Outcomes of Kasai hepatoportoenterostomy in children with biliary atresia in Johannesburg, South Africa

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Background. Without timely surgical intervention, most children with biliary atresia (BA) are not expected to live beyond 2 years of age. The initial intervention, the Kasai hepatoportoenterostomy (KPE), aims to achieve biliary drainage. Liver transplantation (LT) is performed if jaundice fails to clear or when biliary cirrhosis occurs. In under-resourced South African (SA) academic state hospitals, KPE procedures are the standard of care for the majority of children with BA, but LT is becoming more routinely available.
Objectives. To describe the outcomes of children with BA undergoing KPE, and to identify presenting clinical, laboratory and histological features that were associated with a more favourable outcome.
Methods. All children with BA who underwent KPE between January 2009 and June 2012 at the Johannesburg academic-hospital complex were included. Clinical and laboratory parameters, including paediatric end-stage liver disease (PELD) score at the time of KPE, liver histology fibrosis score, clearance of jaundice at 6 months and 24-month survival were determined.
Results. Of 70 children with BA diagnosed during the study period, 43 (61.4%) underwent KPE, but only 12 (27.9%) achieved early resolution of jaundice. By 24 months, 14 (32.6%) of 43 children undergoing KPE were alive with their native liver, and 2 (4.7%) other children underwent LT. PELD score <15 and early resolution of jaundice, but not age at surgery or histological fibrosis score, predicted a favourable outcome.
Conclusion. Children with BA undergoing KPE in SA state hospitals have a poor prognosis. The PELD score at the time of KPE best predicts 24-month survival.

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Over the last 65 years, the Kasai hepatoportoenterostomy (KPE) and liver transplantation (LT) have dramatically improved the outcomes of children with biliary atresia (BA).[1,2] In developed settings, 5-year native-liver survival rates of up to 60%, and overall 5-year survival rates of up to 90%, are reported.[3,4] The majority of South African (SA) children with BA are treated at resource-poor state hospitals where, if diagnosed before the onset of biliary cirrhosis, they undergo KPE. However, the transplant-free survival rates are probably lower than the survival rates reported in developed settings; this may be related to social, medical and genetic factors such as delayed presentation, inconsistent implementation of management protocols and the suboptimal management of pre- and postoperative complications owing to resource constraints. A previous study in Soweto, SA, revealed that only 14% of patients with BA were jaundice free after KPE.[4] Only 3 of 16 patients in a study in Nigeria had KPE, and none of them survived beyond 2 years.[5] Unlike in the UK, where KPE is performed only by a select number of surgeons, to improve outcomes, in Johannesburg KPE is performed by all paediatric surgeons.[6-8]

Patient-related factors also impact on survival rates. These can be broadly separated into factors related to pathogenesis (e.g. BA with splenic malformation syndrome, and anatomy of the biliary remnant), and the degree of hepatic fibrosis at the time of the operation (influenced by age at time of KPE, high aspartate-aminotransferase-to-platelet ratio, histological fibrosis scores, and high portal vein pressures).[2,9,10]

The paediatric end-stage liver disease (PELD) score can be used as a marker to predict the outcome of KPE.[11] This scoring system, which is more commonly used as a LT allocation tool, is a good predictor of outcome in BA.[12] After KPE, resolution of jaundice has been shown to be another reliable prognostic factor, and a recent multicentre study showed that resolution of jaundice by 3 months post KPE conferred better native-liver survival, especially if it was associated with a normal serum albumin (>35 g/dL).[13,14]

The current study describes the outcomes of KPE operations performed at two tertiary hospitals in Johannesburg, SA. The surgery was performed by consultant surgeons using an open approach, fashioning a portoenterostomy after wide dissection of the portal plate, with the jejunojejunostomy construction according to the preference of the operating surgeon. The routine is to administer perioperative antibiotics and steroids to all patients, with the addition of ursodeoxycholic acid when available. The steroid used in the

majority of cases is intravenous methylprednisone 20 mg per day, weaned by 2.5 mg daily. When an intravenous dose of 5 mg is reached, it is changed to oral prednisone 5 mg daily for 1 - 3 weeks. All patients are referred to the dietetics department for ongoing nutritional care. Since the time of this study, LT has become more frequently available to public-sector patients, and predictors of native-liver survival will be useful in planning optimal timing of LT.

