Original article

Does Kasai operation prior to liver transplantation affect peri-operative outcomes in children with biliary atresia?

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Background: Biliary atresia is the most leading cause of death from liver disease in children and the most common indication for pediatric liver transplantation. Although portoenterostomy is the mainstay treatment of biliary atresia, there were some studies found that prior portoenterostomy would adversely affect the liver transplant.

Objectives: To compare the peri-operative outcomes between biliary atresia (BA) children having Kasai operation and those with primary liver transplantation (LT).

Methods: Children with BA (0 - 15 years) who underwent LT between 2003 and 2017 were reviewed. Patients were categorized into 2 groups (Group A: BA children undergoing Kasai operation prior to liver transplantation; and, Group B: BA children receiving primary LT, without Kasai operation). Variables that might affect the outcomes were compared. Unpaired *t* - tests, non-parametric tests, or Fisher's exact tests were used. Data are expressed as mean and standard deviation.

Results: Fifty-two patients were recruited: Group A (36 patients) and Group B (16 patients). Subjects in Group A had older age when having LT (68.5 ± 77.5 *vs.* 12.2 ± 3.3 months, $P = 0.006$) and lower pediatric end-stage liver disease (PELD) score (age <12 years, 13.1 ± 8.8 *vs.* 20.5 ± 6.7, $P = 0.007$). However, there was no statistically significant difference in operative time (605.5 ± 129.6 *vs.* 563.4 ± 74.9 min, $P = 0.235$), warm ischemic time (49.3 ± 14.1 *vs.* 45.8 ± 7.3 min, $P = 0.369$), intraoperative blood loss (149.5 ± 248.8 *vs.* 117.56 ± 126.93 mL/kg, $P = 0.635$), total ICU stays (9.9 ± 9.0 *vs.* 6.9 ± 5.9, $P = 0.232$) and hospital stays (45.3 ± 31.4 *vs.* 48.2 ± 38.3, $P = 0.772$). Postoperatively, there was no significant difference regarding vascular (3/36 *vs.* 2/16, $P = 0.637$) and biliary (5/36 *vs.* 2/16, $P = 1.0$) complications between both groups. Additionally, 3-year survival rates following LT between 2 groups were similar (87.8% *vs.* 93.7%, $P = 0.583$).

Conclusions: Kasai operation probably delayed the need for LT. The severity (PELD score) was less at the time of LT in children with Kasai operation. It did not adversely affect the peri-operative outcomes of BA patients having liver transplantation. Peri-operative complications, early outcomes and survival rates were comparable.

Keywords: Biliary atresia, Kasai operation, portoenterostomy, liver transplantation, outcome.

Biliary atresia (BA) is the disease which intrahepatic and extrahepatic bile ducts are progressively atretic. The patients with BA would present with jaundice, pale stool, and dark yellow urine in the first three months of life. The incidence is approximately 1 in 8,000 to 1 in 18,000.[1] Biliary atresia is the most leading cause of death from liver diseases in children and the most common indication for pediatric liver transplantation.[2] If the patients with BA were delayed diagnosed or left untreated, the patients would be inevitably dead within 2 years from cirrhosis and liver failure.[3] Hepatic portoenterostomy or Kasai operation is still the main therapy to bypass bile to the intestine. Although most patients would undergo Kasai operation in the first few months of life, 60.0 – 70.0% of the patients would need the liver transplant (LT) due to the progression of the disease.[4, 5]

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Some of the BA patients who were delayed diagnosed with the worsening liver function and have the complications from cirrhosis would undergo primary liver transplant. Although Kasai operation is the mainstay of treatment BA, there were some studies found that prior Kasai operation would adversely affect the liver transplant, including increased risk of intestinal perforation, increased vascular and biliary complications, and chances of blood loss and blood transfusion.[6 - 8] However, primary liver transplantation would face with the lack of donors and, moreover, liver transplant in very young children would see more long-term postoperative complication.[9 - 11] Therefore, the objective of this research was to investigate the effect of prior Kasai operation on liver transplantation in BA patients.

