

# Jaundice Clearance and Cholangitis in the First Year Following Portoenterostomy for Biliary Atresia

S Selvalingam, FRCS\*, M N Mahmud, FRCS\*\*, C R Thambidorai, FRACS\*, Z Zakaria, FRCS\*\*, N Mohan, FRCS\*\*, Isa, DCP\*\*\*, M Sheila, M Med (Paeds)\*\*\*\*, \*Departments of Surgery & \*\*\*Pathology, Hospital University Kebangsaan Malaysia, \*\*Departments of Pediatric Surgery & \*\*\*\*Pediatrics, Institute Pediatrics, Kuala Lumpur

## Summary

Sixty-one patients with biliary atresia, who underwent portoenterostomy (PE) between 1992 to 1998 in the Institute of Pediatrics, Kuala Lumpur and were followed for a period of one year, were studied to analyze the factors associated with jaundice clearance and cholangitis following PE. Sex distribution was equal. Majority of patients were Malays. Mean age in days at admission to the surgical ward was 66.90 +/- 23.36 and mean age at PE was 75.85 +/- 24.05. At the end of one-year follow-up, six patients (10%) had died, 35 (57%) developed one or more attacks of cholangitis, 35 (57%) had portal hypertension, eight (13%) liver failure and six patients had esophageal variceal bleeding. Thirty-three patients (54%) had jaundice clearance with a mean clearance time of 85 days after PE.

The study shows that when the ductules in the porta hepatis were < 150  $\mu$  in size, persistence of jaundice after PE and the incidence of cholangitis in the first post-operative year were higher; patients with cholangitis in the first year had lower rate of jaundice clearance. Jaundice clearance was achieved in more patients when their postnatal age at the time of PE was lower but the relationship was not linear. Age at PE also did not have a linear temporal relationship to the incidence of cholangitis and the size of portal ductules.

Prospective, multi-center based local studies on a bigger patient population are needed to identify other indicators of successful outcome following PE. This would help to define the indications for primary liver transplantation in the local population.

**Key Words:** Biliary atresia, Portoenterostomy, Cholangitis, Biliary ductule

## Introduction

Biliary atresia is an idiopathic, progressive and potentially fatal disease. If uncorrected, 90% of patients die before three years of age<sup>1</sup>. Biliary atresia treated by portoenterostomy (PE) or Kasai

operation has been shown to have a five-year survival of 30% to 75%<sup>1</sup>. In Malaysia, Kasai operation currently remains the primary treatment for biliary atresia.

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Corresponding Author: C R Thambidorai, Department of Surgery, Hospital University Kebangsaan Malaysia, Jalan Tenteram Cheras, 56000 Kuala Lumpur

Cholangitis is a frequent complication following PE in patients with biliary atresia and adversely affects the long-term outcome<sup>2</sup>. Cholangitis frequently occurs within the first few months after surgery. In patients followed up for five years after Kasai operation, most attacks of cholangitis occurred between 1.5 to 19 months after surgery<sup>1</sup>. Cholangitis contributes to poor bile flow and development of liver cirrhosis.

Jaundice clearance has often been used to evaluate the success of PE. Ten-year survival rates from 73% to 92% have been reported in infants in whom jaundice cleared following PE<sup>3</sup>. Patients in whom jaundice remained and bile flow was inadequate, the three year survival rate fell to 20%<sup>3</sup>. We analysed the factors associated with cholangitis and persistent jaundice following PE in this study.

## Materials and Methods

This is a retrospective study involving 61 patients. These patients had been followed-up for at least one year, following Kasai operation performed at the Institute of Pediatrics, Kuala Lumpur, from January 1992 to January 1998. The protocol for the investigation of suspected biliary atresia included blood tests to detect congenital infections known to cause neonatal jaundice, hypothyroidism and alpha-1-antitrypsin deficiency. Liver function tests were done in all patients. Ultrasound and HIDA scans were performed to evaluate the biliary tree. Patients in whom biliary atresia could not be excluded underwent either a percutaneous transcholecystic cholangiogram or an on-table-cholangiogram (OTC). On confirmation of biliary atresia, the Kasai procedure was performed. The portoenterostomy was done without an external stoma. A 45cm. Roux en-Y intestinal segment was anastomosed, end to side at the porta hepatitis. All patients had a liver biopsy and biopsy of the tissue from the portal mound. Post-operatively, the patients were followed up in the surgical clinic for a minimum period of one year and evaluated by a pediatric surgeon. As there was no definite policy in the

unit with regard to use of prophylactic oral antibiotics after Kasai operation, the patients receiving antibiotics were not identified in this study. All patients received fat-soluble vitamins during follow-up.

