

Combined Paediatric Liver-Kidney Transplantation: Analysis of our experience

Dr Bernd Ströbele

A research report submitted to the Faculty of Medicine, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Masters of Medicine in the speciality of General Surgery

Johannesburg, 2014

DECLARATION

I, Bernd Ströbele, declare that this research report is my own work. It is being submitted as partial fulfilment for the degree of Masters of Medicine in the speciality of General Surgery, to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg.

It has not been submitted for any degree or examination at this or any other university.

Dr Bernd Ströbele

26 May, 2014

PUBLICATIONS

South African Medical Journal 2013;103(12):925-929

DOI: 10.7196/samj.7304

ABSTRACT

Background. Renal insufficiency is increasingly common in end-stage liver disease and allocation of livers to this category of patient has escalated. The frequency of combined liver-kidney transplantation (CLKT) has consequently increased. Indications for CLKT in children differ from those for adults and typically include rare congenital conditions; subsequently limited numbers of this procedure have been performed in paediatric patients worldwide. Scant literature exists on the subject.

Methods. Subsequent to institutional approval, a retrospective chart analysis of all paediatric CLKTs performed at the Transplant Unit, Wits Donald Gordon Medical Centre, University of the Witwatersrand, Johannesburg, South Africa between January 2005 and July 2013 was conducted.

Results. Defining children as younger than 18 years of age, 43 patients had received a liver transplant since 2005, of whom 8 received a CLKT. Indications included autosomal recessive polycystic kidney disease ($n=3$), primary hyperoxaluria type 1 ($n=4$) and heterozygous factor H deficiency with atypical haemolytic uraemic syndrome ($n=1$). Graft combinations included whole liver and one kidney ($n=5$), whole liver and two kidneys ($n=1$) and left lateral liver segment and one kidney ($n=2$), all from deceased donors. Patient age ranged from 4 to 17 years (median 9) and included 4 females and 4 males. Weight ranged from 13 to 42 kg (median 22.5). We describe one in-hospital mortality. The remaining 7 patients were long-term survivors with a survival range from 6 to 65 months.

Conclusions. Although rarely indicated in children, CLKT is an effective treatment option, appropriately utilising a scarce resource and significantly improving quality of life in the recipient.

Table of Contents

DECLARATION	2
PUBLICATIONS	3
ABSTRACT	4
LIST OF TABLES	6
INTRODUCTION	7
METHODS	8
RESULTS	9
DISCUSSION AND LITERATURE REVIEW	12
CONCLUSION	22
CONFLICT OF INTEREST	23
ETHICS CERTIFICATE	26

LIST OF TABLES

TABLE 1. INDICATIONS FOR COMBINED LIVER-KIDNEY TRANSPLANTATION IN CHILDREN.....	13
TABLE 2. REPORTED COMBINED LIVER-KIDNEY TRANSPLANTS IN CHILDREN.....	14
TABLE 2 CONTINUED. REPORTED COMBINED LIVER-KIDNEY TRANSPLANTS IN CHILDREN	15
TABLE 2 CONTINUED. REPORTED COMBINED LIVER-KIDNEY TRANSPLANTS IN CHILDREN	16

Combined Paediatric Liver-Kidney Transplantation: Analysis of our experience

INTRODUCTION

The Wits Donald Gordon paediatric liver transplant program was established in November 2005 and is one of two such units in Sub-Saharan Africa. It forms part of the solid organ transplant unit run by the Wits Donald Gordon Medical Centre (WDGMC) Transplant Division, a public-private partnership catering to an ever-increasing patient population. The program has performed 42 paediatric liver transplants to date. Of these 8 were combined liver-kidney transplants, the first of which was performed on the 18th August 2007.

Since the first successful kidney and liver transplants in the 1950s and 1960s respectively, both patient and graft survival have improved dramatically (1). The first successful combined liver-kidney transplant (CLKT) was subsequently performed by Margreiter in Austria in 1984 (2). Both the liver and kidney were transplanted from a single deceased donor into a 28 year-old recipient who had liver failure as a result of chronic hepatitis B infection, as well as end stage renal dysfunction. One month following transplant both kidney and liver function had normalised, the patient had returned to a pre-morbid level of functioning, and the procedure was deemed a success. Renal insufficiency, secondary to a variety of causes, is a common problem in patients suffering from end-stage liver disease, particularly in adults (3). Renal impairment in liver transplant patients amplifies the risk for both postoperative chronic kidney disease (CKD) and procedure-related mortality. With the introduction of the model of end-stage liver disease (MELD) score for liver transplantation the allocation of organs to patients with renal insufficiency has increased (1,2,4).

