

Preoperative Low Dose Recombinant Activated Factor VII Effect during Liver Transplantation

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Abstract

Background: End stage liver disease patients are prone to coagulopathy and frequently require blood transfusion during transplantation.

Methods: Prospective study (2008-2011) to investigate the effect of prophylactic intravenous administration of low dose recombinant activated factor VII (rFVIIa) (20 µ/kg) 30 min prior to surgery and repeated one hour later on Standard Coagulation Tests (SCTs), Rotational Thromboelastometry (ROTEM) and Blood Transfusion (BT) requirements during Living Donor Liver Transplantation (LDLT). SCT include Prothrombin Time (PT), International Normalized Ratio (INR) of prothrombin time, Activated Partial Thromboplastin Time (aPTT), fibrinogen and platelets blood levels. ROTEM include EXTEM and INTEM representing coagulation extrinsic and intrinsic pathways respectively, and FIBTEM for fibrinogen activity. Blood transfusion was guided by ROTEM parameters. Control group (C), n=25 and rFVII group, n=25.

Results: Both groups preoperative MELD scores, ROTEM and SCTs were comparable (P>0.05). After initial dose to end of dissection, a reduction in INR and aPTT in rFVII group versus control were observed, associated with a reduction in clotting time (CT) and increased alpha angle in ROTEM (P<0.05) with no hypercoagulability or thromboembolic findings. Mean BT reduced significantly in rFVII group (p<0.05). 4% of controls received no BT versus 36% in rFVII group (P<0.05). Duration of dissection, hemoglobin (HB) at induction were comparable (p>0.05). BT correlated positively with dissection time (r=0.7, p<0.01), but weakly with preoperative HB (r=-0.3, p<0.05).

Conclusion: Low dose rFVII monitored by ROTEM improved coagulation and reduced BT requirements with no evidence of thromboembolic events. Dissection time was another important contributing factor.

Keywords: Recombinant factor VII; Liver transplant; Coagulopathy; Blood transfusion

Introduction

Recipients undergoing liver transplantation require varying amounts of blood products due to the haemostatic changes relating to severity of the end stage hepatic dysfunction, portal hypertension and collateral circulation [1]. The procedure still carries a risk of excessive blood loss that is associated with a higher risk of morbidity and mortality [2-4].

Activated recombinant factor VII (rFVIIa) was initially introduced to treat hemophilic patients, but during the last years, it had been proposed for a large number of off-label treatments [5]. Prophylactic intraoperative correction of coagulopathy in patients with end stage liver disease undergoing liver transplantation with rFVIIa was investigated previously by several studies but frequently at higher doses and with different outcomes [6-8]. The impact of a prophylactic intravenous administration of rFVIIa at a low dose (40 µ/Kg), prior to the surgical incision and during adult living donor transplantation will be the focus of this current study. This involves studying the effect on coagulation parameters and blood products transfusion requirements (BT), together with reporting any adverse events observed during the study period with particular focus on vascular thrombosis.

Patients and Methods

After ethical committee approval (MD 15 -2008, Chair of committee Prof Magdy Kamal) at the Liver Institute, Menoufiya University, Egypt and written informed consent, 50 adult patients scheduled for living donor liver transplantation were included in the study. The study

included 50 patients divided into 2 equal groups of recipients for living donor liver transplantation operated upon by the same surgical team.

Exclusion criteria; age <18 years, renal impairment, hypertension, history of genetic coagulation disorder and massive surgical bleeding due to accidental vascular injury. Patients were divided into two equal groups: control group (C Group) (25 patients) as a placebo and treatment group (R Group) (25 patients) which received an intravenous infusion of rFVIIa (rFVIIa, Novoseven, NovoNordisk A/S, Bagsvaerd, Denmark) 20 µ/kg, 30 min prior to the induction of anesthesia followed one hour later by another dose to cover the dissection phase. Anesthesia was induced with Propofol 2 mg kg⁻¹, Rocuronium 0.9 mg kg⁻¹ was given to facilitate rapid sequence orotracheal intubation with a cuffed tube. Anesthesia was maintained with Desflurane in oxygen and air mixture (FiO₂=0.4), Rocuronium and Fentanyl to keeping the Spectral Entropy (GE Healthcare, Helsinki, Finland) value between 40 and 60.

Head and extremity wraps, and warmer systems in the form

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of forced warming system (Model 750-Bair Hugger Temperature Management Unit, Arizant Healthcare Inc, USA) was applied to each patient to maintain body temperature and to prevent intraoperative hypothermia during liver resection by keeping core body temperature > 36°C.

