

Title:

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Liver transplantation in hemophilia A and von Willebrand disease type 3: perioperative management and post-transplant outcome

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ABSTRACT

Introduction: infection with the hepatitis C virus (HCV) causes significant morbidity and mortality in patients with hemophilia. Finally, patients are considered for a liver transplantation (LT) due to cirrhosis and/or hepatocellular carcinoma (HCC).

Material and methods: we report the cases of congenital coagulopathy and HCV infection that underwent LT in our institution. There were three patients with hemophilia A and one patient with von Willebrand disease (vWD) type 3. The coagulopathy outcome, perioperative management, factor and blood product usage and post-transplant survival were assessed. The deficient factor was initially administered in a direct bolus one hour before surgery with a target level of 100 IU/dl, which was sustained until stable hemostasis was reached.

Results: all three patients with hemophilia A were cured of their coagulopathy following transplantation. Factor VIII (FVIII) was 93 IU/dl at eleven years, 59 IU/dl at 13 months and 109 IU/dl at nine months post-transplant, in each case. The mean perioperative usage of FVIII concentrates was 175 IU/kg; concentrates were infused for an average of 36 hours post-transplant. The natural course of the bleeding symptoms of the patient with type-3 vWD was attenuated, with no detectable hemostatic levels of von Willebrand factor antigen (vWF:Ag) after transplantation.

Conclusions: after transplantation, hemophilia A cure and improved bleeding phenotype of type-3 vWD reduced morbidity and mortality. However, potential graft reinfection with HCV and relapsing HCC cast a shadow over these optimum results.

Key words: Hemophilia. Von Willebrand disease. Hepatitis C. Liver transplant.

INTRODUCTION

During the 1970s, the vast majority of the population with hemophilia and to a lesser extent of the population with von Willebrand disease (vWD) were infected with hepatitis C virus (HCV). This was due to the transfusion of blood products and coagulation factor concentrates. The cumulative incidence of advanced liver disease and hepatocellular carcinoma (HCC) was very similar for patients with hemophilia and those with vWD. According to some studies, around 3-6% of hemophiliacs with HCV-related cirrhosis developed HCC every year (1). Liver transplantation (LT) became the sole potentially curative treatment available for advanced liver cirrhosis and early-stage HCC.

In 1985, the first LT procedure was successfully carried out in Pittsburgh in a 15-year-old patient with hemophilia A and active chronic hepatitis (2). In Spain, the first LT procedure was performed in 1995 at Hospital La Paz, Madrid, in a 5-year-old child with hemophilia A and congenital biliary atresia (3). With regard to vWD, initial LTs performed in 1975 in pigs with the same condition resulted in ephemeral, modest increases in the vWF antigen (vWF:Ag) (4). In 1991, Mannucci et al. reported the case of a patient with type-3 vWD who underwent LT due to HCV-associated HCC (5). There was no increase in vWF ristocetin cofactor (vWF:RCo) or vWF:Ag activity following transplantation. However, the bleeding episodes subsided considerably, which represented a phenotypic shift to type-1 vWD. Overall, the experience reported in hemophiliacs undergoing LT TH (6-8) has been satisfactory thus far, both in terms of their congenital coagulopathy and liver disease.

We report about four patients diagnosed with congenital coagulopathy and HCV infection who underwent LT at the Hospital Clínico Lozano Blesa, Zaragoza, Spain. The goal was to assess the clinical and biological course of congenital coagulopathy, to quantify the usage of the deficient factor and blood products perioperatively and to monitor the HCV serology and/or viral load both pre- and post-transplant.

METHODS

This was a retrospective, observational study. All patients diagnosed with congenital coagulopathy who received a liver transplant from December 1998 (start-up of the LT program at our site) to January 2018 at the Hospital Clínico Lozano Blesa, Zaragoza, Spain, were included. Three patients had mild hemophilia A and one had type-3 vWD. Clinical and laboratory data were retrieved from the medical records. Information was collected via telephone contact with patients and the practitioners involved for cases in follow-up in other centers. The presence of anti-FVIII neutralizing antibodies (inhibitors) was ruled out. Inhibitors reduce the efficacy of replacement therapy and result in a higher morbidity.

