Original Article

Anaesthesia and intensive care for simultaneous liver-kidney transplantation: A single-centre experience with 12 recipients

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Access this article online

Website: www.ijaweb.org

DOI: 10.4103/0019-5049.186025

Quick response code

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ABSTRACT

Background and Aims: The perioperative management of patients presenting for simultaneous liver and kidney transplantation (SLKT) is a complex process. We analysed SLKTs performed in our institution to identify preoperative,intraoperative and post-operative challenges encountered in the management. **Methods:** We retrospectively studied the case records of 12 patients who underwent SLKT between 2009 and 2014 and analysed details of pre-operative evaluation and optimisation, intraoperative anaesthetic management and the implications of use of perioperative continuous renal replacement therapy (CRRT) and the post-operative course of these patients. **Results:** Of the total 12 cases, 4 were under 16 years of age. The indications for SLKT were primary hyperoxaluria (5), congenital hepatic fibrosis with polycystic kidney disease (2), ethanol-related end-stage liver disease (ESLD) with hepatorenal syndrome type 1 (1). Four patients had ESLD with end-stage renal disease due to other causes. Six recipients received live donor grafts and 6 patients received cadaveric grafts. Seven patients received intraoperative CRRT. Mean duration of surgery was 12.5 h. Cardiac output monitors used were trans-oesophageal echocardiogram (2), pulmonary artery catheter (1) and pulse contour cardiac output monitor (3). There was 1 sepsis-related mortality on 7th post-operative day. **Conclusion:** A thorough pre-operative evaluation and optimisation, knowledge and anticipation of potential problems, and meticulous intraoperative fluid management guided by appropriate monitoring and use of CRRT when needed can help in achieving successful outcomes.

Key words: Anaesthesia for combined solid organ transplants, combined liver-kidney transplantation, intraoperative renal replacement therapy, primary hyperoxaluria, simultaneous liver-kidney transplantation

INTRODUCTION

The first successful simultaneous liver-kidney transplantation (SLKT) was reported by Margreiter *et al*. in 1984[1] Since then, SLKT is emerging as the preferred treatment for patients with certain metabolic disorders and those with end-stage liver and kidney disease. Pre-operative optimisation, intraoperative haemodynamic stability and appropriate fluid management in the perioperative period can markedly improve graft and patient survival. Long and complex surgery, requirements for intraoperative renal replacement therapy (RRT) and the complex multisystem changes in these patients, present

How to cite this article: Rajakumar A, Gupta S, Malleeswaran S, Varghese J, Kaliamoorthy I, Rela M. Anaesthesia and intensive care for simultaneous liver-kidney transplantation: A single-centre experience with 12 recipients. Indian J Anaesth 2016;60:476-83.

unique challenges to the anaesthesiologist. A good understanding of these factors will help in thorough pre-operative evaluation and successful intraoperative management. To understand some of these issues, we retrospectively analysed pre-operative, intra-operative and post-operative challenges we encountered in the management of 12 cases who underwent SLKT.

METHODS

After obtaining institutional approval, a retrospective review of SLKT case records performed between 2009 and 2014 was done. Data were collected from anaesthetic and Intensive Care Unit (ICU) case record sheets. Data collected include (a) pre-operative parameters: Demographic profile, indications for transplantation, comorbidities and details of pre-operative dialysis; (b) graft details: Type of graft, cold ischaemia times (CITs); (c) intraoperative details: Surgical details, duration of surgery, anaesthetic agents used, monitoring, fluid management, transfusion requirement, haemodynamic variables, vasopressor use, urine output, intraoperative RRT, peak lactate and lactate at the end of operation, antibiotics and immunosuppression used and (d) post-operative parameters-duration of mechanical ventilation, RRT, ICU stay and hospital stay, immunosuppression and any adverse events noted during the hospital stay.

RESULTS

Our study included four children and eight adult patients. The age, sex, indications for SLKT and the type of grafts used are given in Table 1. In our series, one patient with primary hyperoxaluria (PH) had an isolated kidney transplant 5 years earlier, which failed. All others underwent SLKT for the first time.

