Original Article

Factors that predict mortality rate in biliary atresia

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Summary:

Background: B.A is a relatively rare obstructive condition of the bile ducts causing neonatal jaundice. The etiology is unknown but is the result of a progressive obliterative process of variable extent. If not treated, B.A is fatal within the first 2 years of life.

Objectives: The aim of this study was to analyze & discuss the impact of many patients' factors on short-term outcome of patients with B.A who underwent Kasai operation in our department.

Methods: A prospective study on 34 patients with B.A surgically managed at pediatric surgical department /Medical City during the period Nov. 2006 to Sept. 2013. The patients were followed-up for 2-3 months and the outcome were evaluated by morbidity and mortality rates according to different patients' parameters (preoperative, intraoperative and postoperative factors) .

Results: the mean age of the infants was (61.6 ± 8.1) days with a female to male ratio of 1.27:1. All the patients had type III biliary atresia. Infants with body weight < 3.5 kg were about 10 folds more likely to die than those with body weight > 3.5 kg. Infants who passed greenish bowel motion at the 4th – 5th postoperative day were about 6 folds more likely to die p.value= 0.026. Infants with postoperative anastomotic leak were about 7 folds more likely to die than those with no leak p.value = 0.013. Strong highly significant correlation had been found among high death rate and reoperation rate ($r = 0.78$ and $p < 0.001$). of the thirty four infants, 24 (70.6%) survived, unfortunately, 10 infants (29.4%) died. the ratio of death to survival was 0.4: 1.

Conclusions: The survival with native liver following drainage surgery for biliary atresia in our center, compared favorably with other international figures. Body weight, significant impaired liver function, severe associated anomalies, anastomotic leak and re-intervention, all, greatly contribute to increase mortality rate of those infants.

Keywords: Biliary atresia BA, Kasai operation, Cholangitis, Cirrhosis.

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Introduction:

B.A is a relatively rare obstructive condition of the bile ducts causing neonatal jaundice. It occurs in between 1- 10,000 to 1 - 18,000 live births. With slight female predominance, female to male ratio ranging between 1.4 to 1.7:1(1).

Microscopically, the biliary tracts contain inflammatory and fibrous cells surrounding miniscule ducts that are probably remnants of the original embryonic duct system. The liver parenchyma is fibrotic and shows signs of cholestasis. Proliferation of biliary neoductules is seen and this process develops into end-stage cirrhosis if good drainage cannot be achieved(2).

Despite intensive interest and investigation, the cause of B.A remains unknown. Two different forms are described : either Syndromic B.A (embryonic type) (10% to 20%), the other form is Non-syndromic B.A (perinatal type) may have its origins later in gestation (2).

The cardinal signs and symptoms of B.A are: Jaundice (persists beyond 2 weeks of life), Clay-colored stools and dark brown urine .

Before Kasai described his operation in 1959 and it became worldwide known in 1968, BA was a lethal disease for most patients, except for the rare "correctable" cases(5).

The major complications after Kasai operation: cholangitis (40%), cessation of bile flow, portal hypertension. The major determinants of satisfactory outcome after portoenterostomy are: age at initial operation (before 60 days of age), successful achievement of postoperative bile flow, presence of microscopic ductal structures at the hilum (>150 mm in diameter), the degree of parenchymal disease at diagnosis and the technical factors of the anastomosis. Liver transplantation should be indicated for liver failure of initial portoenterostomy with no bile drainage and progressive liver disease; episodic or inefficient bile drainage with slow deterioration of liver function and development of growth failure and the development of one or more complications of chronic liver disease such as cholangitis or portal hypertension that cannot be easily managed despite an apparently functional portoenterostomy (1,2).

Patients and Methods:

A prospective hospital based study of 34 infants (15male and 19female) with B.A were studied. Patients were surgically managed at the Department of Pediatric Surgery /Children Welfare teaching hospital / Medical City / Baghdad from November 2006 to September 2013.

The patients were followed for 2-3 months and the outcome was evaluated by morbidity and mortality during this period. It was difficult to follow the patients who were doing well

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or died for long term because of social and cultural reasons. We evaluated patient's factors that may be associated with morbidity and mortality of these cases.

Preoperative factors (age and weight of the patient, type of presentation, total serum bilirubin level, liver enzymes, PT and PTT level, associated anomalies and ultrasonography findings) . Intraoperative factors (small or atretic gallbladder, presence or absence of the common bile duct, operable/inoperable and associated predoudenal portal vein, polysplenia and asplenia)

Postoperative factors (time of passing greenish bowel motion postoperatively, decline of TSB, anastomotic leak, cholangitis, histopathological result of the liver biopsy and mortality)

Abdominal ultrasonography was the cornerstone for diagnosis of biliary atresia in our study. The finding of atretic gallbladder associated with absence of common bile duct or small non-contractile gallbladder associated with atretic or patent distal common bile duct were frequently encountered . All of our patients were managed by Kasai operation. Postoperatively, the patients received intravenous antibiotics, ursodeoxycholic acid capsule (dose of 10-15mg/kg/day), hydrocortisone vial (10mg/kg/dose) twice daily or methylprednisolone vial (1.5-1.7mg/kg/day) and then {prednisolone tablet (1-3 mg /kg/day), fat-soluble vitamins (a, d, e, and k)} at discharge.

