Combined liver and kidney transplantation in children and long-term outcome

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Abstract

Combined liver-kidney transplantation (CLKT) is a rarely performed complex surgical procedure in children and involves transplantation of kidney and either whole or part of liver donated by the same individual (usually a cadaver) to the same recipient during a single surgical procedure. Most common indications for CLKT in children are autosomal recessive polycystic kidney disease and primary hyperoxaluria type 1. Atypical haemolytic uremic syndrome, methylmalonic academia, and conditions where liver and renal failure co-exists may be indications for CLKT. CLKT is often preferred over sequential liver-kidney transplantation due to immunoprotective effects of transplanted liver on renal allograft; however, liver survival has no significant impact. Since CLKT is a major surgical procedure which involves multiple and complex anastomosis surgeries, acute complications are not uncommon. Bleeding, thrombosis, haemodynamic instability, infections, acute cellular rejections, renal and liver dysfunction are acute complications. The long-term outlook is promising with over 80% 5-year survival rates among those children who survive the initial six-month postoperative period.

Key Words: Combined liver-kidney transplantation; Immunoprotection; Long-term outcomes; Renal allograft survival; Acute cellular rejection; Autosomal recessive polycystic kidney disease

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INTRODUCTION

The first successful combined liver-kidney transplantation (CLKT) in an adult was reported in 1984. After that it has become more common in adults but remains a relatively infrequent procedure in children. Between 1988 and 2007, there were 2829 CLKT procedures performed in the United States of which only 166 were carried out in children. Combined liver-kidney transplantation is a challenging form of surgery in the paediatric age group with only about thirty surgical procedures being performed worldwide over a given year. CLKT is a procedure in which a liver (whole or in part) and kidney allografts, from the same deceased or living donor, are transplanted during a single surgical procedure. Sequential liver-kidney transplantation is isolated transplantation of the liver (or kidney) followed by the transplantation of the kidney (or liver) after a certain time interval.

Limited numbers of this surgical procedure are due to rarity of clear indications for surgery, long waiting times for the surgery and shortage of suitable donors. With the advancement of medical practices and innovative surgery, it is crucial that clinicians are insightful about when would CLKT be the right choice for a child, as compared to alternative therapeutic and surgical interventions. In the paediatric age group, CLKT can be considered for: (1) Children with profound and irreversible liver and kidney disease, e.g. autosomal recessive polycystic kidney disease; (2) Children with metabolic liver diseases causing end-stage renal disease, e.g. primary hyperoxaluria and atypical haemolytic uremic syndrome. A minority of children undergo CLKT following combined liver and renal failure. CLKT has been shown to be associated with immunoprotection of the kidney allograft and reduced rejection rates as compared with sequential kidney and liver transplantation or kidney transplantation alone. However, the experience of this observation is limited in paediatric studies due to a lack of comparative paediatric studies.

This review focuses on clinical indications, procedures, and acute, short and long term outcomes of combined liver-kidney transplantation in the paediatric age group. The review also discusses the evidence that supports the immunoprotective effects of CLKT on renal graft survival.

Indications

Autosomal recessive polycystic kidney disease: Autosomal recessive polycystic kidney disease (ARPKD) is a rare renal cystic disease in children with an incidence of 1:20000. It is also known as fibro-polycystic liver and kidney disease and the most common renal cystic/ciliopathy disease in children. In ARPKD there is a mutation in PKHD1, a gene located on chromosome 6p12. The defective gene encodes for fibrocystin and leads to the defective tubular formation in renal tubules and hepatic bile ducts, leading to the early development of cysts. Most severe variants are associated with pulmonary hypoplasia and high neonatal mortality. Approximately 50% of children develop the end-stage renal disease (ESRD) during the first decade of life. Hepatic fibrosis is also seen early in life leading to recurrent cholangitis and manifestations of chronic liver disease which includes portal hypertension, splenomegaly and variceal haemorrhage. However, chronic liver failure has a variable age of onset as opposed to early-onset ESRD, making management of these
children quite a challenge. These children undergo early nephrectomy and renal transplantation followed by sequential liver transplantation\(^{12}\) or combined liver-kidney transplantation.

