.
RBCs	r	- 0.419	-0.054	0.216	0.198	-0.031	0.329	- 0.633	0.14	- 0.118	- 0.038
	P- value	< 0.05*	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	< 0.01*	> 0.05	> 0.05	> 0.05
Platelets	r	- 0.584	- 0.271	0.538	0.432	-0.492	0.393	0.03	0.136	- 0.212	- 0.023
	P- value	< 0.01*	> 0.05	< 0.05*	> 0.05	< 0.05*	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05
Cryopre.c	r	- 0.027	- 0.638	0.086	0.397	-0.029	0.123	- 0.249	0.193	0.244	- 0.457
	P- value	> 0.05	< 0.01*	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05*
Plasma	r	- 0.213	- 0.019	0.498	0.632	-0.311	0.041	- 0.234	0.357	0.023	- 0.050
	P- value	> 0.05	> 0.05	< 0.05*	<0.01*	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

*indicates statistically significance (p<0.05)

Table 5: Spearman's correlation between blood products transfused and different studied variables in RAB group.

Variables	Cut level	Sensitivity%	Specificity%	AUC	Accuracy%	SE	CI
HB (gm/dl)	11.85	71.4	80	0.89	90.1	0.05	0.78 – 0.99
Ex MCF (mm)	53	35	90	0.68	72.6	0.08	0.52 – 0.84
Ex CFT (Sec)	175	81.0	75.0	0.86	72.6	0.05	0.75 – 0.97
Ex CT (Sec)	81	79	73	0.83	71.3	0.06	0.72- 0.93
Ex α (deg)	64	70	89	0.69	70	0.07	0.87–0.98
Fib MCF (mm)	11.5	55.0	91	0.78	72.5	0.07	0.64 – 0.92

AUC: area under the curve. Preoperative Extern CT, CFT, and HB cut off values are highly sensitivity for admission to rFVIIa while cut of all parameters are highly specific to avoid giving rFVIIa

Table 6: Sensitivity, specificity and accuracy of preoperative Extern CT,CFT, MCF angle alpha, Fibtrem MCF and HB for admission of rFVIIa in NRNB group versus RNB group.

Variables	Cut level	Sensitivity%	Specificity%	AUC	Accuracy%	SE	CI
HB (gm/dl)	10.8	100.0	75.0	0.88	87.6	0.06	0.76 – 0.99
Ex MCF(mm)	45	100.0	85.0	0.99	98.2	0.01	0.96 – 1.01
Ex CFT(sec)	215	100.0	100.0	1	72.6	0.00	1 – 1
ExCT (sec)	95	92	83	0.86	80	0.05	0.82-0.91
Ex α (deg)	50	91	79	0.91	89	0.03	0.89 0.99
Fib MCF(mm)	9	95.2	75.0	0.94	92.9	0.04	0.87 – 1

AUC: area under the curve. All cut off values of the selected parameters are highly sensitive and specific for detection of rFVIIa responders and non responders

Table 7: Sensitivity, specificity and accuracy of preoperative Extern CT, CFT, MCF, angle α , Fibtrem MCF and HB for response to rFVIIa. in RNB group VS. RAB group.

