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Original Article

Clinical Parameters and Outcomes of Biliary Atresia in Children: A Single Centre Study

Raazia Nawaz, Farooq Ikram, Bilal, Saba Idrees, Ifnan Shamraiz, Samina Tabassum

Department of Pediatric, Combined Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To assess the clinical and laboratory parameters, interventions and their outcomes in children presenting with biliary atresia at a tertiary care hospital.

Study Design: Prospective longitudinal study.

Place and Duration of study: Pediatric Gastroenterology and Hepatology Department of Combined Military Hospital, Rawalpindi Pakistan, from Feb 2021 to Jan 2022.

Methodology: Patients diagnosed with extrahepatic biliary atresia on the basis of liver histopathology and intra operative cholangiogram were enrolled consecutively during this period. The clinical parameters, liver function tests, radiological investigations and histopathology findings were recorded and correlated. The impact of Kasai procedure on outcome and prognosis of biliary atresia patients was noted along with an interval analysis at 1 year of age.

Results: Forty patients were studied including 26 males and 14 females. Thirty (75%) patients underwent Kasai at a median age of 3.14±1.2 months with a success rate of 66.6% (p-value<0.01). No significant correlation was established between age at Kasai Hepatic Portoenterostomy and success of Kasai Hepatic Portoenterostomy (p-value>0.05). A statistically significant relation was established between one-year outcomes of patients undergoing Kasai Hepatic Portoenterostomy and without Kasai Hepatic Portoenterostomy (p-value 0.01). A significant difference in survival of patients undergoing Kasai Hepatic Portoenterostomy and those without Kasai Hepatic Portoenterostomy (p< 0.001) was observed.

Conclusion: Intervention in the form of Kasai Hepatic Portoenterostomy significantly contributes towards an improved outcome in patients with Biliary Atresia.

Keywords: Biliary atresia, Gamma glutamyl transferase, Hepatic portoenterostomy, Jaundice, Kasai.

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INTRODUCTION

Biliary Atresia (BA) is characterized by rapid progression of severe fibro-inflammatory damage to the intrahepatic and extra-hepatic biliary apparatus in neonatal period.[1,2,3]

The incidence of Biliary Atresia is approximated to be 1 in 15000 live births every year which makes it a predictably commonest cause of neonatal obstructive liver diseases and hence the pediatric liver transplant.[4,5] The common clinical features include clay colored stools and progressive neonatal jaundice which begin between 2nd and 6th week of life, while the syndromic form presents even earlier.[6]

An earlier diagnosis is one of the major challenges being faced in patients of BA. Gamma Glutamyl Transferase (GGT) was found to have a significant clinical correlation with diagnosis of EHBA.[7] Liver Biopsy and Per-operative cholangiogram are the most specific tests for diagnosis.[5]

It is imperative that all children with biliary atresia should undergo Kasai Hepato-portoenterostomy (KHPE) before 90th day of life.[7] In KHPE, the obliterated bile duct is removed and a portion of small intestine is attached to portal area through a Roux-en-Y anastomosis thus establishing an alternate pathway for flow of bile.[8] Children who are diagnosed and bridged with KHPE earlier have better success rate i.e. a 65.5% native liver survival at 2years of age if done within 45 days of life.[9]

Thus, the importance of this topic and a paucity of similar studies rationalizes why we studied the various clinical assortments, diagnostic testing, outcomes of KHPE, and long term prognosis of children with BA in a cohort of population.

METHODOLOGY

The prospective longitudinal study was conducted at Pediatric Gastroenterology and Hepatology Department of Combined Military Hospital, Rawalpindi Pakistan, from February 2021

Correspondence: Dr Raazia Nawaz, Department of Pediatric, Combined Military Hospital, Rawalpindi Pakistan

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to January 2022 after approval was obtained from Institutional Review Board (Serial No. 281).

Inclusion Criteria: Patients of either gender diagnosed as extrahepatic biliary atresia, irrespective of their age of presentation were included.

Exclusion Criteria: Patients with normal findings on intraoperative cholangiogram or those without definite diagnosis of extrahepatic biliary atresia, were excluded.