Consequently, the number of CLKT in adults has shown a considerable increase over the last few years.

In children on the other hand, the most common causes for CLKT are congenital diseases affecting both liver and kidney, such as primary hyperoxaluria type 1 (PH-1) and autosomal recessive polycystic kidney disease (ARPKD), amongst others (2). These diseases have a low incidence and, as a result, CLKT in children is still a therapy performed in a very limited number of cases. Little data is available in the literature regarding paediatric CLKT (1).

Methods

All paediatric patients undergoing CLKT at the WDGMC were identified from a prospective database. Overall 8 CLKT's were performed in 8 children between 2007 and the present. In the same time period 34 isolated liver transplants and 49 isolated kidney transplants (25 cadaver kidneys and 24 related living donor kidneys) were performed in children.

The patients were analysed for recipient characteristics as listed in table 1, and the technical details of each procedure were noted. Pertinent intra and postoperative events were documented as were any postoperative complications, particularly those related to vascular, biliary or urinary reconstruction, and graft and patient survival were analysed. Finally, a retrospective English language Pubmed search was conducted from January 2013, looking for all published papers discussing CLKT.

Results

Since 2007, 8 combined liver-kidney transplants have been performed and all are included in this retrospective review. None of the children had received previous transplants. The indications for CLKT were congenital hepatic fibrosis associated with polycystic kidney disease (n = 3), primary hyperoxaluria type 1 (n = 4) and heterozygous factor H deficiency with atypical haemolytic uraemic syndrome (n = 1). The age of the patients ranged from 4 to 17 years (median = 9 years) and included 4 females and 4 males. Their weight ranged from 13 to 42 kg (median = 22.5 kg). Patient waiting times since listing on the active transplant list ranged from 49 to 1383 days (median = 270 days).

The specific surgical techniques for organ procurement, graft preparation and the respective implant procedures are well described, and only when techniques deviate from an accepted standard will they be discussed. Of note is that where recipient weight was less than 20 kilograms, there was a low threshold to establish arterial inflow to the donor kidney directly off the aorta, below the origin of the inferior mesenteric artery. Graft combinations were as follows: whole liver and one kidney (n = 5), whole liver and two kidneys (n = 1) and left lateral segment of liver and one kidney (n = 2). Median anaesthetic time was 7 hours and blood loss ranged from 80 ml to 4970 (median = 1831 ml).

Median blood volume transfused was 900 ml of leukocyte-depleted packed red blood cells and other blood products, and 450ml of cell saved whole blood. Blood group crossmatch was identical in 7 and compatible in 1.

Induction immunosuppression consisted of Daclizumab (Zenepax) and Solumedrol, with dosages adjusted for weight. Postoperative maintenance immunosuppression consisted of mycophenolate

mofetil (CellCept), tacrolimus (Prograf) and prednisone. In one case Everolimus was used. With respect to pre-operative dialysis, 6 patients received haemodialysis, 1 peritoneal dialysis, and 1 patient was transplanted preemptively. All patients with hyperoxalurea received 3 months of post-operative haemodialysis to clear residual systemic oxalic acid. One patient underwent sequential nephrectomies, the first pre- and the second post CLKT, both for severe nephrocalcinosis and recurrent urinary tract infections (UTI's), whilst a 2nd patient had bilateral nephrectomies for recurrent atypical UTIs post transplant. Native kidneys in the remaining patients remained asymptomatic and were left in situ.

There was 1 mortality in this series. The remaining 7 patients are dialysis free, with excellent quality of life subjectively, with a mean follow up of 2,17 years. The mortality was related to surgical complications of hepatic artery and portal vein thrombosis peri-operatively. Although the patient was re-listed, a second liver did not become available and the patient died of acute hepatic failure. In the patient who received the two kidneys as an *en bloc* graft, one kidney infarcted secondary to renal artery thrombosis, although this had no impact on renal function. A further patient developed a wound haematoma which resolved with conservative management. The last patient, who received a reduced left lateral segment graft and single kidney, developed an abdominal compartment syndrome which required urgent decompression and closure with a large mesh.