Co-morbidities included diabetes mellitus in 5, hypertension in 8, seizure disorder in 1 and hypothyroid state in 3 patients. Ten patients were on regular haemodialysis. The duration of dialysis ranged from 45 days to 4 years with a median of 2 years. The average frequency of dialysis was twice per week. Two patients with oxalate cardiomyopathy had low ejection fraction (EF) of 35% and 40%, respectively. The dialysis frequency was increased from twice a week to 5 times a week in the first child and the second child underwent daily dialysis leading to an improvement in EF to 55% and 48% over a period of 2 months and 6 weeks, respectively.

All patients with PH had normal liver function and platelet count. In the remaining, serum bilirubin ranged from 0.4 to 3.14 mg/dL (median of 0.78), albumin from 1.5 to 4.4 mg/dL (median of 2.7), international normalised ratio from 1.04 to 2.29 (median of 1.18) and platelet count from 28,000 to 125,000 cells/mm^3 (median of 82,000 cells/mm^3).

Pre-operative electrocardiogram showed varying degrees of left ventricular hypertrophy (LVH); two-dimensional echocardiogram (ECHO) was normal in 8 patients, with low EF in two patients with PH. Two patients had LVH and moderate diastolic dysfunction with aortic sclerosis. As per our unit policy, four adult patients underwent myocardial perfusion studies, which was normal. Four adult patients underwent coronary angiogram, and atherosclerotic plaques were seen in the left anterior descending artery in one patient. None of the patients required any pre-operative coronary intervention.

Of 12 patients, 5 patients had haemoglobin below 10 g/dL. Except for two patients with pleural effusion, pulmonary function was normal as evidenced by

Table 1: Patient profile

ID number	Age in years	Sex	Aetiology	Type of graft
1	12	Male	Primary hyperoxaluria	Live
2	45	Male	Ethanol-related ESLD with HRS Type I	Cadaveric
3	55	Male	NASH-related ESLD with diabetic nephropathy	Cadaveric
4	21	Female	Congenital hepatic fibrosis with polycystic kidney disease	Live
5	16	Female	Primary hyperoxaluria	Live
6	10	Female	Congenital hepatic fibrosis with polycystic kidney disease	Live
7	30	Female	Primary hyperoxaluria	Cadaveric
8	9	Female	Primary hyperoxaluria	Live
9	53	Female	Primary hyperoxaluria	Cadaveric
10	67	Male	HCV-related ESLD with diabetic nephropathy	Live
11	62	Male	Ethanol-related ESLD with diabetic nephropathy	Cadaveric
12	63	Male	HCV with NASH and diabetic nephropathy	Cadaveric

HCV – Hepatitis C virus; NASH – Non-alcoholic steatohepatitis; ESLD – End-stage liver disease

arterial blood gases and pulmonary function tests. Two patients had oxalate osteopathy.

Of the 12 SLKT, 6 patients received grafts from live donors and the others were from deceased donors. All deceased donor recipients received whole liver graft. Of the living donor liver transplantation (LDLT) recipients, four received left lobe and two patients received right lobe of liver. All patients were transplanted a single kidney.

Eight of the ten patients on regular dialysis received dialysis 4–12 h before surgery. Proton pump inhibitor – esomeprazole was given as a premedication before surgery. Induction was done with fentanyl, propofol and atracurium. Anaesthesia was maintained with isoflurane or sevoflurane in air – oxygen mixture, fentanyl and atracurium infusion.

In addition to standard anaesthetic monitoring, cardiac output monitor was used in six patients. An arterial cannula was placed in the left radial artery in nine patients and the femoral artery in three patients. Ultrasound was used in all patients for performing central venous cannulation. A four-lumen central venous pressure (CVP) line was placed in all the patients. Dialysis catheter was placed in the right internal jugular vein in 8 patients, left internal jugular vein in 1 patient, the right femoral vein in 2 and left femoral vein in 1 patient. Pulmonary artery catheter (PAC) was used in a patient with moderate diastolic dysfunction for guiding fluid management. Transoesophageal echocardiogram (TOE) was used in two patients with cardiomyopathy and pulse contour cardiac output monitoring (PiCCO) was used in three patients. No procedure-related complications were noted in these patients.