Central Venous Pressure (CVP) and Transoesophageal Doppler (TED) (EDM™; Deltex Medical, chichester, UK) passed nasally into the mid-oesophagus till aortic blood flow signals were identified to measure the corrected flow time (FTc) and Stroke Volume (SV) which was used to help guide volume status throughout the procedure [9].

SCT include Prothrombin Time (PT), International Normalized Ratio (INR) of prothrombin time, Activated Partial Thromboplastin Time (aPTT), fibrinogen and platelets blood levels. ROTEM include EXTEM and INTEM representing coagulation extrinsic and intrinsic pathways respectively, and FIBTEM for fibrinogen activity. Blood transfusion was guided by ROTEM parameters.

ROTEM guide intraoperative blood transfusion protocol as prescribed by the study of Gorlinger K [10] was followed in both groups.

Platelets were substituted when maximum clot firmness of (MCFEXTEM)<45 mm and maximum clot firmness of FIBTEM (MCF FIBTEM)>8 mm.

Fresh frozen plasma was administered when clot formation time representing extrinsic coagulation pathway (CFTEXTM) was >240 sec. Haematocrite was kept more than or equal to 25 with packed red blood cells units.

Timing of conventional blood tests sampling was as follows: T1 preoperative, T2 half an hour after the first dose, T3 half an hour after the second dose, T4 at the end of dissection phase, T5 at the end of a hepatic phase, T 6 after reperfusion, T 7 at the end of surgery.

ROTEM (CT, MCF, angle alpha) of EXTEM, INTEM, and MCF FIBTEM were recorded T1, preoperative; T2, half an hour after the first dose; T3 half an hour after the second dose; T4, after reperfusion and T5, at the end of surgery.

Perioperative Doppler Ultrasonography of hepatic vessels was performed after completing the vascular anastomosis, after wound closure and everytwelve hours for 7 days.

Statistical Analysis

Data was collected and entered to the computer using Microsoft Excel before being converted to SPSS (Statistical Package for Social Science) program for statistical analysis, version 13; Inc., Chicago. IL. Quantitative data was shown as mean, and SD. Student t-test was used to compare mean and SD of 2 sets of quantitative normally distributed data, while Mann Whitney test was used when this data is not normally distributed. P-value was considered statistically significant when it is less than 0.05.

Results

Table 1 presented the patients' demographic data. Fifty-two patients were included in the study. Two recipients were excluded, one due to the inoperable conditions of an extending hepatocellular tumor and the other recipient due to severe intraoperative surgical hemorrhage which required massive blood products transfusion.

Results demonstrated in the treatment group (R) a significant

Test name	CT (sec)	CFT (sec)	Angle α	MCF (mm)	ML (%)
EXTEM	38-79	34-159	63-83	50-72	<15
INTEM	100-240	30-110	70-83	50-72	<15
FIBTEM	MCF < 9 mm a sign of decreased Fibrinogen level MCF > 25 mm is a sign of elevated Fibrinogen level				

Table 1: ROTEM parameters of Extrinsicly Activated Thromboelastometry test (EXTEM), Intrinsicly Activated Thromboelastometry test (INTEM) and Fibrinogen Thromboelastometry test (FIBTEM) with normal reference range in a normal volunteer preoperatively [7].

	C Group (n=25)	Rgroup (n=25)	P
Age:	44.84 ± 8.31	44.28 ± 11.20	0.84
MELD:	17.36 ± 3.12	18.40 ± 3.16	0.24
Sex (male/female)	22/3	20/5	0.69
Etiology:			
1-HCV	13	13	
2-HCV-HCC	11	9	
3-Cryptogenic	1	1	
4-Wilson disease	0	1	
5-Alcoholic cirrhosis	0	1	

C, the control group; R, rFVIIa group; HCV, hepatitis C virus; HCC, hepatocellular carcinoma. Data are represented as Mean ± SD

Table 2: The demographic data of the patients involved in the study.

decrease in both the INRand aPTT during the dissection phase, followed by a significant increase after reperfusion until the end of surgery when compared with their preoperative values, while in control group (C) their values were in a steady increase during dissection (Table 2).

The comparison between the two groups revealed that there is statistically significant decrease in R group (P<0.05) in comparison to the C group until the end of the dissection phase after which the comparison was insignificant.

Platelets count showed no significant changes between the two groups throughout the study period. Fibrinogen level showed significant decrease throughout the study period compared with the base line value in both group (Table 2).