Technical details of the CLKT

The purpose of this description of the technical aspects of CLKT is not to repeat the basic steps of the operation that have been published extensively and remain the gold standard, but rather to highlight where we have deviated from, or modified, the standard procedure and give an explanation as to why we did so.

Our liver transplant technique was routine. All donor kidneys were placed extraperitoneally via a right-sided Rutherford-Morrison incision. We did not encounter the theoretical risk of skin bridge necrosis at the lateral aspects of the right subcostal and Rutherford-Morrison incisions where the two approximate. The right-sided extraperitoneal approach allows excellent access to the relevant vasculature, particularly the distal aorta and inferior vena cava, which may be required to establish adequate arterial inflow and venous outflow respectively. This is especially important when a large donor kidney is implanted into a small child, when up to 25-30% of the circulating blood volume is taken up by the transplanted kidney on release of clamps. Inadequate arterial inflow will compromise perfusion, causing subsequent necrosis of the graft.

DISCUSSION AND LITERATURE REVIEW

The relative infrequency of CLKT in children is as a result of limited indications, which are rare conditions with low incidences that have not changed over the years (2). This leaves a challenging problem in determining the optimal indications for CLKT. In our patient cohort the indications for CLKT are listed in Table 1. According to the UNOS database, only 231 CLKT's were performed in children from 1988 to date, these in 41 transplant centres (5). The median number of transplants per centre was 3 (average = 6). It is evident, even with the small numbers that we are reporting on, that our indications and numbers mirror those of the world literature. We will discuss the three most common indications for CLKT, namely primary hyperoxaluria type 1 (PH1), autosomal recessive polycystic kidney disease with congenital hepatic fibrosis, and heterozygous factor H deficiency with atypical haemolytic uraemic syndrome.

Table 1. Indications for combined liver-kidney transplantation in children

Our cohort		Literature	
Primary hyperoxaluria type 1	4	Primary hyperoxaluria type 1	49
Polycystic kidney disease	3	Polycystic kidney disease/ congenital hepatic fibrosis	17
Heterozygous factor H deficiency with atypical haemolytic uraemic syndrome	1	Factor H deficiency	7
		Methylmalonic acidaemia	7
		Alpha-1-antitrypsin deficiency	4
		Cyclosporin toxicity	2
		Failed prior liver transplant	2
		Cystinosis	1
		Drug toxicity	1
		Glycogen storage disease 1a	1
		Autoimmune hepatitis/ hepatorenal syndrome	1
		Sclerosing cholangitis/ interstitial nephritis	1
		Biliary atresia	1
		Liver disease secondary to parenteral nutrition	1

Table 2. Reported combined liver-kidney transplants in children

Author (Reference)	Number CLKT	Indication	Mean age at transplant (years)	Patient survival %	Death censored renal allograft survival %	% of patients with kidney rejection	% of patients with liver rejection	Morbidity/ Mortality
Polinsky et al.	1	PH1	7.5	0	Not reported	Not reported	Not reported	Early postoperative death (cause not specified)
van 't Hoff et al.	1	MMA	13.5	100	100	0	0	
Grewel et al.	12	PKD/CHF (5) alpha-1-antitrypsin deficiency (2) Failed prior liver/ cyclosporin toxicity (2) Other (3)	9.5	67	100 (4.8 yr)	42	42	4 deaths due to sepsis post transplant
Ellis et al.	4	PH1	7.3	75	100	33	0	1 death post transplant (cause not specified)
Shapiro et al.	9	PH1	8.5	78	100 (2.5 yr)	Not reported	Not reported	1 death due to sepsis/ 1 death due to PTLD
Rogers et al.	8	PH1 (3) PKD/CHF (3) Cystinosis (1) Drug Toxicity (1)	10.9	75	50	25	13	1 death due to pneumonia/ 1 death due to PTLD
Gagnadoux et al.	8	PH1	16.4	75	100 (5 yr)	12.5	12.5	2 deaths during transplant not specified
Loreno et al.	1	alpha-1-antitrypsin deficiency	15	100	100	0	100	
Remuzzi et al.	1	Factor H deficiency	2	100	100	Not reported	100	Re-transplanted liver at 1 month
Millan et al.	6	PH1	1.2	100	100 (6.4 yr)	16.70	67	
Nagarajan et al.	2	MMA	15.5	100	100	Not reported	Not reported	