Fluid warmers and warming blankets, thromboprophylaxis with TED stockings and pneumatic compression devices were used. Piperacillin – tazobactam along with fluconazole was used for antimicrobial prophylaxis. Arterial blood gases were performed at hourly intervals along with complete blood count, international normalised ratio, and fibrinogen levels as required. Thromboelastogram was used to monitor coagulation and guide blood products administration. The target haemoglobin for packed red blood cells transfusion was 8 gms%.

Of the 12 patients, intraoperative CRRT was used in seven patients. Five patients with PH received continuous venovenous haemofiltration and two patients with non-alcoholic steatohepatitis disease who were not dialysed in the immediate pre-operative period received continuous venovenous haemodiafiltration. CRRT was initiated during the dissection phase. No anticoagulation was used in the CRRT circuit. No undue bleeding or complication related to vascular access was noted. No clot-related issues were encountered in CRRT circuit.

A restrictive fluid strategy has been used keeping CVP below 6 cm H_2O in the dissection phase. In patients with cardiac output monitors, they were used to guide fluid therapy. Of the 11 surviving patients, 2 patients required bolus of phenylephrine for hypotension at liver reperfusion. All others had uneventful liver reperfusion. The CVP was increased to around 10 at the time of kidney reperfusion. Kidney reperfusion was uneventful in all the patients. Haemodynamics was stable in all the 11 patients. Peak lactate varied from 2.7 to 9 mmol/L with median of 5.7 and a decreasing trend was observed after liver reperfusion. Eleven patients had good urine output after kidney reperfusion.

Intravenous fluids used were both crystalloids (0.45% normal saline) and colloids (gelofusine) and 20% albumin. Cell saver was used in 8 patients and the cell saved blood was transfused in 3 of them. Details of intraoperative fluids are given in Table 2. Duration of surgery ranged from 11 to 18 h with a mean of 12.5 h.

The CIT for the cadaveric liver recipients was found to range from 205 to 675 min with a mean of 320 min while in live liver recipients, it was found to be 27–200 min with a mean of 93.6 min. In cadaveric kidney recipients, CIT ranged from 480-915 min, the

Table 2: Intraoperative fluids and blood products

Parameters	≤16 years (4 patients)	Adults (8 patients)
Mean crystalloid volume	91.1 ml/kg	3.475 L (range: 2.0-5.5 L)
Mean colloid volume	87.04 ml/kg	2.937 L (1.5-6.0 L)
Mean PRBC volume	46.6 ml/kg (all children)	8.375 units (range: 3-16 units; all patients)
Mean FFP volume	5.78 ml/kg (2 children)	3.5 (range: 0-11 units; 5 patients)
Mean single donor platelet volume	3.2 ml/kg (1 child)	1.75 units (range: 0-5 units; 6 patients)
Mean pooled cryoprecipitate volume	2.13 ml/kg (1 child)	0.87 units (range: 0-3 units; 4 patients)
20% albumin	100 ml (1 child)	137.5 ml (5 patients)

PRBC – Packed red blood cells; FFP – Fresh frozen plasma

mean being 583 min and in live recipients, it was found to be 40–120 min with a mean of 64 min.

One patient in our series who received a deceased donor graft died on the 7th post-operative day (POD) due to initial poor graft function. He had reperfusion syndrome after liver reperfusion requiring adrenaline bolus and required moderate doses of adrenaline and noradrenaline infusion throughout surgery. His lactate continued to rise throughout surgery and he remained anuric on CRRT until death. However, the liver graft function had improved and the patient was extubated after 94 h. He succumbed to overwhelming sepsis 7 days after surgery.

All patients were electively ventilated following surgery. Duration of ventilation ranged from 8 to 36 h. Haemodynamics was stable in all the 11 patients. All recipients received methylprednisolone before liver reperfusion and basiliximab before kidney reperfusion. Methylprednisolone was continued post-operatively and 2nd dose of basiliximab was given on 4th POD. Tacrolimus was started in all patients on POD 1, and mycophenolate mofetil was started between POD 1–3.