Objectives

The primary objective was to describe the outcomes of patients undergoing KPE in Johannesburg. The secondary objective was to identify potential prognostic factors at the time of KPE that predicted survival with a native liver at 24 months.

Methods

A retrospective analysis of all children who underwent KPE in a 30-month period between January 2009 and June 2012 at two academic hospitals in Johannesburg was undertaken. Clinical, laboratory and histological parameters (date of birth, gender, age at surgery, serum albumin and total bilirubin (SBR) concentration, international normalised ratio (INR), weight and height, histology and outcome data) were obtained from clinical records and abstracted into an electronic database. PELD scores at the time of KPE (within 72 hours before the procedure and prior to correction of clotting defects) were calculated as described.[12] SBR levels at 3 - 6 months post-KPE were also retrieved.

Histological slides from liver biopsies taken at the time of surgery were retrieved and examined by a single pathologist who was blinded to the patient's outcome. Liver fibrosis secondary to BA was graded as follows: mild fibrosis (grade I) was defined as fibrosis involving <50% of portal tracts, ranging from fibrous expansion of the portal tracts to bridging fibrosis; moderate (grade II) as bridging fibrosis involving >50% of portal tracts without nodular architecture; and severe (grade III) as bridging fibrosis with >50% of portal tracts involved with nodular architecture.[15]

Outcomes recorded include early resolution of jaundice, defined as achieving bilirubin values <34 µmol/L (2 g/dL) by 6 months post surgery, and long-term success, defined as survival with native liver at 24 months of age. Death or LT were events that contributed to failure of survival with a native liver. Participants who were lost to follow-up were censored at the time of their last visit.

Data were entered into an Excel 2010 (Microsoft, USA) spreadsheet and analysed using Stata Intercooled version 11 (StataCorp, USA). Chi-square tests, Wilcoxon rank tests, and Kaplan-Meier survival curves with Cox proportional hazard tests were used to estimate odds ratios and 95% confidence intervals. Spearman's correlation coefficients were calculated to detect correlations between prognostic factors.

Ethics permission was obtained from the University of the Witwatersrand (Wits)'s Human Research Ethics Committee (Medical) (ref. no. M120954).

Results

Seventy children presented with BA during the study period. Forty-three (61.4%) of them underwent KPE. Their general characteristics are shown in Table 1.The remaining 27 did not have KPE performed for the following reasons:

- One mother refused surgery for her child
- Four children underwent laparotomy but not KPE because of the presence of a strong clinical suspicion of cirrhosis (nodular appearance of the liver): three with the absence of a portal plate and one with vascular abnormalities
- One child had situs ambiguus with inoperable complex cyanotic congenital heart disease
- Twenty-one children presented late and had established biliary cirrhosis, and therefore were not referred for KPE.

The mean age of the children at the time of KPE was 64 days (range 24 - 121). The PELD score at the time of surgery could be calculated for 35, and for 25, biopsy slides were retrieved. Six (24%) of these were core biopsies, with the remainder being wedge biopsies. Only 2 biopsies were graded as showing severe or grade III fibrosis (Table 1). Of the 43 children undergoing KPE, 12 (27.9%) achieved early resolution of jaundice, while 6 (14.0%) patients were already lost to follow-up by 6 months, and 7 (16.3%) had died. The 7 early deaths included 1 child with postoperative complications and nosocomial pneumonia, 1 with upper gastrointestinal bleeding and suspected sepsis, 1 with HIV World Health Organization stage-IV infection and chronic diarrhoea, and 1 with septicaemia. The cause of death for the other 3 was unknown. By 24 months post KPE, 14 (32.6%) were alive with their native liver, 2 (4.7%) had been transplanted, a further 4 (9.3%) had died and 9 (20.9%) others were lost to follow-up (Fig. 1). This added up to a total of 11 (25.6%) deaths, and 16 (37.2%) children lost to follow-up by 24 months of age.

Table 1. Demographic characteristics of children with biliary atresia undergoing Kasai hepatoportoenterostomy in Johannesburg, South Africa

Characteristic*	Median (IQR)†
Age (days), range‡ (*N*=43)	64 (46 - 83)
Gender (*N*=43), *n* (%)	
Female	30 (70)
Male	13 (30)
HIV-positive, (*N*=32), *n* (%)	1 (3)
Weight-for-age *z*-score (*N*=33)	–2.42 (–3 - –1.2)
Length-for-age *z*-score (*N*=32)	–2.04 (–2.92 - –0.57)
Weight-for-length *z*-score (*N*=31)	–0.63 (–1.93 - 0.19)
Total bilirubin (µmol/L) (*N*=38)	195 (153 - 244)
PELD score (*N*=38)	11 (8 - 16)
Histological score (*N*=25), *n* (%)	
Mild	14 (56)
Moderate	9 (36)
Severe	2 (8)

IQR = interquartile range.
*Missing observations varied between variables.
†Unless otherwise specified.
‡Range (days) = 24 - 121.