Table 2 continued. Reported combined liver-kidney transplants in children

Author (Reference)	Number CLKT	Indication	Mean age at transplant (years)	Patient survival %	Death censored renal allograft survival %	% of patients with kidney rejection	% of patients with liver rejection	Morbidity/ Mortality
Remuzzi et al.	1	Factor H deficiency	3	0	Not reported	Not reported	Not reported	Split liver - intraop hypotension, early postoperative death
Saland et al.	1	Factor H deficiency	5.5	100	100	0	100	
Kasahara et al.	5	MMA	15.1	100	Not reported	Not reported	Not reported	
Belingheri et al.	1	Glycogen storage disease 1a	19	100	100	0	0	
Zanus et al.	4	PH1 (3) alpha-1-antitrypsin deficiency	6	50	25	Not reported	Not reported	2 deaths early post operative period (cause not specified)/ 1 renal allograft loss
Jalanko et al.	2	Factor H deficiency	9.5	100	100	0	50	
De La Cerda	10	PH1 (5) Autoimmune hepatitis/ hepatorenal syndrome (1) Sclerosing cholangitis/ interstitial nephritis (1) Biliary atresia/CsA toxicity (1) Liver disease secondary to parenteral nutrition/CKD unknown etiology (1)	10	100	90	10	0	1 acute allograft rejection due to patient non compliance with medication
Chava et al.	4	Not specified						
Mehrabi et al.	4	PH1 (3) PKD/CHF (1)	8.8	Not reported	Not reported	Not reported	Not reported	

Table 2 continued. Reported combined liver-kidney transplants in children

Author (Reference)	Number CLKT	Indication	Mean age at transplant (years)	Patient survival %	Death censored renal allograft survival %	% of patients with kidney rejection	% of patients with liver rejection	Morbidity/ Mortality
Herden et al.	14	PH1 (7) PKD/CHF (7)	8	100	93	Not reported	Not reported	Primary non function of the liver graft and impaired kidney function requiring re-CLKT (x2 livers) One re-liver transplant for outflow problem with toxic liver damage
Khan et al.	1	Factor H deficiency	3	100	100	100	100	Delayed renal graft function
Sakamoto et al.	1	Caroli's disease/ARPKD	4.3	0	Not reported	Not reported	Not reported	One death

CLKT, combined liver-kidney transplantation; PH1, primary hyperoxaluria type 1; PKD, polycystic kidney disease; CHF, congenital hepatic fibrosis; MMA, methylmalonic acidemia; PTLN, post-transplant lymphoproliferative disorder

PH1 is an autosomal recessive metabolic condition caused by a congenital deficiency of alanine-glyoxylate aminotransferase (AGT), a hepatic peroxisomal enzyme. Patients with this deficiency metabolise glyoxylate to oxalate and glycolic acid, instead of to glycine (6). The kidneys are subsequently burdened with eliminating the large oxalate load, which results in deposition of calcium-oxalate crystals in the kidney and progression to chronic renal failure. The condition is often more severe in infants, with end stage renal disease (ESRD) presenting before two years of age. By 15 years of age 50% of patients will have developed ESRD (1-3,7). As the glomerular filtration rate drops, oxalate is deposited systemically into bone and soft tissues including the retina, blood vessels, nerves and heart (6). If the condition is diagnosed early, and before significant renal failure is established, isolated liver transplantation (iLT) is an acceptable option, with excellent survival (7). However this only addresses the issue of oxalate formation, and it does not resolve the problem of an already high burden of oxalate which would force the kidneys to eliminate the remaining stores. This can contribute to progressive chronic kidney disease requiring a renal transplant at a later stage.

The converse is however not acceptable – graft survival after isolated kidney transplantation (iKT) for PH1 approximates 18 percent at 3 years, based on data from the European Dialysis and Transplant Association registry (8). This obviously occurs due to progressive nephrocalcinosis and urolithiasis and early graft failure, as hepatic AGT is still deficient, and oxalate over production continues.

