

The Use Of Recombinant Activated Factor VII In Small-For-Size Syndrome After Liver Transplantation

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Abstract

A small-for-size syndrome was diagnosed on a 41-year-old patient who underwent a combined liver-kidney transplant using organs from a paediatric donor. The syndrome was clinically, analytically and histologically demonstrated and was mainly characterized by coagulopathy and life-threatening bleeding. Recombinant activated factor VII proved to be a useful drug to improve coagulation while the graft recovered and the syndrome was reversed. The patient is now in good conditions, with fully recovered liver function and kidney functions. rFVIIa could be a useful drug to improve coagulation while the graft recovers and the syndrome is reversed.

INTRODUCTION

There is large evidence suggesting high post-transplant morbidity, including poor organ function and vascular complications, when using paediatric liver donors in adults recipients.⁽¹⁾ One of the most severe manifestations of organ malfunction is small-for-size syndrome (SFSS), which has been observed when grafts smaller than 0.8% of recipient body weight are used, and is mainly manifested by progressive cholestasis, portal hypertension, coagulopathy and abundant ascites.⁽²⁾

Recombinant activated factor VIIa (rFVIIa, NovoSeven®, NovoNordisk A/S. Bagsvaerd, Denmark) is registered worldwide for treating bleeding episodes in haemophilic patients. Still new experiences are being gathered on the use of this haemostatic agent for the management of intractable bleeding in patients without pre-existing coagulopathy.^(3,4) This report outlines a case of a SFSS with severe coagulopathy resulting from an adult liver transplant using a paediatric donor, successfully treated with rFVIIa, while recovering.

CASE REPORT

A 41-year-old man with chronic hepatitis C and advanced liver disease (recurrent encephalopathy and severe fatigue, Child-Pugh score: B7, UNOS: 2), with associated end-stage renal disease secondary to mesangial IgA glomerulonephritis and previous history of failed kidney transplant, was

scheduled for combined liver-kidney transplantation. At the moment of transplantation the patient was on haemodialysis and anthropometrics showed that the patient was 161cm tall and weighted 61kg.

The donor, a 9-year-old male, had died from a severe craneoencephalic traumatism, with a weight of 40 kg and a stature of 137 cm. The recipient underwent orthotopic liver transplantation, without venovenous by-pass using standard surgical technique.⁽⁵⁾ The graft was reperfused after 355 minutes of cold ischaemia time and 37 minutes of warm ischaemia time. Resulting Donor Liver Weight (DLW)/Estimated Recipient Liver Weight (ERLW) ratio was 0.7 when used as an indicator of graft size matching.⁽⁶⁾ There was immediate function of the liver and after complete haemostasis was achieved, heterotopic kidney transplant was performed in left iliac fosse using standard technique.⁽⁷⁾ Total blood requirements for the combined procedure were 11 U of packed cells, 11 U of fresh frozen plasma, and 7 U of platelets.

The immediate postoperative course was characterized by delayed kidney graft function (creatinin 7.40 mg/dl), requiring haemodialysis. Initial liver function seemed to be preserved, although there was certain tendency to prolonged Prothrombin Time (figure 1). On the following days, hyperbilirubinemia was manifested, with a clear coagulopathy and bleeding (figures 1 and 2). On day 4,

bleeding became severe and generalized with manifested hemodynamic instability. A laparotomy showed general oozing and no specific site for bleeding. Abdominal clots were removed, a liver biopsy was made, and two subsequent rFVIIa doses of 240 KIU (70µg/kg) were given, in an attempt to re-establish haemostasis.

Figure 1

Figure 1: Coagulation times variations during post transplant days. Arrows indicate the moment of rFVIIa usage. PT. Prothrombin Time, PTT. Partial Thromboplastin Time.

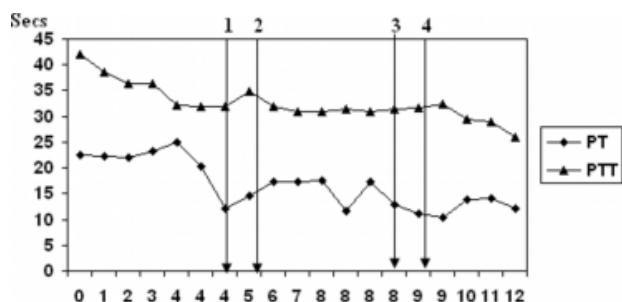
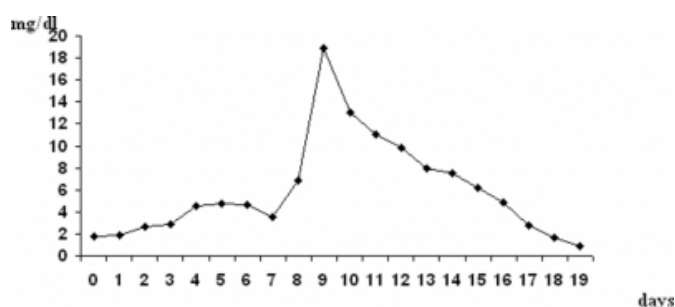


Figure 2

Figure 2: Progression of serum total bilirubin over post transplant days.