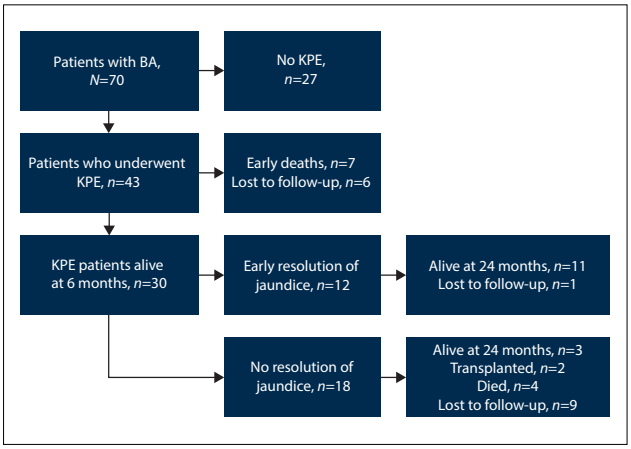

Fig. 1. Study flow diagram. (BA = biliary atresia; KPE = Kasai hepatoportoenterostomy.)

Outcomes

There was poor correlation between age and PELD score, age and degree of fibrosis, and PELD score and degree of fibrosis (Spearman's correlation coefficients 0.23, 0.03 and 0.07, respectively; not significant). Age and histological fibrosis score were not significant predictors of early success. A PELD score <15 was a good predictor of resolution of jaundice at 6 months post KPE (likelihood ratio (LR): 6, p=0.024; Table 2).

Survival analysis revealed that a higher preoperative PELD score predicted worse native-liver survival (p=0.013). Surgery after 60 days of age (p=0.79) or higher histological fibrosis score (p=0.45) did not predict worse native-liver survival. Achieving a total SBR below 34 µmol/L (2 g/dL) within 6 months after KPE predicted transplant-free survival (p=0.0001) (Fig. 2, Table 3).

Discussion

In this resource-poor setting, children with BA present late, with more than a third not able to receive KPE. Furthermore, of those who undergo KPE, the results are not as favourable as compared with outcomes in well-resourced settings. A large percentage of patients defaulted on follow-up post KPE. There was no other paediatric hepatology service in Johannesburg at the time, and it seems likely that most of these children did not survive beyond 24 months of age. To the best of our knowledge, none of the children in the group that did not have KPE or those who defaulted on follow-up received a LT, giving an overall 2-year survival rate of 21%, or 19% with native liver. The present study is one of the first to describe the outcomes seen in children with BA, some of whom undergo KPE, in a low- or middle-income country setting. This information is likely to be useful when clinicians discuss the prognosis of children with BA with their parents. Furthermore, in low-resourced settings, the effects of future therapeutic interventions in children with BA can be measured against the baseline that we have described.

The survival rates are poor when compared with outcomes reported in developed-country settings.[3,16] This is relevant because the incidence of BA in black SA infants may be among the highest of the world: in 1998, preliminary data in the same setting estimated the local incidence to be between 1 in 2 500 and 1 in 8 000 live births.[4] Elsewhere, incidences have been described ranging from 1 in 5 000 in Taiwan to 1 in 20 000 in European populations.[9]

Healthcare in SA is highly inequitable. In 2014, 84% of the population did not have private medical insurance and accessed care in the state health sector, where 30% of the country's doctors are employed.[17] The state sector's annual per capita expenditure on health is USD40, compared with USD1 400 in the private sector. As a consequence, interventions such as LT are frequently inaccessible to the majority of patients in need, as was reflected in this study.

In order to improve outcomes for children with BA, three areas need to be addressed:

(*i*) timeous diagnosis and referral
(*ii*) optimal medical and surgical interventions by an expert team
(*iii*) close monitoring and follow-up with early identification of those who require LT.

