The Relationship between Clinical Outcomes After Kasai Operation and Related Factors in Infants with Biliary Atresia

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Background: *Biliary atresia (BA) has unclear etiology, leading to cholestasis and cirrhosis. Kasai portoenterostomy has been accepted worldwide as the primary treatment for establishing biliary drainage. Successful Kasai operation increases the survival and reduces the incidence of subsequent liver transplantation. Several prognostic factors have been related to the results of this procedure.*
Objective: *To study the relationship between clinical outcomes after Kasai operation and related factors in infants with BA.*
Design of study: *Retrospective charts review.*
Material and Method: *The medical data of 48 infants with BA who underwent Kasai operation in the Division of Pediatric Surgery at Siriraj hospital (from January 1st, 2006 to May 31st, 2015) were retrospectively reviewed. Ten patients were excluded due to incomplete clinical data. Finally, 38 patients were enrolled in this study. The variables including clinical, laboratory database, radiologic findings, operative findings, and post-operative conditions were chosen for study.*
Results: *The median onset of visible jaundice was 4 (0 to 16) weeks of age. The median age at Kasai operation was 82 (34 to 204) days. There were 25 (65.8%) cases who could achieve post-operative jaundice clearance. The incidence of post-operative cholangitis was 30 (78.9%) cases. The age at the time of Kasai operation had a significant impact on post-operative jaundice clearance in patients with (p-value = 0.028). The cut-off age, defined by the ROC curve analysis, was 90 days (p-value = 0.042). Odds ratio for age at the operation of less than or equal to jaundice clearance in patients with 90 days was 4.78 (95% CI 1.13 to 21.32).*
Conclusion: *The age at the time of Kasai operation has a significant impact jaundice clearance in patients with on the ability to achieve post-operative jaundice clearance. The patients whose ages at the operation of more than 90 days have a significant risk for delay clearance of jaundice compared to those of ages less than or equal to 90 days.*

Keywords: *Biliary atresia, Kasai operation, Portoenterostomy, Age, Outcome*

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Biliary atresia is a perinatal disease of unclear etiology, which is characterized by inflammation and obliteration of intrahepatic and extrahepatic bile duct, leading to cholestasis and cirrhosis. There are several levels of obliteration from the porta hepatis to the opening of the common bile duct into the duodenum. If left untreated, biliary atresia will lead to cholestasis, hepatic fibrosis, and development of cirrhosis[1]. The patients will present with obvious signs of conjugated jaundice, pale stool, dark urine, and hepatomegaly[2].

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Kasai portoenterostomy has been accepted worldwide as the primary surgical treatment for establishing biliary drainage[3]. The subsequent liver transplantation will be needed because of failure to restore biliary flow after Kasai operation and/or because of decompensated cirrhosis[3]. The Kasai operation was introduced in 1959, and consists of constructing a new bile drainage system, generally by creating an anastomosis of a Roux-en-Y ascending limb of the jejunum to the porta hepatis region to re-establish a connection between the intrahepatic bile ducts and the intestine. If successful, Kasai operation increases the survival of children with biliary atresia[4]. Nevertheless, the survival of patients with biliary atresia might vary, as several factors were associated with the prognosis of biliary atresia[5]. Shinkai et al reported

that the 5-, 10-, and 20-year survival rates of patients with their native livers after Kasai operation were 63%, 54%, and 44%, respectively[3].

Several prognostic factors of the Kasai operation have been related to the short-term results of this procedure. Among them are many that cannot be altered, such as the anatomy of the biliary remnant, histology of the liver, portal pressure at the time of Kasai operation, or association of biliary atresia with polysplenia (biliary atresia splenic malformation syndrome). Other prognostic factors of biliary atresia are related to the organization of care for these patients, and therefore are improvable: including the age at Kasai operation, accessibility to liver transplantation, experience of the center in the management of patients with biliary atresia[6]. Marie-Odile Serinet et al reported that large series concordantly show that short-term results of the Kasai operation are better when surgery is performed early in life. Whether an age threshold exists remains unclear[6]. Patrick Ho Yu Chung et al also reported that the presence of associated anomaly, operation with laparoscopic surgery, delayed clearance of jaundice, and repeated cholangitis were associated with adverse outcome, whereas the use of adjuvant steroid at post-operative period appeared to be protective[7].

