
DISCUSSION

How can biliary atresia be treated?

Various surgical techniques were proposed in the first half of the 20th century, attempting to restore the biliary drainage. Only about 10 to 20% of the patients with biliary atresia have an extra hepatic bile duct large enough to perform a mucosa-to-mucosa anastomosis with the intestine. These cases with correctable-type can undergo hepatico-enterostomy with good outcome.^(18,120,121)

The remaining patients -about 85 to 90%- don't have any bile duct amenable to a conventional anastomosis. The only effective treatments for biliary atresia at the moment are Kasai portoenterostomy and liver transplantation. Kasai portoenterostomy increases the survival of children with biliary atresia and postpones subsequent liver transplantation.⁽¹²²⁾

Hepatoportoenterostomy was first described by *Morio Kasai* in 1959. There have been numerous subsequent modifications, but the success of this operation remains critically dependent on the meticulous dissection of the porta hepatis and its subsequent anastomosis to a Roux-en-Y limb of jejunum.⁽⁹⁾

What are the prognostic factors of Kasai portoenterostomy?

Several prognostic factors of Kasai operation have been related to the short-term results of this procedure. Among them are many that are non-modifiable which affect prognosis directly. These include anatomy of the biliary remnant -that is; type of biliary atresia- histology of the liver at the time of operation, portal pressure at the time of operation and association of biliary atresia with polysplenia syndrome. Other prognostic factors of biliary atresia are related to the organization of care for these patients and therefore are improvable or modifiable like case load, age at Kasai and accessibility of liver transplant.⁽¹⁰⁴⁾

Although many studies have focused on prognostic factors associated with the portoenterostomy, it is still controversial as to which of these indicators predict a successful or failed portoenterostomy.⁽¹²³⁾

Although the care of children with biliary atresia has improved tremendously in the last decades, there are several controversies regarding the best care of these patients. We have to understand that we know more about treatment than about pathophysiology of the disease and hopefully that in the future more studies could be directed to increase the understanding of the disease in order to achieve better treatment facilities and hence better outcome. Again and more importantly that national or even multinational specialized centers should cooperate in order to achieve the best results for these miserable patients as one of the most important factors controlling the outcome is the surgical experience.

The aim of this work was to study the predictors of the clinical outcome after Kasai portoenterostomy done for cases with biliary atresia.

How many patients did our study include?

Our prospective clinical study included 20 patients with biliary atresia. Open Kasai portoenterostomy was done for all patients over one year during the period from January 2013 to January 2014. Sixteen patients were operated in National Liver Institute, Menoufia University and four patients were operated in Pediatric Surgery Unit, Alexandria University. Most publications studying the prognosis of Kasai operation done for patients with biliary atresia are retrospective and fewer numbers of studies conducted in prospective direction.

In a retrospective study conducted in Turkey by *Aydoğdu S et al.*; 27 patients were included evaluating the surgical success, the survival rate and the relationship of the parameters of the outcome and the age at diagnosis and at operation of patients with BA in Izmir, Turkey.⁽¹²⁴⁾

Chan, KWE et al. in a study conducted in 2014 in China included 27 patients retrospectively reviewed evaluating the clinical outcome after reintroduction of open Kasai portoenterostomy following the era of laparoscopic Kasai. These patients were operated over 5 years between 2007-2012.⁽¹¹⁹⁾

A retrospective indian study conducted by *Sanghai SR et al.* in 2009 included 32 patients diagnosed from May 2005 to July 2007 assessing the incidence of biliary atresia among neonatal cholestatic syndromes and evaluating the prognosis of biliary atresia after Kasai portoenterostomy.⁽¹²⁵⁾

On the other hand; fewer studies were conducted prospectively like a Malaysian study conducted in 2009 by *Lee, Way Seah et al.* including 57 patients referred to the University of Malaya Medical Centre during the period from 1996 to 2005 aiming to determine the outcome of the Kasai operation done for children with biliary atresia at a tertiary pediatric referral center in Malaysia.⁽¹²⁶⁾

Does Kasai portoenterostomy succeed in all patients?

The clinical outcome of surgery for biliary atresia can be assessed by measuring the rate of clearance of jaundice (serum bilirubin within normal range) postoperatively, by survival with native liver and by overall survival. Portoenterostomy may be considered successful if serum bilirubin normalized and jaundice disappeared after operation.

Clinical improvement as well as improvement in laboratory investigations was observed in 55% of our patients postoperatively. It goes in the same levels as in many publications like what had been concluded from high-volume centers suggesting that clearance of jaundice can be achieved in 50 - 60% of infants, with 10-year native liver and real survival rates of 45% and 90%, respectively.⁽¹²⁷⁾

Actuarial native liver 5-year survival rates range from 30% to 60% after portoenterostomy, and about 20% of all patients undergoing Kasai portoenterostomy during infancy survive into adulthood with their native liver.⁽¹²⁸⁾

In Western countries the short-term clearance of jaundice can be achieved in 50% to 60% of the patients after Kasai portoenterostomy.^(101,127)

In Japan, the rate of early clearance of jaundice is 57% in the national registry & 15% to 75% in Sendai. The reasons for the discrepancy of med-term results between Japan and Western countries remain unclear but may be due to centralization of surgical and medical resources.⁽¹⁰¹⁾

In a French study; the rate of jaundice clearance was 38%⁽¹³⁰⁾ which differs from England & Wales in which the rate of bilirubin clearance is about 55%.⁽¹⁰²⁾

In China; *Kin Wai E. Chan et al.* in their retrospective study concluded that the success rate of Kasai portoenterostomy approaches 81%. This may be due to higher experience and centralization of services.⁽¹¹⁹⁾

Given adequate perioperative care the question here is that: can more be done to improve the chances of eventual success?