CT, CFT, MCF, angle α , and Fibtrem MCF had high significant predictive value to the response to rFVIIa (p<0.01) as well as HB and fibrinogen levels (P<0.01), while age, MELD score, and platelet count were not predictor to response to rFVIIa table 4. The correlation of blood products required in 3rd group with different studied parameters shown in table 5. Preoperative platelet's count, INR and MELD score did not correlate with any of blood products required. PRBCS transfusion was negatively correlated with ExMCF (R=-0.4) and preoperative HB (R=-0.6), FFPS was positively correlated with CFT (R=0.49) and CT (R=0.63), platelet transfusion was negatively correlated with EXMCF (R=-0.5) and positively correlated with CFT (R=0.5) and cryoprecipitate transfusion was negatively correlated with FIBTEM MCF (R=0.63) and fibrinogen level (R=-0.4). For admission of rFVIIa (need or do not need rFVIIa to achieve bloodless surgery), table 6, HB cut off level of 11.85 gm/dl had sensitivity, specificity and AUC of 71%, 80%, 0.89 respectively, cut levels of ROTEM parameters with their sensitivity and specificity and AUC were also shown. All sensitivity and specificity values of selected cut levels are greater than 70% except Ex MCF and FIB MCF which had sensitivity of (35% and 55%) respectively. For response to rFVIIa (identify in which patients rFVIIa can improved coagulation state to allow bloodless surgery and those needed blood products and could not achieve bloodless surgery in spite of giving rFVIIa), cut off values of HB, and ROTEM were shown in table 7 with their sensitivity, specificity and accuracy. All selected cut off values had sensitivity and specificity more than 70%. Interestingly, a cut off value of EX CFT of 215 sec had a sensitivity 100%, specificity of 100% and AUC of 1, Also both HB of 10.8 gm/dl and Ex MCF of 45 mm

had sensitivity of 100%. ROC curves of preoperative hemoglobin level for prediction of the need for admission figure 1 and response figure 2 to rFVIIa were given. The results of this study also reported two cases of hepatic artery thrombosis one in RAB group and the other in RNB group and two cases of portal vein thrombosis were recorded in NRNB group and RAB group within the 1st month after surgery

Discussion

This study used some preoperative Rotem parameters as a screening method before prophylactic giving rFVIIa to recipients of ALDLT and could put cut values, which may help to answer the questions; when rFVIIa is not needed (receptients those can have liver transplantation without any blood products without the need of rFVIIa) and when it is most probably required as a hemostatic support allowing bloodless LT and when its use may be futile as its administration will not prevent blood transfusion and the benefit may not be equivalent to cost and risk.

Some studies have investigated many preoperative factors trying to predict blood loss and transfusion requirement during LT and found them of poor or limited value [28-29].

This study depended on Rotem rather than CCT. Kang Y [30] concluded that monitoring of clinical coagulation, not laboratory coagulation, should be an essential tool in coagulation management to avoid prophylactic administration of a large dose of pharmacological agents and so prevent thrombotic or other complications and to help

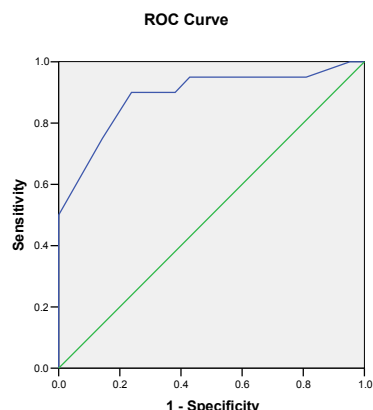


Figure 1: Receiver operating characteristic (ROC) curve of preoperative hemoglobin to predict the need for admission of rFVIIa. (Line in blue represents preoperative hemoglobin and line in green represents reference line).

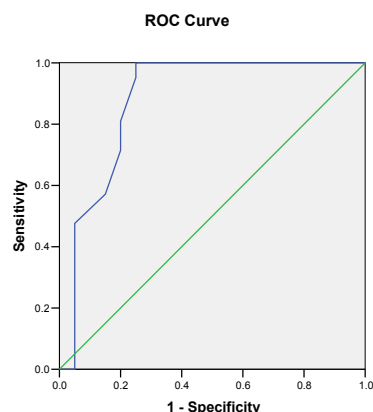


Figure 2: Receiver operating characteristic (ROC) curve of preoperative hemoglobin to predict the response to rFVIIa. (Line in blue represents preoperative hemoglobin and line in green represents reference line).

its appropriate use in maintaining acceptable blood coagulability. This exactly what we mean by rational use of rFVIIa.

