ORIGINAL ARTICLE

GMJ.2014;3(2):109-14
www.gmj.ir

Received: 24 Sep 2013
Revised:13 Oct 2013
Accepted: 19 Oct 2013

Long-term Outcome of Kasai Operation on Children with Biliary Atresia between 2001-2010 (1380-9) in Namazi Hospital, Shiraz, Iran

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Abstract

Background: Biliary atresia is a 100% fatal disorder without any treatment in infants as a leading cause of cirrhosis and Kasai operation, as the only operative choice, which plays a crucial role in increasing their rate of survival. Nonetheless, many patients end up with liver transplantation in the future owing to various inevitable hepatic and biliary problems which do remain after the Kasai operation. In this study, we aimed to assess the prognosis and influential factors on the outcome of this procedure on children attending Shiraz Namazi Hospital. **Patients and Methods:** A database of medical records of 61 patients (F=41, M=20) with biliary atresia, aged between 30 to 100 days (65.27±18 days) at the time of operation, who had undergone the Kasai operation in Shiraz Namazi Hospital from 2001 to 2010 was examined in a retrospective review. Risk factors of failure (death and liver transplantation) were analyzed by Kaplan-Meier test. **Results:** Age at the operation time, type of atresia, and dilatation of the bile ducts were identified as the risk factors; 29 patients had signs of hepatomegaly, 6 patients had liver transplantation. Among them, 3 survived. **Conclusion:** Of the patients, 61% with biliary atresia survived for more than 5 years with their native liver while the overall survival rate among 52 patients was 85.30±5.96 months. Postoperative care and regular checkups should be considered for all survivors as a lifelong procedure to prevent any possibilities of future hepatic deterioration. **[GMJ.2014;3(2):109-14]**

Keywords: Biliary Atresia; Kasai Operation; Liver Transplantation; Outcome

Introduction

Even though biliary disorders are not common among children, their threatening high rate of morbidity and mortality in the case of occurrence calls for accurate and precise diagnosis and urgent intervention [1]. Among such conditions, biliary atresia (BA), a progressive fibro-obliterative cholangiopathy, with the incidence of one in 20,000 live births can be mentioned [2]. This disorder can involve both intra- and extra-hepatic bile ducts and may ultimately lead to cirrhosis and portal hypertension [3]. Despite the massive investigations, the exact pathologic process is still unclear, but some underlying causes such as abnormalities in development of bile ducts, immune system, and bile acid production as well as viral infections have been suggested [4]. Biliary atresia can be 100% fatal if no in-

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tervention is done. Clinical management is a primary portoenterostomy (Kasai procedure), which is designed to repair the bile flow and improve jaundice in cases with extra-hepatic biliary atresia [3,4]. Introduced 50 years ago in Japan, Kasai operation is an operative treatment with the purpose of regaining the bile duct flow and consequently improving the jaundice and minimizing the cholangio-destructive process in the liver [5]. Patients who suffer from intra-hepatic bile duct atresia are more likely to develop cirrhosis and thus need earlier liver transplantation. In addition, cases of extra-hepatic bile duct atresia, whose Kasai operation fails or have already developed cirrhosis, are other likely candidates of liver transplantation [3]. Problems regarding liver transplantation are shortage of donor and complications pertaining to immunosuppressive therapies [4]. The rate of success in this operation depends largely on the time of the intervention which means that the earlier the operation is done after birth the higher the survival chance will be [6]. Therefore, infants who have persistent jaundice should be under careful observation to allow an acceptable and adequate investigation for timely detection of this condition [7]. The other influential factor is that the operation achieves its best results if the surgery is performed before the liver comes close to a cirrhotic state. The outcome also depends on skillfulness of the surgeons. Given these conditions, half of the patients are expected to enjoy a long-term survival and a good quality of life in succeeding years [4]. Briefly, Kasai is the only surgical choice for early treatment, after which two thirds of patients regain their biliary flow, but unfortunately only one third live up to one decade with their own livers and the rest of the patients are obliged to undergo liver transplantation, making this disorder as the number one cause of liver transplantation in children. Both of these procedures together help the patients have a survival rate of 90% if early referral and proper specialist care are met [8]. In regards to the importance of biliary atresia and the controversies over the long-term outcome of Kasai operation, we designed this cohort study in Namazi Hospital of Shiraz, as one of the major centers performing Kasai surgery in the south of Iran (an average of 6 cases per year), to evaluate the efficacy of Kasai operations undertaken for young children in this center.

