

Use of Recombinant Factor VIIA as a Risk Factor for Graft Loss after Orthotopic Liver Transplantation Due to Hepatic Artery Thrombosis

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Abstract

Background: The genetically engineered recombinant activated factor VII (rFVIIa) was primarily developed for the treatment of bleeding episodes in haemophilia patients with inhibitors. Different outcomes have been described in a number of studies evaluating the off-label use in patients with liver disease and consequently with complex coagulopathies. We here evaluated the use of rFVIIa in patients undergoing orthotopic liver transplantation (OLT). The aim of this study was to determine the safety within this patient population.

Methods: Overall, 1343 OLTs were performed at Hannover Medical School between 2002 and 2014. Out of this group we selected patients having received rFVIIa in the early phase after OLT. We retrospectively analyzed the outcome of patients treated with rFVIIa and compared our findings to those from other transplant centers.

Results: In a single center retrospective analysis we identified eight patients after OLT who received treatment with rFVIIa (0.59%). Five out of eight (62.5%) patients suffered graft loss due to hepatic artery thrombosis (HAT). None of these patients had a history of thrombosis or signs of hypercoagulopathy. 60% of the patients who developed HAT had a primary graft non-function. Interestingly, rFVIIa administration was the only risk factor for HAT and consequently for graft loss in our cohort. Other known risk factors such as cold ischaemic time, number of anastomoses, donor age of > 60 years and CMV status could be excluded.

Conclusion: This study shows that rFVIIa treatment is a highly likely risk factor for the development of HAT and consequently graft loss in patients after OLT. Thus, usage of rFVIIa in this patient population should be avoided.

Keywords: Liver transplantation; Hepatic artery thrombosis; Bleeding; rFVIIa; NovoSeven[®]

Abbreviations: CIT: Cold Ischaemia Time; ESLD: Endstage Liver Disease; FFP: Fresh Frozen Plasma; HAT: Hepatic Artery Thrombosis; HCC: Hepatocellular Carcinoma; ICU: Intensive Care Unit; OLT: Orthotopic Liver Transplantation; PVT: Portal Vein Thrombosis; RBC: Red Blood Cells; rFVIIa: Activated Recombinant Factor VII; TF: Tissue Factor

Introduction

Orthotopic liver transplantation (OLT) is the standard of care and the only definitive treatment for patients with end-stage liver disease (ESLD). The most common indications for OLT in adults in the Western world are all causes of ESLD (69%), malignant diseases (14%) and acute liver failure (9%) [1,2]. While OLT was initially considered an experimental procedure in the 70s, the introduction of novel immunosuppressive drugs like calcineurin- or mTOR- inhibitors and mycophenolate mofetil as well as improvements in surgical techniques have continuously enhanced survival rates and the long-term outcome over the past 15 years [3].

OLT is a major surgical procedure making the occurrence of complications unavoidable. Most life-threatening complications associated with OLT occur within the perioperative period and include primary graft dysfunction, severe infections and technical complications such as hepatic artery thrombosis (HAT) or biliary leaks [4,5]. Although advancement in surgical and pharmacological treatment has led to high rates of graft and patient survival, one major source of post-operative morbidity in patients receiving OLT continues

to be extensive bleeding [6]. Reasons for post-operative bleeding are multifactorial and include technical difficulties and graft dysfunction with ongoing severe coagulopathy.

Extensive bleeding requires various amounts of blood and blood product transfusion. The administration of red blood cells (RBC), platelets and fresh frozen plasma (FFP) as well as coagulation factor concentrate still remains the mainstay of therapy for these disorders [6]. However, general guidelines have not been established and strategies for the management of extensive post-operative bleeding vary between the various liver transplant centers. Assessment of post-operative OLT bleeding complications and subsequent treatment is therefore of paramount importance in ensuring the best possible outcome in transplant therapy as well as a cost-efficient treatment.

The genetically engineered recombinant activated factor VII (rFVIIa; Novo Seven[®], NiaStase RT[®], Novo Nordisk) has been shown to improve coagulopathy and haemostasis in a variety of conditions [7].