Statistical analysis: By using statistical package for social sciences version 20, IBM.US, Data were entered and analyzed with appropriate statistical tests and procedures. Descriptive statistics were presented as frequency and proportion for all variables, additionally, the mean age was calculated. Analytic statistics for the correlation of the outcome with the different parameters were performed by using cross-tabulation and bivariate analysis. Odds ratio and the 95% confidence interval (95%CI) were calculated to estimate the risk of each parameter in relation to the outcome and the significance of the correlation was assessed by using chi square test to find the significance (P.value) of the correlation. In some variables where the odds ratio couldn't be calculated, bivariate analysis was used and the correlation coefficient (R) was calculated in addition to P.value.Level of significance (P.value) of $\leq$ 0.05 indicated a significant correlation. The value of R of $<$ 0.4 indicated weak correlation, 0.4 – 0.7 indicated moderate correlation and $>$ 0.7 indicated strong correlation. Finally Results and findings of this study were presented in tables and figures with appropriate explanatory paragraph for each by using Microsoft office software.

Results:

Kasai operation was done to 34 infants (19 female ,15 male) who had B.A (type III) were included in this study, patient's factors that predicted higher mortality rates were:

Weight: Body weight of the infant of $<$ 3.5 kg was significantly associated with higher mortality, 6 of 9 infants (66.7%) whose weight $<$ 3.5kg died compared to 4 of 25 infants (16%) of those weighed $>$ 3.5 kg. The odds ratio was 10.5 and the 95% confidence interval was (1.8-50.5), P.value =0.009. This indicates that infants with body weight $<$ 3.5 kg were about 10 folds more likely to die than those with body weight $>$ 3.5 kg.

Passing greenish bowel motion at the 4th – 5th post-operative day: It was significantly associated with higher mortality than other time, 54.5% of infants who passed greenish bowel motion at the 4th – 5th postoperative day were died and 45.5% survived [odds ratio 5.7] , [95%CI =1.15-28.3] and P.value= 0.026 . This indicates that infants with this parameter were about 6 folds more likely to die, and this parameter was significant predictor of mortality.

Post-operative anastomotic leak: This parameter was a significant predictor of high mortality rate. Infants with post-operative anastomotic leak were about 7 folds more likely to die than those with no post-operative anastomotic leak [odds ratio=7], [95%CI =1.36-36.1] and P.value= 0.013.

Elevated liver enzymes: It was significantly correlated with higher mortality rate; all dead infants had elevated liver enzymes, while none of those with normal liver enzymes died [R= -0.36, P=0.038].

Syndromic presentation: It was significantly correlated with higher mortality rate, 2 patients only with syndromic presentations, both died [R=0.39, P=0.024].

Reoperation : Strong highly significant correlation had been found among high mortality rate and reoperation , all the 6 patients who needed reoperation died compared to those who didn't need reoperation [R=0.78, P<0.001] .

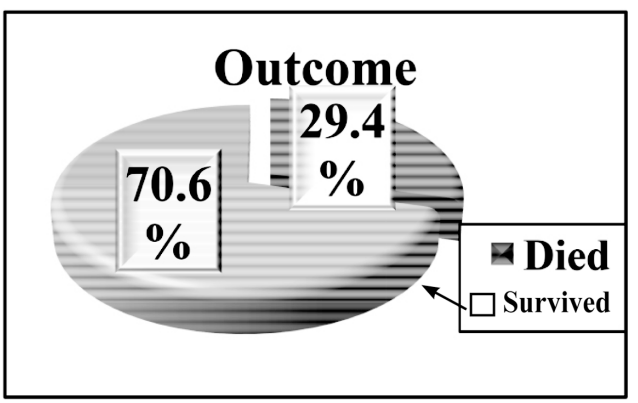

Figure 1. Outcome of the 34 infants with biliary atresia underwent Kasai operation

Table1. Correlation between outcome and patient's parameters of the 34 operated infants with biliary atresia.