In the Division of Pediatric Surgery at Siriraj Hospital, there are patients with biliary atresia who are surgically treated with Kasai operation about 2 to 5 cases per year. The aim of this single-center review is to study about the relationship between clinical outcomes after Kasai operation and related factors in infants with biliary atresia. The result of this study may reveal the improvable or modifiable factors, which could lead to a better outcome of treatment.

Material and Method

A retrospective review of 48 infants with biliary atresia who underwent conventional Kasai operation in our institution from January 1st, 2006 to May 31st, 2015 was conducted. Ten patients were excluded due to incomplete clinical data. Finally, 38 patients were enrolled in this study. The diagnosis of biliary atresia was confirmed based on patients' clinical, biochemical, radiological, and operative findings.

The variables including clinical, laboratory database, radiologic findings, operative findings, and post-operative conditions of the patients were chosen for study. These were sex, onset of visible jaundice, age at operation, body weight at operation, complete blood count (hemoglobin, hematocrit, white blood cell count with differentiation, and platelet count), BUN, Creatinine, Liver function test (total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), albumin, and globulin), ultrasonographic findings, findings from intraoperative cholangiography, intra-operative findings, use of adjuvant steroid (starting dose at 2 mg/kg per day and then reduced by half every week until completely tapered off), jaundice clearance (defined as total bilirubin <1 mg/dl at post Kasai operation), post-operative cholangitis, and the necessity of redo-Kasai operation.

Ethical approval

This study received the approval of Siriraj Institutional Review Board.

Statistical analysis

Descriptive statistical analysis was performed using Predictive Analytics Software (SPSS) Statistics version 18.0. Results were analyzed using independent-samples t-test and Mann-Whitney U test for continuous variables. The categorical data were analyzed using Pearson Chi-square test and Fisher's exact test. The cut-off age was defined by receiver-

Table 1. Demographic data and results

Variables	n = 38 (%) or median (minimum, maximum)
Sex	
Male	12 (31.6%)
Female	26 (68.4%)
Onset of visible jaundice (weeks)	4 (0, 16)
Age at Kasai operation (days)	82 (34, 204)
Body weight at operation (kg)	5.3 (3.5, 6.6)
Jaundice clearance	
Yes	25 (65.8%)
No	13 (34.2%)
Post-operative adjuvant steroid use	
Yes	36 (94.7%)
No	2 (5.3%)
Post-operative cholangitis	
Yes	30 (78.9%)
No	8 (21.1%)
Redo-Kasai operation	
Yes	3 (7.9%)
No	35 (92.1%)

operating characteristic (ROC) curve analysis using Odds ratio with 95% confidence interval. A *p*-value of less than 0.05 was regarded as statistically significant.

Results

A total of 48 cases were identified, which 10 excluded due to incomplete clinical data. The 38 patients were eligible for analysis as demonstrated in Table 1. There were more female than male patients (26: 12). The median onset of visible jaundice was 4 (0 to 16) weeks. The median age at Kasai operation was 82 (34 to 204) days. There were 25 (65.8%) cases who could achieve jaundice clearance after the operation, while the other 13 (34.2%) cases failed to achieve normal bilirubin level. There were 36 (94.7%) cases who received adjuvant steroid after the operation. The incidence of post-operative cholangitis was 30 (78.9%) out of 38 cases. Furthermore, there were 3 (7.9%) cases who had the necessity of redo-Kasai operation. The median follow-up time was 17 (2 to 104) months. There were 5 cases who later received a liver transplantation.

In patients with biliary atresia who underwent Kasai operation, the ability to achieve jaundice clearance was defined as a good outcome. Table 2 showed the results of the factors that related to the ability to achieve good post-operative outcome in our study. The age at the time of Kasai operation resulted in significant impact on the ability to achieve jaundice clearance (*p*-value = 0.028).