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It has been approved by the FDA for the prevention of bleeding during surgery in patients with haemophilia with inhibitors to factor VIII or factor IX, in patients with congenital factor VII deficiency, as well as for the prevention of bleeding in surgical interventions or invasive procedures in Glanzmann's thrombasthenia with clinical refractoriness and/ or platelet-specific antibodies [8].

There has been an increased off-label use of rFVIIa in patients with non-hemophiliac conditions. Some transplant centers have used rFVIIa off-label during or after OLT when conventional haemostatic methods failed to control bleeding [9]. However, arterial and venous thromboembolic adverse events have been reported after treatment with rFVIIa.

The off-label use of rFVIIa in patients with ESLD and consequently with complex coagulopathies undergoing OLT showed inconclusive results in different studies for prophylactic administration [10-12]). In a pilot study with six patients, Hendriks et al. reported reduced blood transfusion requirements after a prophylactic dose of rFVIIa in patients with liver cirrhosis undergoing OLT [13]. However, one patient developed a HAT postoperatively.

A review report analyzed the safety of prophylactic rFVIIa administration upon initiation of OLT in 215 patients with liver cirrhosis, observing no effect on mortality or thromboembolic events [14]. In contrast, off-label use of rFVIIa in cardiac surgery and in intracranial hemorrhage was associated with an increased risk of thromboembolism [14,15].

No study has comprehensively examined the use and safety of rFVIIa for the post-operative treatment in patients undergoing OLT. The assessment of possible complications with special regard to the development of thromboembolism is therefore of great importance.

The aim of this retrospective study was to analyze the use of rFVIIa in the early post-operative phase in patients undergoing OLT and determine the efficacy and safety within this patient population.

Patients and Methods

In this single-center analysis we retrospectively reviewed 1343 OLTs at the Hannover Medical School Germany between January 2002 and December 2014. All adult patients were screened for post-operative usage of rFVIIa starting two hours after OLT for up to five days. No patients were excluded from this analysis due to loss of follow-up (Figure 1). rFVIIa was available in our center since approval by the European Medicines Agency (EMA) in 1996.

Patient and donor demographics were collected from the electronic

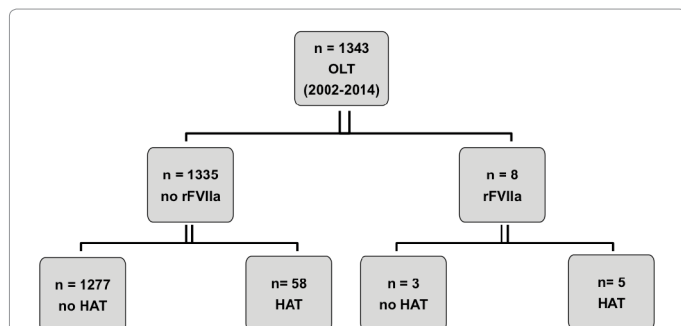


Figure 1: All adult patients were screened for post-operative usage of rFVIIa starting two hours after OLT for up to five days. No patients were excluded from this analysis due to loss of follow-up.

medical records of the Hannover Medical School. The administration of rFVIIa was determined by analysis of operative and post-operative charts and documentation from the local blood bank. The time of rFVIIa administration was obtained by medical and pharmaceutical order entry records. The dose of rFVIIa was determined by pharmaceutical dispensing records.

Severe bleeding was defined as permanent bleeding leading to hypotension, hypervolemia, anaemia (haemoglobin drop of > 5 points) and the need of continuous substitution of packed red cells, FFPs and vasopressor therapy.

Thromboembolic and other severe adverse events as well as primary graft non-function were recorded. Thromboembolic complications were classified as HAT or portal vein thrombosis (PVT). Other recorded clinical outcomes included the need for re-transplantation, the duration of time spent on intensive care unit (ICU) and in hospital. The outcome of patients who developed HAT after rFVIIa treatment was compared to patients without HAT after OLT. Well-established risk factors for the development of HAT after OLT were taken from the literature.