CLKT addresses both the primary metabolic insult, namely hepatic AGT deficiency, and the consequent end organ damage secondary to oxalosis, that being chronic renal failure. Reported outcomes have been varied however. Again the largest series of patients is from the European PH1

Transplant Registry. 127 transplants were performed in 117 patients between 1984 and 2005, 99 CLKTs, 22 iLTs, and 6 patients underwent iLT followed by iKT. 10 year survival was 69% for all groups (9). Factors which were clearly shown to affect outcome and improve survival were the overall clinical condition of the patient at the time of transplantation, earlier diagnosis, and aggressive pretransplantation dialysis (1,2,4,9).

Of interest is that despite a new liver, more than 50% of renal graft failures following CLKT were due to oxalate deposition in the new kidney, and that hyperoxaluria was detectable up to 45 months post transplantation. This oxalate burden should not be underestimated (2,10). Our current protocol is to dialyse all our PH1 cases for 3 months post transplantation, to decrease the oxalate stores and to mitigate any damage they might cause to the renal allograft by nephrocalcinosis or urolithiasis. Consideration should also be given to the shortage of deceased donor organs, and the pressure that this applies to other patients on the waiting list. Thus alternatives that should be considered once the decision to list has been taken include the feasibility of Related Living kidney donation as and when a Deceased Donor liver becomes available, as well as consideration of both Related Living kidney and liver transplantation simultaneously (1,11).

Autosomal recessive polycystic kidney disease (PKD) is a disease with an incidence of 1 in 20 000 live births and demonstrates a variable clinical progression (2,12). The most severely affected children present with ESRD either in the perinatal period or during early infancy. Liver involvement is a result of congenital hepatic fibrosis or Caroli disease, which may progress to portal hypertension, hypersplenism, thrombocytopaenia, and recurrent ascending cholangitis (Caroli syndrome) (6,13). As the liver disease is chronic and may not necessarily progress to failure, isolated kidney transplantation has been the standard intervention for ESRD secondary to PKD with minimal liver disease. Reported data on isolated kidney transplantation shows patient survival to be 89% and death censored graft survival at 100% at 5 years (14). However Khan et al reported on 14

patients who had received isolated kidney transplantation in the presence of hepatic disease; 4 of the 5 deaths in this series were due to complications from hepatic disease and 56% of the remaining survivors had complications related to congenital hepatic fibrosis at a mean of 6.3 years post transplantation (15). Davis et al published another retrospective study of 203 patients who received isolated kidney transplantation for similar indications (13). What is of particular interest in this study is the percentage of sepsis related deaths, 64%. Whilst sepsis is acknowledged as a common cause of death among the paediatric group of kidney transplant recipients, the North American Paediatric Renal Trials and Collaborative Studies registry report this at 28.9% (6,16). Although not proven, this may hypothetically suggest an increased rate of cholangitis related to congenital hepatic fibrosis, and the fact that these patients already have a heavily colonized biliary tree. This situation is possibly accentuated by subsequent immunosuppression (7,13).

Whilst liver disease is always present in these patients, it does not always warrant transplantation, and isolated kidney transplant is often all that is required. When there is liver disease causing progressive and severe complications, CLKT is advocated. Although limited, outcome data following CLKT is favourable in both the adult and paediatric literature. CLKT should be considered when ESRD (as a result of ARPKD) and severe congenital hepatic fibrosis or hepatic failure are present. On occasion, liver disease secondary to the congenital hepatic fibrosis dominates the clinical picture, however we are not aware of any cases reported in the literature of isolated liver transplantation, and currently CLKT is recommended in this scenario (8,11).

Heterozygous factor H deficiency with atypical haemolytic uraemic syndrome (HUS) is a very unusual indication for CLKT, with only 7 cases described in the literature to date. Factor H is produced in the liver and regulates the activation of the complement cascade via the alternative pathway. Qualitative or quantitative deficiencies in Factor H can result in the uninhibited deposition of complement, destruction of microvasculature and the phenotype of HUS. There are more than 60

heterozygous factor H mutations which are responsible for approximately 30% of recurrent cases of HUS. They carry a poor prognosis, resulting in ESRD or death in 50% of patients (3,9,17,18).

