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ORIGINAL ARTICLE

A retrospective study of the ideal operation time for preterm biliary atresia patients

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Abstract

Objective To study the ideal Kasai portoenterostomy (KPE) time for preterm infants with biliary atresia (BA) through evaluation of the postoperative effects.

Methods Retrospectively, 34 preterm infants with BA from 2012 to 2016 were recruited in the present study. The following three groups were established according to their chronological and corrected age at the time of KPE operation: chronological age ≤ 90 days, chronological age > 90 days and corrected age ≤ 90 days, and corrected age > 90 days. For chronological age ≤ 90 days at operation, patients were further divided into another three groups: chronological age ≤ 60 days, chronological age > 60 days and corrected age ≤ 60 days, and corrected age > 60 days. Postoperative effects were then followed up and recorded.

Results First, of those patients divided according to 90-day chronological and corrected age, postoperative total bilirubin levels (TBL), direct bilirubin levels (DBL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) of the group whose chronological age was ≤ 90 days were lower than the levels of the group whose chronological age was > 90 days and corrected age ≤ 90 days ($P = 0.0472$, $P = 0.0358$, $P = 0.0083$, and $P = 0.0491$), and the group whose corrected age was > 90 days ($P = 0.0383$, $P = 0.0392$, $P = 0.0043$, and $P = 0.0107$). Second, for those patients whose chronological age was ≤ 90 days, the group whose corrected age was > 60 days showed a higher ALT level than the other two groups with chronological age ≤ 60 days ($P = 0.0472$) and chronological age > 60 days and corrected age ≤ 60 days ($P = 0.0258$).

Conclusion According to the present study, the ideal KPE time for preterm BA infants should meet two conditions: chronological age ≤ 90 days and corrected age ≤ 60 days. The groups with a chronological age ≤ 60 days, and chronological age > 60 days and corrected age ≤ 60 days show similar postoperative effects.

Keywords Biliary atresia · Preterm · Kasai · Operation time

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Introduction

Biliary atresia (BA) is an irreversible progressive cholangiopathy that manifests as inflammatory obstruction of both the intrahepatic and extrahepatic biliary tree during the early infancy [1, 2]. While the etiology of BA remains unclear, it is mainly attributed to virus infection and immune system dysfunction [3]. Some BA infants are found to harbor rotavirus (RRV) infection, and newborn mouse models of BA are induced by RRV. CD8+ cytotoxic T cells, B cells, NK cells, and macrophages have been found to be responsible for the progressive obstruction of the biliary tree [4, 5]. BA eventually leads to biliary cirrhosis and hepatic failure [6]. BA is the most common indication for liver transplantation in the pediatric population. The incidence of BA is 7.55 per

10,000 among Asians and Pacific islanders, which is higher than that among whites or blacks [7].

Without treatment, BA patients usually die before the age of 2 years. Kasai portoenterostomy (KPE) is the first effective operative choice for the treatment of BA [8–10]. KPE also provides time for BA patients to await liver transplantation. Successful bile drainage after operation is a key indicator of a good postoperative prognosis. Cholangitis is the most frequent complication [11]. The timing of the operation has been the subject of much discussion [12]. Most reports indicate that operating at an early age improves the prognosis. Surgeons typically perform KPE at ages younger than 60 or 90 days [13]. Stool color cards and prompt referral systems have been designed to facilitate the KPE timing [14]. The timing of this operation is of great concern, as it is closely correlated to the postoperative effects.

Preterm birth is a poor prognostic factor in BA. In addition, the prevalence of BA in preterm infants is greater than that of term infants [15]. However, the ideal time for KPE in preterm BA patients has not been extensively studied. This is an important area of investigation, because preterm infants differ from term infants and are usually diagnosed late [16]. The present study included preterm BA patients at our medical center and investigated the proper age to perform KPE to guarantee a satisfactory prognosis.

Patients and methods

Patients

In total, 34 preterm BA patients were retrospectively recruited from January 2012 to June 2016 at a single medical center. Preterm patients refer to those who are born greater than or equal to 28-week gestation and less than 37-week gestation. Prior to the surgery, both the purpose and the associated risk of surgical procedure were fully explained to the legal guardian of the patient. The legal guardian then signed the consent forms. All patients completed the entire therapeutic course under the care of one surgeon at the pediatric surgery department of our medical center. This study was approved by the ethics committee of Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology.