Diagnostic evaluation of thrombosis included laboratory tests, duplex Doppler ultrasound examination and/or contrast-enhanced computer tomographic (CT) scans (VolumeZoom; Siemens, Forchheim, Germany). Ultrasound examinations were performed using a Toshiba Nemio system (pulse inversion, contrast harmonic imaging mode; Toshiba, Otawa, Japan).

The primary clinical outcomes included graft and patient survival five years after OLT, HAT or other thromboembolic events and duration of stay on ICU and in hospital.

Ethical aspects

This study was based on hospital databases and patient medical histories and was performed in accordance with the principles stated in the Declaration of Helsinki. The study had been approved by the local ethics committee of Hannover Medical School, Germany.

Software and statistical analyses

Data were analyzed using Excel (MS Office 2010, Microsoft Corp., Redmond, WA, USA). Unpaired two-sided student's t-test was performed accordingly to determine significance. A p-value of less than 0.05 was considered to indicate statistical significance.

Results

Clinical characteristics of patients treated with rFVIIa

Between January 2002 and December 2012, a total of 1343 OLTs were performed at the Hannover Medical School Germany. Of these, eight (0.59%) adult patients received rFVIIa on the day of OLT or on the first postoperative day.

In seven out of eight patients the indication for rFVIIa administration was severe diffuse bleeding during or directly after OLT (within 6 hours after operation). One patient had a traumatic liver rupture one month prior to transplantation. All patients received additionally high amounts of blood products like RBC, platelets and coagulation factor concentrates. In two cases the graft had a liver laceration with hepatic artery injury due to complications at organ harvesting. 3 out of 8 patients had an initial graft non-function, all of the patients with initial graft non-function developed HAT.

The clinical characteristics of patients treated with rFVIIa are

shown in Table 1. Mean age at the time of OLT was 51 years (range 25-64 years). One out of eight patients was female and all patients were Caucasian. None of these patients had a history of thrombosis or signs of hypercoagulopathy. The main indication for liver transplantation was cirrhosis due to chronic Hepatitis C virus infection (4/8, 50%). Median MELD score was 19 (range 12-40). Two patients had a CHILD-Pugh B and six patients CHILD-Pugh C cirrhosis.

Clinical course and outcome after rFVIIa administration

5 out of 8 patients (62.5%) treated with rFVIIa developed severe HAT 0-6 days after rFVIIa administration (median 1 day, Table 2), while three patients showed no signs of arterial or portal vein thrombosis. The patient treated with the highest dose of rFVIIa also developed a PVT. The dose range of rFVIIa administration was 400-13600 IE in patients who developed HAT and 1200-4100 IE in patients who did not develop thromboembolic events (mean 3680 IE versus 2566 IE, median 1200 IE versus 2400 IE, respectively). None of the eight patients experienced a coronary arterial thromboembolic event. In comparison, the overall rate of HAT development after OLT independently from rFVIIa was 4.3% (58 out of 1335 OLTs).

Ultrasound was performed in eight patients (8/8, 100%) and contrast-enhanced CT scans in five patients (5/8, 62.5%), respectively. Schematic representation of arterial reconstruction by gastroduodenal artery/gastrooduodenal artery (GDA/GDA) branch patch from donor to recipient is shown in Figure 2A. An example of HAT diagnosed by CT scan is shown in Figure 2B.

After diagnosis of HAT, all patients underwent re-OLT. Two out of five patients died 18 and 96 days after OLT, respectively (Table 2).

Patient No.	Age	Sex	Origin	Blood Group	CHILD	MELD	Underlying LD
1	44	m	Caucasian	O	C	18	HBV/HDV
2	53	m	Caucasian	A	C	16	HCV
3	25	m	Caucasian	A	B	14	HCV
4	61	m	Caucasian	A	C	12	HCC
5	64	m	Caucasian	O	B	25	HCV
6	49	m	Caucasian	B	C	40	AIH
7	27	m	Caucasian	A	C	39	liver rupture (traumatic)
8	58	m	Caucasian	A	C	20	HCV

