Factors Influencing Outcome after Hepatic Portoenterostomy for Biliary Atresia: A Logistic Regression Analysis

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Background/Objective: *The association of many factors with the outcome in Biliary atresia (BA) after hepatic portoenterostomy has drawn the attention of many pediatric hepatologists and hepatobiliary surgeons. Understanding these factors will become an important subject in prediction of the postoperative status and in indicating further proper management.*
Material and Method: *During the last 9 years, 159 BA babies were treated by hepatic portoenterostomy. The authors reviewed the following factors and how they related to outcome: age at operation, total bilirubin (TB) level, type of BA, postoperative bile drainage, hepatic histological features at operation, preoperative and postoperative cholangitis. A multiple logistic regression analysis was used to indicate the factors which significantly influenced the outcome.*
Results: *Of the 159 BA babies, clearing of jaundice confirmed by the color of stool and postoperative serum bilirubin level less than 2 mg % was observed in 54 patients (Group A). Bile drainage with mild jaundice (TB 2-5 mg%) was detected in 65 patients (Group B). The operation failed to create bile flow clinically and biochemically in 40 patients (Group C). Some patients in the last group died during follow-up due to hepatic disease. The multiple logistic regression analysis revealed that the age at operation (> 8 weeks of age), and the presence of portal and parenchymal inflammation at operation significantly related to the failure of portoenterostomy which was followed by portal hypertension with or without esophageal varices. The presence of cholangitis was also significantly related to a poor outcome.*
Conclusion: *The age at operation, portal and parenchymal inflammation and the presence of cholangitis are significant factors which relate to the poor prognosis of BA. Recognition of these will lead to proper long-term management*

Keywords: *Biliary atresia, Prognostic factors, Hepatic portoenterostomy*

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The long term prognosis of biliary artesia (BA) after hepatic portoenterostomy is still controversial. Although jaundice may be relieved in 50-60% postoperatively, there is evidence of continuing liver deterioration in some long-term survivors. Raised portal pressure with subsequent ascites, esophageal varices and liver failure has been recognised. The present study aimed to identify significant factors at the time of the intial corrective procedure and post-operative period which may predict the prognosis in such patients.

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Material and Method

Between 1985 and 2000, 183 babies with biliary atresia were treated by surgery at King Chulalongkorn Memorial Hospital (Fig. 1). The number of patients treated a year had apparently increased in 1991, with

Fig. 1 The number of BA patients operated in each year

nearly double the number seen in 1990, and the number rose to about 20 cases per year after 1992. The authors chose to study the BA patients from April 1991 - March 2000 because all the data could be successfully collected from this group, whereas the data of the patients before 1991 were not complete and the number of patients was small. These 159 babies underwent operative cholangiography to demonstrate the biliary tract. Once the diagnosis of biliary atresia was confirmed, hepatic portoenterostomy was performed for bile drainage. A wedge liver biopsy was taken at the time of operation from the right lobe. The specimens, (liver tissue, fibrous tract and tissue at porta hepatis) were examined by pathologists and then reviewed by the last author (P.S.). Their ages at surgery, type of BA identified intraoperatively, preoperative liver function tests and evidence of preoperative clinical cholangitis were recorded. Bile drainage was evaluated clinically by the color of stool seven days and thirty days postoperatively. The liver function tests were also repeated at the same interval. Any evidence of postoperative cholangitis was also recorded.

The patients were classified into 3 groups according to the clinical level of bile drainage and the postoperative total bilirulin level.

Group A: Bile flow restoration and free from jaundice (Total bilirubin level less than 2 mg%)

Group B: Bile flow restoration with mild jaundice (Total bilirubin level between 2-5 mg%)

Group C: Minimal bile drainage with moderate jaundice (Total bilirubin level more than 5 mg%) or failure to create bile flow (Total bilirubin level not decreased)

The patients in group A and B were evaluated as "satisfactory outcome" while the patients in group C were evaluated as "unsatistactory outcome" The type of BA was classified roughly as:

Type I: obliteration of (distal) common bile duct with patent (proximal) common hepatic duct or cyst of the proximal duct

Type II: total obliteration of the common hepatic duct with residual right and left duct.