The following data were collected for each patient: sex, race, age at which jaundice was first detected, age on admission to the surgical ward and age at Kasai operation. The size of the bile ductule remnant at the porta hepatitis was measured (in  $\mu$ -microns) from the portal mound specimen. During the follow-up at monthly intervals, complications including cholangitis, upper gastrointestinal bleed, liver failure and portal hypertension were noted. Portal hypertension for this study purpose was defined as the presence of one or more of the following features: splenomegaly with dilated veins in the abdominal wall, hematemesis due to documented varices or presence of ascites with normal albumin levels. Liver failure was defined as low albumin levels (<25g/L) or prolonged prothrombin time uncorrected by administration vitamin K or failure to thrive in the presence of adequate oral intake. Jaundice clearance was defined as the absence of clinical jaundice with a total serum bilirubin of less than 18 $\mu$ mol/L. Cholangitis was defined as the presence of fever and leukocytosis (without any other obvious cause) associated with either a rise in direct bilirubin or elevated serum levels of liver enzymes, or passage of stools paler than before the onset of fever. A positive blood culture was not mandatory for the diagnosis<sup>2</sup>.

For statistical analysis, student's t-test was used for continuous variables and chi-square test, for categorical variables. Fischer's exact test was used when the data were sparse.

## Results

### Characteristics of the study group

There were 39 (64%) Malay infants, 16 (26%) Chinese and 6 (10%) Indians. Sex ratio was equal among the three races. Mean age on admission to the Institute of Pediatrics was 66.90 +/- 23.36 days

and mean age at PE was 75.85 +/- 24.05 days. At the time of PE, 20 patients (33%) were less than 60 days old (Group 1), 24 (39%) were between 60 to 89 days of age (Group 2), 14 (23%) were between 90 to 120 days of age (Group 3) and 3 patients (5%) were more than 120 days old (Group 4). Although not statistically significant, there was a tendency for Malay and Indian patients to present at an older age. At the time of presentation to Institute Pediatrics, all patients had pale stools and dark- coloured urine. Thirty patients (45%) had splenomegaly and the incidence of splenomegaly was the same in all age groups (about 45%). None of the patients had clinical ascites on admission. All patients had elevated total and direct bilirubin levels. Mean albumin level was 41.1 +/- 5.14 gram/L and alkaline phosphatase levels varied between 98 U/L - 885 U/L with a mean of 398.2 +/- 256.6 U/L.

At the end of the one-year follow-up, 33 patients (54%) had jaundice clearance, 35 patients (57%) had cholangitis, 35 patients (57%) had portal hypertension, eight patients (13%) had liver failure and six patients (10%) developed gastrointestinal bleeding due to oesophageal varices. Six patients (10%) had died. Of the six patients who died, five died of liver failure and one of cholangitis.

When the patients were grouped according to age at operation (Groups 1 - 4) there was no statistical difference in the rate of jaundice clearance between the various groups. The mean age of patients who had jaundice clearance was 75.45 +/- 23.15 days compared to 76.32 +/- 25.49 days in those with persistent jaundice. ( $p > 0.05$ ) However, patients operated after 90 days of age had a clearance rate of only 28% compared to patients operated before 90 days of age, who had a 72% jaundice clearance rate. Among the 33 patients who achieved clearance, the mean clearance time was 85 +/- 39 days (2.85 +/- 1.38 months) after surgery. There were six patients who took six months to achieve jaundice clearance.

Among the 35 patients with postoperative cholangitis, 8 patients had more than one episode of cholangitis while 27 patients had only one episode, during one year of follow-up. Eighteen patients developed cholangitis within three months after PE, 14 patients between three to six months and in 3 patients cholangitis occurred six months after surgery. Cholangitis developed in 23% of Group 1 patients compared to 77% in the other groups. However, there was no statistical difference in the rate of cholangitis between the various age groups. The mean age at the time of PE for patients who developed cholangitis was 80.29 +/- 26.48 days compared to 69.88 +/- 19.24 days in those with no cholangitis. ( $p > 0.05$ ). It was also noted that patients with post-operative cholangitis had a significantly lower jaundice clearance rate (37%) compared to patients who did not develop cholangitis (77%). ( $p < 0.05$ ). This was more obvious among infants with 'early onset' cholangitis, which is defined as cholangitis occurring within three months after PE<sup>3</sup>. Ninety one percent of such infants had persistent jaundice. On the contrary, when cholangitis occurred more than three months after PE, only 23.5% of infants had persistent jaundice.