What were the factors which affected the postoperative clinical outcome?

❖ Preoperative workup

★ Impact of age at operation

If a bile-obstructed liver is left alone for long time, then delayed surgery will be associated with worse results as the liver ultimately becomes cirrhotic and unsalvageable. So that early diagnosis & intervention is recommended.⁽³¹⁾

The age of the infant at operation plays a major detrimental effect on the clinical outcome, although this is not as clear-cut as was once thought. It is not a linear effect, and it is difficult to determine a real variation in the outcome at anywhere up to 80 days of age. Beyond that, fibrosis does begin to be detrimental with worse prognosis. In contrary; even beyond 100 days Kasai procedure can have advantages and even long-term jaundice-free survival.⁽¹³¹⁾

The median age of our studied patients at Kasai operation was 60 days. The age at operation affected the clinical outcome postoperatively with better results detected in the younger age group. This may be explained by the little degree of pathological liver affection and consequently better hepatic physiological condition.

It was observed that in the industrialized world, the median age at Kasai operation is about 60 days also and this does not differ among countries. The age at Kasai operation is slightly lower in the UK (median 54 days) where efforts have been made to educate parents and health care staff to detect the early clinical signs of neonatal liver diseases.⁽¹³²⁾

Many researchers studied the effect of age on the clinical outcome of Kasai portoenterostomy and many of the published studies examining the effect of age at Kasai operation on the post-operative clinical outcome concluded that early operation had good effect on the outcome.⁽⁷⁴⁾

These studies explained the higher success rate in earlier age group by patency of the intrahepatic bile ducts in early infancy and presence of minute bile ducts in the cone-shaped fibrous tissue, replacing extra hepatic biliary radicles. Little or no hepatic fibrosis had occurred in earlier age group with better liver functions, better general condition and hence better outcome.^(9,74)

Willemien de Vries et al. examined the outcome of biliary atresia aiming to identify the prognostic factors of it using a national database in Netherland and concluded that the exact optimal timing of surgery remains to be determined, but their findings indicate that efforts should be directed to perform surgery at least before 60 days of age to obtain better outcome. No additional benefit of very early surgery (age < 45 days) compared with surgery between 45 and 60 days had been detected.⁽¹³³⁾

The median age at surgery in a Malaysian study conducted by *Way-Seah Lee et al.* for all patients was 70 days (96±67 days) with success rate of 44% in patients with median age 58 days. They concluded that earlier referral & surgical intervention had very good effect on the outcome. They briefly explained the main factors of delayed patients' referral by repeated reassurance by inexperienced medical and paramedical staffs that misdiagnose the condition due to the high prevalence of neonatal physiological jaundice, failure of hospital services at referral hospitals and initial parental reluctance for referral. They also recommended reversal of this disadvantageous points.⁽¹²⁶⁾

Masaki Nio et al. declared that increased age at surgery has a negative impact on results of Kasai operation for biliary atresia in infancy and early childhood. It remained unclear if an age threshold exists and if this effect persists with extended follow-up. They retrospectively reviewed 695 patients with biliary atresia upon whom Kasai portoenterostomy was done between 1986 and 2002. They detected that doing Kasai portoenterostomy before 46 days of age can spare up to 5.7% of all liver transplantations performed annually in France for patients younger than 16 years old and concluded that age at Kasai operation had a significant impact on jaundice clearance rates ($p < 0.001$).⁽¹⁰⁸⁾

Performing Kasai portoenterostomy at younger age group affected directly the clinical outcome greatly in many other studies with better outcome if the operation was done at an earlier age group. These studies include those conducted by *Giorgina Mieli-*

Vergani et al.⁽¹³⁴⁾, *Serinet MO et al.*⁽¹⁰⁸⁾, *Vivas-Colmenares GV et al.*⁽³⁾ and by *Khalil BA et al.*⁽¹³⁵⁾

On the other hand some other researchers found in their studies that the age at Kasai portoenterostomy didn't affect the final post-operative clinical outcome.