Type III: obliteration of the entire extrahepatic bile duct

Type III a: obliteration of the proximal common hepatic and common bile duct with patent (distal) common bile duct

Babies with biliary hypoplasia were not included in the present study since for these, conservative treatment was given without portoenterostomy. Liver transplantation may be offered later to these patients.

Each factor was individually analysed for correlation with the "satisfactory" or "unsatisfactory" outcome. Then all the factors were re-analysed using the multiple logistic regression technique to sort out the significantly related factors from among the many others.

Results

Age at operation: 80 babies were operated upon when they were between 4-8 weeks old and 43 babies were operated upon at the age of 8-12 weeks. Only 11 and 25 patients were treated when they were less than 4 weeks old and more than 12 weeks old respectively (Table 1). Eighty-four of the 91 babies who were operated upon before the age of 8 weeks had a satisfactory outcome, whereas 33 of the 68 babies operated upon after 8 weeks of age had unsatisfactory result (Table 1).

Bilirubin level: Forty of 48 babies whose bilirubin level was less than 10 mg.% had a satisfactory bile flow after operation. Fifty eight of 74 and 21 of 37 patients with bilirubin 10-15 or more than 15 mg% respectively also had a satisfactory results (Tables 2, 3).

Type of biliary atresia: There were 5 cases identified as type I BA and 2 cases as type II. All of them had satisfactory results. Seventy eight of 115 babies with biliary type III BA had satisfactory bile drainage after surgery. It was noticed that there were 37 patients (23.3%) who had an atretic proximal common bile duct but a patent distal bile duct - which was a higher rate than various reports. In this group, 34 had satisfactory outcomes (Table 3).

Hepatic Histology: Unfortunately, the pattern of pathological study and report varied according to

Table 1. The relationship between age at operation and outcome

Total Number	Age at operation (wks)	Outcome (group)		
		Satisfactory		Unsatisfactory
		A	B	C
11	<4	4	7	0
80	4-8	41	32	7
43	8-12	5	23	15
25	>12	4	3	18
159		54	65	40

Table 2. The relationship between preoperative total bilirubin level and outcome

Total Number	Preoperative Total bilirubin level (mg%)	Outcome (group)		
		Satisfactory		Unsatisfactory
		A	B	C
48	5-10	22	18	8
74	10-15	28	30	16
37	>15	4	17	16
159		54	65	40

Table 3. Type of biliary atresia versus outcome post-operatively

Total Number	Type of Biliary Atresia	Outcome (group)		
		Satisfactory		Unsatisfactory
		A	B	C
5	I	5	-	-
2	II	2	-	-
115	III	32	46	37
37	IIIa	15	19	3
159		54	65	40

the attending pathologist. Thus, the study of specific findings could not be completed. Hepatic fibrosis was reported in 90 of 159 cases and showed that all 69 patients who had no fibrosis had satisfactory outcomes.

In 90 patients who had hepatic fibrosis, 50 had satisfactory results but 40 failed to drain bile.

Portal tract inflammation and parenchymal inflammation were reported in 118 and 105 patients respectively. The number of patients in the 2 groups (with inflammation and without) inflammation was nearly the same and the respective outcomes are shown in Table 4.

A statistical analysis was carried out to indicate any possible relationships between the presenting factors and outcomes. Patients were assigned by age into 2 groups, age 8 weeks or less and age more than 8 weeks. The present study revealed that age at operation of 8 weeks or less was significantly related to a good outcome (The odds ratio for AGE was 11.180). The presence of cholangitis, hepatic fibrosis, parenchymal inflammation or portal inflammation also related to a poor outcome (Table 6).