Patients were divided into two groups based on size of the biliary ductules, assessed from the tissue taken in the portal mound: 38 patients (62%) had ductule size more than or equal to 150  $\mu$  and 23 patients (38%) had size less than 150  $\mu$ . The mean ductule size among those with jaundice clearance was 240.26 +/- 118  $\mu$  and in those without jaundice clearance was 122.61 +/- 95.64  $\mu$  ( $p < 0.01$ ). Patients with ductule size more than or equal to 150  $\mu$  had a significantly higher jaundice clearance rate (76%), compared to patients with ductule size less than 150  $\mu$  who had only 17% jaundice clearance rate ( $p < 0.05$ ). Patients with ductule size more than or equal to 150  $\mu$  also had a significantly lower cholangitis rate (45%), compared to patients with ductule size less than 150  $\mu$ , 78% of whom had cholangitis. ( $p < 0.05$ ). On further analysis, 47.1% of patients with early onset cholangitis had ductule size less than 150  $\mu$

compared to 26.4% of patients who developed cholangitis more than three months after PE ( $p>0.05$ ). Multivariate analysis showed the ductule size to be an independent predictor of cholangitis and jaundice clearance. However, the jaundice clearance rate as well as the size of the portal ductules did not show any temporal relation to the age of patients at PE.

## Discussion

Our study has shown that after PE, 54% of patients studied had jaundice clearance. Fifty-seven percent of patients developed post-operative cholangitis within one year of surgery. A significant proportion of patients with 'early onset' cholangitis (cholangitis occurring within three months after PE) had persistent jaundice. Although jaundice clearance rates decreased with increasing postnatal age at PE, the relationship was not directly linear. Patients who had biliary ductules at the porta  $< 150 \mu$  in size, were more likely to have persistent jaundice and also to develop cholangitis within the first year following PE. The lower rate of jaundice clearance when the diameter of the biliary ductules was  $<150 \mu$ , has been documented previously<sup>3</sup>.

Cholangitis is the most common complication seen following PE and is known to have a negative impact on the long-term results<sup>2,4</sup>. The reported incidence of cholangitis ranges between 40 - 60%. 'Early-onset' cholangitis is said to result from insufficient volume of bile flow and a partially obstructed biliary tree<sup>2,5</sup>. The poorer outcome following PE in patients who develop cholangitis is likely to be due to progressive damage to the biliary ductules and hepatic parenchyma with each attack of cholangitis.

The lack of linear relationship between age at PE and i) jaundice clearance rate, ii) incidence of cholangitis and iii) the size of the remnant portal ductules has also been noted in other studies<sup>6-11</sup>. A single center study based on 205 patients has shown that sparsity or absence of ductules at the porta hepatis and absence of portal inflammation

were predictors of poor outcome following PE<sup>6</sup>. These histological features may represent the "burnt out" end result of the disease process. Macroscopic appearance at portoenterostomy (MAP), based on liver consistency, size of portal remnants, grade of portal hypertension and associated extrahepatic anomalies have been used to calculate a MAP score. MAP score has shown statistically significant correlation with postnatal age at PE but the actual degree of association between the two was only moderate<sup>8</sup>. Although increased bile excretion and short-term good outcome were related to early operation, there was a plateau effect in which decreasing age had a diminishing effect on outcome<sup>6,8</sup>. Data from biliary atresia registry also showed similar effect<sup>9</sup>. This implies that factors other than age at PE may determine the degree of liver damage<sup>8-10</sup> and it is postulated that although biliary atresia is a progressive disease, the progression with age is not uniform and there is an unknown effect of prenatal period in the evolution of the disease<sup>8</sup>.

In conclusion, our study has reiterated that the size of the biliary ductules in the porta hepatis gives a good indication of jaundice clearance rate and the incidence of cholangitis following PE. Even though PE at an early age gives better jaundice clearance and reduces the incidence of cholangitis, age alone is not an accurate predictor of outcome. Prospective and multi-center based local studies on a bigger patient population are needed to identify other indicators of successful outcome following PE. This may help to define the indications for primary liver transplantation in the local population.

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