The comparison between both groups denotes that the fibrinogen level was significantly lower in rVIIa group after the 1st dose, after reperfusion and after surgery.

ROTEM parameters revealed a significant improvement in clotting time (CT) and angle alpha in both EXTEM and INTEM after the 1st and the 2nd dose in R group when compared to the corresponding base line values and C group values (Tables 4-7).

MCF in EXTEM, INTEM and FIBTEM showed a statistically significant decrease in R group after the 1st dose when compared to its preoperative and C group values. The comparison later was insignificant after the 2nd dose between both groups. Regarding the transfusion requirement, 36% of patients in R group did not receive any blood products in comparison to 4% of the controls. A significant reduction in transfusion of packed red cells, fresh frozen plasma, platelets and cryoprecipitate were reported in R group when compared to the controls as shown in Table 3.

Discussion

In this current study, the prophylactic correction of the coagulopathy with low dose rFVIIa prior to surgery helped significantly to reduce

	Group	T1	T2	T3	T4	T5
INR	C	1.85 ± 0.40	2.10 ± 0.45*	1.91 ± 0.22	2.14 ± 0.30*	2.40 ± 0.27*
	R	1.89 ± 0.43	1.13 ± 0.13*#	1.27 ± 0.17*#	2.29 ± 0.49*	2.56 ± 0.31*
APTT SEC	C	60.90 ± 17	66.84 ± 14.24	77.52 ± 15.7**	90.5 ± 9.9**	92.48 ± 12.30**
	R	58.80 ± 12.57	42.54 ± 9.55**#	58.94 ± 8.69#	96.6 ± 14.8**	92.04 ± 7.56**
Platelets/mm ³	C	58.8 ± 25.9	63.7 ± 24.43	63 ± 13.42	49.1 ± 13.9	47.56 ± 9.97
	R	62.64 ± 27	64.68 ± 26	61.76 ± 19.60	50.08 ± 15.19	50.52 ± 73.13
Fibrinogen (mg/dl)	C	126 ± 37.3	120.6 ± 24.63	93 ± 24.65*	66.7 ± 16.7*	58.8 ± 11.68*
	R	130 ± 75.2	98.8 ± 48*#	89.6 ± 50.7*	55.6 ± 18.*#	49.8 ± 16.34*#

C, Control group; R, rFVIIa group; INR, International Normalization Ratio; T1, preoperative; T2, half an hour after the first dose; T3, half an hour after the second dose; T4, after reperfusion; T5, at the end of surgery. * P<0.05 relative to the preoperative value of the same group is considered statistically significant. # P<0.05 relative to the similar value of C group is considered statistically significant

Table 3: Conventional coagulation changes of both groups.

	C Group	R Group	P
PRBCs (units)	6.36 ± 4.57	2.36 ± 2.531*	<0.001
FFPs (units)	7.52 ± 4.77	1.76 ± 3.072*	<0.001
Platelets (units)	13.44 ± 8.7	4.32 ± 6.8*	<0.001
Cryoprecipitate (Units)	5.80 ± 6.311	2.64 ± 5.75*	<0.05

Data are represented as mean ± SD. C, Control Group; R, rFVIIa Group; PRBCs, Packed Red Blood Cells; FFPs, Fresh Frozen Plasma

*P<0.05 relative to preoperative value of the same group is considered significant

Table 4: Total blood transfusion requirements for both groups.

Variable	Group	T 1	T2	T3	T 4	T 5
EXTEM	C	57.3 ± 10.7	51.6 ± 10.1	46.7 ± 11.4*	42.6 ± 6.8*	38 ± 6.3*
	R	54.9 ± 8.6	59.6 ± 7.1*#	61.8 ± 8.1*#	44.5 ± 7.3*	39 ± 5.5*
INTEM	C	53.8 ± 8.07	51.6 ± 7.05	45.4 ± 5.7*	42 ± 5.8*	39 ± 4.5*
	R	52.4 ± 13.2	60.2 ± 11.1*#	58.6 ± 9.9*#	43 ± 6.6*	40 ± 7.2*

C, control group; R, rFVIIa group; T1, preoperative; T2, half an hour after the first dose; T3, half an hour after the second dose during the dissection phase; T4, after reperfusion; T5, at the end of surgery. *P<0.05 relative to the preoperative value of the same group is considered statistically significant. #P<0.05 relative to the similar value of C group is considered statistically significant

Table 5: Angle alpha in degrees (α) of Extrinsicly (EXTEM) and Intrinsicly (INTEM) Activated Thromboelastometry test for both groups during the study period.

blood products administration. There are no official guidelines or consensus for the off-license use of rFVIIa [11]. Clearance of rFVIIa is approximately 30-35 ml/kg/h in adults, this requires repeating the dose every 2 hours to maintain the effect [12]. A second dose was only given during the dissection phase and this was not repeated to prevent any query about thrombosis of the vascular anastomosis.

