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Correlation between Histological Changes of Liver and Early Surgical Outcome of Kasai Portoenterostomy in Biliary Atresia

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Abstract **Original Research Article**

Background*:** Biliary atresia (BA) is a progressive fibrosing obstructive cholangiopathy involving both resulting in the intrahepatic and extrahepatic bile ducts. Hepatic portoenterostomy was first described by Kasai and Suzuki in 1959 to re-establish bile flow in biliary atresia patients. Currently, the accepted management of infants with biliary atresia is to re-establish bile flow by Kasai portoenterostomy followed by liver transplantation when indicated. ***Purpose*:** The purpose of this study is to correlate the surgical outcome following Kasai portoenterostomy with liver histology at the time of extended Kasai Portoenterostomy for biliary atresia who are operated in this institution. ***Methods: This prospective study was done in the department of Pediatric Surgery, BSMMU, with study period from October 2017 to march 2020.Wedge biopsies of liver was taken at the time of Extended Kasai portoenterostomy. Liver biopsies were graded as mild (grade-1), moderate (grade-2) and severe (grade-3) degree of fibrosis by single pathologist. Serial measurement of serum bilirubin were made preoperative and postoperatively to assess the degree of bile drainage in relation to degree of liver fibrosis. ***Results*:** A total of thirty infants underwent Extended KPE during study period. The mean age at the time of surgery was 89.7 (±23.4SD) days ranging from 57days to 140 days. 16 infants were operated before 90 days and rest 14 were operated beyond 90 days of life. Out of 30 infants, 3 cases were grade -1 fibrosis, 15 cases were grade- 2 and 12 cases were grade-3 fibrosis. 12(40%) infants cleared jaundice at three months after surgery, of which only 2 patients belonged to grade-3 fibrosis. 9(30%) infants were jaundice free at 6 months, among them 8 infants belonged to lower degree of fibrosis (grade-1 and grade-2). Only 1infant belonged to higher degree of fibrosis (grade-3). ***Conclusion*:** Currently, the concept for management of infants with biliary atresia considers successful establishment of liver drainage by Extended Kasai portoenterostomy as the preliminary mainstay. This study reveals that higher grade of fibrosis is uniformly associated with poor prognosis. Therefore, this study concludes that the degree of liver fibrosis is the most significant prognostic factor for surgical outcome of portoenterostomy and native liver survival in biliary atresia.

Keywords: Biliary Atresia (BA), Kasai Portoenterostomy (KPE), Extended KPE, degree of liver fibrosis, Jaundice clearance, bile drainage, Native Liver Survival Rate (NLSR) Liver Transplantation (LT).

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INTRODUCTION

Biliary atresia is a destructive inflammatory cholangiopathy of neonates that affects both intra-hepatic and extra-hepatic bile duct leading to obstruction of bile flow and cholestatic jaundice. Biliary atresia accounts for 25-30% of the total neonatal cholestasis. The incidence varies from 1 in 8000 to 1 in 18,000 live births. Biliary atresia can be divided into two main group. The perinatal or acquired group presents around one month of age and represents 80-90% cases. The pathophysiology of this group is not fully understood and proposed etiologic factors includes