Among these studies was the study conducted by *Sookpotarom P et al.* who concluded that the age at Kasai didn't affect the outcome. They explained that by the briefness of the follow-up period. They also recommended conducting a campaign to highlight the importance of early referral of neonates with jaundice and longer postoperative follow up periods.⁽¹³⁶⁾

In the same way, *Chen G et al.* in their study concluded that even some patients over 90 days of age at surgery can still benefit from Kasai procedure and the age at operation has minor detrimental effect on the outcome.⁽¹³⁷⁾

Lucky Gupta, et al. didn't find a statistically significant difference in the outcome in relation to age at operation and concluded that age at Kasai may not be as significant factor as has been made out in the past with regard to the surgical outcome.⁽¹¹⁸⁾

Chardot C et al. in their French study conducted in 2013 concluded that Kasai operation can be done at any age without age threshold in order to postpone the need for liver transplant.⁽¹³⁰⁾

★ Did the clinical outcome differ between male and female?

The difference in sex didn't affect the clinical outcome in our study (P=0.092). In 2011; a study conducted by *Superina R et al.* disclosed that no association with the clinical outcome was detected with sex difference.⁽¹⁰⁴⁾

Biliary atresia develops with slight female predominance. In our study there was 11 females (55%) and 9 males (45%). In a retrospective study conducted by *Dzakovic A et al.* females constituted 60% of the studied group and males constituted 40%.⁽¹³⁸⁾

Similar distribution was found in *Ana Carceller et al.* study in which 65% were females and 35% were males.⁽¹³⁹⁾ *Aydogdu, S et al.* in a Turkish study included 14 females (51%) & 13 males (49%).⁽¹²⁴⁾

In contrast some few studies have a reversed percentage like in *Lucky Gupta et al.* study in which there was 29 males (74%) and 10 (26%) females.⁽¹¹⁸⁾

Another study with reversed percentage is the spanish one published in 2014 by *Vivas-Colmenares GV et al.* which included 29 patients from whom 59% were males and 41% were females.⁽³⁾

★ Did the clinical presentation affect the clinical outcome?

→ Family history of similar conditions

There was no family history among our studied patients and there was a few number of publications in which there was a positive family history of biliary atresia. *Kobayashi K et al.* published Mother-to-daughter occurrence of biliary atresia in 2008 and they concluded that in their knowledge, these patients were the first occurrence of biliary atresia in a transmission pattern from mother to daughter.⁽¹³⁹⁾

→ Ascites

The presence of preoperative ascites affected the clinical outcome of our studied patients; as there was statistically significant difference between the two outcomes. The four patients who had preoperative ascites were presented in the icteric group postoperatively. This seems to be related to the degree of liver fibrosis at operation. *Aydogdu, S et al.* in their Turkish study conducted in 2004 concluded that the degree of preoperative ascites was higher in those who had high post-operative levels of bilirubin i.e. failed Kasai PE.⁽¹²⁴⁾

→ Splenomegaly

Correlation of preoperative splenomegaly with the clinical outcome didn't show statistically significant difference between the two groups (P=1). This was observed also in *Shalaby A et al.* study in which they concluded that splenic size is moderately correlated to invasive portal venous pressure measurement and again of limited use as a prognostic index of the outcome and indeed in the later development of varices.⁽¹⁴⁰⁾

→ Presence of associated congenital anomalies

Isolated biliary atresia was the commonest finding among our patients accounting for 85%. Associated anomalies had been encountered in 15% of patients in the form of cardiac anomalies, situs inversus and preduodenal portal vein. Cardiac anomalies were found in two patients. This was similar to the rate of isolated biliary atresia in *Davenport M et al.* study in which 81 % of studied patients had isolated biliary atresia.⁽¹⁰²⁾

The presence of associated congenital anomalies didn't show statistically significant difference between the two groups in our study may be due to small sample size. However, association with other congenital anomalies adversely affects the clinical outcome. Associated anomalies like urological and GIT malformations even if these can benefit from successful management, appeared to be related to bad clinical outcome of biliary atresia. This is because the presence of these anomalies plays a detrimental role in development and severity of prenatal biliary atresia and so a high rate of liver failure. Moreover, the presence of multiple congenital anomalies could support the hypothesis of a deregulated embryonic development probably based on a generalized disruption of mesenchyme-epithelial interactions (i.e. esophageal and biliary atresia, anorectal and urinary tract malformations).⁽¹⁴¹⁾

This relation was approved in many publications as in *Patrick Ho Yu Chung et al.* study.⁽¹⁴²⁾ Also *Davenport M et al.* concluded in their study that the outcome after KPE was worse in those patients with other congenital anomalies.⁽¹⁰²⁾

The association between cardiac anomalies and biliary atresia had been studied during 2012 by *Andrew J et al.* who decided that there is high incidence of cardiac anomalies in patients with BA with incidence of 13.8%.⁽¹³¹⁾

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★ To which extent did the results of preoperative investigations affect the clinical outcome?

➔ Did the results of preoperative laboratory investigations affect the clinical outcome?

A. Liver and cholestatic enzymes

Preoperative total serum bilirubin in the non-icteric group was about (16.86±1.67 mg/dl). However in the icteric group it was (21.44 ±1.85 mg/dl). Direct bilirubin was also lower in the non-icteric group (13.6±2.26 mg/dl) than in the icteric one (17.33±1.97 mg/dl). The same was observed in the preoperative levels of ALT and AST being lower in the non-icteric group (178.36±11.81U/L) & (195.67±3.91 U/L) than in the icteric group (232.09±22.7 U/L) & (195.67±3.91 U/L) respectively. In the same way the cholestatic enzymes (GGT and ALP) were lower in the non-icteric group (520.82±53.47 U/L) & (1004.18±77.62 U/L) than in the icteric group (1261.11±140.93 U/L) & (967.22±74.8 U/L) respectively.

