ANESTHETIC MANAGEMENT DURING COMBINED LIVER AND KIDNEY TRANSPLANTATION

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Abstract

Combined liver and kidney transplantation is a highly demanding and challenging procedure for anesthesiologists due to the lengthy and complicated nature of the procedure, the critical patient condition and the need to balance the intravascular volume to maintain the venous outflow of the hepatic allograft and also the diuresis of the renal allograft. Intravascular volume management and coagulation control, seem to be the most important issues during combined liver and kidney transplantation. There is sparsity of data in the literature concerning the anesthetic and fluid management in CLKT. We present and discuss the anesthetic management in a case series in three patients, who underwent combined liver and kidney transplantation in our institution during the last two years.

Keywords: Liver Transplantation; Kidney Transplantation; coagulation management; fluids management; Prothrombin Complex Concentrate; antifibrinolytic agents.
**Introduction**

With advancements in anesthetic techniques, surgical skills and perioperative management, patient survival following liver transplant has been increased considerably, showing a 10 years liver and patient survival above 50\%\(^1\). It was found that about 18\% of the liver transplant patients would suffer from kidney insufficiency requiring dialysis 13 yr after the surgery \(^2\). This deterioration of kidney function was attributed to calcineurin inhibitor-induced nephrotoxicity. Furthermore, the adverse influence of decompensated liver on the kidney function among patients waiting for liver transplant has resulted in chronic renal insufficiency in 10-20\% of them, and up to 8\% receive hemodialysis prior to liver transplant \(^3,^4\). Pre liver transplant renal dysfunction is an important risk factor for post-operative sepsis, poor outcome and also it will increase the overall cost of transplantation \(^5,^6\). Moreover, the incidence of renal failure following liver transplant ranges from 12\% to 70\% \(^7\), and if a renal replacement therapy is needed, the mortality rate increases up to 40-90\% \(^8\). To overcome these problems, there is a more trend to perform combined liver kidney transplant (CLKT).

The United Network for Organ Sharing (UNOS) data revealed that from 2001 to 2006, the number of performed CLKT was almost tripled reaching about 400 CLKT in 2006 \(^1\). This was attributed to the introduction of Model for End-Stage Liver Disease (MELD) scoring system, to allocate donor livers to the patients with a higher risk of mortality on the waiting list of liver transplant, due to the heavily weighted serum creatinine value used in its calculation.

**Anesthetic management**

Standardized anesthetic technique including general anesthesia and tracheal intubation was used in our patients with some modifications done on case by case basis. After the patient’s informed consent was obtained they were taken to the operating room. Upon arrival, standard monitoring consisting of electrocardiogram, pulse oximetry, and noninvasive blood pressure was established. General anesthesia was induced with 2 mg.kg\(^{-1}\) propofol and 2 mcg.kg\(^{-1}\) fentanyl. Endotracheal intubation was facilitated with 0.2 mg mg.kg\(^{-1}\) cis-atracurium. The patients were mechanically ventilated with oxygen/air mixture keeping arterial carbon dioxide and oxygen tension between 35-40 mmHg and 100-200 mmHg, respectively. Anesthesia was maintained with sevoflurane, continuous infusion of intravenous fentanyl, and neuromuscular blockade with continuous infusion of cis-atracurium. The left internal jugular vein was cannulated, using a triple lumen-central venous catheter for continuous infusion of intravenous medications, bolus fluid administration and continuous central venous pressure (CVP) monitoring. A Swan-Ganz catheter introducer was placed also through the left internal jugular vein for massive volume replacement. The right internal jugular was avoided because of the presence of a dialysis line in the right subclavian vein. The left femoral artery and the left radial artery were cannulated for continuous arterial blood pressure monitoring, arterial blood gases and laboratory sampling. Cell saving was performed and salvaged blood was retransfused to the patients.

Pharmacologic hemodynamic management was achieved with norepinephrine infusion.

