Anaphylaxis on Graft Reperfusion during Orthotopic Liver Transplantation: A Case Study

Nada Andjelić, Svetlana Erdeljan, Radmila Popović, Teodora Božić
Clinical Center of Vojvodina, Clinic for Anaesthesia and Intensive Care, Novi Sad, Serbia

SUMMARY
Introduction Hemodynamic instability is a common occurrence during liver transplantation (LT). Hypotension and hemodynamic instability during graft reperfusion are most commonly consequences of the postreperfusion syndrome (PRS).
Case Outline In this report, we present a case of severe cardiovascular collapse leading to cardiac arrest which occurred in the course of graft reperfusion during LT. Persistent hypotension, non-responsive to regular measures such as volume filling and the use of vasopressors, yielded the question of whether other mechanisms were involved in causing it. Diffuse redness of the face and body, swelling of the face, lips and tongue with tongue prolapse, accompanied with severe cardiovascular collapse indicated that it was an anaphylactic reaction. This caused a dilemma as to what instigated the reaction. The trigger may have been the pharmacological substance administered during the graft reperfusion, or the one administered immediately prior to the reperfusion. The substances in question would most likely be either the University of Wisconsin preservation solution (UW), which was administered during the reperfusion, or Hepatect, which the patient received immediately prior to reperfusion.
Conclusion The clinical syndrome resulting from degranulation of mast cells and basophils in anaphylaxis is very similar to the PRS in LT. Clinical features play the most important role in establishing a timely diagnosis and early treatment of anaphylaxis. Swift administration of epinephrine reduces the chances of a fatal outcome. Better information on both donor and recipient can improve the efficiency of therapy and prophylaxis for anaphylaxis.
Keywords: liver transplantation; graft reperfusion; anaphylaxis

INTRODUCTION

Hemodynamic instability during LT is most prominent during unclamping of the inferior vena cava (IVC), the portal vein or the hepatic artery. Hypotension occurring during the period of graft reperfusion and the first five minutes upon establishing blood flow, which lasts more than one minute and is followed by a decrease in mean arterial pressure (MAP) by more than 30% in relation to its value during the anhepatic phase, is by definition a PRS [1, 2]. Persistent hypotension which requires extended use of vasopressors and is characterized by irregular rhythm, asystole and severe fibrinolysis is typical of severe cases of PRS [1-4]. Such changes are caused by irrigating harmful products, accumulated during ischemia, from graft into the blood flow. These products include cold UW solution, acids as products of anaerobic metabolism, proinflammatory cytokines (IL-6, TNFα), as well as cellular products responsible for systemic inflammatory reactions [2-5]. The PRS incidence shows wide variations ranging from 5.9% to 61.3% [1]. Such wide variation is due to different surgical approaches and techniques, different intraoperative hemodynamic treatments, duration of different phases during surgery, duration of cold and warm ischemia, as well as demographic factors regarding donor and recipient [1, 2, 5, 6, 7].

CASE REPORT

The operation was performed at the Clinical Centre of Vojvodina in Novi Sad in April 2011. A 54-year-old man, with a weight and height of 78 kg and 180 cm, respectively, suffering from a chronic hepatitis B infection and cirrhosis of the liver underwent orthotopic liver transplantation. The patient was also exhibiting signs of portal hypertension and grade II/III esophageal varices. The model for end-stage liver disease (MELD) score was 13 and the Child–Pugh score was A(5). He had no previous history of allergic reactions. His chronic therapy consisted of beta blockers (propranolol) and the angiotensin-converting enzyme (ACE) inhibitor fosinopril and diuretics (furosemide and Aldactone).

The patient was premedicated with midazolam; anesthesia was induced with propofol, succinylcholine and fentanyl, and then maintained by using sevoflurane with the addition of fentanyl and cisatracurium. He was mechanically ventilated using pressure control ventilation, with a frequency of 12 breaths per minute and a positive end-expiratory pressure of +5cmH_2O, FiO_2 0.4. Monitoring: ECG- II and lead V, pulse oximetry (SpO_2), capnography values ($etCO_2$), central venous pressure (CVP), invasive blood pressure (IBP), blood gas analysis, body temperature and coagulation status (platelets, traditional coagulation tests, rotation thromboelastometry).