Perioperative hemostatic protocol

All patients received replacement therapy for their specific factor deficiency as IV bolus during the perioperative period. Exogenous administration of deficient factors was deemed necessary over a few hours until the healthy grafts started to synthesize FVIII:C in hemophilia A cases. Recombinant FVIII (rFVIII) concentrates (Refacto®) were used for patients with mild hemophilia A; vWF and FVIII concentrates (Haemate-P®) were used for patients with vWD type 3. Concentrate administration was initiated one hour before surgery in doses estimated to achieve a target factor level of 100 IU/dl.

Hemostatic status was frequently monitored during the procedure via prothrombin time, activated partial thromboplastin time, platelet count and fibrinogen levels, in order to guide blood product administration. FVIII:C (in hemophilia A patients) and FVIII:C, vWF:RCo and vWF:Ag (in vWD patients) monitoring was performed at 12-hour intervals on the first day and at 24-hour intervals thereafter. Administration was discontinued following a good hemostatic control. Patients with thrombocytopenia received preoperative platelet transfusions in order to increase the platelet count to $100,000 \times 10^9/l$.

Immunosuppression protocol

The standard immunosuppression regimen in our site included tacrolimus or cyclosporine and corticosteroids. Some patients with impaired kidney function received mofetil mycophenolate or everolimus.

RESULTS

Four male patients with a mean age of 58 ± 6 years, diagnosed with congenital coagulopathy and HCV-related chronic liver disease, received a liver transplant. None were seropositive for

HIV. Patient clinical data (age, sex, liver disease, relapsing tumor, recurrent HCV, survival), laboratory values (pre- and post-transplant coagulation panel) and donor characteristics (age, sex) are listed in table 1.

Case report 1

A 52-year-old male with mild hemophilia A (FVIII = 13 IU/dl) and Child-Pugh B grade HCV-1b-related cirrhosis for the past 14 years underwent an LT due to stage A liver carcinoma according to the Barcelona Clinic Liver Cancer (BCLC) classification. Surgery was technically challenging due to the graft size, prolonged ischemia and anastomotic issues with the superior vena cava. There was profuse intraoperative bleeding, which required the administration of 12 red blood cell concentrates (RBCs) and eight units of fresh frozen plasma (FFP) during the perioperative period. Replacement therapy with rFVIII concentrates was maintained for eight hours post-transplant. The patient required a total of 179 IU/kg during the perioperative period. The FVIII level was 109 IU/dl at 4.5 months post-transplant. Tacrolimus was administered during the postoperative period but was soon replaced by cyclosporine due to renal toxicity. HCV recurrence was noted at one year post-transplant. The patient received pegylated interferon and ribavirin and maintained a sustained virological response (SVR). Eleven years after transplantation, the patient remains alive, with a stable liver function and a FVIII level of 93 IU/dl.

Case report 2

A 57-year-old male patient with mild hemophilia A (FVIII = 25 IU/dl) developed BCLC stage-A hepatocellular carcinoma due to alcoholic cirrhosis and HCV infection. HCV-RNA levels (RT-PCR) were undetectable and he was positive for anti-HCV antibodies that were subsequently negative without treatment prior to transplantation. The viral load was undetectable post-transplant. The LT was uneventful and no blood product transfusions were required. A total of 194 IU/kg of rFVIII treatment was used during the perioperative period and factor replacement was required until 48 hours after transplantation. The FVIII level was 59 IU/dl at 13 months after the procedure. The patient has been on immunosuppression therapy with tacrolimus until now. He is still alive at 41 months post-transplant and his liver function shows no impairment.