Discussion

The etiology and pathogenesis of biliary atresia are still unknown. The disease is mostly believed to be the result of an inflammatory destruction of the extrahepatic bile ducts accompanied by a variable degree of intrahepatic damage. The process is progressive in untreated cases, the average survival being 11-20 months[1-3]. No attempted surgical treatment had been effective[1] until Kasai introduced the portoen-terostomy in 1959[4]. The restoration of bile flow can now be achieved and there is an increasing number of long-term survivors. Nevertheless, such surgical treatment can not cure all patients. The five-year survival rate still ranges from about 50% to

Table 4. Variations of hepatic histological findings related to outcome of surgery

Total		Hepatic Histology	Outcome (group)		
			Satisfactory		Unsatisfactory
			A	B	C
159	90	Fibrosis (maturity + quantity)	10	40	40
	69	No fibrosis	44	25	0
118	60	Portal tract inflammation	18	22	20
	58	No portal tract inflammation	20	20	18
105	57	Focal parenchymal inflammation	15	24	18
	48	No parenchymal inflammation	20	14	14

Table 5. The relationship between evidence of cholangitis and outcome of surgery

Total	Evidence of cholangitis	Outcome (group)		
		Satisfactory		Unsatisfactory
		A	B	C
83	Present Y	6	42	35
76	Abseent N	48	23	5
159		54	65	40

80%. It is well established that the success rate, in terms of long term survival without jaundice, is inversely related to the age at operation[2,5,6]. Most studies have indicated that the survival rate is higher in patients operated on by eight weeks of age[7,8]. In addition to age, the liver pathology at the time of portoenterostomy may correlate to the outcome. Liver fibrosis, parenchymal degeneration and giant cell transformation seem to be matched with unfavorable results[2,8-10]. Progressive liver deterioration after surgery usually occurs in patients with inadequate bile flow, but it may also occur even though the patient has developed an excellent bile flow[11-14]. This progression has been observed after attacks of ascending cholangitis[15]. Progressive liver damage is manifested by the development of portal hypertension, ascites and esophageal varices. Many correlated factors may be found in the history of such a patient and it may be complicated to determine a truly valuable prognostic indicator.

Portoenterostomy is the key to success in creating bile flow from the existing of small bile canaliculi at the porta fibrous remnant. The drained acini recover and regenerate with ductular proliferation while the undrained ones show scarring and fibrosis. This fibrotic progression may occur before the operation, especially when the operation is performed after eight weeks of life. There have been some observations that a greater size and number[2,16,17] of ductal remnants at the porta hepatis is associated with better results. These studies showed no clear relationship between the timing of surgery or the ductal patency[18], the outcome reflected the ratio between the recovered and damaged liver tissue only. Bile drainage does not always show that the liver tissue is entirely normal. It appears that the timing of onset of BA, the size and number of bile canaliculi or ductules and the liver pathology vary from case to case.

The review of literature revealed that most studies focused their analysis on only individual factors; whereas the authors believed that the outcome of treatment was influenced by multiple factors which could not be analysed by a single

Table 6. Risk estimate according to various factors affecting the outcome

Group comparison	Factors	Odds Ratio Value	95% Confidence Interval		Statistical significant
			Lower	Upper	
>8 wk	Age at op	11.180	4.517	27.669	significant
<12 / >12 mg%	Preop. TB	1.667	0.799	3.475	no significant
Y/N	H. Fibrosis	0.153	0.056	0.417	significant
Y/N	Portal inflammation	0.677	0.600	0.765	significant
Y/N	Parenchymal inflammation	0.217	0.072	0.652	significant
Y/N	Cholangitis	0.050	0.015	0.172	significant

Table 7. Risk estimation for the unsatifactory outcome after multiple logistic regression

Factors	B	Adjusted Odds ratio Exp. (B)	R	Statistical significant
Age at op	2.6761	14.5285	0.3381	significant
Preop. TB	0.0130	-	0.0000	no significant
H.Fibrosis	1.4664	-	0.0000	no significant
Portal inflammation	-8.5051	0.0002	0.0000	significant
Parenchymal inflammation	-2.0598	0.1275	-0.1869	significant
Cholangitis	-2.2406	0.1064	-0.2120	significant

individual factor technique.

Thus, the present study was undertaken to identify valuable prognostic factors among multiple possible related factors. Age at operation was found to show a significant influence on the outcome and even with the logistic regression technique, was still a significant factor.

The finding of inflammatory cells at the porta hepatis or in the remnant did not influence the clinical outcome or the chance of estabistment of bile flow. Only fibrosis of the liver was found to significantly influence the outcome. This finding may explain those patients who were operated on within 8 weeks of age but for whom a satisfactory outcome could not be obtained. Perhaps the liver had already undergone deterioration and fibrosis at the time of operation.