Correspondence to:
Nada ANDJELIĆ
Veselina Masleše 70/23
21000 Novi Sad
Serbia
andjelicnada2@gmail.com

The hemoglobin (Hgb) level was maintained above 90 g/l, the platelet count (Plt) above 50×10^9/l. Clinically significant hemorrhaging and irregularities in coagulation status were treated with fresh frozen plasma, cryoprecipitate and antifibrinolytics (tranexamic acid) depending on the changes in the Hgb level, Plt count and coagulation tests.

Immunosuppressive therapy in the early part of the anhepatic phase consisted of 1,000 mg os methyl-prednisolone, while at the end of the anhepatic phase the patient received 10,000 IJ of Hepatect at a rate of 0.1 ml/kg/h. During the anhepatic phase, continued infusion of calcium gluconate in the dosage of 20–30 ml/h was administered. There was no hemostatic disturbance. In the dissection phase and in the anhepatic phase the patient was hemodynamically stable, with continued administration of low doses of norepinephrine (0.02–0.04 μg/kg/min intravenously).

The donor liver was prepared and preserved with UW solution and washed in 1,000 ml of Ringer's solution immediately prior to initiating grafting. No data was available on potential allergic reactions of the donor. Surgery was performed with total clamp on IVC and without veno-venous bypass so that the initial graft reperfusion and establishment of blood flow was done by unclamping the suprahepatic and intrahepatic IVC.

During the anhepatic phase the patient was hemodynamically stable with average systolic blood pressure of 115–120 mmHg, MAP of 85–90 mmHg and heart rate (HR) of 75–80 beats/min. Immediately following unclamping of the IVC and restarting blood circulation there was a sudden drop in blood pressure to 45/30 mmHg and MAP to 35 mmHg, an increase in HR to 135–140 beats/min, with a drop in $etCO_2$ and in SpO_2 and signs of acidosis (pH 7.16; pCO_2 55 mmHg). Hypotension persisted despite volume filling with resuspended erythrocytes and fluids and administration of vasopressors (intravenous norepinephrine was increased to 0.4 μg/kg/min with additional bolus injections of 10 μg intravenously). There was no visible external hemorrhaging. Further investigation into the cause of hypotension revealed diffuse redness of the face and body of the patient, as well as swelling of the face, in particular the lips and the tongue, accompanied by prolapse of the tongue in the oral cavity, indicating that it was an allergic reaction in question. Immediate therapy was administered with intravenous epinephrine in a continuous dosage of 0.04 μg/kg/min and bolus doses of 10 μg, chloropyramine 20 mg intravenously. Cardiovascular collapse intensified by ventricular tachycardia resulting in cardiac arrest. The patient was ventilated with 100% oxygen, and volume control ventilation, external cardiac massage and defibrillation of 200 J were administered. Heart rate and blood flow were re-established after a few minutes, and bradycardia was treated with atropine in a full dosage of 3 mg. Additional medication administered to the patient were as follows: methylprednisolone 240 mg, ranitidine 50 mg, sodium bicarbonate 100 ml, calcium gluconate, amiodarone 150 mg. Acidosis was corrected. His hemodynamic status gradually improved and after 35 minutes systolic pressure values remained steady at 90–l00 mmHg.

DISCUSSION

In this report we have presented a case of severe cardiovascular collapse resulting in ventricular tachycardia type cardiac arrest, which occurred while performing graft reperfusion during LT. Hypotension and hemodynamic instability are common in the course of unclamping and re-establishing blood circulation and are a consequence of PRS.

Persistent hypotension, non-responsive to regular procedure, brought to the fore the question of whether other mechanisms were at play in causing it. The differential diagnosis included the following: myocardial dysfunctions (intracardiac thrombosis, infarctions, heart failure, etc.), pulmonary embolism, anaphylaxis, electrolyte imbalance, acute graft rejection [2-8]. Extended invasive hemodynamic monitoring could have solved some of the differential diagnostic dilemmas.