Case report 3

A 58-year-old male with mild hemophilia A (FVIII = 20 IU/dl) and Child-Pugh B grade HCV-1b-related cirrhosis was managed with pegylated interferon and ribavirin. He then received sofosbuvir and daclatasvir due to a detectable viral load and responded with undetectable levels prior to transplantation. The patient underwent an LT due to frequent decompensation events manifesting with edema and ascites, which was uneventful. He required two RBCs during the perioperative period. In all, the rFVIII concentrate administration amounted to 152 IU/kg, which was maintained until 48 hours after surgery. The FVIII levels rose to 109 IU/dl at nine months post-transplant. He received immunosuppression therapy with tacrolimus and mofetil mycophenolate. The patient is still alive at 27 months after transplantation and the liver function remains within the normal range.

Case report 4

A 67-year-old male with vWD type 3 (FVIII = 5 IU/dl, vWF:Ag < 1 IU/dl, vWF:RCo < 1 IU/dl, and overall impairment of platelet function tests) on regular (three times a week) prophylaxis with Haemate-P®. He also had Child-Pugh A grade HCV-3a-related cirrhosis for more than 20 years and a positive viral load, despite antiviral therapy with alpha and beta interferon plus ribavirin. He underwent a LT due to BCLC stage-A hepatocellular carcinoma, with a favorable outcome; 468 IU/kg of Haemate-P® was used during the perioperative period and was maintained until day 10 post-transplant. The patient received a total of five RBCs, three units of FFP and one of platelets during the perioperative period. He started an immunosuppressive regimen with tacrolimus.

During follow-up, the vWF:Ag and vWF:RCo levels remained impaired, with values of approximately 3 and 1 IU/dl, respectively. The FVIII level was 12 IU/dl at 30 months post-transplant. However, the patient had a favorable phenotypic shift in his coagulopathy, which allowed prophylactic therapy to be discontinued. He was re-infected with HCV early during the post-transplant period. The hepatocellular carcinoma relapsed four years later, which led to his demise at 63 months post-transplant.

DISCUSSION

LT for liver cirrhosis secondary to infection with HCV was a curative therapy for congenital coagulopathy in all three patients with hemophilia A. Correcting hemophilia A was also a relevant factor for the absence of post-transplant morbidity and the survival of all three cases. These patients still have well-functioning grafts as of today.

With regard to the patient with type-3 vWD who underwent an LT due to HCV-related cirrhosis and HCC, no hemostatic levels of vWF:Ag were detected and bleeding symptoms improved considerably. This allowed prophylactic treatment with Haemate-P® to be discontinued. His postoperative period was uneventful and the liver function was normal post-transplant.

A stringent control of perioperative coagulation parameters is required in patients with congenital coagulopathy undergoing surgery for appropriate deficient factor replacement. Dosing regimens for deficient factor concentrates vary among reported studies (9). The optimal factor plasma levels and treatment duration required to prevent bleeding complications during invasive procedures are not definitively established. Hermans et al. (10), on behalf of the European Hemophilia Therapy Standardization Board (EHTSB), reviewed 35 clinical studies regarding replacement therapy for major invasive procedures. In most studies (26/31), target plasma levels for patients with hemophilia A were above 80 U/dl (10). In our patients with hemophilia A, the perioperative administration of rFVIII concentrates was maintained for an average of 36 hours post-transplant (range: 8-48 h). This is consistent with the experience of other authors (6). The average amount of FVIII that was perioperatively administered was 175 IU/kg.

Deficient factor concentrates may be administered using intravenous boluses, continuous infusion or both. Boluses were used in our center, since exogenous factor supply is deemed necessary for just a few hours in the LT setting. Some authors have pointed out that perioperative transfusion requirements in patients with hemophilia A or vWD that undergo LT, regardless of severity, are similar to those of non-hemophiliacs (5), provided that adequate replacement therapy is provided, even though LT is a surgery with a high bleeding risk. Transfusion requirements were not high for our patients, except for case no. 1. High doses of RBCC and FFP were administered in this patient, mainly due to the complex surgery during the hepatectomy phase of the LT.

Previous studies have shown that survival rates in hemophiliacs undergoing LT do not differ from those of non-hemophiliacs (11). In our study, all three patients with hemophilia remained alive at 12 years and 41 and 27 months post-transplant. In one of the scarce Spanish series reported (eleven patients) (7), overall survival after transplantation was 91% (eleven patients with hemophilia A or B who underwent LT between 1995 and December 2008 at six Spanish hospitals).