immunological factors, genetic predisposition, ischemia and infections. The rarer fetal group presents much earlier and accounts only 10-20%. The fetal group has worst outcomes even when surgical intervention is done in early course of disease. Kasai portoenterostomy is the initial treatment of biliary atresia. The overall 5-year survival rates following Kasai portoenterostomy is about 50% and 10 year survival rate is about 30%. Before reaching adulthood, about67% of patients develop chronic liver disease and ultimately need liver transplantation. Prognostic factors for biliary atresia after Kasai portoenterostomy have been widely studied and results so far contradictory. Age at initial operation, anatomical type of biliary atresia, size and number of bile ductules and histological changes of liver are thought to be prognostic indicators [1]. In 1959, Professor Morio Kasai (1922-2008) of Japan first performed hepatic Portoenterostomy as a breakthrough for biliary atresia claiming good bile drainage. This operation popularly known as Kasai portoenterostomy has become standard treatment for all children with biliary atresia diagnosed early. Kasai Portoenterostomy has undergone modification with wide dissection of the portal plate at the hilum, known as Extended Kasai portoenterostomy [2]. The operation should preferably be done before 8 weeks of life but in developing countries, most of the cases present late even after 5 months. So it is thought to analyse the histological changes of liver in biliary atresia with advancing age at presentation and trend of survival in such cases [3]. Although biliary atresia is a rare disorder with higher incidence reported in Asian countries, we do face many patients of biliary atresia in our institution. Biliary atresia is the most common indication of pediatric liver transplantation in developed country. But childhood liver transplantation is not available in our country. So Kasai operation may be the survivability of native liver as long as possible for biliary atresia patients in our country. There are studies from Western and Asian countries showing effective bilirubin clearance and long-term survivability, even for more than 15 to 20 years with their own liver and jaundice free after kasai portoenterostomy. Accurate early prediction of poor prognosis after Kasai portoenterostomy for biliary atresia permits focused anticipatory guidance and monitoring related to potential complications of advancing liver disease and early consideration of liver transplantation. The surgical outcome following Kasai portoenterostomy is assessed by clearance of jaundice and proportions of native liver survival. Clearance of jaundice (TB<2.0mg) within 3 months enhance early surgical outcome [4]. Outcomes after KPE depend on factors like age at initial operation, successful achievement of post-operative bile drainage, presence of microscopic ductal structures at the hilum, and technical factors at the anastomosis. Among these factors effective bile drainage after Kasai procedure is important hallmark for the success of operation and longtime survival with native liver in children with biliary atresia. Surgical success is defined by clearance of jaundice within three 3 months after KPE [5]. Bilirubin at 3 months is the best predictor of native liver and overall survival [6]. After KPE if jaundice resolves by 3 months, the 10 years transplant free survival is 75%-90%. Conversely, if jaundice persists, the 3 years transplant free survival is only 20%. Thus, the children who do not demonstrate good bile flow and clearance of jaundice by 3 months after KPE should be evaluated for early liver transplantation [7]. So reduction in jaundice is the evidence of bile drainage and determines the effectiveness of bile drainage. The purpose of this study is to determine the effectiveness of bile drainage in relation to degree of liver fibrosis after extended Kasai portoenterostomy in patients with biliary atresia.

MATERIALS AND METHODS

Study Type: Prospective analytical study.
Study Place: Department of Paediatric Surgery, BSMMU, Bangladesh.
Study Period: October 2017 to March 2020.
Study Population: Infants who were operated as Extended Kasai portoenterostomy for Biliary Atresia.
Sample Size: 30 (Thirty).

Inclusion Criteria:

- Infants who underwent Extended Kasai Portoenterostomy for biliary atresia.

Exclusion Criteria:

- Parents of infants not willing to participate in the study.
- Patients who died early postoperative period.

History and Clinical Examination: Relevant history was taken and physical examinations was done for each patient and recorded in pretested data collection sheet.
Pre-Procedure Evaluation / Investigations: Diagnosis of Biliary Atresia was made by laboratory findings of liver function tests, ultrasonography of hepatobiliary system, hepatobiliary scintigraphy and core needle liver biopsy.
Operative Procedure: Surgical procedure – All the patients in this study underwent Extended type of Kasai Portoenterostomy, which includes mobilization and exteriorization of liver, wide dissection of portal plate and funnel shaped portoenterostomy to ensure adequate bile drainage. Biopsy was taken from right lobe of liver and sent for histopathology with preservative. Histopathological study was done by single histopathologist in Department of Pathology, BSMMU and histological findings was graded as Grade I (mild/fibrosis 1+) fibrosis comprised cases with portal fibrous expansion to porto-portal bridging fibrosis involving less than 50% of portal tracts. Grade II (moderate/fibrosis 2+) fibrosis included cases with porto-portal bridging fibrosis involving greater than 50% of portal tracts without nodular hepatic architecture. Grade III (severe/fibrosis 3+) fibrosis ranged from porto-portal and porto-central bridging

fibrosis involving greater than 50% of portal tracts associated with nodular hepatic architecture.