Materials and methods

This was a retrospective study, including patients aged 0 - 15 years diagnosed with BA who underwent liver transplantation (LT) between 2003 and 2017 at King Chulalongkorn Memorial Hospital. The patients were categorized in two groups: patients who underwent Kasai prior to LT group (Group A) and patients receiving primary LT group (Group B). The primary outcome was considered as the impact of Kasai operation on the perioperative results of LT. Perioperative variables were analyzed including age at transplant, gender, weight, height, pediatric end-stage liver disease or PELD score (PELD score including age, bilirubin, albumin, international normalized ratio (INR), growth failure in order to assess the severity of liver disease in each patient), operative time, intraoperative blood loss, ischemic time (warm and cold), intensive care unit (ICU) stays, hospital stays, vascular complications, biliary complications, primary graft survival and overall survival. PELD score was calculated exclusively in BA patients who were < 12 years old at the time of LT.

This study has been approved by the Institutional Review Board (IRB), the Faculty of Medicine, Chulalongkorn University (IRB No. 543/61).

Statistical analysis

An unpaired *t* - test was used for continuous variables, and Chi-square test or Fisher's exact test were used for categorical variables, when appropriate. A *P* - value of < 0.05 was considered as statistically significant. Kaplan-Meier method and log-rank test were used for evaluation the survival analysis. All analyses were performed using the SPSS 22.0 (IBM Inc., USA). Survival analysis was performed using GraphPad Prism program version 8 (GraphPad Inc., USA). Data are expressed as mean and standard deviation.

Results

Fifty-two patients were recruited in the study. Thirty-six patients (67.9%) underwent Kasai operation prior to LT and 16 patients (30.8%) underwent primary LT. None of the subjects underwent redo-Kasai operation. Twenty-nine patients (55.8 %) were female and twenty-three patients (44.2 %) were male. The mean age of liver transplant was 51 months.

The demographic data of BA patients in group A and group B are shown in Table 1. The BA patients in group A had age at LT, weight, and height significantly higher than those of patients in group B. However, PELD score of patients in group A was significantly lower than the score of patients in group B.

Peri-operative data and complications are demonstrated in Table 2. Operative time in both groups were not statistically significant different. Intraoperative blood loss in group A was higher than group B but if considered in the details, intraoperative blood loss per body weight (ml/kg) was not statistically different in both groups. Total ischemic time and cold ischemic time in the group A were longer than in group B, but the warm ischemic time in both groups were not significantly different. Total ICU stay and hospital stay were no statistically significant difference in both groups.

As for complications, they were categorized into three groups including vascular complications, biliary complications, and respiratory complications (Table 2). Vascular complications were subgrouped into hepatic arterial thrombosis or stenosis, portal vein thrombosis or stenosis, and hepatic vein thrombosis or stenosis. All vascular complications were not different between both groups. We considered vascular thrombosis as a significant vascular complication. Vascular complications in group A and B were not different (3/36 *vs*. 2/16, $P = 0.637$). Biliary complications were considered as leakage or stricture. There was no significant difference between 2 groups (5/36 *vs.* 2/16, $P = 1.0$). For respiratory complications which included atelectasis, pleural effusion, and pneumonia, difference in both groups was not observed ($P = 1.00$). Additionally, 3-year survival rates following LT between 2 groups were similar (87.8% *vs.* 93.7%, $P = 0.583$). Comparison of survival curve after LT using log-rank test revealed no statistically significant difference between both groups (Figure 1).

Table 1. Preoperative status of patients of Group A (prior-Kasai) and Group B (primary LT).
*PELD score was calculated exclusively in BA patients who were < 12 years old at the time of LT (28 patients in group A and 16 patients in group B).

Variables	Group A	Group B	*P* - value
Gender			0.209
Male	18	5	
Female	18	11	
Age at LT (month)	68.5 ± 77.5	12.2 ± 3.3	0.006
Weight (kg)	20 ± 18.5	7.4 ± 1.5	0.009
Height (cm)	95.8 ± 39.4	69.6 ± 7.4	0.012
PELD score*	13.1 ± 8.8	20.5 ± 6.7	0.007

LT: liver transplantation, PELD: pediatric end-stage liver disease

Table 2. Perioperative variables and complications.