Shooting high levels of preoperative serum bilirubin, its direct fraction, ALT, AST, GGT and ALP affected the final outcome and showed statistically significant difference between the non-icteric and the icteric groups. Poor clinical outcome developed in these patients with higher preoperative levels of these tests. This may be attributed to the higher pathological hepatic affection as disclosed by these tests.

The same was observed in the study conducted by *Seung Min Hahn et al.* who compared pre & post-operative levels of these tests declaring that there was statistically significant difference between patients who developed liver related complications and those who didn't develop complications being higher in those who developed complications, concluding that these tests can be used as predictors of the clinical outcome post operatively.⁽¹⁴³⁾

Lucky Gupta et al. in their study concluded the same result that the liver function tests were found to have a better correlation with the surgical outcome. Higher degrees of cholestasis showed definite correlation with poor surgical outcome.⁽¹¹⁸⁾

On the contrary the *Sanghai SR et al.* in their study concluded that none of these tests affected the clinical outcome.⁽¹²⁵⁾

Elevated direct/indirect bilirubin ratio above normal shortly after birth -even if the total bilirubin is still below phototherapy level- has been studied by *Sanjiv Harpavat et al.* as a prognostic factor of BA. This test proved effectiveness in the early detection of BA with early referral & intervention resulting in better results. They concluded that early screening of this relationship in all neonates rather than of only that who appeared jaundiced is effective in early diagnosis of BA.⁽¹⁴⁴⁾

B. Plasma proteins and serum albumin levels

In the current study the difference in the preoperative plasma proteins and serum albumin were statistically significant between the two groups affecting the clinical outcome. They were higher in the non-icteric group (4±0.31 g/dl) & (3.13±0.19 g/dl)

respectively than in icteric group (2.3 ± 0.06 g/dl) & (1.78 ± 0.15 g/dl) respectively. This may be attributed to the higher hepatic functional affection in the icteric group.

Seung Min Hahn et al. in 2013 conducted the same results in a retrospective study evaluating the predictors of development of liver related complications after Kasai portoenterostomy which included failed Kasai, liver cirrhosis, varices, ascites and jaundice. They measured serum albumin at Kasai operation as base line and re measured it in the follow up after 3 months. They found that there was statistically significant lower levels of preoperative serum albumin in the group who developed postoperative liver related complications than in those who didn't develop any complications and concluded that lower levels of preoperative serum albumin can predict the clinical outcome postoperatively.⁽¹⁴³⁾

C. PT, PTT, INR

The difference in bleeding profile (PT, PTT, and INR) between the two groups in the current study didn't show statistical significance. This may be attributed to the small sample size.

In contrast to our results; *Seung Min Hahn, et al.* in their study in 2013 which was conducted retrospectively on 69 patients found that there was statistically significant difference regarding PTT and INR between their studied groups. The group who developed post portoenterostomy liver related complications had higher levels of these tests at the time of Kasai operation than in those who didn't develop complications concluding that higher levels of preoperative PTT & INR can predict bad outcome.⁽¹⁴³⁾

→ **How can the preoperative findings of US abdomen affect the clinical outcome?**

A. Preoperative hepatomegaly & hepatic echogenicity

The size of liver margin below costal margin varied between the non-icteric and the icteric groups with statistical significance ($P= 0.038$). The liver size under the costal margin in the non-icteric group was (2.62 ± 0.86) cm being smaller than in the icteric group (3.4 ± 0.85) cm. This may be explained by the more pathological affection of the liver in the icteric group preoperatively which proved to affect the clinical outcome.

Diffuse hepatic parenchymal heterogeneity was detected in 12 patients; 3 from the non-icteric group and the entire icteric group. The difference between the two groups of the clinical outcome regarding this variable showed statistical significance ($P=0.001381$). The liver parenchymal diffuse heterogeneity on US abdomen denotes more diffuse hepatic pathological affection and consequently worse outcome.

The same was observed by *Hahn SM et al* in their retrospective study in which they studied the predictors of the clinical outcome of patients with biliary atresia concluding that the finding of a "heterogeneous" hepatic parenchyma on preoperative ultrasonography was predictive of poor outcome after Kasai PE but lacked sensitivity.⁽¹⁴³⁾

B. TC Sign

The triangular cord sign (TC sign) was detected in 12 patients preoperatively on US abdomen. Its presence didn't show statistically significant difference between the two outcomes. This may be attributed to the small sample size. However the presence of preoperative TC sign was found in 7 out of the 9 patients who survived icteric post portoenterostomy (78% of the icteric group) and only 5 out of the 11 who survived non-icteric post portoenterostomy (45% of non-icteric group).

