Objective Evaluation of the Therapeutic Effects of Oral Steroids in the Management of Biliary Atresia

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Abstract

Introduction: Biliary atresia is a progressive fibro-obliterativecholangiopathy that affects both intrahepatic and extrahepatic biliary ducts causing cholestasis and neonatal jaundice**.** The use of anti-inflammatory agents such as corticosteroids may decrease inflammation and recurrent stricture**.**

Materials and Methods: This clinical trial had been performed on 24 patients admitted to Children's Hospital with biliary atresia. Prednisolone was not administered in the control group after the operation, but in the intervention group, 2 mg/kg/day of prednisolone was given for 6 weeks and then tapered. Then, its therapeutic effect in the management of biliary atresia was compared.

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Results: The mean age of the patients in the case and control groups was 2.19 and 2 months, respectively. Cholangitis (P= 0.3), direct hyperbilirubinemia (P= 0.6), ascites (P= 0.5), pigmented stools (P= 0.7), and esophageal varices (P= 0.1) between the two groups was not significant. But the age of the patients, outcome of treatment (P= 0.05), total hyperbilirubinemia (P= 0.05), growth failure (P=0.03), worsening grade of splenomegaly (P= 0.04), hepatomegaly (P= 0.03), fecal pigmentation (P= 0.003), death (P= 0.01), and portal hypertension (P= 0.02) in two groups were significant.

Conclusion: Regarding the results, corticosteroids have a significant effect on reducing the bilirubin levels, improving the survival rate, and decreasing the mortality rate, although these results are closely related to the patient's age at the time of surgery.

Keywords

- Biliary atresia
- Corticosteroids
- Kasai procedure
- Stenosis

Introduction

Biliary atresia is a progressive fibro-obliterativecholangiopathy that affects both intrahepatic and extrahepatic biliary ducts causing cholestasis and neonatal jaundice.[1–3] Without treatment, progressive hepatic fibrosis leads to cirrhosis, portal hypertension, liver failure, and eventually death before the age of 2 years.[1, 2]

According to the level of obstruction, biliary atresia has three types, with the third type being the most common form, in which the obstruction takes place in the most proximal part of the extra hepatic biliary ducts at the level of portahepatis.[1]

Kasai procedure remains the first - line surgical treatment in the world, while liver transplantation is the salvage therapy when the surgical procedure fails.[4] The most common complications of a successful Kasai procedure are ascending cholangitis and portal hypertension with or without esophageal varices.[5]

Adjunct medical treatments after the Kasai procedure including various oral antibiotics and corticosteroids are commonly used in order to prevent postoperative cholangitis, induce the biliary stream, and to decrease inflammation and fibrosis. Corticosteroids, in addition to their anti-inflammatory and immunomodulatory effects, cause the biliary current to increase.[4] Approximately 40–60% of the patients suffer from hepatic biliary cirrhosis after the surgery. The likelihood of recurrent stenosis, failure to respond to surgery, and persistent cholestasis rises with inflammation. Hence, the use of anti-

inflammatory agents such as corticosteroids may decrease inflammation and recurrent stricture. As there is still controversy about the role of corticosteroids, performing current research in order to evaluate the effects of oral steroids on the prevention of postoperative recurrent stenosis in patients suffering from biliary atresia seems to be of necessity.

Materials and Methods

This fundamental applied research is a prospective clinical study of the referred infants with biliary atresia to the Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. The aim of this study was to evaluate the therapeutic effects of oral steroids in the management of biliary atresia.

Inclusion criteria: Children under 3 months old with biliary atresia.

Exclusion criteria:

(1) Patients without parental letter of credit.

(2) Patients who passed away for any reason even due to biliary atresia or any other causes.

(3) Patients suffering from cardiac anomalies, hyperplasia of biliary ducts, TORCH syndrome, or inspissated bile syndrome.

In the current study, 24 patients (13 male and 11 female), less than 3 months old, with biliary atresia were evaluated from April 2014 to April 2021. Patients were divided into two groups. In the current study, we had randomized the patients to place in the case or control group based on their medical records, last number on the left side. In case of odd numbers, they would be placed in the case group, while the even numbers would be placed in the control group. Group I included 12 patients (case) who received oral steroids, and group II was composed of 12 patients (control) who did not receive oral steroids. The mean patient age was 2.19 months in group I, and 2 months in group II. It should be noted that informed consent was obtained from the parents and patients' information were kept confidential in their files.

To survey the therapeutic effects of corticosteroids in the prevention of postoperative cholangitis, the patients were divided into two groups of cases (group I) and controls (group II). Preoperative workups such as blood tests, radiography, and abdominal ultrasonography were done for all patients. Intraoperative cholangiogram and liver biopsy were done to confirm the diagnosis of biliary atresia for all patients.