Age at the time of surgery is widely accepted as having an influence on the outcome and success rate of achieving bile drainage and native-liver survival, although the optimal timing is disputed.[8] The average age of this sample was 64 days, which is comparable with several first-world settings.[16,18,19] However, the age of presentation would increase if those children who did not undergo KPE were included in the analysis.

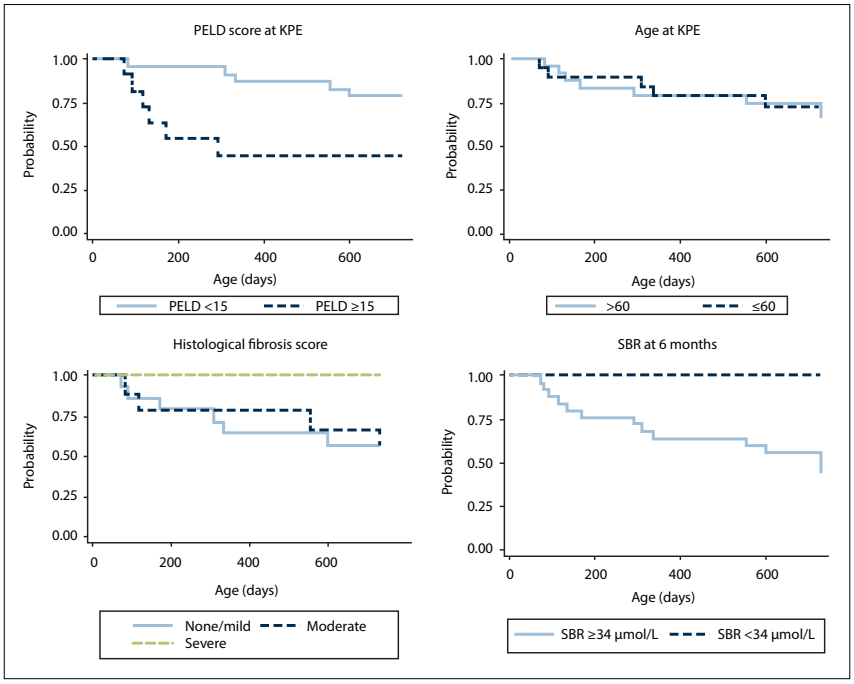

Fig. 2. Kaplan-Meier survival curves by paediatric end-stage liver disease (PELD) score, histological fibrosis score, age at the time of Kasai hepatoportoenterostomy (KPE), and resolution of jaundice by 3 months post KPE. (SBR = total serum bilirubin.)

Table 2. Predictors of early success (6 months post KPE)

Factor	Early success (n=12)	Jaundice not cleared/death (n=25)	Loss to follow-up (n=6)	p-value *†
Age (days), median (IQR)	57.5 (45 - 89)	66 (46 - 75)	66 (37 - 78)	0.88
Age = <60 days, *n*/*N* (%)	6/12 (50)	11/25 (44)	2/6 (33)	0.73
PELD score, median (IQR)	10 (5 - 12)	12 (10 - 18)	9 (8 - 10)	0.06
PELD score <15, *n*/*N* (%)	11/12 (92)	11/21 (52)	2/2 (100)	0.02‡
Histology fibrosis score				
Mild, *n*/*N* (%)	6/9 (67)	8/16 (50)	0	
Moderate, *n*/*N* (%)	2/9 (22)	7/16 (44)	0	
Severe, *n*/*N*, (%)	1/9 (11)	1/16 (6)	0	0.46

*Wilcoxon rank sum and likelihood ratio with Fisher's exact tests used where applicable.
†Comparison between early success v. failure (jaundice not cleared or death) group.
‡p<0.05.

Table 3. Outcomes at 24 months in children with BA undergoing KPE

Factor	Native-liver survival, *N*=14	Death, *N*=11	Liver transplant, *N*=2	Loss to follow-up, *N*=16	*p*-value *†
Age in days when KPE performed, median (IQR)	57.5 (49 - 88)	69 (38 - 101)	49.5 (24 - 75)	65 (49.5 - 76.5)	0.75
Age <60 days *n*/*N*, (%)	7/14 (50)	5/11 (45)	1/2 (50)	6/16 (38)	0.84
PELD score, median (IQR)	9.5 (3 -12)	16 (9 - 18)	11.5 (11 - 12)	11.5 (10 - 18)	0.032‡
PELD score <15, *n*/*N* (%)	12/14 (86)	5/11 (45)	2/2 (100)	5/8 (63)	0.066
Histology fibrosis score					
Mild, *n*/*N* (%)	6/10 (60)	6/9 (67)	0/1 (0)	2/5 (40)	
Moderate, *n*/*N* (%)	2/10 (20)	3/9 (33)	1/1 (100)	3/5 (60)	
Severe, *n*/*N* (%)	2/10 (20)	0/9 (0)	0/1 (0)	0/5 (0)	0.50
Early success (SBR <34 μmol/L within 6 months), *n*/*N* (%)	11/14 (79)	0/11 (0)	0/2 (0)	1/10 (10)	<0.001