This was explained by *Saxena AK et al.* in their study evaluating the prognostic and medicolegal values of TC sign in biliary atresia in which they declared that because TC sign is due to the presence of fibrosis of extrahepatic biliary remnants; it is possible to know that patients with TC sign on preoperative US have poorer outcome than in those in whom the TC sign is absent.⁽¹⁴⁵⁾

Nemati M et al. in their study published in 2009 declared that ultrasonography is a reliable screening method in early diagnosis of biliary atresia and that the TC sign increases its accuracy contributing to the early referral & intervention resulting in better prognosis.⁽¹⁴⁶⁾

Postoperative presence of TC sign denotes inadequate removal of the fibrous cone at portahepatis during portoenterostomy. Post-portoenterostomy TC sign is associated with higher morbidity and mortality; and reflects inadequate surgical technique.⁽¹⁴⁷⁾

→ **Did the preoperative pathological findings of percutaneous liver biopsy affect the clinical outcome?**

In biliary atresia, progression of hepatic fibrosis before the Kasai portoenterostomy may explain why age is a major determinant of survival of the native liver.⁽¹⁴⁷⁾

It's recommended doing pre-laparotomy liver biopsy for all suspected cases of biliary atresia to decrease the frequency of negative laparotomy achieving cost benefit with reduced morbidity.⁽⁷¹⁾

The hepatic histopathological examination in biliary atresia is classically characterized by ductular proliferation, canalicular and cellular biliary stasis, swelling and vacuolization of biliary epithelial cells, portal tract edema and fibrosis, monocytic inflammatory cell infiltration of portal tracts and ductal plate malformation. The severity of intrahepatic biliary cholangiopathy and the extent of hepatocyte injury are important determinants of prognosis.⁽¹¹⁸⁾

In our study the histopathological features appeared to affect the final surgical outcome. Higher degree of cholestasis, hepatocellular alteration, bile ductular proliferation, bile duct inflammation and portal tract edema showed definite correlation with poor surgical outcome. High grade hepatic fibrosis was also associated with poor outcome.

The same was observed *in Lucky Gupta et al.* study in which they concluded that the hepatic histopathological changes (hepatocellular alteration, cholestasis, bile ductular proliferation and inflammation) in the preoperative biopsies affected the clinical outcome implying that the patients with lesser degree of hepatic damage were likely to have better outcome following surgery. However, they detected that although fibrosis was seen in all patients preoperatively the difference in the outcome was not statistically significant among the studied patients. They explained the lack of statistical significance by the small number of patients in their study.⁽¹¹⁸⁾

Salzedas-Netto AA et al. in their retrospective study found that none of the patients who lived non-icteric after Kasai portoenterostomy had grade IV liver fibrosis and that 25 % of patients who had been operated after 60 days and showed failure of procedure; have had grade IV liver fibrosis. They concluded that in addition to the good results which could be achieved with earlier intervention in case of biliary atresia; the rate of grade IV fibrosis is higher in no drainage patients and that all patients with grade IV fibrosis had no biliary drainage after Kasai operation.^(148,149)

The results of the current study coincide with the last publication as the five patients who had grade IV fibrosis in the preoperative liver biopsy survived icteric postoperatively constituting about 5% of the icteric group.

On the contrary; some researchers didn't find any relation between the degree of affection of liver in preoperative liver biopsy and the outcome as in the studies conducted by *Sookpotarom P et al.* and by *Sanghai SR et al.* who concluded that the liver histology did not influence the early outcome, presumably due to the briefness of the follow-up period.^(135,125)

❖ What is the frequency of post-operative cholangitis?

Cholangitis is one of the most important determinants of long-term survival after Kasai procedure. The knowledge on postoperative cholangitis has been increasing in the last 10 years, showing a lower incidence of the disease and better therapeutic results.⁽⁹⁴⁾

Cholangitis occurs most commonly in the first two years following primary surgery in about 30–50% of children. Paradoxically, it only occurs in children with some degree of bile flow and not in those with early failure. Clinically, it is characterized by worsening jaundice, fever and acholic stools. The diagnosis may be confirmed by blood culture or by percutaneous liver biopsy, but it is important to treat suspected cases early with broad-spectrum antibiotics effective against Gram-negative organisms.⁽¹⁵⁰⁾

Often, however, the diagnosis of cholangitis is not obvious and unexplained fever may be the only symptom. Antibiotics are then started empirically, after taking a blood culture and assessing liver function tests, C-reactive protein and full blood count. If the fever responds to antibiotics, these are continued for 5 days.⁽¹³⁴⁾

There was only one patient in the non-icteric group who developed an attack of cholangitis during the follow up period.

Several studies concluded that cholangitis in the early postoperative period is one of risk factors having adverse effect on the clinical outcome after Kasai portoenterostomy, so that prevention and aggressive management of cholangitis should be considered as measures to avoid disease progression in the early stage.⁽¹⁴²⁾

Recurrent cholangitis with resultant intrahepatic cystic dilatations known as biliary lakes, which are readily apparent on US abdomen is a bad prognostic sign and requires liver transplantation.⁽¹²⁸⁾

❖ Did the postoperative use of cholegogues affect the clinical outcome?