Patients and Methods

This study is a retrospective assessment of medical records of 61 children (F=41, M=20), who had congenital biliary atresia and underwent Kasai operation during the years 2001-10 in Namazi Hospital, Shiraz, Iran. The age of the patients ranged from 30 to 100 days at the time of operation (65.27±18). Parents of the participating infants were asked to sign a consent form prior to the study, approved by the Ethics Committee of Shiraz University of Medical Sciences. Inclusion criteria consisted of either intra- or extra-hepatic biliary atresia, based on the morphological type of biliary atresia, and there was no gender limit for selection of subjects. Exclusion criteria were false initial diagnosis of biliary atresia by colangiography during the operation and also positive history of previous biliary surgery. Diagnosis of biliary atresia was confirmed by cholangiography and histopathological investigation of the liver. All patients underwent the Kasai operation for the first time. The patients were followed up in Namazi Hospital with regular medical checkups including blood tests (complete blood count and biochemistry), ultra sonography, HIDA scan (Hepatobiliary Iminodiacetic Acid), as well as upper gastrointestinal endoscopy and liver biopsies, if necessary, in the follow up process. The only operation after the Kasai surgery was liver transplantation in cases with indication of worsening cholestasis, portal hypertension, and recurrent cholangitis. Data to evaluate the outcome of Kasai operation were collected through the records available in hospital archives. Demographic information of patients was obtained from their file records in the hospital, including gender, age, and weight at the time of operation, and also liver function test (LFT) results. For cases whose records were defective, information were collected by using patients' phone number; for those who were still under observation, the information was gathered according to their very last progress notes. The

outcomes of Kasai operation were categorized into three groups: 1- survival after Kasai operation with non-cirrhotic liver, 2- cirrhotic liver (with and without liver transplantation), and 3- death. Finally, the obtained data were analyzed and presented as mean standard deviation. Statistical calculations were performed by IBM SPSS software (ver.14.0). Data are expressed as mean± standard deviation (SD) Survival rate of the patients with natural livers were assessed using Kaplan-Meier method and log rank test with endpoints of death or liver transplant. Chi-square tests were also used for categorical variables.

Results

Sixty one infants were studied (20 male and 41 female). The length of the study was 10 years; and the mean duration of the follow up was 85-86 months (SD=6.95). The following data were analyzed:

Blood tests:
Among the 3 patients who had a plasma albumin lower than 3.5, 2 died and among the 50 patients with an albumin over 3.5, 36 patients survived. Other enzymatic values were as follows: AST (aspartataminotransferase) and ALT (alaninaminotransferase) normal levels were set as 45 and patients were categorized into two groups above and below the 5-folds. In 32 patients from a total of 59 available results and in 9 patients from a total of 59 available cases AST and ALT levels were higher than normal range, respectively. In 46 patients of 59 available results, ALP (alkaline phosphates) levels were above 1200 units.

Ultrasound findings:
Imaging laboratory data, obtained by sonography, showed homogenous echo of the liver of 7 patients in a total of 41 cases. Regarding the size of the gall bladder, from a total of 14 out of 32 was normal, 8 had a smaller gall bladder than normal size, and in 10 patients the organ was not detected. Four patients out of 22 cases were diagnosed with abnormal spleen size while others had normal spleen size.

Hepatic condition and the related tests:
Alcoholic stool, also known as clay color stool, was observed in 43 cases from 49 available data; also no sign of bile duct dilatation was detected in any of the patients. Considering an end stage liver condition, 22 patients

Table 1. Survival Months of Patients and Their Blood Tests

Blood test		Survival time (month)	P value
ALT	0*	93.086	0.002
	1*	40.753	
AST	0*	93.046	0.065
	1*	74.347	
ALP	<1200	62.222	0.616
	>1200	86.166	
ALB	<3.5	13.000	0.043
	>3.5	87.467	

* "0" means < ALT or AST/45×5; "1" means > ALT or AST/45×5

Table 2. Survival Months of Patients and the Related Imaging Studies

Ultrasound findings		Survival time (month)	P value
Liver	0	87.945	0.241
	1	54.004	
Spleen	0	81.884	0.216
	1	43.508	
Gallbladder	0	83.700	0.796
	1	58.010	

Liver: 0 = normal liver echo
1 = homogenous echo
Spleen: 0 = normal size
1 = abnormal size
Gallbladder: 0 = normal size
1 = atretic

had bridging fibrosis in biopsy. Cholangiography of the biliary tree revealed that 2 patients had intra-hepatic atresia, 15 patients extra-hepatic and 29 patients had complete atresia. Data were not available for 15 cases.