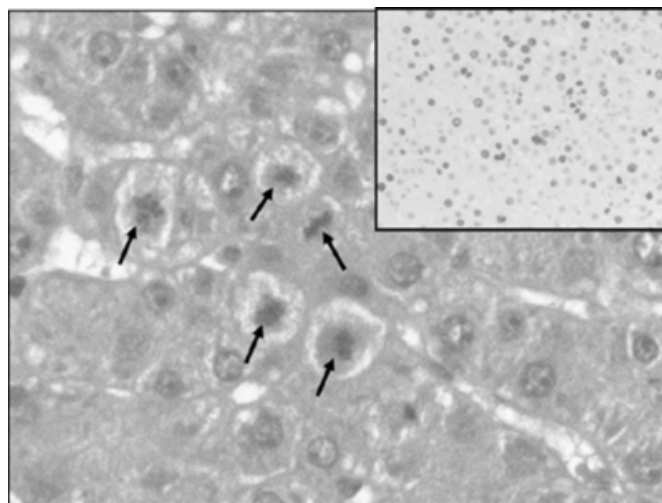


Liver biopsy showed neither ischaemic nor rejection changes. Mitotic figures were numerous in hepatocytes, and immunoperoxidase stain for MIB-1 (Ki-67) was positive in more than 25 % of hepatocytes (figure 3). MIB-1 is a protein expressed by proliferating cells in late G1, S, G2 and M phases. It is detected by MIB-1 (Ki-67) monoclonal antibody staining technique, which is a promising tool for assessing cell proliferation on routine histological material. A MIB-1 cut off of 25% is adequately identified as high proliferation index.⁽⁸⁾

Based on the fact of using a small paediatric donor, the sustained hyperbilirubinemia, the manifest coagulopathy and the high proliferating rate of hepatocytes, the diagnosis of SFSS was made.

Figure 3

Figure 3: Liver biopsy on post transplant day 4 showing dividing hepatocytes with numerous mitotic figures (arrows). HEx200. Inset: positive immunoperoxidase stain for MIB-1 (Ki-67) is seen in more than 25 % of hepatocytes.



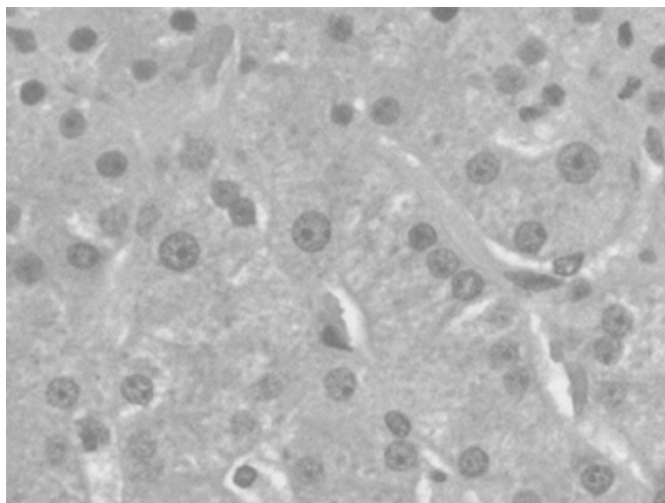
days

The patient continued under medical treatment and two further rFVIIa doses were required on day 8 because of severe bleeding and significant hematocrit decapitation, in spite of no peak coagulogram deviations. These complementary rFVIIa treatment resulted successful in controlling bleeding and in decreasing the need for blood products.

Gradual normalisation of liver function was achieved, as well as partial kidney graft function. A liver biopsy on day 30 showed normal structure of liver plates without proliferation of hepatocytes, and a proliferation index less than 1% on MIB-1 staining technique (figure 4), corresponding with clinical status and laboratory results.

Figure 4

Figure 4: Biopsy taken on post transplant day 30 showing a normal structure of liver plates without proliferation of hepatocytes (HEEx200). MIB-1 staining was positive in less than 1% (image not included).



The patient is now symptomatically well and discharged from the hospital four months after the combined transplant, with fully recovered liver and kidney functions.

DISCUSSION

Although paediatric donor livers are ideally used for paediatric recipients, they are occasionally allocated to adult recipients. Several studies have focused on the safety of using paediatric donor livers on adults and results remain controversial. Still there is a general agreement in an increased morbidity for such transplanted patients and eventually lower graft survival. Vascular complications, specially hepatic artery thrombosis, have been highlighted as one of the main reasons for decreased graft survival, being reported as high as 40%.⁽⁹⁾ Yet, the main risk with those grafts is that they may fail secondary to inadequate liver volume.^(1,9)

Experiences with living related liver transplantation in adults have shown that graft weight to recipient body weight ratio (GRBWR) should be close to 1 to ensure a proper balance between liver regeneration and liver function, and avoid SFSS.⁽²⁾ Further studies have demonstrated more accurate estimation by using the DLW/ERLW ratio, being 0.4, the safety threshold for this indicator.⁽²⁾

This paper reports a documented SFSS in an adult receiving a paediatric liver. Even when the donor was only 9 years old, weight matching was within tolerated range and the DLW/ERLW ratio was 0.7. We therefore hypothesized that

the syndrome could have been caused by a hyperperfusion injury from excessive portal vein inflow and not for insufficient liver mass, as previously described.⁽⁶⁾

Coagulopathy and subsequent bleeding became a life-threatening condition for this patient, and based on personal and reported experiences, we decided to use rFVIIa as a rescue drug.⁽¹⁰⁾ Satisfactory results were obtained with only two pairs of separated doses, allowing better coagulation status and lower blood products consumption, as a bridge therapy until liver graft recovery was fully achieved.

In conclusion, the use of paediatric livers in adults may always be at risk of developing a small-for-size syndrome. Should that occur, recombinant activated factor VII could be a useful drug to improve coagulation while the graft recovers and the syndrome is reversed. Yet, further studies are required to evaluate the insight of this treatment, the potential risk of thrombosis and assays for validation.

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