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CASE REPORT

Donor heparinization is not a contraindication to liver transplantation even in recipients with acute heparin-induced thrombocytopenia type II: a case report and review of the literature

R. Bachmann,[1] S. Nadalin,[1] J. Li,[1] J. Lange,[1] R. Ladurner,[1] A. Königsrainer[1] and A. Heininger[2]

1 Department of General Visceral and Transplant Surgery, University Hospital Tübingen, Tübingen, Germany
2 Department for Anesthesiology and Intensive Care Medicine, University Hospital Tübingen, Tübingen, Germany

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Correspondence
Robert Bachmann MD, Hoppe-Seylerstr. 3, Tübingen, Germany. Tel.:/fax: 00497071/2986611; e-mail: robert.bachmann@med.uni-tuebingen.de

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Summary

Heparin-induced thrombocytopenia (HIT) type II is caused by an immune-mediated side effect of heparin anticoagulation resulting in a clotting disorder. In the setting of urgent liver transplantation, the question arises whether a graft from a heparinized donor can be safely transplantated in a recipient with even acute heparin-induced thrombocytopenia type II. We report on a patient with end-stage liver disease and acute HIT II waiting for liver transplantation. Despite the risk of life-threatening complications, an organ procured from a heparinized donor was accepted. Assuming heparin residuals within the graft, the donor organ was flushed backtable with increased amounts of Wisconsin solution. The subsequent transplantation and the postoperative course were uneventful; neither thromboses nor graft dysfunction occurred. Even in acute episode of HIT II with circulating antibodies, a patient may receive an organ from a heparin-treated donor, if adequate precautions during organ preparation are observed.

Introduction

A severe and common side effect of the use of heparin is the immune-mediated development of thrombocytopenia, called heparin-induced thrombocytopenia (HIT) [1]. In HIT, the immune system forms IgG antibodies against heparin when it is bound to a protein called platelet factor 4 (PF4) resulting in platelet activation, leading to thrombocytopenia [2]. The clinical probability of HIT can be scored by the 4Ts test [3]. For screening, the immunologic assays – particle gel immunoassay (PGIA) and heparin/PF4-ELISA – are used to detect antibodies against PF4-/heparin. The confirmative functional assays – serotinine release assay (SRA), heparin-induced platelet activation assay (HIPA) or platelet aggregation test (PAT) – are detecting antibodies that induce heparin-dependent platelet activation [4,5].

Systemic anticoagulation is a requisite part in organ recovery procedure to avoid microvascular thromboses of the removed organs. Heparin residues, e.g. bound to the epithelial surfaces of the allograft, could initiate the coagulation cascade in a recipient suffering from acute HIT. To exclude the risk of life-threatening thromboses or organ dysfunction, some surgeons might refuse to transplant an organ from a heparinized donor in an acute HIT-positive patient.

The purpose of this report was to document the management strategy used during liver transplantation of a HIT-positive recipient, who received an allograft from a deceased heparin-treated donor.

Case presentation

A 57-year-old female patient with end-stage liver disease caused by alpha-1 antitrypsin deficiency and a model of end-stage liver disease (MELD) score of 18 (Child-Pugh C) was urgently admitted to our intensive care unit

because of a hydropic decompensation leading to a perforated umbilical hernia. After surgical repair, a transjugular intrahepatic portosystemic stent shunt (TIPSS) was performed because of therapy refractory ascites. The progressive liver failure with an increased MELD score of 32, the need of catecholamine therapy, the continuing hepatorenal syndrome and the increasing signs of hepatic encephalopathy made a timely transplantation indispensable. Transfusions of fresh frozen plasma, red blood cells or platelets were not required. In this time of immobilization, low-dose intravenous anticoagulation with unfractionated heparin was started as deep vein thrombosis prophylaxis resulting in a significant decrease of the platelet count (Fig. 1). The clinical pretest probability in the 4 **T**-Test (**T**hrombocytopenia, **T**iming of platelet fall, **T**hrombosis, o**T**her cause of thrombocytopenia) showed with six points a high probability for HIT. Fortunately, there was no evidence of thromboses. The antibody screening test done as gel-sedimentation-test and platelet-factor-4 (PF4)/heparin-ELISA showed a high level of heparin-induced antibodies. The result of the HIPA, obtained 7 days later, confirmed the diagnosis of HIT.

On the day that the acute HIT was confirmed by the PF4/heparin-ELISA, Eurotransplant offered a liver from an adult deceased donor matching our patient. At this time point, she had a platelet count of 63 000/µl and no evidence of thrombosis; and her MELD score was 30 (serum bilirubin 24.7 mg/dl, creatinine 1.7 mg/dl, international normalized ratio 1.8).