Variables	Group A	Group B	*P* - value
Intraoperative blood loss (mL)	1948.7 ± 2003.2	754.4 ± 688.8	0.026
Intraoperative blood loss (mL/kg)	149.5 ± 248.8	117.6 ± 126.9	0.635
Intraoperative blood transfusion (mL/kg)	66.5 ± 108.4	69.7 ± 78.3	0.918
Total ischemic time (min)	217.5 ± 161.7	107.8 ± 19.7	0.013
Warm ischemic time (min)	49.3 ± 14.1	45.8 ± 7.3	0.369
Cold ischemic time (min)	168.1 ± 157.7	62 ± 21.3	0.013
Biliary complications			
Leakage	5/36	1/16	0.674
Stricture	1/36	1/16	0.525
Total	5/36	2/16	1.000
Vascular complications			
Hepatic a. thrombosis/ stenosis	4/36	1/16	0.629
PV thrombosis/stenosis	8/36	4/16	0.835
Hepatic v. thrombosis/ stenosis	3/36	3/16	0.555
Vascular thrombosis	3/36	2/16	0.637
Respiratory complications (atelectasis/ pleural effusion/ pneumonia)	28/36	14/16	1.000
Reoperation			
Bleeding	3/36	1/16	0.712
Intestinal perforation	2/36	0/16	0.541
Total ICU stays (days)	9.9 ± 9	6.9 ± 6	0.232
Hospital stays (days)	45.3 ± 31.4	48.3 ± 38.3	0.772