Rotem Extrem and Fibtrem values were selected in this study to put a guide for the cut values for rFVIIa administration. According to Daniel Bolliger et al. [31] EXTEM and FIBTEM are used primarily to evaluate overall clot stability and fibrin polymerization, respectively. FIBTEM and EXTEM should be performed simultaneously as first-line ROTEM tests in bleeding surgical patients [32] Armando Tripodi et al. [33] in their study concluded that CFT and MCF are the most interesting parameters to be considered for future clinical studies needed to assess bleeding-risk and prognosis in cirrhotic patients.

Patients in NRNB group had almost within normal range preoperative ROTEM values indicating good coagulation reserve, which was sufficient to undergo blood less LT without rFVIIa. Cammerer et al. [34] in their study found that patients with normal ROTEM results are unlikely to bleed for haemostatic reasons and bleeding in these patients is probably caused surgically. The selected cut values of admission of rFVIIa have high specificity, which means above these values, patients have higher chance to have bloodless LDLT without supplementation of rFVIIa. In agreement with this, two studies [34,35] found Rotem of high negative predictive value for the

prediction of bleeding in the early postoperative period after cardiac surgery. Furthermore, these cut values are of high sensitivity (except MCF) indicating that they could predict when the coagulation reserve of the patients has to be supported by rFVIIa to have blood less surgery.

To our knowledge no study investigated the ability of Rotem to predict blood transfusion during liver transplantation. However, Cammerer et al. [34] and Davidson et al. [35] found preoperative Rotem analysis was not useful in predicting those patients who would bleed excessively after routine cardiac surgery but unlike current study, they did not exclude multiple factors influencing blood loss in such operation including surgical causes so positive predictive value as large as the negative predictive value cannot be expected.

Blood loss during liver surgery is a complex issue affected not only by the clotting reserve but also by operative procedures and presence of other factors such as portal hypertension which may play a more important role in the bleeding tendency of these patients [36]. Exclusion of cases with surgical bleeding mishaps as vascular injury could improve the ability of Rotem to predict intraoperative bleeding.

Regarding response to rFVIIa, RAB (non responders) group had the worst ROTEM values which are significantly disturbed compared to those values of RNB group. Marcin Wasowicz et al. [37] found that patients with abnormal baseline TEG values were less likely to respond to rFVIIa than those with normal baseline TEG values. This can be explained by understanding that for rFVIIa to work in patients with blood loss, an adequate number of clotting substrates need to be present [38-40].

The cut values of response to rFVIIa are both highly sensitive and specific indicating that they can predict rFVIIa responders (better than these values) who achieved bloodless surgery and non-responders (worse than these values) who would need blood transfusion in spite of giving the drug. In agreement with us, ROTEM was found to be more useful for predicting and monitoring the effects of rFVIIa [24,40,41].

Patients with ROTEM values in the range between the cut values of admission and response are most probably good candidate for rFVIIa as an appropriate pharmacological hemostatic support to maintain acceptable coagulability, permitting blood less surgery.

Some of the selected cut ROTEM values in this study were not normal and even, as an absolute values, are triggering levels for transfusion, this may be explained by the strategy for blood transfusion, which depends beside ROTEM parameters on the clinical assessment of the surgical field and holds prophylactic transfusion, unless there is diffuse surgical bleeding.

In this study fibrinogen level was an important factor in response to rFVIIa, because fibrinogen is required for the thrombin burst to produce a fibrin clot [42], Ganter MT et al. [43] in their study of a model of severe dilutional coagulopathy suggest that fibrinogen is a key component in the coagulation process and that adequate levels of fibrinogen should be present before considering the administration of rFVIIa.

Besides ROTEM parameters, this study found preoperative HB level an important factor in achieving blood less LDLT. It was statistically significant higher in NRNB group than RNB group and the latter was significantly higher than RAB group which indicates that a higher HB level is protective against transfusion in the absence of surgical bleeding. Some Studies [44-46] concluded that preoperative HB seems to be one of the most significant predictive factors for intraoperative

RBC transfusion requirements and preoperative normalization of HB levels can diminish the number of blood transfusions during LT.