The definite diagnosis was established on the basis of liver biopsy histopathology findings and/or intraoperative cholangiogram findings. The Seven feature, fifteen points scoring system was used to differentiate biliary atresia from neonatal hepatitis on liver histopathology.[10] All patients were enrolled consecutively after taking informed consent. The data was obtained during indoor stay and scheduled appointment outpatient visits. A total of 40 patients were registered during this period,

The clinical parameters including age of onset of jaundice, stool color, gender and weight and the age of KHPE procedure was noted most pertinently. The presence of extrahepatic associations such as polysplenia, gut malrotation, intrauterine growth retardation (IUGR), congenital heart disease(CHD) and TORCH (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes Simplex Virus) infections was also recorded.

The results of preoperative testing of liver functions including Serum Total Bilirubin (STB) levels, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase(ALP), Gamma Glutamyl Transferase(GGT) and synthetic functions such as Serum Albumin and Prothrombin time(PT), Activated Partial Thromboplastin(APTT) and Complete Blood Counts were obtained. Diagnostic modalities such as Ultrasonography (USG) Abdomen, Hepatobiliary Imino Diacetic Acid (HIDA) Scan and intraoperative Cholangiogram results when performed, were also recorded amongst laboratory testing information.

The Kasai Procedure was defined to be successful when an infant cleared serum bilirubin levels (<20micromol/l) by 6 months of age.[11] All patients were placed on supportive management postoperatively in the form of ursodeoxycholic acid at 30mg/kg/day and rotating prophylactic antibiotics such as cefixime at 8mg/kg/d or ciprofloxacin at 10mg/kg/day. Impact of different factors on outcome of Kasai procedure were also assessed.

Outcome of all patients was meticulously measured at one year of age in terms of number of episodes of cholangitis, growth failure, portal hypertension, hypersplenism, synthetic dysfunction and need for liver transplantation. The presence of portal hypertension was assessed through surveillance endoscopy, Doppler USG and splenomegaly. Cholangitis was defined as an episode of high-grade fever in absence of any other focus of infection, acholic stools, rise in bilirubin levels or jaundice and a positive blood culture.[12]

The data was recorded on Microsoft Excel and analyzed with Statistical Package of Social Sciences (SPSS) version 28.0. Descriptive statistics were presented using frequency, percentages, mean, median and standard deviation. Association between different categories was measured using Chi-Square test and paired sample t-test. One-year survival analysis was assessed using Kaplan-Meier curves.

RESULTS

A total of forty infants were evaluated constituting 65% (26) boys and 35% (14) girls. Sixteen infants (40%) had onset of jaundice since their first week of life, overall average weight was 5.1±0.13kg and clay colored stools were seen in all of the patients.

KHPE was done in thirty patients (75%) with a median age of 3.14±1.2mo (94days). KHPE was successful in twenty patients (66.6%). The most common immediate post-operative complication observed in patients undergoing KHPE was cholangitis in nineteen (63.3%) patients (Table-I).

Biliary Atresia Splenic Malformation (BASM) was found in four patients (10%) followed by IUGR in three (7.5%), Ventricular Septal Defect in two (5%) and Malrotation in 2 patients (5%). Eight patients (20%) were found to be CMV positive. The presence of association did not significantly impact the one-year outcomes with 17.5% of the patients, having no extrahepatic association, doing well.

The mean levels of Serum Bilirubin were 172.6±60.3micromol/L, Alanine aminotransferase level of 221.55±124.4 U/L, AST level of 246.2±147.2U/L, ALP 750.8±194.2U/L and GGT were 633.3±276.9U/L (Table-II).