The cut-off age was defined by the receiver-operating characteristic (ROC) curve analysis (area under the curve = 0.71, *p*-value = 0.034). The result showed that the cut-off age was 90 days (*p*-value = 0.042). Odds ratio for age at the operation less than or equal to 90 days was 4.78 (95% CI 1.13 to 21.32), which means that the patient who was more than 90 days of age at the operation has 4.78 times of risk for delayed jaundice clearance more than who was less than or equal to 90 days of age.

Among 25 cases who could achieve jaundice clearance, there were 8 cases (32%) who were more than 90 days of age at the time of the operation. The maximal age at the operation of the jaundice-free patient in this study was 162 days.

There were 13 cases (34%) who could not achieve jaundice clearance. Most patients in this group had bilirubin level at 1 and 3 months after the operation lower than the preoperative value. Three of them (23%) could live with their native liver (maximal age in this study = 6 years and 5 months). In addition, this operation could delay the time for liver transplantation in 2 cases (15%).

Discussion

Currently, biliary atresia is still problematic because of the progressive inflammation, hepatic fibrosis, and development of liver cirrhosis that would lead to end-stage liver disease or even death if left untreated[5]. Identification of prognostic factors related with outcome after Kasai operation is an important question to enable improvements in outcome[7]. Kasai portoenterostomy has been accepted as the primary therapeutic option for establishing biliary drainage. This operation is still required as the primary treatment to avoid liver transplantation because of the shortage of transplant organs, especially for infants, and because of the morbidity and mortality associated with liver transplantation[3]. However, it is unknown which factors provide clues to patients prognosis. Several studies showed that the earlier the surgery, the better the outcome[6,8].

The outcome of the Kasai operation has been reported to be influenced by various factors such as the type of BA, age at the initial operation, experience of the surgical center, era in which surgery was performed, and postoperative medical care[9]. The majority of published studies show that the best surgical results are obtained in infants who are 60 to 80 days of age at the time of operation[10]. Our study demonstrated that patients' age at the time of the Kasai operation is the significant prognostic factor on the ability to achieve jaundice clearance after the operation. The age at the time of operation of less than or equal to 90 versus more than 90 days of age resulted in significant difference in jaundice clearance. The patients whose age at the Kasai operation more than 90 days have significant risk for delayed clearance of jaundice more than who was less than or equal to 90 days of age. However, there were some patients who could also achieve jaundice clearance after underwent the operation at age more than 90 days. It is concordant with the result from the study of Davenport et al that showed the potential for reasonable medium-term survival is present in about one third of infants 100 days or older coming to primary corrective surgery[11]. This result also supported the use of this procedure, if possible, even in the older infants. Therefore the operation after 90 days of age is not contraindicated.

In some patients who could not achieve jaundice clearance, the level of postoperative bilirubin level at 1 and 3 months were lower than the preoperative value. Some of them could live with their native

Table 2. The factors that were related to the ability to achieve jaundice clearance