**Primary hyperoxaluria type 1:** Primary hyperoxaluria type 1 (PH-1) is a rare disorder of oxalate metabolism which has an incidence of 1:120000\(^{13}\). It is an autosomal recessive disease and the most common indication for CLKT in children. Primary hyperoxaluria is characterized by elevated plasma and urinary oxalate levels due to the defective liver-specific peroxisomal enzyme alanine/glyoxylate aminotransferase\(^{14}\). Increased accumulation of glyoxalate leads to increased oxalate and formation and deposition of insoluble calcium salts in the kidney\(^{15}\). Children with PH-1 develop early-onset nephrocalcinosis, nephrolithiasis and ESRD\(^{16}\). With the development of ESRD and impaired excretion, oxalate is deposited in other tissues such as the retina, blood vessels, nerves and heart\(^{17}\). PH-1 often has a variable age of onset for ESRD and oxaluria is responsive to pyridoxine in some children. Therefore, it is important that pyridoxine responsiveness is evaluated and DNA analysis is performed to confirm the diagnosis in all children before planning CLKT\(^{14}\).

The definitive treatment is CKLT to prevent early recurrence of nephrocalcinosis in the transplanted kidney\(^{14}\). However, in developing countries, isolated kidney transplantation is considered initially unless a child is referred to a centre performing CLKT\(^{18}\). Hyperhydration is recommended in the immediate post-operative period to prevent the surge of plasma oxalate due to mobilization of oxalate from other tissues and subsequent damage to the transplanted kidney\(^{14}\). Hyperhydration should be supplemented by post-operative haemodialysis and use of crystallization inhibitors (e.g. citrate) for the same reason\(^{14}\).

**Atypical hemolytic uremic syndrome:** Atypical hemolytic uremic syndrome (aHUS) is a rare disorder of the alternative complement pathway involving impaired synthesis or function of factor H, a complement control protein. This leads to a triad of microangiopathic haemolytic anaemia, thrombocytopenia and renal dysfunction\(^{29}\). For aHUS CLKT was previously the treatment of choice as it corrected both the renal failure and the underlying problem with factor H which is produced by the liver. However, this procedure is no longer recommended as the first choice of definitive treatment due to promising effects of Eculizumab (anti-C5 monoclonal antibody) as a medical treatment and significant incidence of long term postoperative complications of CLKT. Eculizumab has been shown to inhibit complement activation in an alternative pathway that leads to microangiopathy\(^{28}\), thereby avoiding the need for liver transplantation. However, there are certain genetic variants such as DGKE (diacylglycerol kinase-epsilon) mutations for which Eculizumab is not effective\(^{21}\). An international consensus statement recommends either liver transplant or CLKT as the only treatment of cure for severe aHUS or defective complement factors synthesized in the liver (CFH–Complement factor H, CFB–Complement factor B, C3–Complement 3) although Eculizumab is also given to reduce post-transplant recurrence in those who only had renal transplantation\(^{13}\). Use of Eculizumab is limited by lack of availability and very high cost.

**Methylmalonic acidemia:** Methylmalonic acidemia is a rare inherited autosomal recessive metabolic disorder mainly due to defective vitamin-B12-dependent enzyme, methylmalonyl-CoA mutase leading to increased formation of methylmalonic acid. Children with methylmalonic acidemia are at high risk of multi-organ complications including heart, kidney, eyes and nervous system\(^{20}\). These children can also present with acute metabolic crises with profound metabolic acidosis and seizures\(^{22}\). Methylmalonic acidemia leads to renal tubular interstitial injury and up to 60% of children develop ESRD during adolescence\(^{24}\). Since methylmalonyl-CoA mutase activity is present in both liver and kidney, transplantation of one organ will lead to only partial recovery with a risk of recurrence\(^{27}\). CLKT has been shown to improve methylmalonic acidemia, renal dysfunction\(^2\) and overall quality of life\(^{20}\).

However, even after the CLKT, some systemic disease manifestations (such as neurologic or muscle impairment) may persist despite normal liver and kidney graft function due to abnormal methylmalonic acid metabolism in other tissues, including the muscles and skin\(^{21}\). Therefore, it is crucial to provide lifelong specific high-calorie diet low in propiogenic amino acid precursors despite organ transplantation, due to on-going production of methylmalonic acid from skeletal muscles\(^{29}\).

**Combined liver and kidney failure:** Combined liver and kidney failure occurs in certain metabolic diseases such as alpha-1 antitrypsin deficiency, glycogen storage disease type 1A, Boichis syndrome (nephronophthisis with congenital hepatic
fibrosis), and medical conditions such as hepatorenal syndrome and liver tumour with nephrotoxicity. CLKT had been variably successful in children with these conditions[31].

Hepatorenal syndrome (HRS) is one of the main complications of end-stage liver disease with high morbidity and mortality. It results from hypoperfusion of kidneys due to combined effects of intrarenal arteriolar vasoconstriction and peripheral vasodilatation, mainly in the splanchnic circulation. There are two types of HRS, type 1 (with the worst prognosis) is rapidly progressive with renal failure while type 2 has slowly developing renal dysfunction in patients with liver cirrhosis.