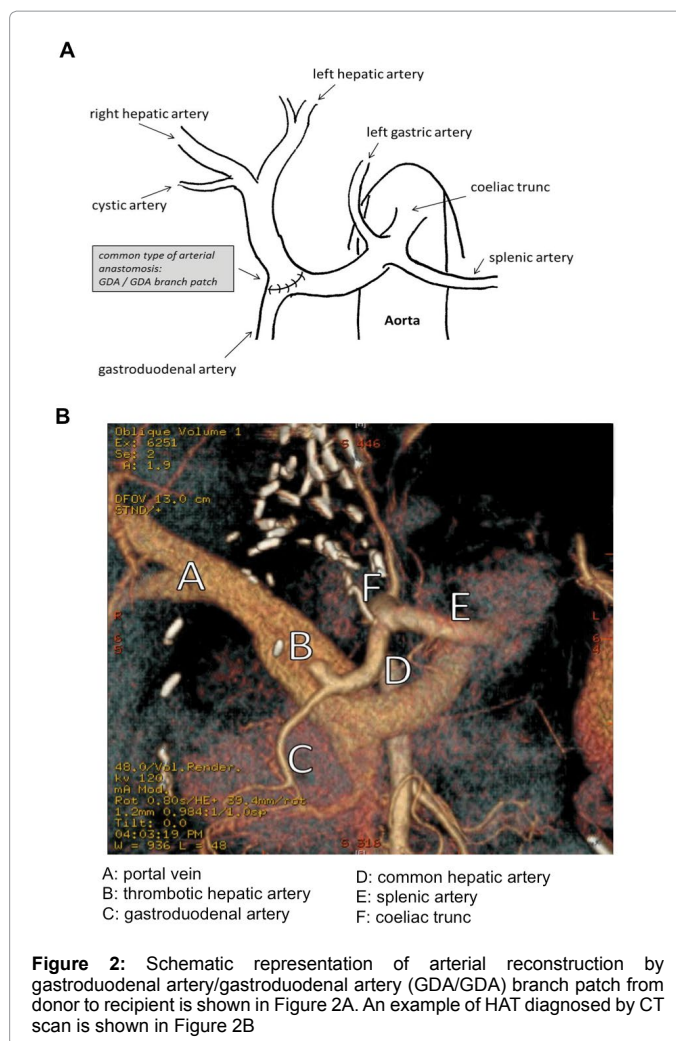
m= male, f= female, LD= liver disease, HCV= Hepatitis C virus infection, HBV= Hepatitis B virus infection, HDV= Hepatitis D virus infection, AIH= autoimmune hepatitis

Table 1: Patient characteristics.

Patient no.	rFVIIa dose (IU)	No. of appl.	Days post OLT	HAT	PVT	Days after rFVIIa	Hospital stay (days)	ICU stay (days)
1	400	1	0	yes	no	0	68	52
2	2400	1	1	yes	no	6	died (d 96)	died (d 96)
3	1200	1	1	yes	no	1	82	48
4	800	1	1	yes	no	4	226	226
5	13600	6	0	yes	yes	0	died (d 18)	died (d 18)
6	1200	2	1	no	no	n.a.	19	7
7	4100	3	1	no	no	n.a.	59	59
8	2400	1	0	no	no	n.a.	34	13

HAT= hepatic artery thrombosis; PVT= portal vein thrombosis; rFVIIa= recombinant factor VIIa; ICU= intensive care unit; appl.= applications

Table 2: Outcome after rVIIa administration.



Both patients died due to sepsis with multiple organ failure. The other three patients had longer ICU and in-hospital stays after re-OLT in comparison to the patients who received rFVIIa but did not develop HAT.