Variables	Jaundice clearance		*p*-value
	Yes (n = 25)	No (n = 13)	
Sex: female	18 (72.0%)	8 (61.5%)	0.714
Onset of visible jaundice (weeks)	3 (0,16)	4 (0, 8)	0.874
Age			
Age at Kasai operation (days)	91±36	121±43	0.028
Age ≤90 days at operation	17 (81%)	4 (19%)	0.042
Body weight at operation (kg)	5.2±0.8	5.5±0.5	0.226
Complete blood count			
Hb	10.4±1.1	10.5±1.2	0.963
Hct	31.5±3.2	31.4±3.1	0.984
WBC	14,034±3,949	14,941±4,052	0.510
% Neutrophil	26.5±7.0	30.1±10.1	0.208
% Lymphocyte	60.9±11.5	59.1±12.2	0.194
Platelet	413,000±174,694	355,153±11,003	0.286
BUN	7.2±2.9	5.6±1.5	0.079
Creatinine	0.2±0.7	0.17±0.41	0.055
Liver function test			
Total bilirubin	10.2±3.9	2.1±3.6	0.153
Direct bilirubin	7.9±2.7	9.6±2.9	0.072
Aspartate transaminase (AST)	242.7±223.7	332.5±238.9	0.106
Alanine transaminase (ALT)	144.1±93.4	152.4±66.9	0.779
Alkaline phosphatase (ALP)	457.3±164.0	514.2±162.8	0.316
Gamma-glutamyl transpeptidase (GGT)	753.6±345.2	759.2±639.2	0.673
Albumin	3.87±0.49	3.72±0.56	0.389
Globulin	2.16±0.57	2.35±0.48	0.308
Ultrasonographic findings			
Presence of gallbladder	11 (44%)	10 (76.9%)	0.034
Presence of atretic gallbladder	8 (72.7%)	3 (30%)	0.086
Presence of triangular cord sign	7 (28%)	1 (7.7%)	0.222
Presence of extrahepatic duct	3 (12%)	2 (15.4%)	1.000
Presence of normal liver parenchyma	24 (96%)	12 (92.3%)	1.000
Intra-operative cholangiography (n = 25)			
Presence of gallbladder	3 (23.1%)	6 (66.7%)	0.079
Presence of biliary tree connection	0 (0%)	1 (11.1%)	0.409
Patency of cystic duct	6 (46.2%)	4 (44.4%)	1.000
Patency of common bile duct	3 (23.1%)	4 (44.4%)	0.376
Atresia of porta hepatis	13 (100%)	8 (88.9%)	0.409
Presence of bowel connection	3 (23.1%)	4 (44.4%)	0.376
Intra-operative findings			
Normal appearance of the liver	5 (21.7%)	3 (27.3%)	1.000
Presence of ascites	22 (95.7%)	9 (81.8%)	0.239
Patency of cystic duct	2 (8%)	4 (30.8%)	0.154
Patency of common bile duct	2 (8%)	5 (38.5%)	0.034
Presence of fibrous porta hepatis	24 (96%)	11 (84.6%)	0.265
Post-operative adjuvant steroid use	23 (92%)	13 (100%)	0.538
Post-operative cholangitis	19 (76%)	11 (84.6%)	0.609
Redo-Kasai operation	1 (4%)	2 (15.4%)	0.265

liver. Lykavieris et al reported that 23% of the children survived with their native liver for at least 20 years after the Kasai operation[12]. The study of Hartley Jane L. et al showed that transplantation is usually

indicated within 6 months to 2 years of age in infants whom bile drainage is not achieved, while about 50% of the patients who underwent Kasai operation received secondary liver transplantation[13]. From our study, few cases who could not achieve jaundice clearance could delay the time of liver transplantation. This result indicated that Kasai operation should be done for bridging before liver transplantation in some cases.

In our study, there was an inconsistency of the statistical significance between the presence of common bile duct from intraoperative cholangiography and the patency of common bile duct from intraoperative findings. It may be resulted from the small sample size of this study. The result of no statistical significance in jaundice clearance in post-operative steroid treatment may derive from the most of the patients in this study received steroid in post-operative period along with small sample size.

Conclusion

The age at the time of the Kasai operation has significant impact on the ability to achieve jaundice clearance after the operation. The patients whose ages at the operation of more than 90 days have significant risk for delayed clearance of jaundice compared to those with the age of less than or equal to 90 days. However, it is possible for the patients in this group to achieve jaundice clearance after the operation. Early detection and urgency operation will improve outcome of this operation. Even though some patients could not achieve jaundice clearance, some of them could live with their native liver with lower bilirubin level than the preoperative value. Moreover, this operation could delay the time for liver transplantation in some cases.

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What is already known on this topic?

Biliary atresia is a perinatal disease of unclear etiology. Kasai portoenterostomy has been accepted worldwide as the primary therapeutic option for establishing biliary drainage. Strong evidence suggests that age at operation is an important factor in outcome from multiple reports. The exact cutoff where outcome from surgery become predictably poor is unknown. Therefore most centers usually have the goal to accurately obtain a provisional diagnosis and operate before the age of 60 days.

What this study adds?