BA = biliary atresia; KPE = Kasai hepatoportoenterostomy; IQR = interquartile range; SBR = total serum bilirubin.
*Comparison between native-liver survivor group versus patients who died or received a liver transplant.
†Wilcoxon rank sum and likelihood ratio tests used.
‡$p<0.05$.

As has been noted before, there are no reliable prognostic markers predicting the success of KPE for BA. This is in part due to the heterogeneity of the disorder, with different aetiological pathways leading to the same end pathology.[20] The lack of association between age of presentation and histological score in this study was surprising. However, older children with established cirrhosis were excluded from surgical intervention, and the histological score used may not be sensitive enough to be used as a predictor of outcome in our setting. While the PELD score was a better predictor than young age and histological score, two children with a score >15 did survive to 24 months with their native liver. We would therefore not recommend avoiding KPE based on this result, particularly given the scarcity of LT options in this setting. Nevertheless, offering KPE to children who present late with established cirrhosis and features of chronic liver failure is unlikely to result in a successful outcome. These children should be referred primarily for an evaluation by the LT team.

Achieving adequate biliary drainage and low SBR by 6 months post KPE was highly predictive of native-liver survival to age two, and therefore these children should be followed-up closely and monitored for complications.

Optimising outcomes in BA starts with early diagnosis and referral. Introduction of a stool-colour card has been shown to be successful, and would help to raise awareness of the disease.[19] However, early identification alone will not necessarily result in improved outcomes, as this study has shown.

Once the diagnosis has been made, it is beneficial to have a centralised model of care for these patients, with a few specialised surgeons performing the KPE in a few institutions.[16] Several peri- and postoperative multidisciplinary interventions have also been used to improve outcomes of the surgery.[7] Once again, centralisation of the management of this condition should improve adherence to these protocols, and therefore improve outcomes. The authors therefore recommend centralisation of care for children with BA, with all KPE operations being performed at selected centres by a team of experienced surgeons. After discharge, all these children require thorough follow-up and monitoring, early detection of complications and appropriate nutritional support.

The definitive surgical link in the chain of managing children with BA is LT. SA currently has two paediatric LT services: one at the Red Cross War Memorial Children's Hospital in Cape Town, and the other at the Wits Donald Gordon Medical Centre in Johannesburg. The latter has the expertise to perform living-donor LTs, which assists greatly in light of the shortage of deceased-donor organs that exists locally and worldwide.[21,22] Increasingly, children in the state sector are gaining access to this therapeutic option, albeit on a limited basis. Factors that have contributed to this low rate of transplantation include poor social circumstances and lack of accessible transport, delays in diagnosis, work-up and referral to the transplant centre, and limited remuneration and support from the National Department of Health (NDoH) for the LT programme, including post-transplantation medical and supportive care. For children with BA who present to state facilities, support from the NDoH for a LT programme is vital to improving outcomes.

Recognised study limitations include a small sample size, difficulty in obtaining clinical information, including the anatomical classification of the biliary tree, other malformations such as splenic malformations or dextrocardia, loss to follow-up, and lack of details regarding the direct cause of death in those who died. Only 25 subjects' liver biopsies could be retrieved and reviewed. Detailed clinical information about the patients' medical management and healthcare professionals' adherence to treatment guidelines is not known, but the study aims to describe outcomes in resource-poor settings.

Conclusion

BA continues to carry a poor prognosis in many developing countries. Despite this, good outcomes are achievable, and efforts should be ramped up to promote awareness, increasing the chances of early diagnosis. Referral to a centre with KPE expertise is strongly recommended, with close follow-up by a multidisciplinary team thereafter.

As BA is the most common indication for paediatric LT in SA, successful KPE will have a positive impact on the transplant programme, and hopefully result in fewer young children requiring transplants. Nevertheless, equal access for indigent patients to the LT programme must be addressed urgently, and improved buy-in from the NDoH is critical.

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