The hemodynamic situation of our patient was marginal intermittently requiring infusion of norepinephrine despite the treatment with 8 mg desmopressin per day and albumine replacement. Taken together, she was undeniably dependent on intensive care treatment exposing her to the well-known increased hazard of infections, which might in turn lead to a situation prohibiting transplantation. Thus, the liver transplantation was considered highly urgent for this patient despite of a MELD of 'only' 30.

At organ recovery performed by an external explantation team, a standard systemic anticoagulation was carried out with a bolus of 15 000 IU of unfractionated heparin (230 IU/kg body weight) central-venously administered 12 min before clamping the abdominal aorta. For organ preservation, a cold aortal perfusion with 5000 ml of organ preservation solution (University of Wisconsin solution, Viaspan, Bristol-Myers Squibb, Bruessels, Belgium) (77 ml/kg body weight) was performed over 20 min; portal venous perfusion was not carried out. The total surgery time (explantation of liver and two kidneys) took 2:30 hours. Thus, the increased risk of secondary thromboses triggered by potential residues of heparin within the graft had to be weighed against the risk of ongoing end stage liver disease. Finally, the liver from the heparinized donor was accepted.

The backtable preparation of the donor liver consisted in the use of University of Wisconsin Solution with direct flushing of the great liver vessels to wash out the possibly remaining heparin ingredients. The volume was chosen

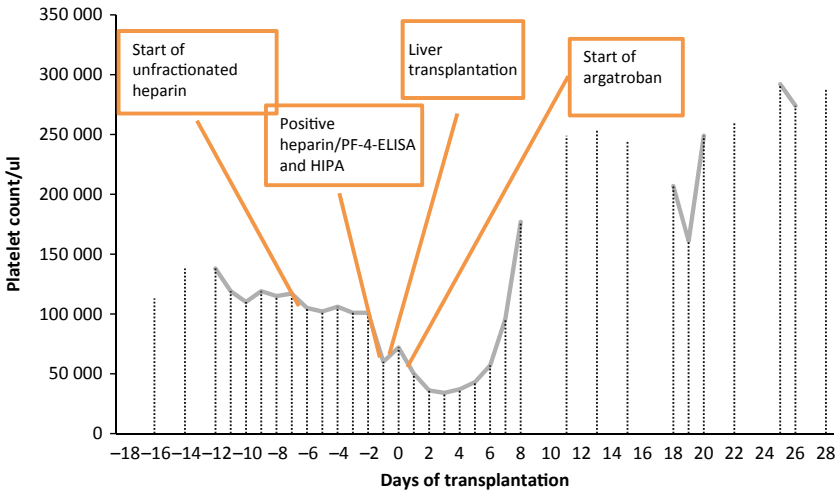

Figure 1 Shows the course of platelets before and after liver transplantation. 6 days before transplantation, an intravenous unfractionated heparin administration was started for deep vein thrombosis prophylaxis. The day before transplantation the platelet count fell over 50%, the heparin/PF4-ELISA and HIPA showed an acute heparin-induced thrombocytopenia with high antibody titer. On day 0, an uneventful transplantation could be performed. Six hours after transplantation the anticoagulation with the direct thrombin inhibitor argatroban was started. The increase of the thrombocytes after transplantation was caused by perioperative platelet transfusion. The decrease in the following days was caused by postoperative consumption. The platelet count normalized within 8 days.

Table 1. The course of the relevant labor parameters. After a short increase after transplantation, there is a normalization of the liver enzymes. The platelet count (PLT) is increasing with normalization within 8 days. The increase after transplantation is caused by perioperative thrombocyte transfusion, the decrease thereafter by postoperative consumption. The activity of heparin-induced thrombocytopenia (HIT) is measured with PGIA (particle gel immunoassay), heparin/PF4-ELISA and HIPA (heparin-induced platelet activation). After transplantation, there was no activity to detect with a clearance of the antibodies within 6 days.

Time (days)	PLT ($\times 10^3$/µl)	INR	PTT (s)	Krea (mg/dl)	GOT/AST (U/l)	GPT/ALT (U/l)	Bili (mg/dl)	LDH (U/l)	PGIA	ELISA (OD-level)	HIPA
−1	63	1.8	37	1.5	86	58	24.7	278	+	+++(2.089)	+
0	87	1.6	57	1.6	2522	1225	9.8	3319			
4	28	1.2	35	1.8	114	403	2.9	261			
6	57	1.3	49	1.1	22	109	1.5	162	–	–	–
8	177	1.2	35	1.2	21	83	1.3	153			
12	249	1.0	27	1.3		43	0.9	159	–	–(0.141)	
17	244	1.0	30	1.1	27	34	0.9	204			
21	161	1.1	33	1.1	24	36	0.9	171			
32	271	1.1	33	1.2	22	16	0.9	180			
47	246	1.0	33	0.8		25	1.0	291			
90	289	0.9	26	1.1	16	48	1.9	161			
180	205	0.9	26	1.0	35	68	1.2	235			
240	175	0.8	24	0.9	36	64	1.7	306	–	–(0.150)	