There are no clear standards for administering anesthesia and monitoring a patient during a liver transplantation [9-12]. At our center, the type of monitoring and choice of extended invasive monitoring to be applied depends on the patient's Child status as well as on the extent of systemic changes and accompanying diseases [11, 12]. In this case, the recipient's health status was generally good, with a Child A score, no significant systemic changes or accompanying diseases so we opted for CVP and IBP measuring.

The presence of diffuse redness of the face and body, swelling of lips and tongue with tongue prolapsed from the oral cavity coincident with a severe cardiovascular collapse indicated that this was an anaphylactic reaction [13, 14].

Anaphylaxis is a rare occurrence during anesthesia with an incidence rate of 1/5,000 to 1/20,000 anesthetics [13]. Bearing in mind that the recipient had no history of previous allergic reactions, the likely cause of anaphylaxis was the direct pharmacological stimulation of mast cells and basophils and instigating inflammatory-mediated reactions (non-allergic anaphylaxis) [13]. The symptoms of anaphylaxis during anesthesia can vary. The dominant symptoms in our patient were severe cardiovascular collapse, visible skin changes and angioedema. The severe cardiovascular collapse resulting in cardiac arrest from ventricular tachycardia occurred as a consequence of the inflammatory-mediated reaction and the severe hypotension. In addition, the direct stimulation of mediators released from mastocytes of the cardiac muscle can cause coronary vasospasm, arrhythmia and cardiac arrest [13].

A contributing factor to the severe hypotension and cardiovascular collapse could also have been the use of β-blockers and ACE inhibitors reducing vasoconstricting response of the blood vessels [13, 14]. Chronic use of diuretics has a similar effect reflected in an increase of salt and water excretion.

Changes on the skin and swelling of lips and tongue during anesthesia can be difficult to detect because the patient is often fully covered with surgical drapes and warming blankets, as was the case with our patient. When we noticed the changes, the differential diagnosis dilemma was resolved. It is of paramount importance to make an early diagnosis on

doi: 10.2298/SARH1508467A

the basis of clinical criteria and start therapy promptly. It is believed that early administration of epinephrine reduces the incidence of fatal outcome in anaphylaxis [13, 14].

We had a dilemma as to what triggered the anaphylactic reaction. It could have been a pharmacological substance that entered the blood circulation during graft reperfusion or immediately prior to the reperfusion. In this case it is most likely the UW solution [15, 16, 17]. The components in the UW solution that are known to cause an allergic reaction are:

- Hydroxyethyl starch with an incidence of severe forms of anaphylaxis of 0.006% [14];
- Adenosine can be the direct cause of mast cell degranulation [15, 18, 19];
- Allopurinol with an incidence of severe forms of anaphylaxis of 0.43% [20, 21];
- Penicillin 200,000 IU/l with an incidence of severe forms of anaphylaxis of 1/1,000 [14].

Another possible trigger is 10,000 IU of Hepatect administered immediately prior to starting reperfusion. Hepatect consists primarily of IgG (95%), IgA (5%) and has a content of antibodies to hepatitis B virus surface antigen of 50 IU/ml. It is made from human plasma and is a protein solution and immune response modulator, which thereby makes it a potential trigger of allergic reactions [22].

The role of blood and blood products used immediately prior to, and during, reperfusion also cannot be completely ruled out as culprits in causing anaphylaxis.

We did not have enough information about the donor, but if the donor had a history of severe forms of allergic reactions, passive transfer of IgE from the donor liver can cause degranulation of mast cells in the recipient and an anaphylactic reaction [23]. This is why it is tremendously important to have precise information about both donor and recipient so that prophylaxis and treatment can be more efficient.

In order to document and confirm an allergic reaction the levels of tryptase in serum need to be measured within 15 minutes to three to four hours after onset of a reaction. The total increase in serum tryptase and increase in β-tryptase, which is specific to degranulation of mast cells in anaphylaxis, should be measured in series and compared to control values. We did not determine the tryptase level (the procedure is not available at our institution), and we consider this a disadvantage. Furthermore, determining the level of serum tryptase is of more importance in clinically unclear cases, especially during anesthesia [24]. In this case study we were able to determine the diagnosis on the basis of the clinical features, and the diagnostic criteria were completely clear.