Data Processing and Analysis: All the data were compiled and sorted properly and the numerical data were analyzed by using standard statistical tools – percentage, proportion, ratio, mean ± SD, Paired t- test and Chi-Square test and p value of <0.05 was considered as the level of significant.

RESULTS

A total of thirty (30) patients had undergone Extended Kasai Portoenterostomy and were enrolled for the study. Effectiveness of bile drainage in early post-operative period after Extended Kasai Portoenterostomy was studied in terms of degree of bile drainage in relation to degree of liver fibrosis.

Table 1: Distribution of study population according to sex (n=30)

Sex	Number	Percentage (%)
Male	18	60
Female	12	40

Table 2: Distribution of study population according to age at Kasai (n=30)

Age	Number	Percentage (%)
>90	14	46.7
≤90	16	53.3

The mean age at Kasai Procedure of the study population was found to be 89.7 (±23.4 SD) days. The eldest one being operated at 140 days and the junior most was operated at 57 days of age. 53.3% of the study population was operated at or before 90 days of age. Rest 46.7 % infants were operated late beyond 90 days of age.

Table 3: Distribution of the study subjects according to degree of fibrosis (n=30)

Subjects according	Number	Percentage (%)
Grade 1	3	10
Grade 2	15	50
Grade 3	12	40

The degree of fibrosis of study population was observed. Total 3(10%) patients are grade-1 fibrosis, 15(50%) patients are grade- 2 fibrosis and 12(40%) patient are grade- 3 fibrosis.

Table 4: Comparison of age at operation with degree of fibrosis (n=30)

Operation	Age ≤90 days		Age >90 days		P-value
	N	%	N	%	
Grade 1	6	20.0	0	0.0	0.073^{S}
Grade 2	17	56.6	13	43.4	
Grade 3	7	23.4	17	56.6	

Comparison of age at operation with degree of fibrosis is shown in figure: observed that total 3 cases were grade -1 fibrosis and all belonged to group operated below 90 days, 15 cases were grade-2 fibrosis among them 9 were operated below 90 days and 6 were operated beyond 90 days, another 12 cases were grade-3 fibrosis among them 4 belonged to group below 90days and 8 cases were operated beyond 90 days. Significance was studied and p-value was 0.073 which shows statistically not significant.

Table 5: Pre and post-operative (after 3 months and 6 months) total serum bilirubin at different degree of fibrosis (n=30)

	Total serum bilirubin(mg/dl)			p-value	
Degree of fibrosis	Pre operative	After 3 months of operation	After 6 months of operation	Pre vs 3 month	Pre vs 6 month
Grade 1	15.93 ± 4.68	6.67 ± 8.11	1.50 ± 0.72	0.304	0.042
Grade 2	11.00 ± 3.40	7.00 ± 7.54	2.36 ± 2.24	0.066	<0.001
Grade 3	10.20 ± 2.60	6.45 ± 5.22	7.65 ± 6.35	0.110	0.560

Paired t test was done

Serial total serum bilirubin in pre and postoperative period of each study sample was obtained in relation to different degree of fibrosis of infants. In grade-1 fibrosis, the mean preoperative total serum bilirubin was15.93± 4.68, after 3months and 6months the mean total serum bilirubin was 6.67± 8.11 and 1.50± 0.72(p-value 0.04) which was significant. In grade-2 fibrosis mean preoperative serum bilirubin was 11.00± 3.40, after 3months and 6months it was7.00± 7.54 and 2.36 ± 2.24(p- value<0.001) which was also significant. In case of grade-3 fibrosis, mean preoperative total serum bilirubin was 10.20± 2.60, after 3 months and 6 months was 6.45± 5.22 and 7.65±

6.35 (p-value 0.56) which was not statistically significant.