In most instances, HRS resolves with liver transplantation alone thus HRS is not being considered routinely for CLKT[34]. However, as prolonged HRS can progress to irreversible renal damage some patients with both the end-stage liver and kidney failure may be candidates for CLKT[35].

**Procedure**

In CLKT, both kidney and either whole or part of the liver from a donor (usually cadaveric) is transplanted to the same recipient during a single surgical procedure. Sequential liver-kidney transplantation is performed in two stages where the recipient initially undergoes isolated organ transplantation (either kidney or liver) followed by the other organ (liver or kidney) from two different cadaveric donors or a single living donor. It is of the paramount importance to keep the cold ischemic time shorter to avoid delayed graft function.

Whole cadaveric liver transplantation would help to reduce the post-transplant complications (e.g. bleeding, bile leak) by avoiding prolonged cold ischemic time for both liver and kidney, compared to partial liver graft transplantation. The liver graft is transplanted first to reduce the risk of cold ischaemia to liver and cold ischaemic time is usually kept to less than 8-10 h for the liver and 10-12 h for the kidney. After hepatic vascular anastomoses are performed, renal vessels are anastomosed to the common iliac vessels to achieve early re-perfusion. Uretero-vesical and biliary anastomoses are performed only after hepatic and renal vascular reperfusion is achieved.

**Acute complications and short term outcomes**

CLKT is a complex major surgical procedure and immediate post-operative complications are frequently reported. Analysis of the Scientific Registry of Transplant Recipients (https://www.srtr.org/) of 152 primary paediatric CLKTs performed from October 1987 to February 2011, revealed a total of 32 deaths (21.1%) during the first 30-mo postoperative period[32]. The main causes of death were: Infectious (18.7%), cardiovascular (18.7%), respiratory (6.2%), gastro-intestinal and haemorrhage (6.2%). However, with the advancement of surgical and medical interventions, the rate of complications has been progressively reducing over the last decade.

Post-operative hyperoxaluria and graft dysfunction is a major problem following CLKT for primary hyperoxaluria and ESRD and these patients should be managed with postoperative renal replacement therapy. Many studies reported that the acute post CLKT complications were higher in primary hyperoxaluria compared to other causes[33].

Further complications including, post-operative bleeding, bile leaks, hepatic artery thrombosis, and acute liver failure can lead to graft loss and even mortality. Due to bleeding and multiple vascular anastomoses, patients are at risk of hypovolaemia and shock or fluid overload due to multiple transfusions. Therefore, fluids and diuretics should be used carefully. A liver graft can suffer cold ischaemia with longer anastomosis times and the risk is higher with partial liver transplantations compared to whole liver transplantations[34].

Mortality during the initial six months following CLKT remains high. Septicaemia and multi-organ failure are common causes of mortality while on high doses of immunosuppressive medications[35]. Acute organ rejection was reported in 14% of CLKT patients during the first postoperative year in one study[36]. The combination of basiliximab and daclizumab reduces acute rejection in renal transplantation when used during the induction phase of immunosuppression[37]. Calinescu et al[38] examined 152 patients who had CLKT for short and long term outcomes. Overall, the one-year patient survival was 86.8% and the survival of the kidney and liver grafts was 83.4% and 81.9% respectively.

**Immunoprotective effects of CLKT on renal allograft**

In CLKT patients, the liver allograft confers immunoprotection of the kidney allograft. This was first demonstrated in animal model[39,40]. Later clinical studies of CLKT have
shown reductions in both acute cellular rejection and chronic rejection of kidney allograft in those who undergo CLKT when compared to cadaveric renal transplantation\cite{36,37}. The molecular basis of immunoprotection is yet to be precisely defined but it is thought that the transplanted liver can modify the immune system of the recipient by neutralizing circulating autoantibodies\cite{38}. Further, a liver graft provides HLA-G antigens that inhibit natural killer cells thought to be involved in acute rejection\cite{39}. Improved renal outcomes from such immunoprotection in part explain the fact that CLKT has better outcomes as compared with sequential organ transplantation in patients with combined liver and renal impairment. Liver rejection rates were not different in those with CLKT when compared to isolated liver transplantations\cite{40}. Rapamycin, a calcineurin inhibitor, is the mainstay of immunosuppression following CLKT. Use of Rapamycin has been associated with reduced rates of hepatic rejection in adult studies\cite{41}.