All five patients with PH underwent post-operative dialysis as a means of reducing the oxalate load to the newly transplanted kidney. Two other patients also required post-operative dialysis, of which one patient had acute tubular necrosis of the kidney and required CRRT for 4 days following, which his kidney function recovered well. The other patient developed acute rejection of renal graft in the 3rd post-operative week after surgery and had to go on regular dialysis. She underwent retransplantation 8 months later and is currently well.

Relaparotomy was performed for two patients (one patient had bleeding from renal bed and the other had intestinal obstruction and required adhesiolysis). Other post-operative complications observed were acute tubular necrosis (1), urinary tract infection (4), cytomegalovirus infection (1), deep vein thrombosis at the site of femoral dialysis catheter (1), tacrolimus-induced seizures (1), febrile neutropenia (1), steroid induced myopathy (1) and superficial wound infection (1).

The duration of ICU stay ranged from 3 to 11 days with an average of 6 days. Hospital stay ranged from 8 to 36 days with average of 20 days.

DISCUSSION

The introduction of model for end-stage liver disease (MELD) score for organ allocation in 2002 significantly altered the scenario for patients requiring SLKT by prioritising patients with renal dysfunction due to the heavily weighted serum creatinine value in the MELD score calculation. This lead to a marked increase in the number of deceased donor SLKT[2] and the favourable outcomes encouraged performance of live donor SLKT. The indications for SLKT agreed by the expert panel of representatives from the Organ Procurement Transplantation Network as well as experts from the previous consensus conference assembled in Los Angeles are listed in Table 3.[3] Figure 1 illustrates the indications in our series. Managing patients presenting for SLKT is very challenging because of (a) multisystem changes, (b) long duration of surgery and the nature of surgery and (c) the need for intraoperative RRT.

Table 3: Indications for simultaneous liver and kidney transplantation

OLT candidates with persistent AKI≥4 weeks with one of the following
Stage 3 AKI as defined by modified RIFLE (i.e., a 3-fold increase in serum creatinine from baseline, serum creatinine≥4 mg/dL with an acute increase of≥0.5 mg/dL or on renal replacement therapy
eGFR ≤35 mL/min (MDRD-6 equation) or GFR ≤25 mL/min (iothalamate clearance)
Candidates with CKD, as defined by the National Kidney Foundation, for 3 months with one of the following
eGFR ≤40 mL/min (MDRD-6 equation) or GFR ≤30 mL/min (iothalamate clearance)
Proteinuria ≥2 g a day
Kidney biopsy showing >30% global glomerulosclerosis or >30% interstitial fibrosis
Metabolic disease

RIFLE – Risk Injury Failure Loss End-stage criteria; AKI – Acute kidney injury; eGFR – Estimated glomerular filtration rate; OLT – Orthotopic liver transplantation; MDRD-6 – Modification of diet in renal disease-6; CKD – Chronic kidney disease