There is no fixed recommended dose of rFVIIa in LT. The selected dose of rFVIIa followed our institute protocol and it was lower than some recommendations. Ranucci et al. [47] recommended dose of at least 50 ug/kg to achieve a significant effect. Other studies, however, have recommended lower doses [38,48]. The protocol of rFVIIa administration aims to limit its effect to dissection and hepatectomy phase as it could theoretically precipitate thrombosis in transplantation surgery as the endothelium in transplanted organs may expose TF due to ischemia-reperfusion [49]. Two studies [40,50] noticed that rFVIIa increased the clot strength in a dose-dependent manner as measured by TEG. However, whether this is similarly useful and safe in RAB group can be investigated on risk-benefit ratio bases in a future study.

In spite of exclusion of cases with history of thrombosis, the relatively low dose of rFVIIa with early administration away from reperfusion phase and the local institution protocol of postoperative thromboprophylaxis, we recorded 4 cases of vascular thrombosis. The role of rFVIIa as an inducing agent is difficult to be estimated due to other contributing factors as surgical vascular anastomosis. Safety of rFVIIa in OLT patients has been demonstrated in previous trials [9,12,13]. Nevertheless, a few thrombotic events as cerebrovascular events, myocardial ischemia and portal vein thrombosis in patients with advanced liver disease following rFVIIa administration have been reported [51,52] thus raising some concerns regarding its safety and making its rational use mandatory in this setting.

Cost issues of such an expensive drug cannot be ignored, especially in the face of a rapid rise in health-care costs. Haemostatic support of RAB group, including price of both rFVIIa and given blood products, was significantly higher than RNB group, and it was zero in NRNB group. Evaluating cost effectiveness is not easy [53] considering the indirect and long-term effects of blood product administration.

Blood loss was significantly higher in RAB group compared to RNB group, which may be explained by the lowest coagulation reserve as indicated by worst ROTEM values. While the comparison was insignificant between RNB and NRNB group indicating that rFVIIa could improve the blood coagulability to a level allowed comparable blood loss with NRNB group. This was reflected as significant higher colloid transfusion in RAB compared with RNB group. Cell saver was not used for any of the cases as it was not available in our institute at the study period. Traneximic acid was given to 9 cases 2 cases in NRNB group, 3 cases in RNB group and 4 cases in RAB group. It is to note that one of the multiple advantages of the ROTEM is to give information not only about the formation of the clot but also about the dissolution of the clot which provides real-time recognition of hyperfibrinolysis and allows early treatment [54].

RFVIIa has no effect on hyperfibrinolysis, as explored in vitro in the study by Dirkmann et al. [55] using thromboelastometric assays of whole blood and by Lisman T et al. [56]. Therefore, before administering rFVIIa, adequate levels of fibrinogen should be ensured, and direct acting antifibrinolytic agents should be used, if required.

In this study the RAB group tended to have the highest MELD values but the comparisons of RAB group and RNB group and that between NRNB group and RNB group were insignificant. In this study MELD failed to predict patients who would response to rFVIIa to achieve bloodless surgery. In the 3rd group (RAB group) MELD score did not correlate with any blood products required. This is consistent with the study by Massicotte et al. [57] and the study of Rouillet et al.

[29] who concluded that MELD score did not appear to be a risk factor for bleeding or transfusion requirements during OLT.

Of limitation is that we stacked to a fixed dose of rFVIIa according to local institution protocol, which did not allow evaluation of dose/response relationship. Also the small number of cases that may not allow firm judge. In conclusion, this study does not recommend indiscriminate administration of rFVIIa, as a prophylactic haemostatic support during LT. Selected ROTEM cut values may help rational prophylactic rFVIIa use, considering safety and cost, to achieve bloodless surgery. Preoperative hemoglobin is another important parameter. Regarding non responders, correction of preoperative HB and trying higher rFVIIa doses may improve response. The balance between risk and benefit should guide our decisions as long as rFVIIa is available for off-label use. A large-scale study is required to get firm guidelines.

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