The coagulation profile reported in the current study showed a significant improvement in aPTT and INR in the treatment group throughout the dissection phase after which the effect faded away this could be explained due to the relatively low dose given to target the dissection phase. This was also reported by the Surudo et al. study [13] but with a higher rFVIIa dose of 68.4 μ/kg. The effect did not extend further than the dissection phase for fear of thrombosis that can affect the anastomosis vessels.

In this study, Rotem has been used to guide the transfusion requirements and to monitor the effects of recombinant activated factor VII. Fayed et al. [14] in their study used preoperative Rotem parameters to guide rFVIIa administration during liver transplantation to have bloodless surgery, also Wasowicz et al. [15] found that TEG may be a useful tool for predicting response to rFVIIa in the setting of refractory hemorrhage after cardiac surgery. Yuji Hirasaki et al. [16] in a letter to editor in anesthesia and analgesia journal found that Rotem could be a beneficial tool to monitor the effect of this hemostatic agent. Othman

et al. [17] reported an improvement of global haemostatic parameters as early as 15 min following drug administration, with a peak for factor VIIa activity in plasma at the same time. There was a significant correlation between plasma FVIIa and TEG parameters 15 min post injection, and the baseline TEG profile influences the individual post drug administration outcome. Together, these data support the value of TEG not only as an effective monitoring haemostatic test, but also as a tool for individualization of therapy to achieve the best haemostatic and cost effectiveness of rFVIIa therapy. This study showed such a large both intra- and inter-patient variability following in vivo administration of recombinant activated FVII that the authors concluded that the use of either method was unsuitable for dose-response prediction in the clinical setting. Also, Fayed et al. [14] in their study described a group of patients as non responders to rFVIIa at a dose of 40 and identified them using cut off values of some ROTEM parameters and supposed that higher dose may be beneficial. The effect of inter patients variable response may be partially limited by the fact that the base line values of the haemostatic parameters in both groups were insignificant and patients selection in both groups was randomized and the use of ROTEM monitoring. In this study we were dealing with cases with end stage liver disease while kenet et al. [18] were dealing with haemophilia cases with different haemostatic disturbances.

ROTEM demonstrated a significant improvement of all parameters in treatment group when compared to the control except for the maximum clot firmness (MCF) of EXTEM, INTEM and FIBTEM after the second dose, which was not significantly affected; this could be explained due to the associated decrease in fibrinogen blood level rather than the decrease in thrombin generation. Niemann et al. study [19] explained that the repeated dosing of rFVIIa may exhaust and deplete the coagulation reserve which may be aggravated by continuous surgical blood loss and accompanied haemodilution.

Several studies reported a reduction in blood transfusion requirements with similar results and outcome to our current study but they all used higher doses that can reach 3 to 4 times the dose used by the our study. Hendriks et al. [20] used a single dose of 80 ug/kg of rFVIIa prior to skin incision, while Niemann et al. study [21] infused a single mean dose of 58 mg/kg of rFVIIa.

In contrast, to the current results, Planinsic RM et al. and Lodge JPA et al. [7,8] have published two prospective multicentre randomized double blind studies of the prophylactic use of rFVIIa for the reduction of blood loss and bleeding complications in adult liver transplantation. Despite the substantially higher and repeated doses used in their studies, there was no effect of rFVIIa on mean blood loss or blood transfusion. This could be attributed to the fact that both studies used only the conventional coagulation tests as triggers for blood

Variable	Group	T1	T2	T3	T4	T5
EXTEM	C	68.6 ± 9.4	73.7 ± 10.3	78.3 ± 10.8*	151.32 ± 54.78*	161.72 ± 79.29*
	R	70.2 ± 10.7	59.7 ± 12.3*#	56.9 ± 12*#	134.92 ± 40.25*	149.32 ± 75.32*
INTEM	C	188.1 ± 22.6	190.9 ± 19.1	209.2 ± 20.7*	241.44 ± 89.8*	266.2 ± 69.13*
	R	184.6 ± 28.6	149.4 ± 23.2*#	157.8 ± 65.4*#	218.96 ± 94.36*	250.4 ± 75.15*

C, control group; R, rFVIIa group; T1, preoperative; T2, half an hour after first dose; T3, half an hour after second dose during dissection phase; T4, after reperfusion; T5, at the end of surgery. *P<0.05 relative to preoperative value of the same group is considered statistically significant. #P<0.05 relative to the similar value of C group is considered statistically significant

Table 6: Clotting Time in Seconds (CT) of Extrinsically (EXTEM) and Intrinsically (INTEM) activated Thromboelastometry tests for both groups all over the study period.