The authors have observed in the liver pathology taken liver transplantation recipients that the same liver pathology is not regularly found over the whole liver. Thus, a large piece of liver is recommended to be taken at biopsy.

In conclusion, using the multiiple regression analytic technique, the factors which significantly influenced the outcome of portoenterostony in biliary atresia are age at operation and hepatic fibrosis presenting at the time of surgery.

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ปัจจัยที่มีอิทธิพลต่อผลการผ่าตัด Hepatic portoenterostomy ในโรคทางเดินน้ำดีตีบตัน โดยการวิเคราะห์แบบ logistic regression

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ความเป็นมา: *ความสัมพันธ์ของปัจจัยต่าง ๆ ที่มีอิทธิพลต่อผลการผ่าตัด hepatic portoenterostomy ในโรคทางเดินน้ำดีตีบตันทำให้กุมารแพทย์โรคตับและศัลยแพทย์โรคตับส่วนใหญ่มีความสนใจที่จะศึกษา การที่เข้าใจปัจจัยต่าง ๆ เหล่านี้จะทำให้มีประโยชน์ต่อการพยากรณ์โรคและการให้การรักษาหลังผ่าตัด*

วัสดุและวิธีการ: *ในระยะเวลา 9 ปี มีเด็กที่เป็นโรคทางเดินน้ำดีตีบตัน 159 คนที่ได้รับการผ่าตัด hepatic portoenterostomy ผู้นิพนธ์ได้ทบทวนปัจจัยต่าง ๆ ที่มีความสัมพันธ์กับผลการผ่าตัดรักษา คือ อายุเมื่อได้รับการผ่าตัดรักษา ระดับซีรั่มของ total bilirubin ชนิดของโรคทางเดินน้ำดีตีบตัน การระบายน้ำดีหลังผ่าตัด พยาธิสภาพของตับเมื่อผ่าตัด การติดเชื้อทางเดินน้ำดีหลังผ่าตัด การวิเคราะห์หาปัจจัยที่มีอิทธิพลต่อผลการรักษาใช้การวิเคราะห์แบบ logistic regression*

ผลการศึกษา: *จากผู้ป่วยทั้งหมด 159 คน ผู้ป่วย 54 คนหายเหลืองและมีระดับซีรั่มของ total bilirubin ต่ำกว่า 2 mg% (กรุ๊ปเอ) ผู้ป่วย 65 คนเหลืองลดลงและมีระดับซีรั่มของ total bilirubin อยู่ระหว่าง 2 ถึง 5 mg% (กรุ๊ปบี) และผู้ป่วย 40 คนที่การผ่าตัดไม่ได้ทำให้ผู้ป่วยมีอาการตัวเหลืองลดลงเลย (กรุ๊ปซี) ผู้ป่วยจำนวนหนึ่งในกรุ๊ปซีเสียชีวิตระหว่างการติดตามการรักษาหลังผ่าตัดจากโรคตับวายเรื้อรังระยะสุดท้าย การวิเคราะห์แบบ logistic regression พบว่าการผ่าตัดหลังอายุ 8 สัปดาห์ไปแล้ว และการพบพยาธิสภาพของตับที่มีการอักเสบบริเวณพอร์ทัล และพาเรนไคมัลเมื่อผ่าตัด มีความสัมพันธ์กับผลการผ่าตัดที่ไม่ได้ผล นอกจากนี้การมีการติดเชื้อทางเดินน้ำดีหลังผ่าตัดก็มีความสัมพันธ์กับการพยากรณ์โรคที่ไม่ดี*

สรุป: *อายุของผู้ป่วยทางเดินน้ำดีเมื่อขณะผ่าตัด พยาธิสภาพของตับที่มีการอักเสบบริเวณพอร์ทัลและพาเรนไคมัลและการติดเชื้อทางเดินน้ำดีหลังผ่าตัดเป็นปัจจัยสำคัญที่มีความสัมพันธ์กับการพยากรณ์โรคที่ไม่ดี ผลจากการศึกษานี้จะทำให้การรักษาในระยะยาวมีความเหมาะสมมากขึ้น*