Table 6: Association of jaundice clearance with degree of liver fibrosis at 3 month (n=30)

Grading of Fibrosis	n	Persistent jaundice (n=18)	Jaundice free (n=12)	p-value
Grade 1	3	0(0.0)	3(25.0)	
Grade 2	15	8 (44.4)	7 (58.3)	0.023
Grade 3	12	10 (55.6)	2 (16.7)	
Total	**30**	**18 (60.0)**	**12 (40.0)**	

Chi-Square test was done to measure the level of significance

The jaundice clearance of the study population is shown in table 6. Only 12 (40%) infants have serum total bilirubin level below 2 mg/dL at 3 months post-surgery, of which 3 (out of 3) belonged to grade-1 fibrosis, 7(out of 15) belonged to grade-3 fibrosis. Only 2 (out of 12) infants cleared jaundice in grade-3 fibrosis and p-value was 0.023 which shows statistically significant.

Table 7: Association of jaundice clearance with degree of liver fibrosis at 6 month (n=30)

Grading of Fibrosis	n	Persistent jaundice (n=21)	Jaundice free (n=9)	p-value
Grade 1	3	0 (0.0)	3 (33.3)	
Grade 2	15	10 (47.6)	5 (55.6)	0.007
Grade 3	12	11 (52.4)	1 (11.1)	
Total	30	21 (70.0)	9 (30.0)	

Chi-Square test was done to measure the level of significance.

Association of jaundice clearance with degree of liver fibrosis is shown in table 7. Total 9(30%) infants continued jaundice free at 6 months of post-surgery. Among them 8 infants belonged to lower degree of fibrosis (grade 1 and grade 2). Only 1infant belonged to higher degree of fibrosis (grade 3) and p-value was 0.007which also shows statistically significant.

DISCUSSION

Biliary atresia is considered to be a progressive fibro-inflammatory cholangiopathy of unknown etiology where both the extra and intra hepatic biliary ducts are gradually destroyed. It is rare but devastating disease of infants and is a burning topic for research in respect of the operative technique, post-operative care, complications, outcome and the most importantly liver transplantation for its success, appears to be an early drainage of the liver by kasai portoenterostomy before substantial liver damage has taken place and thereby, enable the patient to survive with the native liver for a considerable length of time when they eventually may require liver transplantation for further prolongation of survival time. Since decades Kasai Portoenterostomy has become the standard surgical procedure for biliary atresia worldwide. The surgical outcome is thought to be influenced by various factors such as the type of anatomical abnormality, age at initial operation, surgical experience. Several authors have studied the short and long term outcome and prognostic factor. Most of the recent studies have focused on improved outcomes with early diagnosis and younger age at surgery [8,9]. Where some studies have reported showing no significant effect of age at the time of [10,11]. Liver histology, a less studied prognostic factor seems to be an important as age at initial operation in predicting both short and long term outcome. As biliary atresia is considered as a progressive disease that destroys and obliterates the drainage apparatus sequentially from distal to proximal, there is an ongoing deposition of collagen and progressive hepatic fibrosis resulting in liver failure and death in first few years of life. But after successful portoenterostomycholestasis and portal inflammation decrease. Resolution of cholestasis and reduction of portal inflammation after successful kasai portoenterostomy is associated with slower progression of fibrosis and improve native liver survival Hukkinen *et al.,* [6]. In this study mean age at operation was 89.7±23.4 days. As there is a delay indiagnosis and referral system in Bangladesh, we found most of the patients present late. Sharma *et al.,* [3] showed that there was no significant difference in relation to the age less than or more than 90 days in the grading of liver fibrosis. Gupta, Gupta and Bhatnagar [12] also showed that grades of fibrosis were worse in increased age but this difference was not statistically significant. In this study comparison of age at operation with grading of liver fibrosis was done and found grades of fibrosis higher whose age more than 90 days but statistically was not significant (p-value>0.05). Gupta, Gupta & Bhatnagar [12] concluded that high grade of hepatic fibrosis was associated poor outcome but did not achieve statistical significance. Webb *et al.,* [13] have shown that absence of bridging fibrosis in liver histology at the time of Kasai portoenterostomy was the only prognostic factor found to be significantly associated with improved native liver survival at 5 years. Mukhopadhyay *et al.,* and Muthukanagarajan *et al.,* [1, 8] in their study have demonstrated that lower