All the patients in our study received post-operative Ursodeoxycholic acid (UDCA). However, double blinded controlled study is recommended to study its effect on the clinical outcome.

UDCA administration seemed to be beneficial in patients with type III biliary atresia in increasing bile flow and reducing cholangitis by hepatocyte protection.⁽¹⁵¹⁾

In the same way *Willot S et al.* in a cross over French study conducted in 2008 concluded that there was a great improvement in liver function tests with introduction of UDCA.⁽¹⁵²⁾

On the other hand; *Davenport M et al.* in their study concluded that the role of adjuvant medical therapy post-portoenterostomy is unclear and evidence of benefit is lacking. Nonetheless, the use of post-operative steroids, prophylactic antibiotics and choleric agents such as ursodeoxycholic acid is common.⁽¹²⁷⁾

❖ Do we have to use postoperative corticosteroids?

We didn't use regular postoperative corticosteroids in our study. Some authors believe that there is no beneficial effect on the outcome and others recommend regular postoperative steroids preventing against cholangitis by immunological and anti-inflammatory effects, increasing biliary flow by inducing canalicular electrolyte transport and prolonging the period of survival with native liver.⁽¹⁵³⁾

Although the efficacy of postoperative steroids which had been used for the last 30 years is still unknown, about 50 % of patients in USA receive postoperative steroids on regular basis.⁽⁸⁹⁾

There is a great controversy whether to use steroids post portoenterostomy or not due to deficiency of clear evidence of its efficacy. This is because biliary atresia is rare and few centers can see more than 5 cases yearly. This is aggravated by the great variations among surgeons and the disease stages. The result is that most of the published studies are retrospective and uncontrolled with only few published prospective studies.^(133,159)

From these prospective studies; one was conducted by *Petersen C et al.*⁽¹⁵⁴⁾ using a high-dose steroid regimen to treat 20 consecutive patients after Kasai portoenterostomy and compared them with a historical control group, while *Davenport et al.*⁽¹⁵⁵⁾ performed a prospective, double-blinded, randomized, placebo-controlled trial of low dose oral prednisolone in 71 children with biliary atresia. Neither study showed any difference in overall survival, liver transplant frequency, survival with native liver, or jaundice-free survival with native liver.

The same conclusion was reached by *Sarkey A et al.*⁽¹⁵⁶⁾, by *Bezerra JA et al.* in 2014.⁽¹⁵⁷⁾

On the other hand *Rui Dong et al* in their study concluded that the clinical outcome of Kasai operation could be improved with longer periods of survival with native liver with regular high dose of postoperative steroids which should be started parenterally then shifted to oral route.⁽⁹⁰⁾

What were the indications of for liver transplantation in our study?

All of the patients who survived icteric postoperatively in our study were scheduled for liver transplantation. They developed progressive deterioration of liver functions with increasing amounts of ascites and enlarging spleen.

Hadzic N in his publication concluded that the only effective treatment for 'failing' Kasai portoenterostomy is liver transplantation. However, to maximize the patient's chances to achieve the proclaimed >95% survival with sequential liver transplantation, medical follow-up and treatment must be planned carefully. This includes routine fat-soluble vitamin supplementation with cholagogues, aggressive nutritional support, regular ultrasonography, optimal general pediatric care, and psychological support for the family once complications arise. Careful timing of liver transplantation is of critical importance, although recent trends include earlier consideration of it in children with biliary atresia. This management can only be offered through centralized, specialized national services.⁽¹⁴²⁾

There was great increase in the overall survival in case of biliary atresia after the wide spread of application of liver transplantation worldwide. Survival with native liver was 39 % at 10 years before the era of liver transplantation. With the application of liver transplant, overall 10-year survival for patients with biliary atresia was 94.9 %.⁽¹⁵⁸⁾

Bondoc, Alexander J et al. in a recent study concluded that revision of Kasai portoenterostomy in selected cases may be undertaken in order to get reestablishment of this successful bile drainage pattern and return them to the more favorable long-term outcome subgroup associated with persistent biliary drainage.⁽¹⁵⁹⁾

However, surgical revision of an unsuccessful portoenterostomy is generally discouraged, as repeat abdominal surgery potentially increases the technical difficulty of subsequent liver transplantation. Portoenterostomy revision results in more adhesions that, with the development of cirrhosis and portal hypertension, become vascularized. These adhesions magnify the complexity of the transplant procedure increasing blood loss, prolonging anesthetic and operative times, and increasing the risk of enterotomy or damage to other intra-abdominal structures. Although there is increased morbidity for patients undergoing transplantation after revision of portoenterostomy, there is no significant increase in mortality.⁽¹⁶⁰⁾

Selection of patients who will be subjected to redo Kasai should be precise including (1) a patient who initially experienced a successful PE but abruptly develops jaundice, refractory to medical therapy and (2) a patient who experiences recurrent episodes of cholangitis but has no other manifestations of progressive liver disease.⁽¹⁴²⁾

So, what is the independent predictor of the clinical outcome?