Methods

Following recruitment of 34 preterm BA patients, relevant information during hospitalization was recorded. Demographic information included sex, gestational age (GA), chronological age, and corrected age at KPE operation. Corrected age at operation was calculated by subtracting the number of days of prematurity from the chronological age. In addition, preoperative total bilirubin levels (TBL), direct bilirubin levels (DBL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were recorded [17].

Afterwards, patients were divided into three groups according to their chronological ages and corrected ages at operation. The time point was 90 days old. The patients were divided into three groups comprised of those whose chronological age was ≤ 90 days (Group A), those whose chronological age was > 90 days and corrected age was ≤ 90 days (Group B), and those whose corrected age was > 90 days (Group C). Their clearance of jaundice (COJ), TBL, DBL, ALT, and AST was followed up within 6 months following the operations. COJ was defined as TBL < 20 μmol/L. Furthermore, the middle-term follow-up recorded any conditions of recurrent cholangitis, 2-year survival with native liver, liver transplantation, and death by outpatient visits, telephone calls, or mail. Following collection of data from the three groups, patients with a chronological age ≤ 90 days were again divided into three groups to obtain further conclusions. The time point was 60 days old, with the three groups divided into the following: patients whose chronological age was ≤ 60 days (Group A1), those whose chronological age was > 60 days and a corrected age ≤ 60 days (Group A2), and those whose corrected age was > 60 days (Group A3). The follow-up parameters above were then compared among these three groups. The flowchart was shown in Fig. 1.

Statistical analysis

Statistics for all variables were calculated by SPSS Version 17.0. Student's *t* test and analysis of variance (ANOVA) were used to analyze the measurement data. Student's *t* test was used for comparison between two groups and ANOVA among three groups. Chi-square test and Fisher's exact test were applied to analyze enumeration data. All statistical tests were two-tailed. A P value < 0.05 was considered statistically significant difference.

Results

Prior to operation, the GA, sex, and laboratory examinations, including DBL, TBL, ALT, and AST, showed no statistically significant differences among all the groups (Tables 1, 2). Thereafter, follow-up results were as follows.

First, patients were divided into three groups by the 90-day-old time point (chronological and corrected age). Postoperative TBL, DBL, ALT, and AST of Group A were lower than Group B ($P = 0.0472$, $P = 0.0358$, $P = 0.0083$, and $P = 0.0491$) and Group C ($P = 0.0383$, $P = 0.0392$, $P = 0.0043$, and $P = 0.0107$). COJ showed no statistically significant differences among three groups ($P = 0.3825$).

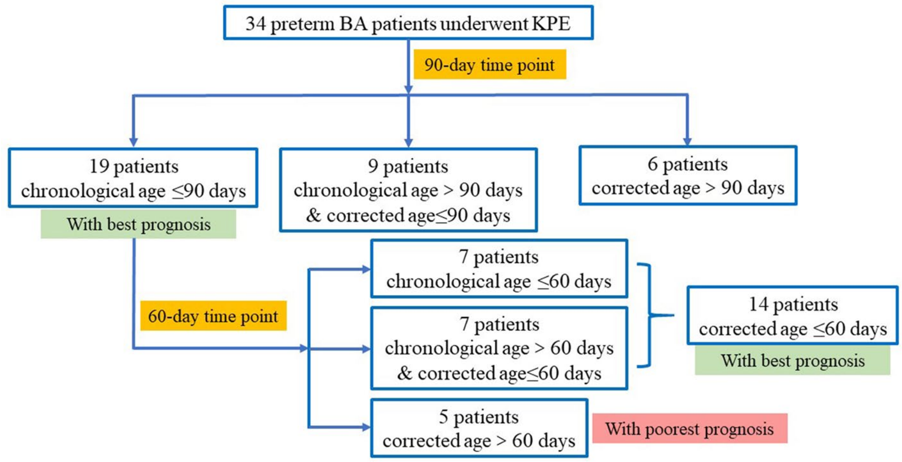

Fig. 1 Flowchart of the study. Thirty-four preterm BA patients are included. First, they are divided by 90-day point and the group with best prognosis is picked up. Then, they are divided by 60-day point and the group with best prognosis is found out. *BA* biliary atresia, *KPE* kasai portoenterostomy