ICU: intensive care unit

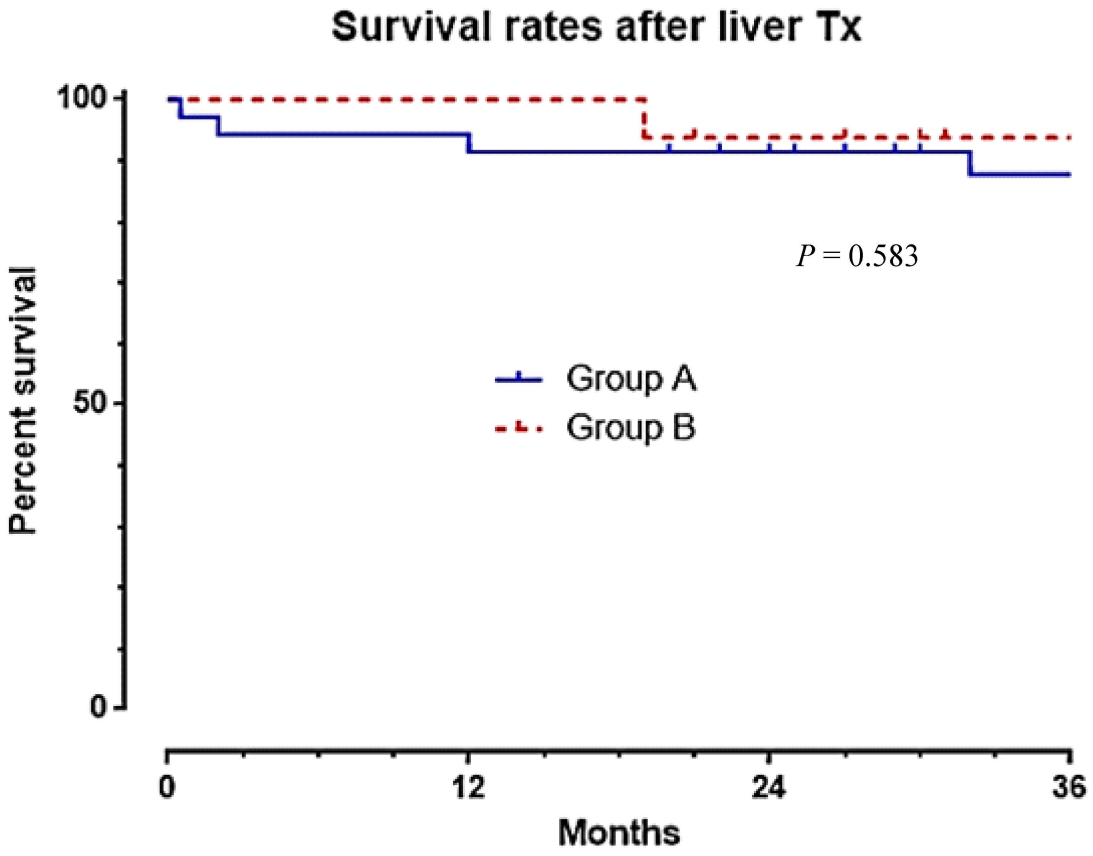

Figure 1. Survival curves of BA patients with prior portoenterostomy and primary LT.

Discussion

Kasai operation has been the mainstay treatment of biliary atresia for years. [12] However, some patients were diagnosed late and thus inevitably underwent primary LT as the only therapeutic option.[1] Unfortunately, some patients with BA who underwent Kasai operation were clinically worsening due to progressive fibrosis and having complications from cirrhosis. Thus, these patients with prior Kasai operation with progressive disease eventually need LT later in their lives. Interestingly, some authors claimed that the patients who underwent prior Kasai operation would have more adhesion and could cause troublesome during performing LT.[10, 13]

However, the idea of primary liver transplantation as the first treatment of choice is not widely accepted in many countries including Thailand because of the shortage of the organs, the long-term complications and technical difficulties and complexities when performing liver transplantation in infants.[8]

This study compared the preoperative status of the patients, perioperative outcomes and complications, and overall survival between two groups of patients who underwent prior Kasai operation and those who underwent primary LT.

In our institution, which is a tertiary care center, we found that the preoperative status of patients in two groups were quite different. Age at liver transplantation, weight, and height were higher in the BA patients with prior Kasai operation. This suggests that Kasai operation can probably delay the need of LT by approximately 3 - 4 years. While PELD score in the BA patients with prior Kasai operation was lower than the primary LT group. It could infer that patients with prior Kasai operation would have less burden and less severe symptoms with their native livers. On the other hand, the patients with primary LT may suffer more severe liver disease pre-operatively.

Intraoperatively, blood loss seems to be higher when considered as mL alone. However, if we consider this issue in volume per weight as mL/kg, there was no statistically significant difference. Our observation may explain why transplant surgeons usually felt that blood loss was more in patients with prior Kasai operation.[11, 13] In fact, when comparing weight by weight, the blood loss was comparable.

Nevertheless, surgical skills and transplant surgeons' experience may take into account when talking about blood loss during the operation. Our results were consistent with other reports. [7, 13, 14]

Based on ischemic time, significant differences were observed in total ischemic time and cold ischemic time, but no significant difference was observed in warm ischemic time (defined by the time from the liver brought out of ice storage until the time of reperfusion the anastomosed portal vein). This is probably due to a proportion of BA patients with prior Kasai operation underwent cadaveric donor LT whereas all the patients receiving primary LT underwent living donor LT.

Postoperative complications including vascular complications, biliary complications, and respiratory complications were not statistically different in our study. As for the outcome of LT, survival rates in both groups were not different. In our series, 3-year survival rates following LT between 2 groups were comparable.

Although we demonstrated in this study that Kasai operation did not significantly affect peri-operative outcome of LT, there are some scientific limitations. Firstly, this was a retrospective study. There is likely to have some selection bias of the patients. Secondly, the small sample size in each group of patients may account for the non-different findings in this study. Finally, LT is a complex operation needing highly skilled surgeons. Therefore, our results may not be reproducible if the skills of the surgeons are different. More studies as a prospective controlled trial can perhaps answer all these questions more accurately.

Conclusion

Kasai operation probably delayed the need for LT. The severity (PELD score) was less at the time of LT in children with Kasai operation. It did not adversely affect the peri-operative outcomes of BA patients having liver transplantation. Peri-operative complications, early outcomes and survival rates were comparable. Therefore, Kasai operation is still instrumental to the treatment of BA.

Conflict of interest

The authors, hereby, declare no conflict of interest.

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