according to the liver weight, using 1 ml/g liver weight. The subsequent transplantation took 5:48 hours with a total cold ischemia time of 8:36 hours and a warm ischemia time of 48 min. Intraoperatively, the patient's estimated blood loss was 2000 ml and she required transfusions of six units of packed red blood cells and seven units of fresh frozen plasma. In the two following days, she received two units of packed red blood cells, of thrombocytes and of fresh frozen plasma. After this, the patient required no further transfusions. The immunosuppression was achieved with steroids, basiliximab, tacrolimus and mycophenolate mofetil.

The liver showed good primary function and the postoperative course was uneventful. Intravenous anticoagulation was started 6 h after transplantation with intravenous argatroban (0.067 µg/kg/min), and the patient did not manifest any signs or symptoms of HIT. Her platelet count rose above 96 000/µl within 1 week of transplantation. The postoperative HIT-monitoring showed 6 days after transplantation negative results (Table 1).

Seven days after transplantation, the patient was transferred to the normal ward and after further stabilization of the organ functions and the blood count, the anticoagulation was switched into fondaparinux (Arixtra), a subcutaneously administrable factor Xa inhibitor. 6 weeks after transplantation, she could be discharged from the hospital.

Discussion

The management of anticoagulation in patients with HIT is a challenge, particularly in the context of organ transplantation. To prevent thrombosis in the donor, a systemic anticoagulation with heparin is carried out according to the standard protocol given as a bolus before organ explantation [6,7]. In the setting of HIT, the applicated heparin during organ recovery aggravates the transplantation. Whether heparin residuals remain within the graft is influenced by quantity, route of administration (aortal and/or portal venous), and duration of rinsing with preservation solution during the explantation. Degradation of heparin because of its dose-dependent half-life time (in this case 90–120 min) can be assumed as marginal because of the short time span of 12 min until the cold perfusion started. During the cold ischemia period of 8:36 h, further degradation would have been extremely retarded if not arrested altogether. Therefore, residues of heparin within the graft, e.g. bound to the epithelial surface, must be assumed, that could lead to a reexposition.

Patients with remote HIT can be safely treated with heparin for a short period of time, since the titer of HIT antibodies can be expected to decline below the detection level within 3 months [8,9]. Patients with history of HIT and negative antibody titers have been reexposed to heparin in heart and liver transplantation procedures without any problems [10,11]. Even patients with history of HIT and still existing weak HIT antibody titers have been reexposed to heparin in heart transplantation procedures without organ dysfunction or clotting disorder [12].

In our case, the direct flushing of the liver with 1500 ml UW solution was done to remove most of the entrapped heparin. Argatroban was further postoperatively applied for therapeutical anticoagulation because of

the rapid clinical effect (1–3 hours), the short half-life (39–51 min) and a predictable pharmacokinetic dose response; furthermore, argatroban does not interact with or induce heparin-dependent antibodies, and it can inhibit both free and clot-bound thrombin [13,14] therefore it can prevent further thrombotic events or worsening of existing thrombosis [15].

An additional approach to avoiding the re-exposure in the transplant setting is the use of alternative anticoagulation instead of heparin during organ recovery. This has been described in HIT-positive donors [16]. The alternative anticoagulation in organ recovery with argatroban did not affect the transplanted organs including heart, lungs, liver and kidneys. Whether such an approach can be realized depends on the number of removed organs, the available time frames and allocation procedure. In our case, the urgent need for an allograft and the threatening shortage of available allografts precluded this course of action.

The monitoring of HIT with immunologic and functional assays showed an unexpectedly early antibody clearance. The reason for the early postoperative negative result of the HIT test in ELISA and HIPA remains unclear. The phenomenon of early antibody clearance has been reported after heart transplantions as well [11].

Conclusion

In the present case of liver transplantation in a patient with acute HIT, this management strategy resulted in a successful transplantation without any increasing symptoms of HIT, graft dysfunction or perioperative complications.

1 Heparin anticoagulation in the donor is not in general a contraindication for the subsequent transplantation in a recipient with even acute HIT.

2 In case of a heparinized donor, the transplantation procedure should be performed after backtable preparation of the organ including additional flushing with organ preservation solution and postoperative anticoagulation with alternative anticoagulants in the recipient.

Authorship

RB: collated the information, searched the literature, and wrote the article. AH: managed the patient and edited the final version. AK, SN, JL, RL, and JL helped in literature search and preparing the manuscript. All authors read and approved the final version of the manuscript.

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