Table 1 Clinical and laboratory characteristics of all studied patients

	Group A Chronological age ≤ 90 days (*n* = 19)	Group B Chronological age > 90 days and corrected age ≤ 90 days (*n* = 9)	Group C Corrected age > 90 days (*n* = 6)	*P* value
Male:female	10:9	4:5	3:3	0.9214
GA (weeks)	35.25 ± 1.33	34.68 ± 1.59	35.13 ± 1.15	0.5943
Chronological age at operation (days)	60.78 ± 16.79 (29–86)	98.11 ± 3.98 (93–106)	116.00 ± 14.34 (97–129)	–
Corrected age at operation (days)	48.47 ± 17.29 (22–81)	82.00 ± 7.47 (64–89)	103.00 ± 12.31 (91–119)	–
TBL (μmol/L)	141.68 ± 37.87	138.82 ± 58.30	136.87 ± 35.46	0.9679
DBL (μmol/L)	111.01 ± 30.44	91.61 ± 12.84	107.48 ± 29.09	0.2127
ALT (U/L)	134.11 ± 41.37	180.78 ± 121.19	126.17 ± 67.76	0.2525
AST (U/L)	177.11 ± 65.04	196.78 ± 107.54	171.83 ± 68.05	0.7845

Values are expressed as the means ± standard deviation

GA gestational age, *TBL* total bilirubin levels, *DBL* direct bilirubin levels, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

Table 2 Clinical and laboratory characteristics of patients whose chronological age ≤ 90 days

	Group A1 Chronological age ≤ 60 days (*n* = 7)	Group A2 Chronological age > 60 days and corrected age ≤ 60 days (*n* = 7)	Group A3 Corrected age > 60 days (*n* = 5)	*P* value
Male:female	3:4	4:3	3:2	0.0833
GA (weeks)	35.73 ± 0.73	34.37 ± 1.60	35.80 ± 1.09	0.0805
Chronological age at operation (days)	42.00 ± 7.83 (29–52)	66.71 ± 5.99 (61–79)	78.80 ± 6.22 (71–86)	–
Corrected age at operation (days)	33.14 ± 6.94 (22–44)	48.29 ± 12.11 (33–60)	70.20 ± 7.19 (62–81)	–
TBL (μmol/L)	125.13 ± 12.76	164.87 ± 53.94	132.40 ± 17.78	0.115
DBL (μmol/L)	98.96 ± 15.13	129.43 ± 43.33	102.10 ± 7.88	0.127
ALT (U/L)	123.00 ± 47.82	141.57 ± 29.65	139.20 ± 51.05	0.692
AST (U/L)	164.71 ± 62.89	178.57 ± 51.95	192.40 ± 92.15	0.786

Values are expressed as the means ± standard deviation

GA gestational age, *TBL* total bilirubin levels, *DBL* direct bilirubin levels, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

However, COJ of Group A was 42.1%, which was higher than that of Group B (22.2%) and Group C (16.7%). In the middle-term follow-up, no statistically significant differences were found for conditions including recurrent cholangitis, liver transplantation, survival with native liver, and death. Fewer patients in Group A had recurrent cholangitis (57.9%), and more patients of Group A survived with native liver within 2 years (42.1%) compared to Group B and Group C. Detailed data are shown in Table 3.

Second, for patients whose chronological age was ≤ 90 days, Group A3 showed a higher ALT level than the other two groups: Group A1 ($P = 0.0472$), and Group A2 ($P = 0.0258$). However, DBL, TBL, and AST showed no significant difference. The results of middle-term follow-up also showed no significant difference among Group A1, Group A2, and Group A3. Percent of recurrent cholangitis of Group A1, Group A2, and Group A3 was 57.1%, 42.9%, and 60.0%, respectively. In addition, 2-year survival rate of native liver was 42.9% in Group A1, 42.9% in Group A2, and 40.0% in Group A3. Detailed data are shown in Table 4.