Risk factors associated with HAT after OLT

Furthermore we investigated the role of other well-known factors that are associated with an increased risk for the development of HAT after OLT. As shown in Table 3, there were no significant differences in cold ischaemia time (CIT, mean 11:06 versus 9:00 hours), CMV donor and recipient status, blood group compatibility, number of arterial anastomoses, platelet counts or duration of surgery (mean 207 versus 198 min) between patients developing HAT after rFVIIa administration and patients showing no signs of thromboembolic events. Importantly, there were also no significant differences between type of anastomosis and time needed for completion of arterial anastomoses. Patients developing HAT after rFVIIa administration had higher platelet counts at the time of OLT (mean 115400 versus 55000 μ l). However, the difference was statistically not significant (p=0.3). Another well-known risk factor for HAT after OLT is donor age. This is consistent with our results: mean donor age was significantly higher in patients developing HAT compared with patients who did not (mean age 48.4 versus 20.0

Patient No.	Outcome	CIT (h)	Surgery (min)	No. of Anastomoses	Thrombocytes (tsd/ μ L)	CMV D	CMV R	Donor age* (years)	ABO incomp
1	re-OLT	13:23	180	1	53	D+	R+	57	no
2	re-OLT	7:36	165	1	43	D+	R+	67	no
3	re-OLT	7:00	135	1	273	D-	R-	44	no
4	re-OLT	11:02	320	2	113	D+	R+	40	no
5	re-OLT	16:30	235	1	95	D-	R-	34	no
6	n.a.	6:12	192	1	54	D+	R+	17	no
7	n.a.	8:12	165	1	46	D-	R-	18	no
8	n.a.	12:36	237	1	65	D+	R+	25	no

CIT= cold ischaemia time, D= donor; R= recipient, incomp = incompatibility
 Normal range of thrombocytes: 150-450 tsd/ μ L
 * p = 0.013

Table 3: Other risk factors for HAT.

years, p= 0.013).

Discussion

In this study we report the administration and safety of rFVIIa in patients undergoing OLT in one of the largest German transplant centers. In our cohort, the total number of patients who received rFVIIa treatment directly after OLT is low, however with a decisive outcome: 62.5% of the patients treated with rFVIIa within the first 48 hours after OLT developed a HAT and had to undergo re-transplantation and all of them were treated with rFVIIa due to diffuse bleeding during or directly after OLT. 60% of the patients who develop HAT had a primary graft non-function. Of these, two patients subsequently died due to sepsis and multiple organ failure. In comparison, the overall rate of HAT after OLT was only 4.3%. We therefore identified rFVIIa administration shortly after OLT as a potential risk factor for HAT.

In general, HAT is a rare complication after liver transplantation. Literature analysis reveals that HAT developed in 2-9 % of patients after OLT and is associated with a mortality of up to 50% [16]. In our liver transplant cohort around 4% of the patients developed HAT after OLT over a 12-year period. Known risk factors for HAT are the number of anastomoses, donor age, blood group incompatibility, CMV donor status and a CIT >12 hours [17-20]. In line with these data, the mean donor age of our cohort was significantly higher in patients who developed HAT than in patients who did not experienced any vascular/thromboembolic complication. However, in various studies describing donor age as a risk factor, a donor age of >60 years was associated with a higher HAT rate. In our cohort, the mean donor age was 48.4 years. We therefore do not believe that the donor age was a crucial factor for HAT development in our patients. The administration of rFVIIa shortly after OLT seems a more likely cause for the development of vascular complications. In addition, only one out of five patients who developed HAT after rFVIIa administration had HCC. Even if it has been demonstrated that patients with HCC have a higher risk to develop thrombosis in the portal vein, we could not find any correlation in our cohort.

The causes of thromboembolic events during OLT are complex and multifactorial. Abnormal thrombin generation and platelet function along with a lack of efficacy of the profibrinolytic system may trigger the initiation of a procoagulative process. Many additional factors besides cirrhosis can promote a hypercoagulable state in this setting [4]. Factor VII (proconvertin) is an enzyme of the serine protease class. It binds directly to tissue factor (TF) and then activates the clotting cascade. It then increases thrombin generation cleaving fibrinogen to fibrin, thus initiating the formation of a blot clot [21]. It is well known that TF release is enhanced at the site of arterial anastomoses due to

vascular lesion. Therefore, it is not surprising that the substitution of rFVIIa accelerate prothrombotic events at arterial anastomoses.

rFVIIa (Novo Seven[®], NiasStase[®]) was initially developed for the treatment of patients with haemophilia A and B with inhibitors. It was successfully administered for the first time in 1999 in an Israeli soldier with uncontrollable, life threatening bleeding [22]. Additionally, it has been shown that rFVIIa reduces the rate of hematoma growth in patients with intracerebral haemorrhage [23,24]. However, this treatment did not reduce the mortality or rate of severe disability after intracerebral haemorrhage and is therefore not recommended for treatment in these patients [25].