Outcomes following isolated kidney transplantation are equally poor with recurrences in the range of 50 to 100% (3,17). CLKT addresses both the qualitative and quantitative factor H issues and restores renal function.

Recently Eculizimab has been registered for the management of aHUS and the recommendation is to do a kidney transplant combined with lifelong Eculizimab therapy (19). Unfortunately the lifelong cost of this drug is currently prohibitively high. The alternative is CLKT which is a more aggressive treatment option and is associated with greater morbidity and mortality due to the combined organ transplant. In order to reduce this risk an option is to use Eculizimab peri-operatively in CLKTs in order to reduce the complications related to uninhibited complement activation. Where anti-factor H antibodies exist then a CKLT may need to be combined with lifelong plasma exchange and therapy aimed at reducing antibody levels. Our patient did not have anti-factor H antibodies.

At the time of writing, CLKT has been reported in seven patients (including our own case) with factor H-associated HUS. Most recently Khan et al reported on one case which was uncomplicated, apart from a short period of delayed renal graft function of the kidney. Saland et al also published a single case with 100% dual graft survival at 2 years (3). Our case was equally uncomplicated, with dual graft survival more than 2 years post transplant. Plasma exchange has been suggested in the immediate pretransplant period, or intraoperatively, as it restores normal factor H function and inhibits unregulated complement deposition until the new liver has had time to normalise factor H levels and function. Also, because split liver grafts are more susceptible to poor perfusion and the resultant increased complement activation, it is suggested by some units that whole liver grafts be used (18). It should be stated that this is not the practice of our unit, and we would consider the use of split grafts without reservation.

Thus although there are only a limited number of documented cases in addition to our own single case experience, it has been demonstrated that in light of these recent successes as well as the poor outcomes of alternative therapy, CLKT should be considered for this subgroup of patients.

All published CLKTs (including adults) extracted from the PubMed database are shown in Table 2. From 1984 to present, 3568 cases have been reported. A significantly smaller number, 108 cases, have been performed in children, including our series. The majority of transplants were for primary hyperoxaluria type 1 (n = 52, 48.6%), autosomal recessive polycystic kidney disease (n = 20, 18.5%) and atypical Factor H deficiency (n = 8, 7.4%). Immunosuppression varied significantly from tacrolimus or cyclosporin A monotherapy, to multiple drug combinations and even quadruple therapy with antithymoglobulin, cyclosporin A, methylprednisolone and azathioprine. When reported, complications were predominantly sepsis related (n = 7, 6.5%), and invariably resulted in mortality.

Since CLKT's are now more commonly performed, there has been debate as to whether the liver allograft offers "immunoprotection" to the kidney allograft. In 2003, a review of the UNOS database illustrated a lower six-month cumulative acute renal rejection rate for patients receiving CLKT as opposed to isolated kidney transplantation (21.5 versus 30.1%). When reviewing single centre experiences the results appear even more promising, however the small numbers reported in these studies should caution their interpretation. Grewel et al reported a 42% acute renal allograft rejection rate however only two of the five cases were proven by biopsy (20). Rogers et al showed a 25% acute renal allograft rejection rate versus 86% rejection rate in their kidney after liver transplant cohort (21). More recently De La Cerda et al conducted a single center retrospective case-control study which looked at 10 children who had CLKT and survived to 6 months, comparing them to a control group of 20 kidney only transplants matched for age, era and

immunosuppression (22). In the CLKT group only 1 acute renal allograft rejection was reported at 7 years secondary to non-compliance of medication. In the same period the kidney only group had 16 acute rejection episodes. There was also no hepatic rejection in the CLKT. The study was, however, too small to uncover a significant difference in immunologically mediated kidney allograft failure. The same authors therefore looked at UNOS paediatric data - they analysed 111 CLKT and 3798 kidney-only transplants between 1995 and 2005. What they found is that although renal graft loss in the first 6 months was higher in the CLKT (20.1% vs 5.9%), death censored kidney allograft survival at 5 years was significantly better in the CLKT group and that function did not continue to deteriorate as it did in the kidney only group (22).