Corticosteroids were not administered to group II, while the patients in group I were provided with 2 mg/kg/day of oral prednisolone since the fifth postoperative day for 6 weeks, and tapered afterwards based on the protocols. Given the fact that corticosteroids are controversial, the decision to cease to prescribe prednisolone in the control group was of no contradiction with the references.[6]

Surgical technique: Roux-en-Y hepatic portoenterostomy (Kasai procedure), which was approved by the boarding

committee of pediatric surgeons of Mofid Children's Hospital, was the procedure of choice for all patients. All patients underwent transverse laparotomy incisions. After excision of bile duct remnants, end-to-end portoenterostomy with a Roux loop length of 45 cm long was performed to prevent cholangitis for all patients. An antireflux valve by invaginating the proximal intestinal portion of the Roux-en-Y limb into the distal part (Nakajo modification) was created. Then parameters such as birth date, sex, weight, age at the time of diagnosis and surgery, coexisting symptoms including jaundice, chromatic urine, acholic stool, bilirubin level, liver enzymes, platelets, rate of cholangitis, need for transplantation, recovery from hyperbilirubinemia, ascites, malnourishment, splenomegaly, hepatomegaly, time of pigmented feces, death rate, esophageal varices, and portal hypertension in both groups were evaluated. It should be noted that all of the aspects of the treatment except prednisolone in two groups were equal. All patients were followed up for 2 years after the surgery.

Results

Progressive jaundice, acholic stool, and dark urine were the most common preoperative symptoms in both groups, with a rate of 75%. The average serum bilirubin level on admission was 8.4 mg/dl for group I and 8.7 mg/ dl for group II. Significant decrease in serum bilirubin to the levels of less than 2 mg/dl in a 2-month period of follow-up and a decline in the level of the conjugated bilirubin to less than 2 mg/dl in a 3-month period was seen among 75% of the patients of group I compared with the 33.4% in group II (P= 0.06). Other laboratory data such as liver enzymes and the platelet level showed no significant change in either of the two groups (P> 0.05). The rate of cholangitis in the first group was 16.6%, while it happened in 33.4% of the patients of the second group (P= 0.3). Neither of the groups needed a second surgery. Growth abnormalities were seen in 25% of patients of each group (P= 0.03). During the follow-up ultrasound, splenomegaly was seen among 16.6% of patients of group I and in none in-group II (P= 0.04). Ascites was seen in 8.3% of patients of group I and in 16.6% of the cases in-group II (P= 0.5). Pigmented stool was noticed after 2 weeks in 83.4% of the patients of group I and in 24.9% of group II (P= 0.03). In both groups abdominal ultrasound showed shrunken gallbladder among 66.6% of the patients. Death from complications of biliary atresia including liver failure, severe cholangitis, and septicemia happened in two cases of group I, compared with the seven cases of mortality in-group II) P= 0.01). Mortality from causes not related to biliary atresia such as cardiac anomalies happened in one case in-group I and two cases in-group II **Figures 1–4 and Table 1.**

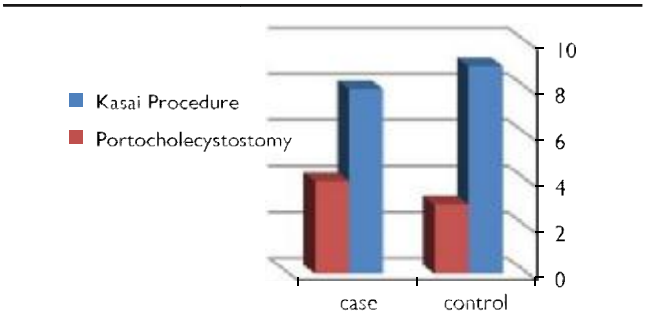

Figure 1: Comparison of the type of surgery in the case and control groups

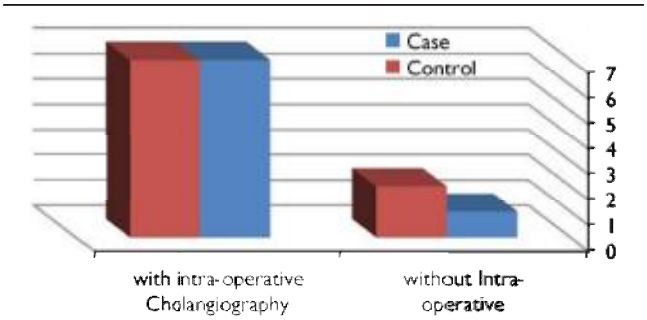

Figure 2: Frequency of intraoperative cholangiography in those who underwent the Kasai procedure in the case and control groups

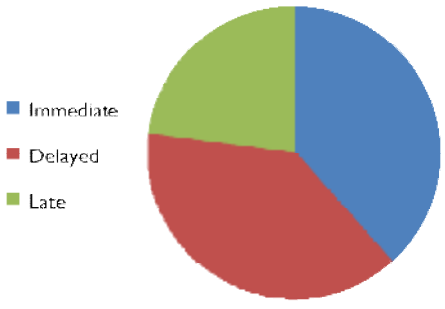

Figure 3: Timing of stool pigmentation in those with initial acholic stool.