This study demonstrated that patient age at the time of the Kasai operation is the significant prognostic factor on the ability to achieve jaundice clearance after the operation. The patients whose ages at the operation of more than 90 days have significant risk for delayed clearance of jaundice compared to those with the age of less than or equal to 90 days. However, it is possible for the patients in this group to achieve jaundice clearance after the operation. The maximal age at operation that could achieve jaundice clearance was 162 days. Therefore Kasai procedure can be use, if possible, even in older infants. Early detection and urgency operation will improve outcome of this operation.

Potential conflicts of interest

None.

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การศึกษาความสัมพันธ์ระหว่างผลลัพธ์ทางคลินิกและปัจจัยที่เกี่ยวข้องในการรักษาด้วยวิธีการผ่าตัด Kasai ในผู้ป่วยทารกที่ได้รับการวินิจฉัยว่าเป็นโรคท่อน้ำดีตีบตัน

มงคล เลาหเพ็ญแสง, พัชรพรรณ ศรีขวัญเจริญ

ภูมิหลัง: *โรคท่อน้ำดีตีบตันนั้นยังไม่พบสาเหตุของการเกิดโรคที่แน่ชัด นำไปสู่การเกิดภาวะน้ำดีคั่งและตับแข็งในที่สุดการผ่าตัด Kasai ได้รับการยอมรับกันทั่วโลกว่าเป็นการรักษาเบื้องต้นเพื่อให้เกิดการระบายน้ำดีได้ การผ่าตัด Kasai ที่ประสบความสำเร็จนั้นเพิ่มอัตราการรอดชีวิตและยืดระยะเวลาในการผ่าตัดเพื่อปลูกถ่ายตับออกไป ซึ่งการผ่าตัดดังกล่าวนี้มีปัจจัยหลายประการด้วยกันที่มีอิทธิพลต่อความสำเร็จ*

วัสดุและวิธีการ: *การศึกษาข้อมูลย้อนหลังของทารกที่ได้รับการวินิจฉัยเป็นโรคท่อน้ำดีตีบตันและได้รับการผ่าตัด Kasai ที่หน่วยกุมารศัลยศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาลในช่วงวันที่ 1 มกราคม พ.ศ. 2549 ถึงวันที่ 31 พฤษภาคม พ.ศ. 2558 จำนวน 48 ราย โดยมีผู้ป่วย 10 ราย ไม่สามารถเข้าร่วมในการศึกษาได้เนื่องจากมีข้อมูลไม่ครบ จึงมีผู้ป่วยทั้งหมด 38 รายที่เข้าร่วมในการศึกษานี้ ข้อมูลที่นำมาศึกษาได้แก่อาการ ผลการตรวจจากห้องปฏิบัติการ ผลการตรวจทางรังสี ผลการผ่าตัด และอาการหลังจากการผ่าตัด*

ผลการศึกษา: *อายุเฉลี่ยของผู้ป่วยที่เริ่มมีอาการตัวตาเหลืองอยู่ที่ 4 สัปดาห์ อายุเฉลี่ยขณะได้รับการผ่าตัด Kasai คือ 82 วัน มีผู้ป่วย 25 ราย (62.8%) ที่หายจากอาการตัวตาเหลืองหลังได้รับการผ่าตัด มีการเกิดภาวะติดเชื้อในทางเดินน้ำดีหลังการผ่าตัด 30 ราย (78.9%) อายุขณะที่ได้รับการผ่าตัด Kasai นั้นมีผลต่อการหายจากอาการตัวตาเหลืองหลังผ่าตัดอย่างมีนัยสำคัญ จากการศึกษาพบว่าการผ่าตัดที่อายุน้อยกว่าหรือเท่ากับ 90 วันนั้นมีผลต่อความสำเร็จของการผ่าตัดอย่างมีนัยสำคัญอีกด้วย*

สรุป: *อายุขณะที่ได้รับการผ่าตัด Kasai มีผลต่อการหายจากอาการตัวตาเหลืองภายหลังการผ่าตัดอย่างมีนัยสำคัญ ผู้ป่วยที่ได้รับการผ่าตัดขณะอายุมากกว่า 90 วัน มีความเสี่ยงต่อการเกิดการลดลงของอาการตัวตาเหลืองช้าเมื่อเทียบกับกลุ่มที่อายุน้อยกว่าหรือเท่ากับ 90 วัน*