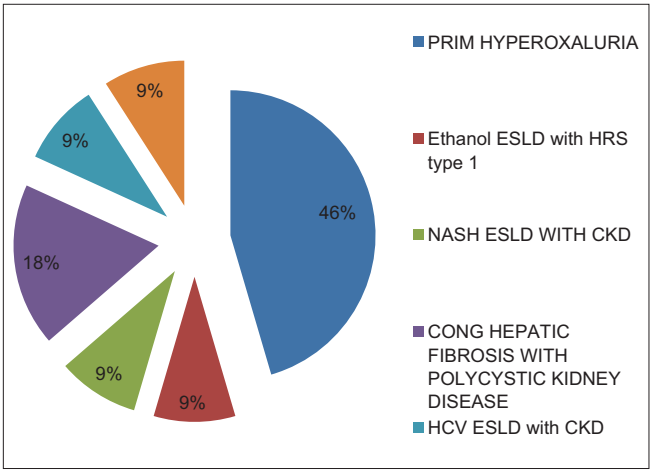

Figure 1: Indications for simultaneous liver-kidney transplantation

Complex changes occur in the various organ systems of the body in patients with end-stage liver and kidney disease and patients with metabolic disorders, that should be identified and addressed during pre-operative evaluation. A good understanding of these manifestations is crucial as it dictates the pre-operative optimisation, intraoperative and post-operative management.[4-9] SLKT recipients can have cardiac issues such as cardiomyopathy due to cirrhosis, uraemia or secondary to infiltrate deposition in metabolic diseases such as propionic academia, hyperdynamic circulation and a high incidence of coronary artery disease. Our patients have undergone cardiopulmonary evaluation as per established guidelines.[10,11] The respiratory challenges for anaesthesiologist in SLKT recipients include pulmonary congestion, arteriovenous shunting, portopulmonary hypertension and pleural effusion. Metabolic issues can be due to primary diseases such as methylmalonic acidaemia, PH or due to renal and liver dysfunction and the severity of such derangement is usually determined by the timing of last dialysis. Anaemia can be present due to impaired erythropoiesis secondary to renal failure, increased bleeding due to coagulation abnormalities secondary to liver disease, Vitamin B6/B12 deficiency, uraemia and drugs such as D-penicillamine-induced bone marrow suppression and repeated blood loss during dialysis. Thrombocytopenia and platelet dysfunction will commonly be seen in patients due to portal hypertension, uraemia-induced bone marrow suppression and interference of platelet function by uremic toxin in blood.[12,13] Complete blood counts, coagulation profile, renal and electrolyte profile and liver function tests should be obtained immediately before the surgery.

PH is a rare autosomal recessive disorder arising due to deficiency of the enzyme alanine glyoxylate aminotransferase located in the liver, which results in excessive oxalate production causing deposition of calcium oxalate crystals in the kidney, progressive renal failure and systemic oxalosis. Isolated kidney transplantation almost always causes recurrence due to unresolved excess oxalate production by the liver. Therefore, SLKT is the solution that results in improved graft and patient survival.[14,15] Varying degrees of cardiac function abnormalities and treatment-resistant anaemia and oxalate osteopathy due to oxalate deposition in the bone marrow have been reported.[16,17] Because of the overwhelming oxalate production in these patients, conventional peritoneal or haemodialysis would be unable to remove sufficient amount of oxalate. Therefore, aggressive strategies need to be used to eliminate plasma oxalate and to limit systemic involvement. Strategies proposed until transplantation are short daily sessions of high flux dialysis, nocturnal dialysis or combination of haemodialysis and nocturnal peritoneal dialysis to keep oxalate levels at an acceptable range below 30–45 μmol per litre.[18-20] In our series, we found that two patients with PH had low EF, which improved with aggressive dialysis following which they were subjected to transplantation. Plasma oxalate levels and urinary oxalate excretion may remain elevated for days after the transplantation because of slow resolubilisation of calcium oxalate, and this can cause oxalate deposition in the new graft. Therefore, haemodialysis or haemofiltration is recommended during surgery and a few days after transplantation depending on the systemic oxalate burden and the adequacy of urine output. Forced fluid intake and occasionally crystallisation inhibitors are used in some patients post-operatively to avoid oxalate deposition in the graft.[21,22] All 5 PH patients in our series had CRRT for 2–3 days. A recent paper from our own centre discusses the aspects of sequential and simultaneous LDLT in these patients.[23]

Caution has to be exercised during induction and extubation because of the potential concern of delayed gastric emptying in patients with renal or hepatic disease.[24] The choice of inhalational anaesthetic agent has not shown to affect any of the outcomes in the renal transplant recipients.[25,26]

Central venous cannulation can be difficult because of the previous cannulation for dialysis, which poses problems with vessel patency. Venous imaging such as real-time ultrasound or magnetic resonance mapping as part of the pre-operative evaluation can facilitate in choosing the best route for venous access. It is important to discuss with the surgeons regarding the site of kidney implantation to avoid that area for venous and arterial access.[27]

In a comparative study, it was found that volumetric monitoring with PiCCO monitors was superior to PAC monitoring during anaesthesia for orthotopic liver transplantation (OLT). A good correlation was observed between intrathoracic blood volume index (ITBVI) and cardiac index (CI) compared to CVP/CI and pulmonary artery occlusion pressure (PAOP)/CI. ITBVI was found to be a more reliable indicator of preload than PAOP

during liver transplantation.[28,29] Another great tool is TEE, which offers the advantage of directly visualising the preload of both right and left sides of the heart in real-time. During increases in intravascular volume, the right ventricle dilates which results in no significant change in CVP despite large increases in volumes, which can easily be picked up by TEE. In our series, three patients were monitored using PiCCO, two patients had TEE for monitoring and one patient had PAC inserted.[30]