Parameter	Died		Survive		Total		Odds ratio (95%CI) *	P
	No.	%	No.	%	No.	%		
Age (months)								
< 2	4	40.0	6	60.0	10	100.0	2(0.42-.58)	0.64
2 – 4	5	23.8	16	76.2	21	100.0	0.5(0.11-2.3)	0.60
> 4	1	33.3	2	66.7	3	100.0	1.2 (0.1-15.3)	0.61
Gender								
Female	7	36.8	12	63.2	19	100.0	2.3 (0.5-11.2)	0.45
Male	3	20.0	12	80.0	15	100.0		
Weight (kg)								
< 3.5	6	66.7	3	33.3	9	100.0	10.5 (1.8-50.5)	0.009
>3.5	4	16.0	21	84.0	25	100.0		

Table2. Correlation between outcome and liver function test of the 34 operated infants with biliary atresia.

Parameter	Died		Survive		Total		Odds ratio (95%CI)*	P
	No.	%	No.	%	No.	%		
Total serum bilirubin								
< 10	3	18.8	13	81.2	16	100.0	0.36 [0.1- 1.7]	0.36
> 10	7	38.9	11	61.1	18	100.0		
Liver enzymes								
Elevated	10	38.5	16	61.5	26	100.0	R= 0.36	0.038
Normal	0	0.0	8	100.0	8	100.0		
Prothrombin time /partial thromboplastin time (PT/PTT)								
Elevated	8	42.1	11	57.9	19	100.0	3.16 [0.58-17]	0.33
Normal	2	13.3	13	86.7	15	100.0		

Table3. Correlation of outcome with presentation and ultrasound findings of the 34 operated infants with biliary atresia.

Parameter	Died		Survive		Total		Odds ratio (95%CI) *	P
	No.	%	No.	%	No.	%		
Presentation								
Associated	1	33.3	2	66.7	3	100.0	1.22 [0.1-15.2]	0.61
Classical	9	29.0	22	71.0	31	100.0		
Syndromic	2	100.0	0	0.0	2	100.0	R=0.39	0.24
Ultrasound findings								
Atretic G.B**, absent CBD***	6	35.3	11	64.7	17	100.0	1.77[0.4-7.9]	0.7
Small G.B, Absent CBD	1	9.1	10	90.9	11	100.0	6.43[0.7-59.2]	0.21
Small G.B, distal normal CBD	3	50.0	3	50.0	6	100.0	0.33 [0.1, 2.1]	0.46

Table4. Correlation of outcome with operative findings and liver biopsies of the 34 operated infants with biliary atresia.

Parameter	Died		Survive		Total		Odds ratio (95%CI) *	P
	No.	%	No.	%	No.	%		
Operative finding								
Absent GB, CBD	6	30.0	14	70.0	20	100.0	1.77 [0.40-7.93]	0.7
Small GB, absent CBD	1	10.0	9	90.0	10	100.0	5.40[0.58-49.98]	0.23
Small GB, Normal CBD	2	50.0	2	50.0	4	100.0	0.10 [0.02-0.58]	0.01
Liver biopsy								
CLD****	4	28.6	10	71.4	14	100.0	0.93 [0.21-4.20]	0.80
CLD mounting cirrhosis	2	16.7	10	83.3	12	100.0	0.35[0.06-2.01	0.41
Cirrhosis	3	42.9	4	57.1	7	100.0	2.14[0.38-12.05]	0.68

Table5. Correlation of outcome with postoperative follow up of the 34 operated infants with biliary atresia.

Parameter	Died		Survive		Total		Odds ratio (95%CI) *	P
	No.	%	No.	%	No.	%		
Postoperative day passing greenish bowel motion								
2nd - 3rd	1	6.7	14	93.3	15	100.0	0.08[0.01, 0.73]	0.027
4th - 5th	6	54.5	5	45.5	11	100.0	5.70[1.15-28.33]	0.026
> 5th	3	37.5	5	62.5	8	100.0	1.63[0.31-8.68]	0.89
Post operative total serum bilirubin								
Decline	6	24.0	19	76.0	25	100.0	0.39 [0.08-1.96]	0.47
Not	4	44.4	5	55.6	9	100.0		
Post operative anastomotic leak								
Yes	7	53.8	6	46.2	13	100.0	7.00 [1.36-36.1]	0.013
No	3	14.3	18	85.7	21	100.0		
Postoperative Cholangitis								
Yes	5	27.8	13	72.2	18	100.0	0.89 [0.31-2.52]	0.87
No	5	31.2	11	68.8	16	100.0		
Reoperation								
Yes	6	100.0	0	0.0	6	100.0	R=0.78	<0.001
No	4	14.3	24	85.7	28	100.0		

*(95%CI) = 95% confidence interval of the odds ratio
**G.B=gallbladder
***CBD=common bile duct
****CLD=cholestatic liver disease

Discussion:

The mean age of the infants at time of Kasai operation was (61.6 ± 8.1) days, which is very close to other international studies that range from 55-65 days(6). The older age group (≥ 4 months) was associated with 1.2 fold of death more than the other groups [P.value = 0.61] , which did not significantly affect the mortality rate. Numerous reports have been published regarding the impact of age at Kasai operation(7). Although many researchers advocated the advantage of early operation(8), some noted an adverse effect of early operation, especially during the first month of life(9).. In a Japanese review(10), the age at operation appeared to be the most predictive factor for long term outcome; 10 years survival for patients who were diagnosed prior to age of 60 days was 68% and for patients diagnosed after age 91 days was 15% , and 0% in age >150 days in Sedani series and French national series(11).