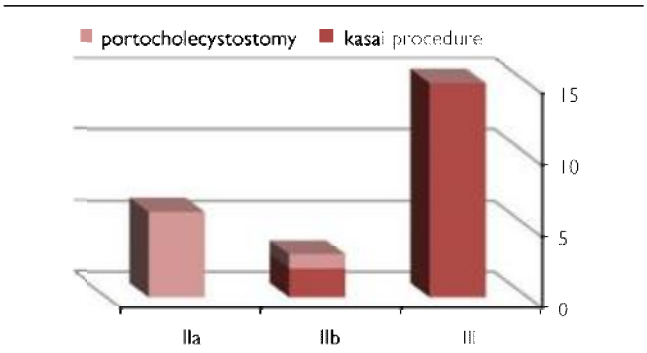

Figure4: Evaluation of the type of biliary atresia and the type of surgical procedure

Table 1: Mean level of transaminase in the case–control groups

laboratory Data	within 10 days	10–14 days	more than 14 days
Case			
AST	192.6	84	309
ALT	91.33	45	138.83
Control			
AST	345.33	32	179.5
ALT	145	45	84.12

Immediate: within 10 days followed by surgery.
Delayed: 10–14 days followed by surgery.
Late: more than 14 days after surgery.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Discussion

There is some degree of neonatal jaundice in the first few weeks of life among more than 50% of live births.[2] Neonatal cholestasis develops in the form of direct hyperbilirubinemia during the first month of life because of a pathologic process due to anatomical abnormality, biliary diseases, infections, metabolic and genetic disorders, toxins, drug intoxication, nutritional disorders, and unknown etiologies. Excluding the neonatal cholestasis due to total parenteral nutrition, the most common disorder associated with cholestasis in a term neonate is the extrahepatic biliary atresia

or idiopathic neonatal hepatitis.[7] On the basis of previous studies regarding the etiology of cholestasis, numerous causes have been postulated, among which extrahepatic biliary atresia and idiopathic neonatal hepatitis are the most common, responsible for 70 – 80% of the cases of cholestasis. The most important step in the evaluation of neonatal cholestasis is to differentiate between biliary atresia and neonatal hepatitis.[8] Biliary atresia is a progressive obliterating fibrous cholangiopathy which impedes both the intrahepatic and extrahepatic bile ducts and causes obstruction of the bile, cholestasis, and neonatal jaundice.[1,2] It is a rare disease, only in neonates, with the prevalence of one in 15 000–19 000 births in the Western world. However, the prevalence is higher in Asian countries.[9]

Currently, there is no effective treatment for the progressive course of hepatic injury in children with biliary atresia. Roux-en-Y hepatic portoenterostomy (Kasai procedure) is the standard therapeutic choice to increase bile flow and to improve icterus; and if it is done in the first 8 weeks of life, the chance of success in maintaining the bile flow is ~ 90%.[7] Without treatment, progressive hepatic fibrosis leads to cirrhosis, portal hypertension, liver failure, and eventually death before the age of 2 years.[1,2] Acute cholangitis is the most common complication after the surgery. Treatment includes broad-spectrum antibiotics, short-term use of corticosteroids, and reoperation in some cases.[10–12] Liver transplantation is another option for patients with a weak response to surgery.[12]

Based on the study by Zhang et al.[13] on the effect of steroids on jaundice, cholangitis, and survival of patients after Kasai procedure, they concluded that the use of steroids causes a decrease in jaundice, cholangitis, and mortality. Based on this study, the effect on cholangitis (P= 0.3) and jaundice (P= 0.06) was inconsequential, while the effect on mortality (P= 0.01) was meaningful. Based on the findings of the study of Dong et al.[14] who determined the role of steroid doses in improving the outcomes of patients with biliary atresia, who underwent the Kasai procedure, found that high doses of corticosteroids due to anti-inflammatory effects caused a decrease in the incidence of cholangitis, decreased bilirubin levels, and improved survival rate. In the current study, the effects of oral steroid therapy on the prevention of stenosis in patients with biliary atresia who underwent Kasai procedure was performed . Based on the results of this study, comparison of cholangitis (P= 0.3), the need for transplantation (P= 0.6), direct hyperbilirubinemia (P= 0.6), ascites (P= 0.5), pigmented stools (P= 0.7), and esophageal varices (P= 0.1) in the intervention and control groups was not significant; but total hyperbilirubinemia (P= 0.05), malnutrition (P= 0.03), intensification of splenomegaly (P = 0.04), intensification of hepatomegaly (P= 0.03), pigmented stools (P = 0.003), death (P= 0.01), and portal hypertension (P= 0.02) in group I and improved survival (P = 0.01) in group II was significant. Also, based on the findings, the age of patients was significantly correlated with the outcome

of treatment (P= 0.05). So, if these patients underwent Kasai surgery before 60 days of age and used corticosteroid at a dose of 2 mg/kg/day for 6 weeks they would have lower serum bilirubin levels and reduced need for liver transplantation.

Conclusion

Considering the results of the current study, oral corticosteroid administration after oral tolerance could have positive effects on patient outcomes but for improving the results, much larger studies with the collaboration of several medical centers with more samples for improving the results is recommended.

Ethical Consideration

This study was approved by Institutional Ethics Committee of Shahid Beheshti University of Medical Sciences and the approval ID is IR.SBMU.REC.1395.15

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Conflict of interests

There is no conflict of interest

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