Survival Rate:
In a total of 60 patients, 29 patients underwent Kasai operation before 60 days of age and 31 patients underwent the operation after 60 days of age. Among the 29 patients who underwent Kasai operation before 60 days of age, 19 survived; (14 patients with cirrhotic liver and 5 patients with non-cirrhotic liver) and among the 31 patients who underwent Kasai operation after 60 days of age, 20 survived; (3 patients with cirrhotic liver and 17 patients with non-cirrhotic liver). The outcome for our 61 subjects is as follows: 17 deaths, 39 alive and 5 cases with unavailable outcome. From the 39 patients alive, 31 had developed cirrhosis. Two cases of deaths were caused by sepsis. Two patients died due to pulmonary hemorrhage, and 2 died after transplantation. Hepatic-encephalopathy, GI bleeding, heart failure, and PTLD (Post- transplant Lymphproliferative Disorder) each was related to one case of death. The cause of death was not available in 7 cases.
Regarding the patients' weights and the time of surgery, 8 patients weighed below 4000 gram and the other 45 were above this weight, with 3 deaths in the first group and 12 deaths in the latter. Three patients in the first group and 27 patients in the second group developed cirrhosis (P value=0.722). The 5 year survival rate after Kasai portoenterostomy was 61%.

Discussion

Studies are suggestive of a 30- 60% five year survival and 20% adulthood with native liver after Kasai surgery [6]. In a study conducted by Bittmann *et al*., five-year survival of the female patients was 88% as compared with 55% of the male patients [3]. In a review study, 88% of the patients (162/184) were reported alive with native liver and 60.5% (98/162) were suffering from hepatic complications. Although patients with biliary atresia may survive more than 20 years, most patients suffer from progressive liver complications in a long term period. In our study, 39 patients survived and only 6 cases (9.8%) had liver transplantation. In this study, biliary atresia was confirmed by cholangiography and histopathological assessment of the liver. As false diagnosis of biliary atresia directly influences the outcome results, minimizing the error rate of diagnosis should be attempted by a multidisciplinary approach of suspected cases. Pathological examination is the critical factor for diagnostic evaluation of this disease [9]. Studies suggest that cirrhosis commonly caused by intrahepatic biliary hypoplasia can be an influential factor in decreasing the rate of success of portoenterostomy [3]. Considering the relationship between the success rate and caseload, Schreiber *et al*. evaluated this connection in 230 patients, divided into 3 groups, who were referred to different centers. There was no significant correlation be-

Table 3. Survival months of patients and their liver biopsy

		Survival time (month)	P value
Fibrosis	Bridging	77.190	0.372
	Moderate	96.102	
Cholangiography of Biliary Tree	completely atresia	83.341	0.572
	extrahepatic atresia	75.575	

tween the success rate and caseload which is also confirmed in our study [10]. Age at the time of operation and absence of cholangitis or liver cysts after the surgery are reported as the determining factors of increasing the native liver 5 year survival [11]. A study evaluating the outcome of prognosis of biliary atresia in Taiwan during 1976 to 2000 showed that the resolution of jaundice and the absence of repeated cholangitis contributed to better outcome [12]. One study revealed that living donor liver transplantation for post Kasai biliary atresia is safe in all age groups both children and adults if the patients do not have other serious comorbidities [13]. Although it is possible that many patients survive into adulthood, there are probable secondary biliary complications such as abnormally high levels of ALT, ALP, and serum bilirubin, pruritis, jaundice, sclerosing cholangitis, bacterial cholangitis, and portal hypertension making liver transplantation inevitable for some patients [14]. Despite the fact that Kasai operation has increased the survival rate of patients, hepatic deterioration calls for a continuous follow up of the patients [15].

Conclusion

Age at operation is a determinant factor influencing the outcome of biliary atresia. The results of this study showed that 61% of the patients with biliary atresia survived for more than 5 years with native liver after Kasai portoenterostomy. However, postoperative care still has to be increased to ensure a promising improvement in both survival rate and condition of survived patients.

Table 4. Result of Kasai procedure until the end of 2012

	Frequency	percent
Alive non-cirrhotic	8	13.11
Alive cirrhotic	28	45.90
Alive transplant	3	4.95
Death without transplant	14	22.9
Death with transplant	3	4.95
missing	5	8.19
Total	61	100

Table 5. Condition of the patients aging less than 60 days and over 60 days at the Kasai operation time

		Frequency	Percent	Survival time(month)	P value
>60 days	Alive non - cirrhotic	3	10.3	89.98	0.216
	Alive cirrhotic	17	58.6		
	Death	9	31.03		
	Total	29	100%		
<60 days	Alive non - cirrhotic	5	18.5	78.85	
	Alive cirrhotic	14	51.8		
	Death	8	29.6		
	Total	27	100		

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