Centres employ several strategies to offset haemodynamic changes at reperfusion, which includes calcium bolus, sodium bicarbonate bolus or small incremental boluses of vasopressors such as epinephrine, phenylephrine or fluids when there is a relative hypovolaemia or unexpected bleeding at reperfusion.[31]

It was demonstrated that maintaining a low CVP and in addition, performing a phlebotomy if required during the preanhepatic phase, reduces blood transfusion requirements without any renal impairment during liver transplantation.[32,33] Higher CVP in the neohepatic phase was thought to impede outflow from the liver allograft leading to allograft dysfunction. Thus, low CVP was preferred during post-reperfusion phase in liver transplantation. However, higher CVP is preferred to optimise the cardiac output and renal perfusion for the subsequent kidney transplantation. Therefore, a CVP, which enables optimal renal perfusion and avoids venous outflow obstruction and liver allograft dysfunction, is favoured. Saner *et al*. have shown that higher PEEP up to 15 cm H_2O does not impair hepatic venous outflow.[34] Therefore, it can be inferred that high CVP in the neohepatic phase would not always cause congestion of liver allograft. Cywinski *et al*. have shown that CVP during the post-reperfusion phase does not affect early post-operative outcomes in liver transplant recipients.[35]

The renal graft function and survival are directly influenced by the transplanted graft perfusion and, therefore, it is essential to keep the patient warm and well perfused by maintaining an adequate mean arterial pressure and optimal fluid status. Those patients who maintained haemodynamic stability had demonstrated better intraoperative graft turgidity. CVP is no longer considered to be a better correlate of intravascular fluid status, and this has been demonstrated in renal transplant patients as well.[36] Several studies have shown better outcomes with CVP-guided fluid therapy in renal transplant recipients.[37,38] Some studies have demonstrated that a slightly restrictive fluid therapy targeting CVP of 7–9 mm Hg have shown no increase in incidence of delayed graft function.[39] In our series, CVP was maintained below 6 until renal graft implantation and has been increased to around 10 at reperfusion. Other cardiac output monitors have been used to guide fluid management in six of our patients.

Transplant teams have different protocols for renal reperfusion. Some teams have advocated 0.5–3 μg/kg/min of dopamine but a recent study showed a higher mortality and prolonged length of ICU stay in patients receiving dopamine for renal transplant surgeries.[40] With the available data, no single vasopressor drug can be deemed superior but it seems prudent to avoid episodes of hypotension during and after reperfusion. Furosemide has been used as a bolus before reperfusion at a dose of 40–250 mg in some centres. This can induce diuresis and prevent oliguria but sometimes, fluid management can become difficult due to the massive diuresis. Mannitol, which acts as an osmotic diuretic and intravascular volume expander, has been used to promote renal blood flow at a dose of 0.25–0.5-g/kg-body weight as a bolus before reperfusion in some centres. Only one patient had received furosemide bolus after reperfusion in our series.

In a study, Townsend *et al*. demonstrated that intraoperative CRRT was logistically feasible and safe, no anticoagulation was generally needed to maintain filter circuit patency, it was possible to maintain neutral or sometimes negative fluid balance with CRRT at the end of surgery and no significant complications attributable to CRRT was noted.[41] In another study of perioperative CRRT during OLT, the authors concluded that CRRT provided greater flexibility to anaesthesiologists in managing metabolic and cardiovascular stability.[42] It was also shown that the incidence of post-reperfusion syndrome is reduced during CRRT usage probably due to mitigation of cytokine storm.[43] In our series, we found that CRRT helped to maintain metabolic and haemodynamic stability. Heparin-free circuits had been used in our series. No complications related to CRRT were noted in our series.

CONCLUSION

A sound knowledge of the complex multisystem changes of patients presenting for SLKT, a thorough preoperative evaluation and optimisation and a safe conduct of anaesthesia with the anticipation of all potential problems can help in achieving successful outcomes with SLKT.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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