**Case 1**

Female patient (44 years, 149 cm height, 67 kg weight, BMI 30kg/m\(^2\)) with end stage liver disease (ESLD) due to hepatitis C liver cirrhosis. The patient’s MELD score was 17. A cadaveric hepatic allograft became available but she refused surgery. Renal function rapidly deteriorated, and dialysis was required for 2 months, fitting the criteria for CLKT. The MELD score deteriorated to 40. Another liver and kidney allografts were available, and CLKT was planned. Preoperative laboratory findings were hemoglobin 89 g/L, platelet count 39,000/mm\(^3\), white blood cell count 3,400 cells/mm\(^3\), international normalized ratio (INR) 3.2, PTT 85 seconds, fibrinogen 0.4 g/L, creatinine 163 µmol/l, electrolytes (K+, Na+, Cl-) within normal range, fasting blood sugar 5.2 mmol/l, and albumin 24 g/l. Preoperative echocardiography and electrocardiogram were unremarkable.
Continuous veno-venous hemodialysis with an output of 250 ml/hour was initiated with the start of surgery. The baseline CVP reading was 9 mm Hg. It was maintained between 5 - 8 mmHg during the preanhepatic, anhepatic phase and neohepatic phases of liver transplant till the start of the renal transplant procedure. Then the continuous veno-venous hemodialysis was stopped and the CVP was slowly increased to 15 mmHg until renal allograft reperfusion using crystalloid hydration with normal saline, and it was kept at this value until urine production was noted. CVP was then gradually decreased again to approximately 10 mmHg until completion of the surgery. Total blood loss was 14 liters. Throughout the surgery, the patient received 21 units (7350 ml) of packed red blood cells, 17 units (3400 ml) of fresh frozen plasma (FFP), 18 units (1260 ml) of platelets, 50 units (1500 ml) of cryoprecipitate, 2500 ml of cell saver blood and 15 liters of normal saline, and produced 120 ml of urine. Additional coagulation management was achieved with single doses of desmopressin (0.3 mcg/kg) and recombinant factor VIIa (rFVIIa) (90 mcg/kg).

Case 2

Female patient (54 years, weight 70 kg, height 154 cm, BMI 29.5 kg/m2) with ESLD secondary to cryptogenic cirrhosis, type 2 diabetes mellitus (insulin treated), hypertension, dyslipidemia, hypothyroidism and end stage renal disease (ESRD). The patient’s MELD score was 25. The laboratory evaluation showed hemoglobin 128 g/L, platelet count 103,000/mm3, fibrinogen 2.1 g/L, INR 1.1, PTT 30.9, albumin 31 g/l, electrolytes (K+, Na+, Cl-) within normal range, fasting blood sugar 5.3 mmol/l and creatinine 738 µmol/l. Electrocardiogram showed prolonged QT interval, and echocardiography showed a right ventricular systolic pressure of 40-50 mm Hg with mild tricuspid valve regurgitation.

Continuous veno-venous hemodialysis was on standby. The baseline CVP was 12 mmHg. CVP was maintained between 7-10 mmHg throughout the 3 phases of liver transplant. Then CVP was gradually increased to 18 mmHg one hour before kidney allograft reperfusion and remained at this level till the end of surgery. Blood loss was 3 liters. The patient received 8 units (2800 ml) of packed red blood cells, 4 units (800 ml) of FFP, 10 units (300 ml) of cryoprecipitate, 500 ml of albumin 5%, and 13 liters of plasmalyte. Two grams of tranexamic acid were given intraoperatively.

After completion of the surgery, the patients were transferred to surgical intensive care unit in a stable condition. They all had a smooth post-operative course, with good function of the liver and kidney grafts, except case 2 whose kidney graft did not work properly requiring hemodialysis, but she was discharged home, and only comes to the hospital for her dialysis sessions.
Discussion

Fluid volume management and coagulation control seem to be the most important issues during CLKT. There is sparsity of literature discussing the anesthetic and fluid management in CLKT. In our cases, in agreement with previous study we tried to make fluid management based on literature of isolated liver transplant and kidney transplant.