Discussion

Popularity of KPE has greatly improved the prognosis and survival rate of BA patients worldwide. The procedure is considered a breakthrough in the field of BA treatment. A long-term follow-up in Hong Kong of China showed that the rate of transplant-free survival post-KPE was 51% [18]. The oldest recipient of KPE, from Japan, was over 60 years old [19]. Moreover, KPE is a bridge for children in need of liver transplantation. Although most BA patients still currently require liver transplantation for a longer survival, successful KPE remains a good prognostic factor and may delay the requirement for liver transplantation.

The preoperative prognostic factors of KPE are age at operation, presence of the biliary atresia splenic malformation syndrome (BASM), center-specific factors, liver histology, and anatomic pattern of bile ducts. In particular, the age at KPE is the focus of many publications [13, 20–22]. The current opinion that a younger age at operation guarantees a better prognosis is accepted by most doctors. From the initial study in 1975, researchers concluded that BA patients whose ages at operation were younger than 60 days had long-term postoperative effects [23]. A study from Canada reported that the 10-year post-KPE survival rate of those undergoing KPE at 30-days old was 49%, while that of those undergoing KPE at 90-days old was only 15% [22]. This long-term follow-up result clearly provides evidence for the view that the age at KPE is an important prognostic factor for BA patients. Moreover, recent research indicates that older age at KPE is associated with significantly higher costs [21]. However, another study found that age at KPE was a useful prognostic factor for short-term follow-up but not the

Table 3 Short-term and mid-term follow-up of all patients

	Group A Chronological age ≤ 90 days ($n = 19$)	Group B Chronological age > 90 days and corrected age ≤ 90 days ($n = 9$)	Group C Corrected age > 90 days ($n = 6$)	P value
Length of follow-up (months)	19.05 ± 5.39	17.89 ± 4.40	16.50 ± 5.24	0.5534
Clearance of jaundice (n, %)	8, 42.1%	2, 22.2%	1, 16.7%	0.3825
TBL (μmol/L)	23.42 ± 11.79	34.22 ± 14.86	36.33 ± 14.94	0.0494* 0.0472※ 0.0383&
DBL (μmol/L)	11.99 ± 8.42	20.96 ± 12.87	21.32 ± 11.24	0.0488* 0.0358※ 0.0392&
ALT (U/L)	40.89 ± 16.23	58.56 ± 12.85	64.00 ± 12.92	0.0200* 0.0083※ 0.0043&
AST (U/L)	42.26 ± 15.64	54.22 ± 10.76	62.17 ± 14.02	0.0107* 0.0491※ 0.0107&
Recurrent cholangitis (n, %)	11, 57.9%	8, 88.9%	5, 83.3%	0.1831
Liver transplantation (n, %)	4, 21.1%	2, 22.2%	2, 33.3%	0.8215
Survival with native liver (n, %)	8, 42.1%	2, 22.2%	1, 16.7%	0.3825
Death (n, %)	7, 36.8%	5, 56.6%	3, 50.0%	0.6930

Values are expressed as the means ± standard deviation

※$P < 0.05$ shows significant difference between "Chronological age ≤ 90 days" group and "Chronological age > 90 days and corrected age ≤ 90 days" group

&$P < 0.05$ shows significant difference between "Chronological age ≤ 90 days" group and "Corrected age > 90 days" group

*$P < 0.05$ shows significant difference among three groups

GA gestational age, *TBL* total bilirubin levels, *DBL* direct bilirubin levels, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

Table 4 Short-term and mid-term follow-up of patients whose chronological age ≤ 90 days