degree of liver fibrosis and younger age at operation were associated with better long term surgical outcome. Of these, degree of fibrosis was the most significant factor. This study was undertaken to analyze the significance of hepatic fibrosis in prognosis of biliary atresia from liver biopsy. The surgical outcome of Kasai Portoenterostomy was assessed by clearance of jaundice which evidence of bile drainage. Then clearance of jaundice was undertaken to determine the effectiveness of bile drainage in relation to degree of hepatic fibrosis after Extended Kasai Portoenterostomy. Redker *et al.,* [14] showed in their study of 121 patients that 47.2% had jaundice clearance at 3 months post Kasai procedure. Shneider *et al.,* [4] have shown that after 3 months of Kasai portoenterostomy 50% had total bilirubin <2.0mg/dl. Webb *et al.,* [13] showed that jaundice clearance within 6 months occurred in 29.2% of infants. In this study of thirty infants, total 40% infants had jaundice cleared by three months of operation, of which three (out of three) were grade-1fibrosis, seven (out of fifteen) were fibrosis grade-2 and only two (out of twelve) were fibrosis grade-3 which was statistically significant. So degree of liver fibrosis at the time of Exteded Kasai portoenterostomy predicted clearance of jaundice at 3 months after surgery which is the most important predictive factor for native liver survival. However, at six months after surgery total 30% patients continued to be jaundice-free, most of the patients belonging to lower degree of fibrosis (Fibrosis grade-1 and grade-2) only one patient belonging to fibrosis grade-3 which was also statistically significant. The remaining children had shown a subsequent rise of bilirubin after initial clearance at three months which never again came to normal indicating disease progression with progressive hepatic parenchymal damage even after initial free drainage of bile was established by Extended Kasai Portoenterostomy. All those infants who did not clear jaundice at any point after Extended Kasai Procedure and those who developed progressive jaundice after initial clearance at three months were destined to progress to early end-stage-liver-failure. These infants require early liver transplantation. It is widely accepted that progression of disease is arrested by establishment of early bile drainage and initial bilirubin clearance is important indicator of sustainability of drainage for longer periods. But fibrosis impairs flow of bile leading to jaundice and poor surgical outcome. This study suggests that the major prognostic indicator appears to be the initial establishment of jaundice clearance which is strongly associated with degree of liver fibrosis and higher degree of liver fibrosis is strongly associated with poor surgical outcome.

CONCLUSION

This study reveals that the major prognostic indicator of Kasai Portoenterostomy appears to be the initial establishment of jaundice clearance which is strongly associated with degree of liver fibrosis and higher degree of liver fibrosis is uniformly associated with poor prognosis even when the cases presented early for surgery.

Limitations of the Study

1. Short term follow up. So I could not see the long time native liver survival.
2. Liver transplantation yet not available in our country, so all the parents cannot be convinced for surgery.

RECOMMENDATIONS

1. All the survivors after Kasai operation need close supervision both for shorter and longer periods.
2. Degree of liver fibrosis can indicate the prognosis of the patient at the time of Kasai Portoenterostomy.

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