**Long term outcome**

The result of CLKT is in part dependent on the aetiology of hepatic and kidney dysfunction. The outcome is also dependent on the child’s pre-transplant clinical condition. Diagnosis of metabolic disease and an early transplantation scenario are good prognostic indicators while multi-organ failure leading to CLKT is a poor prognostic indicator. The long term outcome of the transplanted liver is usually good without evidence of chronic rejection. However, chronic allograft nephropathy of the kidney is apparent in the long term.

Data regarding long term outcomes of CLKT are limited. Quintero Bernabeu *et al.*\cite{42} reported long term outcomes of 14 children who had CLKT. The majority of patients in that cohort had either ARPKD or PH-1. One child had renal re-transplantation following branch renal artery thrombosis of the kidney allograft after it was complicated by severe hypertension and renal dysfunction. One patient had chronic rejection 10 years after the transplant. Two children had BK viral infections which were treated with cidofovir whilst one child died following adenoviral infection 8 mo after CLKT. Several children developed progressive renal dysfunction and severe tubulopathy indicative of allograft nephropathy and needed renal re-transplantation.

Long term outcome was dependent on the primary disorder and patients with PH-1 have slower improvement of renal functions as compared with ARPKD. Five-year renal graft survival and overall survivals were 85.7% and 92.9% respectively. More recently, Ranawaka *et al.*\cite{43} reported long term renal outcomes in a cohort of 40 children who had CLKT with the majority being diagnosed with ARPKD. The investigators observed a statistically significant greater decline of estimated glomerular filtration rate in isolated kidney transplant patients compared to those who had CLKT whilst acute rejection was less in those with CLKT. The investigators observed better outcomes in those with ARPKD compared to PH-1 and comparative to observations made by Quintero Bernabeu *et al.*\cite{42} Although there are several studies which reported long term renal outcomes, only a few studies reported long term liver outcomes of which 5-year graft survival varied from 76.5%\cite{44,45,46}. In one large series, Calinescu *et al.*\cite{47} analyzed data using the Scientific Registry of Transplant Recipients to determine long term outcomes of 152 pediatric CLKT. The liver graft survival at five and ten years was 76.5%, and 72.6 % respectively, and kidney graft survival was 76.5% and 66.8 %, respectively. Patient survival was 82.1% at five years, and 78.9% at ten years, which was much similar to the isolated liver transplant at five and ten years (81.2% and 77.4%). But isolated kidney transplant showed much better results at those points (95.4% and 90%)\cite{48}.

The children with liver and kidney failure are shorter than their peers due to underlying chronic conditions but show improved growth after CLKT. Growth is an important determinant of better functional outcomes in employment, education and marital life\cite{49,50}. North American Paediatric Renal Trials and Collaborative Studies data have shown that better catch-up growth is achieved when CLKT is performed at a younger age, especially below six years\cite{51}. Human growth hormone has a place in this group of children and a recent Cochrane update demonstrated that children who were treated with growth hormone showed an increased height velocity of 3.88 cm/year\cite{52}.

Although life-saving, CLKT may not be curative in all children, and children who had CLKT may suffer from chronic health problems throughout their life. Therefore, the quality of life is an important aspect to assess in long term outcome of transplant recipients. The World Health Organization defines health as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. Thus, it is of the paramount importance to have a holistic approach from the multidisciplinary transplantation team with participation of primary care physicians, community nurse, psychologists, social workers and the school. Such an approach
should extend to address the common attentional, behavioural and peer relationship problems of these children to improve their overall school performance. Furthermore, they should be guided through a proper adolescent transition programme to achieve their ultimate goals in life as young adults.

CONCLUSION

CLKT is a complex surgical procedure which is increasingly performed for a number of indications, especially primary hyperoxaluria type 1 and autosomal recessive polycystic kidney disease. Given the risks of the procedure, selection of patients for this surgery needs to be done carefully taking into consideration, the clinical indication, the functional status of liver and kidney, the patient’s general health, and the skills and expertise of the transplant centre. In CLKT, the early mortality is mostly related to infections and surgical complications of the liver graft. On the other hand, chronic complications with liver graft are fairly rare, and the liver protects the kidney allograft from rejection, which results in stable function and long term survival of the renal allograft.

However, liver survival rates are not different in CLKT compared to sequential liver and kidney transplantation or isolated liver transplantation. Acute complications are not uncommon given the complexity of the surgical procedure. However, these can be reduced by optimal precautions and early detection and management of problems. Long-term outcomes are promising in children who have had CLKT with good overall long-term survival rates when performed in experienced centres with expertise.

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