Multiple logistic regression of the significant factors affecting the non-icteric outcome revealed that only the preoperative total serum bilirubin is a significant predictor of this outcome.

Sangkhathat S. et al, in their retrospective study of perioperative factors predicting the outcome of Kasai portoenterostomy in infants with biliary atresia concluded that age of the infants younger than 60 days and type I biliary atresia were the key determinants of successful hepatic portoenterostomy. Early cholangitis was an accelerator of progressive cirrhosis. Stool color and bilirubin level at one month after surgery can be used as predictors of jaundice clearance.⁽¹⁶¹⁾

Chung PH et al, in their retrospective study aiming at identification of the risk factors that predict early failure of this operation included all patients who received Kasai operation between 1980 and 2012. Patients referred from other centers for liver transplantation because of failed Kasai operation were also recruited. With univariate analysis, the presence of associated anomaly, operation with laparoscopic surgery, delayed clearance of jaundice, and repeated cholangitis were associated with adverse outcome. With multivariate analysis, repeated cholangitis was an independent risk factor for early failure after Kasai operation. Furthermore, it was also considered as a risk factor for failure after 3 year post-Kasai. They concluded that the presence of above mentioned factors drive the procedure to failure in an early stage so that frequent regular monitoring is required and that prevention and aggressive management of cholangitis should be considered as measures to avoid disease progression in the early stage. Lastly, they recommended performing open Kasai operation and using adjuvant steroid which are potentially beneficial.⁽¹⁴²⁾

The cause why the above mentioned study concluded more than one predictor factor of the clinical outcome of Kasai portoenterostomy is that it was a retrospective study conducted in a referral center over 32 years on huge number of patients over long period of follow up. However our study was conducted over one year with 6 months of follow up of only 20 patients. This may explain the detection of only the total bilirubin as being a significant predictor of this outcome.

SUMMARY

Biliary atresia is the most common correctable surgical disorder among the neonatal cholestatic syndromes occurring with slight female predominance. It involves different lengths of biliary tract with type I affecting distal common bile duct, type II extending to common hepatic duct (with or without cystic duct affection). Both of these types are known as correctable and can be treated by hepaticojejunostomy or cholecystojejunostomy. Type III or the uncorrectable type extends to the portahepatis with no evident bile ducts for enteric anastomosis. The two lines of treatment of this last type are Kasai portoenterostomy and liver transplantation.

The clinical outcome following Kasai portoenterostomy has many determinants; some of them are uncorrectable like type of biliary atresia, preoperative degree of pathological affection of the liver, association with polysplenia syndrome and portal venous pressure at time of surgery. The other determinants are correctable factors and include the age of the patient at Kasai operation, surgical experience and accessibility of liver transplantation.

The aim of our work was to evaluate the predictors of the clinical outcome following Kasai portoenterostomy done for cases with biliary atresia.

The study included 20 patients; 11 females and 9 males diagnosed with biliary atresia and operated upon with open Kasai portoenterostomy during the period from January 2013 to January 2014. Sixteen patients were treated in the National Liver Institute at University of Menoufia and the other four patients were operated in Pediatric Surgery Unit at University of Alexandria. These patients were followed up for 6 months for the clinical outcome by measuring the total serum bilirubin, GGT and ALP.

This follow up disclosed that there was no mortalities among the studied patients during the follow up period and that the patients were classified according to their clinical outcome into two groups; the 1st group is the non-icteric group in which patients showed postoperative improvement with success of Kasai operation and the 2nd group was the icteric group which included patients in whom Kasai operation failed. Antibiotics were used for only two weeks postoperatively, no steroids were given and UDCA was used in all patients.

The non- icteric group involved eleven patients and nine patients belonged to the icteric group with success rate of 55%.

There was slight female predominance with male:female ratio of 1:1.2. This difference didn't affect the clinical outcome however there was a great impact of the age at operation on the outcome with significant difference between the two groups. It was lower in the non-icteric group 56.91 ± 5.77 days than in the icteric group 72.78 ± 12.02 days.

Regarding the clinical presentation of the studied patients; all patients were presented by jaundice, hepatomegaly and dark colour urine. Only 75% of the studied patients have associated splenomegaly and clay colour stool. Four patients had ascites and three patients had associated congenital anomalies in the form of VSD, patent foramen ovale, situs inversus and preduodenal portal vein. These associated anomalies were not amenable to

correction in the same setting. The four patients who had preoperative ascites survived in the icteric group postoperatively. This difference in presence of preoperative ascites between the two groups was statistically significant ($P=0.026$). However the presence of preoperative splenomegaly didn't affect the clinical outcome with no statistically significant difference between the two groups ($P=1$). The degree of affection of liver function as measured by Child-Pugh score affected adversely the clinical outcome with statistically significant difference between the two groups. The mean of child-Pugh in the non-icteric group was (7.27 ± 0.47) being lower than in the icteric group (8.22 ± 0.67). This difference was statistically significant ($Z=-2.895$, $P=0.006$). Although all the patients with associated congenital anomalies survived icteric postoperatively; this difference was not statistically significant. ($P=0.07$)