Re-infection with HCV and relapsing HCC shorten survival for LT patients. Overall, liver graft re-infection with HCV is considered as a universal event for all individuals transplanted with a positive viral load. Two of our patients, one with hemophilia A (case no. 1) and the subject with vWD type 3 (case no. 4), had a HCV re-infection of the liver graft. Furthermore, the latter patient had relapsing hepatocellular carcinoma, which caused his demise.

Data reported in the literature on type-3 vWD patients undergoing LT are controversial and limited due to the low prevalence of this congenital coagulopathy (approximately one case per million). This results in a virtually undetectable production of vWF:Ag. Mannucci et al. (5) found that a healthy liver only generates a small proportion of the overall vWF:Ag pool, a fraction much smaller than that required to rectify the primary defect. Similarly, Lechler et al. (12) observed a modest increase (2 IU/dl) in vWF:Ag levels following LT, in a patient with type-3 vWD. There was increase in vWF:Ag and vWF:RCo levels in our patient with type-3 vWD, with values around 3 and 1 IU/dl, respectively. However, the VIII F:C levels rose from 5 IU/dl to 12 IU/dl at 30 months post-transplant. Prophylaxis treatment with Haemate-P® that the patient required before transplantation could finally be discontinued. With regard to the cases reported by Schulman et al. (13) and by Ghinolfi et al. (14), replacement therapy had to be maintained after LT with halved doses of vWF/FVIII. In the published accounts of patients with vWD undergoing LT, short survival primarily resulted from HCV recurrence and/or tumor relapse. Our patient with type-3 vWD died at 63 months after transplantation due to relapsing hepatocellular carcinoma. A multidisciplinary approach is key for an appropriate LT candidate selection and bleeding risk minimization. Optimal doses and dosing intervals to achieve a successful hemostasis have not been established and vary significantly from one site to the next.

To conclude, LT in patients with end-stage liver disease and hemophilia A cures the congenital coagulopathy, which in turn facilitates a favorable course with no bleeding complications post-transplant. Experience with LT in patients with type-3 vWD is very limited. Following LT, patient outcome was modestly favorable from a congenital coagulopathy biologic perspective, while the clinical benefits were substantial, as reflected by a decrease in bleeding events.

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Table 1. Characteristics and coagulation studies (pre-transplant and the last follow-up post-transplant) of four patients with congenital coagulopathy that underwent a liver transplant at the Hospital Clínico Lozano Blesa

| Pat. no. | Recipient sex/age | HCC [†] | Tumor relapse | Recurrent HCV [§] | Sv (months) | Donor sex/age | Factor VIII:C [¶] (60-120 IU/dl) | | vWF:Ag ^{**} (50-150%) | | vWF:RCo ^{††} (50-150%) | |
|-----------------------|-------------------|------------------|--|----------------------------|---------------------------|---------------|---|------|--------------------------------|------|---------------------------------|------|
| | | | | | | | Pre | Post | Pre | Post | Pre | Post |
| 1 H.A.* | M/52 | Yes | No | Yes (treated, cured) | 149 | M/49 | 13 | 93 | | | | |
| 2 H.A.* | M/57 | Yes | No | No | 41 | F/41 | 25 | 59 | | | | |
| 3 H.A.* | M/58 | No | - | No | 27 | F/39 | 20 | 109 | | | | |
| 4 vWD [‡] | M/67 | Yes | Relapsing HCC at 3 years post-transplant | Yes (treated, not cured) | 63 (death) | M/69 | 5 | 12 | 1 | 3 | 1 | 1 |

*H.A.: hemophilia A; †vWD3: von Willebrand disease, type 3; ‡HCC: hepatocellular carcinoma; §HCV: hepatitis C virus; ||Sv: survival; ¶FVIII:C: coagulating factor VIII;

**vWF:Ag: vWF antigen; ††vWF:RCo: vWF ristocetin cofactor. ||As of 01/01/2018.