Significant correlation was observed between ALT and AST (0.712, p-value<0.01), between age of

Table-I Overview of Different Clinical Parameters, Interventions and their Outcomes (n=40)

Clinical Parameters	Categories [n(%) or Mean±SD]
Age of KHPE (months)	3.14±1.2
Gender	Male 26(65) Female 14(35)
Weight (kg)	5.1±0.13
Associations	None 12(30) BASM 10(4) IUGR 3(7.5) Gut Malrotation 2(5) CCHD 2(5)
Types of Biliary Atresia (Intraoperative Cholangiogram)	Type 2a; 3(7.5) Type 2b; 3(7.5) Type 3; 24(60)
TORCH Screen	Negative 31(77.5) CMV 8(20) Toxo 1(2.5)
KHPE done	Yes 30(75) No 10(25)
Outcomes of KHPE	Successful 20(66.6) Not Successful 10(33.3)
Post-Operative Complications	Cholangitis 19(63.3) Sepsis 4(10) Expired 1(2.5)

KHPE= Kasai Hepato-portoenterostomy, TORCH = Toxoplasmosis, Rubella, Cytomegalovirus, Herpes Simplex Virus; CCHD= Complex congenital Heart Disease, IUGR= Intrauterine growth retardation, CMV= Cytomegalovirus, BASM= Biliary Atresia Splenic Malformation

Table-II Laboratory Parameters, Radiological Investigations and Histopathological Findings of Subjects (n=40)

Variables	n(%)
Serum Alanine Aminotransferase (U/L) (Mean±SD)	221.55±124.4
Serum Aspartate Aminotransferase (U/L) (Mean±SD)	246.2±147.2
Serum Gamma Glutamyl Transferase (U/L) (Mean±SD)	633.3±276.9
Serum Total Bilirubin (Mean±SD)	172.6±147.2
Serum Alkaline Phosphatase (U/L) (Mean±SD)	750.8±194.2
Serum Albumin (g/L) (Mean±SD)	36.4±3.7
Prothrombin Time (sec)	16.7±5.1
Activated Partial Thromoboplastin Time (sec) (Mean± SD)	34.6±5.6
Histopathological Characteristics	Bile Duct Plugging 34 (85) Bile Duct Proliferation 40 (100) Portal Bridging and Fibrosis 37 (92.5) Hepatocyte Swelling 8 (20) Neutrophils and Lymphocytes 26 (65)
Ultrasound Abdomen	Non Visualized Gall Bladder 12 (30) Atretic Gall Bladder 3 (7.5) Partially Contracted Gall Bladder 8 (20) Contracted Gall Bladder 9 (22.5) Triangular cord Sign 5 (12.5) Cyst, Small Volume GB, Bile duct abnormalities 1 (2.5) each

KHPE and ALT (0.372, *p*-value<0.01) and STB with AST (0.355, *p*-value<0.01). Serum albumin levels were 36.4±3.7g/l and PT and APTT levels were 16.7±5.1 sec and 34.6± 5.6 sec, Hb 9.5±1.2, TLC 14.8±7.4, Platelets of 363.5±168 respectively.

HIDA scan was done in twenty-three patients with 100% sensitivity. USG Abdomen was suggestive in twenty-four (60%) patients with a non-visualized GB in twelve (30%), contracted gall bladder with intact CBD in nine (22.5%) and triangular cord sign in five patients.

Results of intraoperative cholangiogram were studied in patients undergoing KHPE. Type 3 biliary atresia with atretic GB and biliary channels, and absent

biliary channels with atretic GB was seen in eighteen (45%) and six (15%) patients respectively. Type 2a or cystic EHBA was seen in three (7.5%) patients followed by atretic hepatic ducts and intact GB in three (7.5%) of the infants.

One-year follow-up of patients who had undergone Kasai revealed that ten patients (33.3%) were doing well, five (16.7%) of the patients had expired or had developed portal hypertension each whereas none of the patients were doing well in Non-Kasai group and five (50%) had expired by one year of age (Table-III).

A statistically significant difference between follow-up of patients who had undergone KHPE and without KHPE with a *p*-value<0.05. Kaplan-Meier survival analysis of one year revealed a significant difference in survival ratio of patients undergoing Kasai and those without KHPE, x^2=10.04, *p*<0.001(Figure).