When reviewing the literature there are a few reported cases where patients required re-liver transplant after CLKT for graft non-function or rejection. In one case a patient received two subsequent liver transplants following the initial CLKT (23). Although that patient did not ultimately survive, the feasibility of subsequent transplantation does exist, obviously dependant on the availability of organs. This does raise the question as to whether our patient could have survived had the resource been available, at the same time raising the question of utilizing a scarce resource.

Conclusion

In the paediatric age group, the most common indication for CLKT are metabolic diseases which affect either the kidney alone with or without liver disfunction, or congenital abnormalities affecting both organs simultaneously. CLKT has good results in select groups of patients and long term survival approaches that of liver transplantation alone. What lends itself to more favourable results, is when patients are evaluated early and listed before they become severely ill or manifest systemic complications. In patients with PH1, nephrocalcinosis and systemic oxalosis can become a problem. All patients in our series were dialysed for 3 months post operatively to clear systemic

oxalic acid. The literature presents two conflicting views; some studies show good results following CLKT while others report poorer results. Irreversible renal dysfunction should not exclude children with severe liver disease from consideration for liver transplantation if it is performed with a simultaneous kidney transplant. Factors that negatively affect the outcome of isolated liver transplantation (UNOS status and re-transplantation) must be considered in determining the suitability of any given candidate for CLKT but ultimately ESRD and poor quality of life need to be offset against the potential excellent long-term benefits of a timely CLKT. Similarly our patients with ARPKD showed excellent graft and patient survival. 64-80% of mortality occurring in ARPKD can be attributed to cholangitis or sepsis which is related to their liver disease. As surgical mortality in paediatric liver transplant recipients has been shown to be < 10% at one year, it is a viable option in patients with recurrent cholangitis or complications of portal hypertension, to do a CLKT to decrease overall mortality. There is suggestive clinical evidence that CLKT offers a degree of immunologic protection to the renal allograft.

Our centre demonstrated an excellent survival rate, with satisfactory results in terms of mortality and morbidity in comparison to reported data in worldwide literature.

Conflict of interest

All authors declare that they have no conflict of interest in relation to this publication and. This study is not funded by any source.

References

1. Herden U, Kemper M, Ganschow R, Klaassen I, Grabhorn E, Brinkert F, et al. Surgical aspects and outcome of combined liver and kidney transplantation in children. *Transplant International*. 2011 May 26;24(8):805–11.
2. Sutherland SM, Alexander SR, Sarwal MM, Berquist WE, Concepcion W. Combined liver-kidney transplantation in children: indications and outcome. *Pediatric Transplantation*. 2008 Dec;12(8):835–46.
3. Saland JM, Emre SH, Shneider BL, Benchimol C, Ames S, Bromberg JS, et al. Favorable long-term outcome after liver-kidney transplant for recurrent hemolytic uremic syndrome associated with a factor H mutation. *Am J Transplant*. 2006 Aug;6(8):1948–52.
4. Chava SP, Singh B, Pal S, Dhawan A, Heaton ND. Indications for combined liver and kidney transplantation in children. *Pediatric Transplantation*. 2009 Sep;13(6):661–9.
5. UNOS Database. Combined Liver-Kidney Transplants by Age of Donor.
<http://optn.transplant.hrsa.gov/latestData/advancedData.asp> (accessed 28 February 2013).
6. Ellis SR, Hulton SA, McKiernan PJ, de Ville de Goyet J, Kelly DA. Combined liver-kidney transplantation for primary hyperoxaluria type 1 in young children. *Nephrol Dial Transplant*. 2001 Feb;16(2):348–54.
7. Shapiro R, Weismann I, Mandel H, Eisenstein B, Ben-Ari Z, Bar-Nathan N, et al. Primary hyperoxaluria type 1: improved outcome with timely liver transplantation: a single-center report of 36 children. *Transplantation*. 2001 Aug;72(3):428–32.
8. Broyer M, Brunner FP, Brynger H, Dykes SR, Ehrich JHH, Fassbinder W, et al. Kidney Transplantation in Primary Oxalosis: Data From the EDTA Registry. *Nephrology Dialysis Transplantation*. 1990 Jan 1;5(5):332–6.
9. Jamieson NV. A 20-Year Experience of Combined Liver/Kidney Transplantation for Primary Hyperoxaluria (PH1): The European PH1 Transplant Registry Experience 1984–2004. *Am J Nephrol*. 2005;25(3):282–9.
10. Latta K, Jamieson NV, Scheinman JI, Schärer K, Bensman A, Cochat P, et al. Selection of transplantation procedures and perioperative management in primary hyperoxaluria type 1. *Nephrology Dialysis Transplantation*. 1995 Jan 1;10(sup8):53–7.
11. Telega G, Cronin D, Avner ED. New approaches to the autosomal recessive polycystic kidney disease patient with dual kidney-liver complications. *Pediatric Transplantation*. 2013 Apr 17;17(4):328–35.
12. Zerres K, Mücher G, Becker J, Steinkamm C, Rudnik-Schöneborn S, Heikkilä P, et al. Prenatal diagnosis of autosomal recessive polycystic kidney disease (ARPKD): molecular genetics, clinical experience, and fetal morphology. *Am. J. Med. Genet*. 1998 Mar 5;76(2):137–44.