The clinical syndrome resulting from degranulation of mast cells and basophils in anaphylactic reactions is very similar to PRS in LT. Clinical features have the most important role in early diagnosing and treatment of anaphylaxis. Prompt administration of epinephrine reduces the chances of a fatal outcome [14]. Finally, better information on donor and recipient can improve efficiency of therapy and prophylaxis for anaphylaxis.

ACKNOWLEDGMENT

We would like to thank Professor Zoran Milošević, as well as Professor Radmila Kolak for their unwavering support in launching the liver transplant program at the Clinical Centre of Vojvodina in Novi Sad.

REFERENCES

1. Fukazawa K, Pretto EA. The post-reperfusion syndrome (PRS): diagnosis, incidence and management. In: Abdeldayem H, Allam N, editors. Liver Transplantation-Basic Issues. 1st ed. Rijeka: InTech; 2012. p.385-96.
2. Paugam-Burtz C, Kavafyan J, Merckx P, Dahmani S, Sommacale D, Ramsay M, et al. Postreperfusion syndrome during liver transplantation for cirrhosis: outcome and predictor. Liver Transpl. 2009; 15:522-9.
3. Hilmi I, Horton CN, Planinsic RM, Sakai T, Nikolau-Raducu R, Damian D, et al. The impact of postreperfusion syndrome on short-term patient and liver allograft outcome in patients undergoing orthotopic liver transplantation. Liver Transpl. 2008; 14:504-8.
4. Ramsay M. The reperfusion syndrome: Have we made any progress? Liver Transpl. 2008; 14:412-4.
5. Radojković M, Stojanović M, Zlatić A, Radojković D, Jeremić LJ, Kovačević P, et al. Microcirculatory disorders in ischemic/reperfusion hepatic injury. Vojnosanit Pregl. 2008; 65(12):913-8.
6. Nishida S, Nakamura N, Vaidya A, Levi DM, Kato T, Nery JR, et al. Piggyback technique in adult orthotopic liver transplantation. HPB (Oxford). 2006; 8(3):82-8.
7. Lado L, Figueras J. Techniques of orthotopic liver transplantation. HPB. 2004; 6(2):69-75.
8. Sibulesku L, Peiris P, Taner CB, Kramer DJ, Canabal JM, Nguyen JH. Intraoperative intracardiac thrombosis in liver transplant patient. World J Hepatol. 2010; 2(5):198-200.
9. Schumann R. Intraoperative resource utilization in anesthesia for liver transplantation in the United States: a survey. Anesth Analg. 2003; 97:21-8.
10. Schumann R, Mandell MS, Mercaldo M, Michaels D, Robertson A, Banerjee A, et al. Anesthesia for liver transplantation in united states academic centers: intraoperative practice. J Clin Anesth. 2012; 25:542-50.
11. Singh S, Nasa V, Tandon M. Perioperative monitoring in liver transplant patients. J Clin Exp Hepatol. 2012; 2(3):271-8.
12. Kanabak M, Karagoz AH, Uzumcugil F. Anesthesia in liver transplantations. In: Abdeldayem H, Allam N, editors. Liver Transplantation-Basic Issues. 1st ed. Rijeka: InTech; 2012. p.333-52.
13. Kroigraad M, Garvey LH, Gillberg L, Johansson SGO, Mosbech H, Florvaag E, et al. Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow up of anaphylaxis during anaesthesia. Acta Anesthesiol Scand. 2007; 51:655-70.
14. Simons EFR, Ardusso LRF, Bilo MB, El-Gamal YM, Ledford D, Ring J, et al. World Allergy Organisation Guidelines for the Assessment and Management of Anaphylaxis. J Allergy Clin Immunol. 2011; 2(3):13-36.
15. Anderson A, Eilers H, Spencer YC. Anaphylaxis complicating graft reperfusion during orthotopic liver transplantation: a case report. Transplant Proc. 2010; 42(5):1967-9.
16. Antunovic M, Aleksic D. Preparation and testing of solutions for organ perfusion and preservation in transplantation. Vojnosanit Pregl. 2008; 65(12):913-8.
17. Blisard D, Gaber O, Shapiro R. Current Issues in Organ Preservation [monograph on the Internet]. Newtown (PA): Essential Pharmaceuticals LLC; 2009 Dec cited 2014 Feb 5. 20 p. Available from: http://www.central.com/assets/1927/Preservation%20Monograph%20-%20Final.pdf.