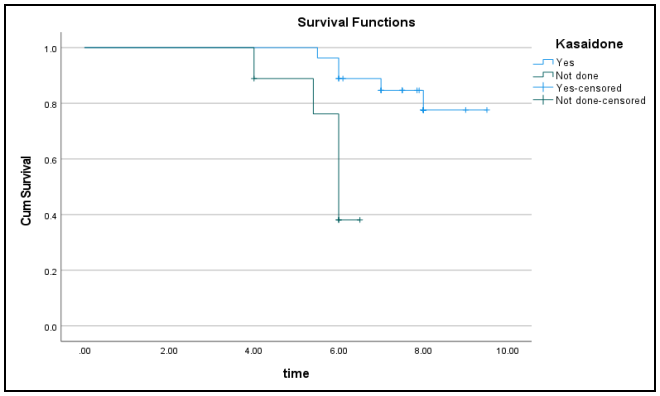

Figure: Graph Showing One-year Survival of Patients with KHPE and Without KHPE

There was a significant difference in serum total bilirubin levels; Pre-Kasai STB (159.82±57.38) and Post Kasai STB (67.43±84.06); t (29) =5.61, *p*=<0.01. (Table-IV)

DISCUSSION

Recent advances in BA are more focused on the etiology, pathogenesis and standardization of a non-invasive diagnostic indicator and treatment.[3] The outcome of KHPE has been appraised in context of age of intervention and hence the chances of native liver survival post KHPE.[13] Biliary Atresia is more common in Asian countries but very little data is available regarding the clinical characteristics and outcomes of KHPE in our region.[6]

Our study showed a predominant male gender distribution which is in accordance with a study conducted at a tertiary care centre of Egypt. Most of the previous studies showed a female predominance,[14] including Japanese registry where 63% of the patients were female and males were only 37%.[15]

The syndromic variety of Biliary Atresia is defined to occur in association with congenital malformations. Our study showed an increased incidence of BASM in comparison with other studies where there was greater occurrence of CHD only.[14] The presence of extra hepatic associations did not significantly affect the follow up outcomes.

The average age of Kasai surgery as per our study was 94 days with an average success rate of 66.6% highlighting the importance of KHPE even at 3 months of life. Yassin *et al*. also reported that the average age of KHPE was 80 days with no impact on outcome.[16] Kumar *et al*. reported 36.7% patients to have cleared their jaundice by 6 months of age out of which 55.6% were operated before 60 days.[17] Studies also show that using newborn screening with total and direct bilirubin levels may help in earlier diagnosis.[18]

Table-III Comparison of One-Year Outcomes of Patients with Kasai and Without Kasai Procedure (n=40)

Outcomes	Patients with KHPE n(%)	Patients without KHPE n(%)	*p*- value
Doing well	10 (33.3)	0 (0)	<0.01
Expired	5 (16.7)	5 (50)	
Failure to thrive	0 (0)	2 (20)	
Synthetic Dysfunction	2 (6.7)	0 (0)	
Portal Hypertension	5 (16.7)	1 (10)	
Hypersplenism	2 (6.7)	1 (10)	
Transplant	3 (10)	0(0)	
Lost to follow-up	3 (10)	1 (10)	

Table-IV Comparison of Bilirubin Levels (n=30)

Characteristics	KHPE (Pre-Kasai) (n=30)	KHPE (Post-Kasai) (n=30)	*p*-value
Serum Bilirubin levels (Mean±SD)	159.82±57.38	67.43±84.06	<0.001

The efficacy of ultrasonography (USG) as a screening test for diagnosing biliary atresia amongst infants with neonatal cholestasis was also assessed by another study which showed a specificity of 77%.[19] As per our study, USG Abdomen findings were suggestive of biliary atresia in 60% of patients with triangular cord sign seen amongst 20.8% of the cases with positive ultrasonography findings. Khayat A *et al*. retrospectively reviewed that patients should be referred for surgical opinions even when late as their survival rates were comparable with other groups which was supported by our study too.[14]

CONCLUSION

Intervention in the form of KHPE significantly contributes towards an improved outcome in patients with Biliary Atresia.

Conflic of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

RN & FI: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

B & SI: Study design, drafting the manuscript, critical review, approval of the final version to be published.

IS & ST: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of

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