It is well known that rFVIIa treatment increases the risk of arterial thrombosis. Mayer et al. reported an absolute increase of 5% in the frequency of arterial thromboembolic serious adverse events in the group receiving 80 μ g of rFVIIa per kilogram of body weight [25]. Furthermore, Simpson et al. evaluated the safety of rFVIIa in patients without haemophilia in 29 published studies and found that administration rFVIIa is associated with a significant increase in total arterial events (RR 1.45; 95% CI 1.02 to 2.05) [26]. Overall, the risk for development of arterial thrombosis was higher in older patients (>65 years). In a placebo-controlled trial of 4468 patients, Levi et al. confirmed that rFVIIa increased the risk of arterial thromboembolic events (9% versus 3.8%; [27]).

In our study we also recorded a substantial increase in the risk of developing HAT after OLT. Interestingly, and in contrast to Mayer et al., the total amount of rFVIIa given to a patient does not seem to correlate with the development of thromboembolic events [25].

In a study by Scheffert et al., preventative and intraoperative administration of rFVIIa was compared in patients undergoing liver transplantation. In this study, intraoperative rFVIIa administration was associated with lower graft and patient survival rates as well as longer ICU stays [28]. However, only two out of 41 patients treated with rFVIIa developed HAT. Chavez-Tapaia et al. also reviewed the use of rFVIIa in 265 patients having undergone liver transplantation [9]. Interestingly, the rate of thromboembolic events did not differ significantly between patients who received rFVIIa or a placebo (OR 1.37; 95% CI 0.68-2.77). The most obvious difference to our study is the fact that we did not administer rFVIIa prophylactically. In addition, one has to keep in mind that in patients with severe bleeding, rFVIIa was given in addition to other blood products like RBC, platelets and coagulation factor concentrates.

In contrast to our findings Busani et al. examined the use of rFVIIa in bleeding episodes within 15 days after liver transplantation but did not find any thrombotic events [29]. However, the time point of

application of rFVIIa was different to our cohort (within 15 days) and in particular no other pro-coagulatory factors except frozen plasma and platelets were given. This might be the main reason for the different outcome of our study and could explain the absence of thrombotic events.

Interestingly, four out of five patients developing HAT had a viral hepatitis as the underlying liver disease. To our knowledge there is no data available showing that patients with viral hepatitis have a higher risk for the development of HAT after OLT. In addition, we have to keep in mind that ESLD due to viral hepatitis is the major indication for liver transplantation in Europe [30].

End stage liver disease itself often result in significant reduction in the synthesis of factors involved in coagulation and in factors controlling fibrinolysis. The high frequency of arterial thromboembolic events after administration of rFVIIa in our patients with ESLD undergoing OLT might therefore be a consequence of the changes in the intrinsic coagulation system in addition to the operative procedure (anastomosis of the hepatic artery). Further studies evaluating the safety of rFVIIa in patients with severe bleeding complications after surgery with arterial anastomoses (e.g. heart or lung transplantation) are missing.

The present study has some limitations: the size of the study cohort, the inhomogenous distribution of rFVIIa administration and the retrospective design. However, to our knowledge there is no other study available that has comprehensively examined the use and safety of rFVIIa for the early post-operative treatment in patients undergoing OLT.

In summary, clarifying risk factors for the development of thromboembolic events after OLT is important. Awareness of these risk factors can aid in the prevention of serious adverse events after OLT.

Taken together, these findings suggest that treatment with rFVIIa in the early postoperative phase results in a high rate of HAT in patients after OLT. Therefore, rFVIIa administration shortly after OLT should be avoided in this patient population.

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