18. Shaw AD, Boscoe MJ. Anaphylactic reaction following intravenous adenosine. Anaesthesia. 1999; 54(6):608-11.
19. Woehlck HJ, Johnson CP, Roza AM, Adams MB. Beta tryptase levels are not elevated in patient undergoing liver transplantation. Liver Transpl. 2003; 9:980-2.
20. Ahmad S. Allopurinol and Enalapril. Drug induced anaphylactic coronary spasm and acute myocardial infarction. Chest. 1995; 108(2):586-90.
21. eHealthMe [Internet]. Review: Anaphylactic reaction in Allopurinol, 2013. Available from: www.ehealthme.com/ds/allopurinol/anaphylactic+reaction.
22. Biotest Pharma GmbH [Internet]. Hepatect, Summary of product, 2001. Available from: B\U:\PDF\aktuelle_Fachinfos\Hyper_igG\englisch\doc\SPC Hepatect_12_01.doc
23. Woehick H, Johnson C, Roza A, Gottschall J, Brumwell M, Cronin D. Anaphylaxis on reperfusion during liver transplantation with coagulopathy. Anesth Analg. 2012; 115:522-5.
24. Bjornsson HM, Graffeo CS. Improving diagnostic accuracy of anaphylaxis in the acute care setting. WestJEM. 2010; 11(5):457-61.

Анафилактичка реакција током реперфузије графта код ортотопичне трансплантације јетре: приказ болесника

Нада Анђелић, Светлана Ердељан, Радмила Поповић, Теодора Божић

Клиника за анестезију и интензивну терапију, Клинички центар Војводине, Нови Сад, Србија

КРАТАК САДРЖАЈ

Увод Хемодинамска нестабилност током трансплантације јетре је уобичајена појава. Хипотензија и хемодинамска нестабилност током периода реперфузије графта углавном су последица постреперфузионог синдрома (ПРС).

Приказ болесника Приказан је случај појаве тешког кардиоваскуларног колапса са застојем срца који се десио за време реперфузије графта током трансплантације јетре. Упорна хипотензија која не реагује на уобичајене поступке, надокнаду волумена и примену вазоактивних лекова довела је до питања да ли су и неки други механизми укључени у њен настанак. Заступљеност дифузног црвенила лица и тела, оток лица, усана и језика, са испадом језика из усне шупљине, заједно с тешким кардиоваскуларним колапсом, указали су на анафилактичку реакцију. Постоји дилема шта ју је покренуло. Фармаколошка супстанца која је доспела у крвоток током реперфузије графта или непосредно пре реперфузије могла је бити окидач почетка анафилактичке реакције. То су, пре свега, заштитни раствор *UW* (*University of Wisconsin Solutions*), који је доспео у крвоток за време реперфузије, или *Hepatect*, који је болесник примио непосредно пре реперфузије.

Закључак Клинички синдром који настаје као резултат дегранулације мастоцита и базофила код анафилактичке реакције је врло сличан ПРС код трансплантације јетре. Клиничка слика има најзначајнију улогу у постављању ране дијагнозе и правовременом лечењу анафилаксе. Рана примена епинефрина смањује могућност фаталног исхода код анафилаксе. Боља обавештеност о даваоцу и примаоцу органа може побољшати профилаксу и ефикасност терапије.

Кључне речи: трансплантација јетре; реперфузија графта; анафилакса

Примљен • Received: 12/02/2014 **Ревизија • Revision:** 16/01/2015 **Прихваћен • Accepted:** 21/05/2015

doi: 10.2298/SARH1508467A