	Group	T1	T2	T3	T4	T5
EXTEM	C	51.8 ± 9.6	49.4 ± 10.1	45.3 ± 8.4*	43.8 ± 7.3*	41.8 ± 7.5*
	R	52.9 ± 10.6	43.8 ± 9.5*#	44 ± 11.2*	43.9 ± 9.4*	42.8 ± 6.5*
INTEM	C	45 ± 7.3	47.6 ± 5.1	42.7 ± 5.4*	41.6 ± 5.3*	42.7 ± 7.9
	R	46.9 ± 9	41.1 ± 4.07*#	41.6 ± 4.3*	40.7 ± 6.8*	40.4 ± 6.4*
FIBTEM	C	9.41 ± 1.6	9 ± 0.77	8.4 ± 1.01*	7.63 ± 0.6*	7.3 ± 0.6*
	R	9.16 ± 1.2	8.1 ± 0.86*#	7.9 ± 0.9*	7.53 ± 0.52*	7.2 ± 0.7*

C, control group; R, rFVIIa group; T1, preoperative; T2, half an hour after the first dose; T3, half an hour after the second dose during the dissection phase; T4, after reperfusion and T5 at the end of surgery. * P<0.05 relative to preoperative value of the same group is considered statistically significant. #P<0.05 relative to the similar value of C group is considered statistically significant

Table 7: Maximum Clot Formation in millimeter (MCF) of Extrinsically (EXTEM), intrinsically (INTEM) and FIBTEM activated Thromboelastometry tests for both groups.

transfusion regardless of surgical field assessment and the ROTEM guided parameters were not used. Wang SC. Et al study [22] provided clear evidence that thromboelastography-guided transfusion decreases transfusion of fresh frozen plasma in patients undergoing orthotopic liver transplantation.

Kang Y et al. and Bolliger D et al. studies [23,24] also reported that thromboelastography-based algorithms reduce both transfusion requirements and blood loss in cardiac surgery, liver transplantation, and massive trauma. Bolliger D et al. study [24] concluded that haemostatic interventions based on classical coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are of limited value for the Perioperative management of surgical patients.

Another difference is the type of graft as our current study population includes Living Donor Liver Transplantation (LDLT) not cadaveric as in the above studies by Planinsic RM et al and Lodge JPA et al. studies [7,8] as LDLT is accompanied by more improvement in coagulation parameters after reperfusion due to shorter ischemia time.

No thrombotic complications were reported in the current study this could be due to the low dose of the rFVIIa used which only meant to target the dissection phase as demonstrated in the results section.

Meijer K et al. [25] in their study concluded that the rFVIIa use in orthotopic liver transplantation might enhance thrombin generation in a localized and time-limited manner, without causing systemic activation of coagulation. Hendriks et al. study [20] reported one patient developing postoperative hepatic artery thrombosis with a single preoperative dose of rFVIIa but at double the dose used in our current study.

Two studies previously mentioned above [7,8] reported that rFVIIa doses ranging from 20 to 120 ug/kg did not increase the rate of acute thromboembolic complications or other serious adverse events in rFVIIa-treated patients when compared with placebo-treated patients. In contrast thrombotic events as cerebrovascular, myocardial and portal vein thrombosis in patients with advanced liver disease following rFVIIa administration have been reported in two studies [26,27].

One of the limitations in this study was not investigating the economic cost of using rFVIIa and its impact on Intensive care unit and hospital stay.

Another limitation of the study was the inability to use Fibrinogen concentrates and Prothrombin complex concentrates products, as they are not yet available in the Middle East, also the small number of patients in the study, which was the only available number at the study time.

In conclusion prophylactic low dose rFVIIa at 40 microgram/kg significantly improved the coagulation parameters during the dissection phase of living donor liver transplantation, which helped to reduce transfusion requirement, but monitoring coagulation and vessel patency with Doppler should always be available whenever rFVIIa is administered during LDLT. A multicenter study with a larger population would be an appropriate further step to plan.

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