French investigators of children older than 3months of age at diagnosis suggest that liver histology and general degree of liver disease are more predictive of outcome than age alone12. There were 19 females (55.9 %) and 11 males (44.1%) in this study forming female to male ratio of 1.27:1.15, and this compare favorably to a study by (Ho Yu Chung Kenneth 2008 (13). Our study was nearly compatible with most of the studies that described the slight female predominance(1,2). The majority of infants in this study weighed > 3.5 kg at the time of Kasai operation; which represent 25 infants (73.5%). The infants with body weight less than 3.5 kg was significantly associated with higher mortality and about 10 folds more likely to die than those with body weight > 3.5 kg [P.value =0.009] . Ruža Grizelj, et al. 2010 (14) & Elisa de Carvalho 2010 (15) stated the mean body weight at the time of kasai operation of 3.2 kg and 3.1 kg , respectively with no significant association with mortality rate . The late age of presentation, association with malnutrition and lack of postoperative nutritional support may be contributed to this variation. The decline in total serum bilirubin postoperatively was reported in 19 patients (76%). Six patients (24 %) of them died [P.value =0.47] which is not significant. Woung et al. showed that considerable percentage of patients over 60days of age achieved excellent surgical outcome and that age up to 100 days has no obvious impact on surgical outcome (16 17) . B.A with associated anomalies (congenital heart disease, polysplenia / asplenia, predoudenal portal vein & situs inversus) , was reported in 2 infants (5.9%) and both of them died [R=0.39], [P.value =0.24] . B.A splenic malformation syndrome (BASM) have the worst prognosis in contrast to non-syndromic B.A(6 18). All of the 34 patients had type III BA. In a study of Gong Chena, et al. 2012 (17), they argued that 490 patients of a total number of 519 patients had type III BA. According to Willemien de Vries study 2008 (18), it was reported that around 80% were of type III BA. The above variation may be due to the difference in the samples size among studies. Liver biopsy was performed in 33 of the studied 34 infants. It was found that 14 (41.2%) had cholestatic liver disease, 12 infants (35.3%) with cholestatic liver disease mounting liver cirrhosis and 7 infants (20.6%) were found to have liver cirrhosis. A Brazilian study of B.A conducted by Elisa de Carvalho, et al. 2010 (15) demonstrated variable

histopathological findings of bile plug, proliferation and fibrosis in 93.8 %, 93.2 % & 84.1% respectively. postoperative anastomotic leak was a significant predictor of high mortality rate, infants with postoperative anastomotic leak were about 7 folds more likely to die than those with no postoperative anastomotic leak [odds ratio=7] ,[95%CI 1.36-36.1] and P.value= 0.013 . Thirteen patients developed postoperative anastomotic leak, 7 patients died .In a study of mortality of BA in children not undergoing liver transplantation in Netherlands at 2010 (19) explained 7% of the patient who died was related to technical complications (anastomotic leaks) .The higher mortality rate in those patients may be due to higher rate of reoperation without waiting on conservative treatment, as the total parenteral nutrition was unavailable. Post- operative cholangitis occurred in 52.9% , five patients (27.8 %) died , (odds ratio=0 , P.value= 0.087) , while Ruža Grizelj , et al. 2010 (14) reported postoperative cholangitis rate of 42.8% , Ho Yu Chung, et al. 2008 (13) 23.1 % . This is because evidence of steroid usage after Kasai operation was not firmly established and there is still no standard protocol regarding the optimal dosage. Steroid due to its anti-inflammatory action help to reduce ductal inflammation and edema, making subsequent fibrosis and sclerosis less prominent beside it is believed to have choleretic effect (13 20). Twenty four patients (70.6%) survived with ratio of mortality rate to survival rate of 0.4:1 and this compare favorably to other studies by Way-Seah Lee, in Malaysia (21) and Christophe Chardot 2009 (5),they found that the overall survival rates of patients with BA with their native liver were 40% and 72-89% respectively .

Conclusion:

The survival with native liver following drainage surgery for biliary atresia in our center compare favorably with other international study. Body weight, significant impaired liver function, severe associated anomalies, anastomotic leak and re-intervention, all, greatly contribute to increase mortality rate of those infants.

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