During kidney transplant, a liberal hydration policy optimizing the cardiac output and renal blood flow is usually employed intraoperatively targeting a CVP between 10 - 15 mm of Hg to decrease the incidence of postoperative renal graft acute tubular necrosis. In contrast, it is believed that maintaining a low CVP limits blood loss during liver resection and orthotopic liver transplant, reducing the need for blood product transfusion and its associated negative impact on postoperative patient outcomes. Although there is no clear evidence for the ideal level during liver transplantation, the CVP is generally maintained between 5-10 mmHg. However, keeping the CVP in the desired range is very difficult in cases where there is both coagulopathy and a need to administer blood products. Additionally, in the CLKT this is obviously controversial, since keeping the CVP low seems to be critical for anesthesia management during liver transplantation, while it has to be increased during renal transplantation.

More controversy comes from that, it has been demonstrated that CVP values <5 mmHg could be a reason for hypotension and deterioration of microperfusion in liver grafts. In our cases we tried to keep the CVP below 10 mmHg during the preanhepatic and the anhepatic phases in accordance with other studies and then CVP was increased to 10 mmHg between the neohepatic phase and 1 hour before the renal allograft reperfusion, where the patients were fully hydrated with crystalloids, with a maximum CVP of 15 mmHg, 17 mmHg and 18 mmHg, in cases 1, 2 and 3 respectively.

During preanhepatic and anhepatic phases, CVP was not allowed to decrease below 5 mmHg. There is increased evidence indicating that CVP values <5 mmHg should be avoided during the anhepatic phase until the end of surgery, since this is associated with elevated creatinine levels, more frequent need for dialysis and increased mortality due to sepsis and graft failure. In contrast, previous studies that Instead of decreasing CVP to an absolute numeric value range, they found that decreasing CVP value 40% from baseline during the anhepatic phase of liver transplant, protected liver function, reduced intraoperative blood loss, and had no detrimental effects on renal function.

In another study comparing CVP above 10 mmHg with CVP below 10 mmHg in the neohepatic phase of liver transplant, the investigators did not find any difference in terms of immediate postoperative allograft function, graft survival, or patient survival. This may support our practice of gradually increasing the CVP in the neohepatic phase in preparation for kidney transplant.

During kidney transplant, hemodynamic stability, better intraoperative renal allograft turgidity, earlier diuresis, and rapid improvement of postoperative renal function, were accomplished with maximal hydration targeting a CVP of 15 mmHg within an hour before renal allograft reperfusion, followed by replacement of urine output targeting a CVP of 8 to 10 mmHg. Although the CVP was low in case 1, the patient presented significantly increased intraoperative blood loss and increased blood products transfusion. However, the patient had a MELD score 40. This supports considering many factors affecting intraoperative blood loss other than the isolated CVP, like the preoperative patient condition, surgical technique and also the donor parameters (donor risk index).

It is important to note that the CVP is being replaced with newer hemodynamic parameters, such as stroke volume variation (SVV), which may be used to guide fluid management in the patients receiving mechanical ventilation. Despite the superiority of SVV to CVP, the promising results of its use in the patients undergoing liver or kidney transplant are still evolving.

According to the European Renal Best Practice (ERBP) Transplantation guidelines there is no evidence to prefer one type of solution for intravenous volume management of the recipient during kidney transplant surgery, with recommendation to monitor for metabolic acidosis when normal saline is used as the only intravenous fluid in the perioperative period. In our case series we used normal saline for crystalloid...
volume replacement in cases 1 and 2, and Plasmalyte in case 3. There is a report comparing normal saline, lactated Ringer's and Plasmalyte, in kidney transplants of living related donors. The conclusion was that all three crystalloid solutions can be safely used during uncomplicated, short-duration renal transplants; however, better metabolic profile was maintained in patients who received Plasmalyte.