The preoperative laboratory investigations disclosed that the total serum bilirubin was lower in the non-icteric group 16.86 ± 1.67 mg/dl than in the icteric group 21.44 ± 1.85 mg/dl. This difference was statistically significant ($P=0.001$). The same was for the direct fraction of bilirubin which was 13.6 ± 2.26 mg/dl in the non-icteric group and 17.33 ± 1.97 mg/dl in the icteric group; this was statistically significant ($P=0.002$). The level of the preoperative liver enzymes (AST & ALT) as well as the cholestatic enzymes (GGT & ALP) differed between the two groups being higher in the icteric group. This difference was statistically significant ($P=0.001$, $P=0.002$, $P=0.000$, $P=0.001$ respectively). The preoperative changes in plasma proteins and serum albumin were lower in the non-icteric group than in the icteric one; both of them showed statistically significant difference ($P=0.000$). However, the difference in bleeding profile between the two groups which showed prolonged times in the icteric group didn't show statistical significance.

The preoperative US abdomen showed variation in the liver size below the costal margin being larger in the group of patients who lived icteric 3.4 ± 0.85 cm than in the non-icteric group 2.62 ± 0.8 cm. This difference was statistically significant ($Z=-2.064$, $P=0.038$). Another parameter in hepatic US which was associated with worse outcome was the diffuse hepatic heterogenous parenchymal appearance which showed significant statistical difference between the two groups ($P=0.001381$). Although the incidence of preoperative TC sign in the non-icteric group was about 45% and in the icteric group was about 78%; this difference wasn't statistically significant ($P=0.19$).

The degree of liver fibrosis showed statistically significant difference between the two groups of the clinical outcome ($P=0.000$). All the patients who had no fibrosis in the preoperative liver biopsy showed good outcome postoperatively. However, patients with preoperative cirrhosis didn't show improvement postoperatively.

Parameters of preoperative liver biopsy rather than fibrosis including hepatocyte alteration, cholestasis, bile ductular proliferation, bile duct edema, inflammation were more severe in the icteric group preoperatively. This affected the clinical outcome directly with statistically significant difference ($P=0.000$).

There was a slight difference between the two groups regarding the operative duration being 161.8 ± 24.8 min in the non-icteric group with median of 150 min and 167.8 ± 30.7 min in the icteric group with median of 180 min. This difference wasn't statistically significant. ($Z=0.594$, $P=0.6$)

Regarding the postoperative complications; nine patients developed non-functioning portoenterostomy postoperatively and all of them developed progressively signs of advanced liver disease with increasing amount of ascites and enlarging spleen. They were subjected to medical management and scheduled for liver transplantation as soon as possible. One patient in the non-icteric group developed cholangitis treated conservatively and another one developed adhesive intestinal obstruction treated surgically with adhesiolysis after abdominal exploration. The last patient who had a postoperative complication belonged also to the non-icteric group and developed biliary anastomotic leakage. He responded to conservative measures.

Multiple logistic regression of the significant factors affecting the non-icteric outcome revealed that only the preoperative total serum bilirubin is a significant independent predictor of this outcome. That is every 10% decrease in the preoperative total serum bilirubin, there are 2.5 times increase in the probability of success of Kasai portoenterostomy and therefore occurrence of the non-icteric outcome.

CONCLUSION

1. Kasai portoenterostomy showed better results with short term follow up if done at an early age.

2. There are several factors that can affect the clinical outcome following Kasai portoenterostomy as following:

A. High scores of Child-Pugh index can predispose to bad outcome.

B. The presence of preoperative ascites adversely affects the clinical outcome with worse results following the operation.

C. Although the presence of associated congenital anomalies didn't show statistically significant difference; there was a predisposition for bad outcome in patients with biliary atresia associated with other congenital anomalies.

D. Low levels of plasma proteins and serum albumin in the preoperative laboratory work up of patients with biliary atresia correlate with bad clinical outcome.

E. Patients with preoperative higher levels of total serum bilirubin and its direct fraction showed bad results after Kasai portoenterostomy.

F. Shooting levels of preoperative liver function tests (ALT, AST, GGT, and ALP) have direct relationship with bad clinical outcome following Kasai portoenterostomy.

G. Higher degrees of hepatomegaly as well as preoperative diffuse parenchymal heterogeneity on US abdominal examination are associated with bad outcome.

H. Although the presence of TC sign in the preoperative abdominal ultrasonography didn't show statistically significant difference between the two groups, it had been noticed that most patients with this sign –which means fibrosis at portahepatis- had worse outcome after Kasai portoenterostomy.

I. Higher degrees of pathological liver affection in the preoperative liver biopsy in the form of cholestasis, hepatocellular alteration, bile ductular proliferation, bile duct inflammation and portal tract edema in addition to high degrees of fibrosis can result in bad clinical outcome after Kasai portoenterostomy.

3. Our study concluded that the only independent factor which can predict good clinical outcome that is non-icteric result is the preoperative total serum bilirubin. This was detected by multiple logistic regression analysis of the factors which showed statistically significant difference between the two groups of the outcome.