	Group A1 Chronological age ≤ 60 days (n = 7)	Group A2 Chronological age > 60 days and corrected age ≤ 60 days (n = 7)	Group A3 Corrected age > 60 days (n = 5)	P value
Length of follow-up (months)	20 ± 4.83	19.29 ± 5.65	17.40 ± 6.54	0.7283
Clearance of jaundice (n, %)	3, 42.9%	4, 57.1%	1, 20.0%	0.4375
TBL (μmol/L)	23.86 ± 13.38	19.43 ± 9.78	28.40 ± 12.40	0.4511
DBL (μmol/L)	10.77 ± 7.80	11.03 ± 8.96	15.06 ± 9.55	0.6624
ALT (U/L)	37.14 ± 13.35	33.86 ± 13.73	56.00 ± 15.48	0.0385* 0.0472※ 0.0258&
AST (U/L)	40.57 ± 11.24	36.43 ± 10.10	52.80 ± 23.56	0.1952
Recurrent cholangitis (n, %)	4, 57.1%	3, 42.9%	3, 60.0%	0.8048
Liver transplantation (n, %)	2, 28.6%	1, 14.3%	1, 20.0%	0.8048
Survival with native liver (n, %)	3, 42.9%	3, 42.9%	2, 40.0%	0.9939
Death (n, %)	2, 28.6%	3, 42.9%	2, 40.0%	0.8453

Values are expressed as the means ± standard deviation

※P < 0.05 shows significant difference between "Chronological age ≤ 60 days" group and "corrected age > 60 days" group

&P < 0.05 shows significant difference between "Chronological age > 60 days and corrected age ≤ 60 days" group and "Corrected age > 60 days" group

*P < 0.05 shows significant difference among three groups

GA gestational age, *TBL* total bilirubin levels, *DBL* direct bilirubin levels, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

long-term follow-up [24]. Doctors from China indicated that a portion of BA patients of greater than 90 days of age at operation could also benefit from KPE [25]. The age at operation is an important factor of KPE. According to these results, generalization of stool color cards and establishment of a referral system would aid in the early diagnosis and early operation time [14, 26, 27].

Prematurity is a poor prognostic factor for COJ and transplantation-free survival in BA patients. In addition, delays in diagnosis occur more frequently in these patients. In the present study, we recruited preterm BA infants to find the appropriate age at which to perform KPE. The goal was to improve the prognosis of preterm BA patients and to provide evidence to support that operative age is an important prognostic factor for KPE. This study includes 90 days and 60 days as the relevant time points. According to their premature days, groups were divided by chronological age and corrected age. The combination of chronological and corrected age allowed the comprehensive comparison of postoperative follow-up in preterm BA patients. Each patient was assigned to a single group. For those with corrected ages > 90 days (Group C), their chronological ages were certainly > 90 days. Afterwards, corrected ages ≤ 90 days were divided into Group A (chronological age ≤ 90 days) and Group B (chronological age > 90 days and corrected age ≤ 90 days). We found that BA patients whose chronological age was ≤ 90 days and corrected age ≤ 60 days had the best postoperative effects. Although they showed no statistical significance, the COJ and 2-year survival with native liver rates in Group A were higher than those of Group B and Group C. The 2-year survival with native liver rates of all the three groups was not higher than the rate mentioned before, which may demonstrate that prematurity itself is a poor prognostic factor of BA. In addition, TBL, DBL, ALT, and AST all showed statistically significant differences among groups divided by the time point of 90 days. Group A had lower TBL (23.42 ± 11.79 μmol/L), DBL (11.99 ± 8.42 μmol/L), ALT (40.89 ± 16.23 μmol/L), and AST (42.26 ± 15.64 μmol/L) when compared to Group B and Group C. The groups were further divided into Groups A1, A2, and A3 by the time point of 60 days. Only ALT levels showed statistically significant differences among the three groups: Group A1 and Group A2 were lower than Group A3. Group A1 and A2 were merged into the group whose corrected age was ≤ 60 days. However, the COJ rate and 2-year survival rate with native liver showed no statistically significant differences. We did not find that a younger age at operation for preterm BA patients had a worse prognosis in this study. Therefore, preterm BA patients with a chronological age ≤ 90 days and corrected age ≤ 60 days may achieve a better prognosis in short-term follow-up. This is in accordance with the theory that early diagnosis and early operation are beneficial for BA. This is a retrospective study and included only 34 patients. Therefore, our conclusions are limited. A prospective clinical study with a larger sample size should be initiated to further validate our findings.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology approved the protocol of the study (Permit Number 2010-HP0761, Wuhan, China). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from the guardians of the patients included in this study.

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