Transfusion and coagulation management during CLRT is challenging and coagulopathy is usually multifactorial. Clinical strategies to reduce blood loss during CLRT include the use of blood products to correct pre-existing or intraoperative coagulopathy. This is achieved by transfusion of fresh frozen plasma (FFP), platelet concentrate, cryoprecipitate and antifibrinolytic agents to correct hyperfibrinolysis that may occur during the procedure. In our cases the coagulation management was guided by thromboelastography (TEG), performed hourly during the surgical procedure, as well as conventional coagulation parameters. The use of TEG for coagulation management constitutes the more recent trend in coagulation monitoring. A major disadvantage of transfusion of blood products such as FFP is volume overload. To correct a prolonged PT during CLRT several units of FFP are needed, which will result in an increase in CVP and portal (splanchnic) venous blood pressure and in fact will increase the bleeding risk.

Prothrombin complex concentrate (PCC) are homostatically active highly purified concentrates, prepared from pooled plasma. They contain all four vitamin K-dependent clotting factors (II, VII, IX and X). In contrast to the traditional infusion of FFP to stimulate coagulation in cirrhotic patients, PCC does not add to the intravascular volume and therefore may be, theoretically, more effective in reducing bleeding complications than FFP infusion.

It has been demonstrated that hypofibrinogenemia is associated with increased hemorrhage during liver transplantation. Fibrinogen concentrate is also produced from pooled human plasma. It is stored as a lyophilised powder at room temperature and can be reconstituted quickly with sterile water and infusion volumes are low, allowing for rapid administration without delays for thawing or cross-matching. In many centers, PCC and fibrinogen concentrate are used “off-label” during LT as a rescue therapy during catastrophic bleeding, when coagulopathy is evident. Although the available data on safety in this population does not suggest an increased risk of thrombotic, thromboembolic and ischaemic events associated with PCC and fibrinogen concentrate use, the data are scarce and need to be confirmed in large trials. Currently the first two multicentre, randomized, double-blinded trial comparing the routine use of prothrombin complex concentrate (PCC) or fibrinogen concentrate with a placebo in patients undergoing LT are still pending.

Recombinant factor VIIa (rFVIIa) was used by Busani et al., in a series of seven patients with persistent severe bleeding after application of a standard transfusion protocol, in a dose similar to what we used in case 1 (90 mcg/kg). Blood losses and need for platelets transfusion significantly decreased after rFVIIa administration; a non-significant decrease in red blood cell and fresh frozen plasma transfusions also occurred. In six patients treatment with rFVIIa was effective; only one patient died because of haemorrhagic shock, and no thromboses were detected among the treated patients. The study suggested that in some challenging cases of massive bleeding rFVIIa should be considered as a useful option to control bleeding.

Tranexamic acid was administrated in case 2, it was given also in case 3. It seems to be the antifibrinolytic agent of choice in liver transplantation, being equally efficacious as the currently unavailable aprotonin. As opposed to a blind prophylaxis with antifibrinolytics in liver transplantation a goal directed therapy, by using thrombelastometry to assess fibrinolysis, has been suggested.

Desmopressin acetate (DDAVP) was used in case 1. Desmopressin increases the levels of factor VIII, vWF, and plasminogen. DDAVP appears to improve blood coagulability during liver transplantation in vitro, possibly by activating coagulation factors and platelets.

In conclusion, CLKT is a highly demanding and challenging procedure for anesthesiologists due to the lengthy and complicated nature of the procedure, the critical patient condition and the need to balance the intravascular volume to maintain the venous outflow of the hepatic allograft and also the diuresis of the renal allograft. Appropriate intraoperative fluid management tailored to each phase of CLRT surgery and targeted coagulation management may have favorable results.
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