13. Davis ID, Ho M, Hupertz V, Avner ED. Survival of childhood polycystic kidney disease following renal transplantation: the impact of advanced hepatobiliary disease. *Pediatric Transplantation*. 2003.
14. Beaunoyer M, Snehal M, Li L, Concepcion W, Salvatierra O, Sarwal M. Optimizing outcomes for neonatal ARPKD. *Pediatric Transplantation*. 2007 May;11(3):267–71.
15. Khan K, Schwarzenberg SJ, Sharp HL. Morbidity from congenital hepatic fibrosis after renal transplantation for autosomal recessive polycystic kidney disease. ... of *Transplantation*. 2002.
16. Smith JM, Stablein DM, Munoz R, Hebert D, McDonald RA. Contributions of the Transplant Registry: The 2006 Annual Report of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS). *Pediatric Transplantation*. 2007 Jun;11(4):366–73.
17. Remuzzi G, Ruggenti P, Colledan M, Gridelli B, Bertani A, Bettinaglio P, et al. Hemolytic uremic syndrome: a fatal outcome after kidney and liver transplantation performed to correct factor h gene mutation. *Am J Transplant*. 2005 May;5(5):1146–50.
18. Jalanko H, Peltonen S, Koskinen A, Puntila J, Isoniemi H, Holmberg C, et al. Successful liver-kidney transplantation in two children with aHUS caused by a mutation in complement factor H. *Am J Transplant*. 2008 Jan;8(1):216–21.
19. Connock M, Wang D, Fry-Smith A. Prevalence and prognosis of paroxysmal nocturnal haemoglobinuria and the clinical and cost-effectiveness of eculizumab. ... (UK): University of 2008.
20. Grewal HP, Brady L, Cronin DC2, Loss GE, Siegel CT, Oswald K, et al. Combined liver and kidney transplantation in children. *Transplantation*. 2000 Jul;70(1):100–5.
21. Rogers J, Bueno J, Shapiro R, Scantlebury V, Mazariegos G, Fung J, et al. Results of simultaneous and sequential pediatric liver and kidney transplantation. *Transplantation*. 2001 Nov;72(10):1666–70.
22. La Cerda De F, Jimenez WA, Gjertson DW, Venick R, Tsai E, Ettenger R. Renal graft outcome after combined liver and kidney transplantation in children: UCLA and UNOS experience. *Pediatric Transplantation*. 2009 Sep 7;14(4):459–64.
23. Chava SP, Singh B, Stangou A, Battula N, Bowles M, O’Grady J, et al. Simultaneous combined liver and kidney transplantation: a single center experience. *Clinical Transplantation*. 2009 Sep 9;24(3):E62–8.

ETHICS CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr BP Strobele

CLEARANCE CERTIFICATE M110932

PROJECT Combined Paediatric Liver-Kidney Trans-
plantation: Analysis of Our Experience

INVESTIGATORS Dr BP Strobele.

DEPARTMENT Department of Surgery/Transplantation

DATE CONSIDERED 30/09/2011

M110932DECISION OF THE COMMITTEE* Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 30/09/2011 CHAIRPERSON 
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Professor M Veller

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. I agree to a completion of a yearly progress report.
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...