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Original Article

Peri-Operative High-Dose *v* Post-Operative Low Dose Steroid Therapy in the Management of Biliary Atresia: a Preliminary Report

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Abstract

Background: The use of high-dose steroid therapy peri portoenterostomy may have a positive impact on the frequency of cholangitis and survival rate.

Methods: A prospective study was conducted on two groups of patients (less than three months of age) suffering from biliary atresia from 1999 to 2005. The patients in group I (G I) were managed peri-operatively by high-dose methylprednisolone while the other group (G II) received low dose methylprednisolone only post-operatively (2mg/k/day for 1 month). Infants in GI (n=30) received methylprednisolone for 3 successive days before operation (10-8-6mg/kg/day), and 10 mg/k at the day of operation respectively. Thereafter the dose was tapered in the next successive 6 days by 8, 6, 5, 4, 3, and 2 mg/kg/day and continued for one month.

Results: Seventy two infants with biliary atresia were operated (39 girls and 33 boys). Twenty-six of the 30 patients (86%) in G I became jaundice-free within 90 days after portoenterostomy while only seven (15%) of the 42 patients in G II had normal bilirubin (P<0.0001). Episodes of postoperative cholangitis in G I were 20% (6 of 30), and 53% (24 of 42) in G II (P<0.005). The difference in 3-year survival rate between the two groups is also remarkable: Eighty seven percent (26 of 30) in GI versus 29% (13 of 45) in G II (P<0.005). Death related to biliary atresia occurred in 1 (3.3%) patient in GI compared with 12 (29%) patients in G II (p<0.005).

Conclusion: These results provide strong evidence that peri-operative high dose steroid therapy is not only safe in this patients population, but because of its anti-inflammatory and cholerrhetic effects has a positive impact on preventing recurrent cholangitis, and ultimately survival.
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Keywords ● Biliary atresia ● cholangitis ● steroid

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Introduction

Biliary atresia is a progressive obstructive cholangiopathy, which ultimately leads to hepatic failure and death if not treated within 12 weeks after birth.[1,2] However, with surgical intervention, the chance of survival is higher and the course of the disease can be modified.[3-5]

Portoenterostomy, which was introduced by Kasai in 1959, has resulted in better prognosis and an increased survival rate for patients with biliary atresia.[3,6] Infants and children, who do not benefit from Kasai Portoenterostomy or its modifications, need hepatic transplantation as a sequential strategy.[7] However, all of these procedures are palliative. None of them are able to stop the pathological process.

Considering the immunologic mechanism as a possible etiology for destruction of biliary ductus and ultimately the hepatic cells, immunosuppressive and anti-inflammatory pharmacotherapy, should probably be effective in reducing the destructive process.[1,8] Until now, most studies have focused on the efficacy of prophylactic steroid therapy during postoperative period to increase the chance of improvement and reducing the need for hepatic transplantation.[1,8-13] Although surgery is the mainstay in the management of biliary atresia,[10,14] some pharmacologic agents have proven to be effective as well; Phenobarbital, ursodeoxycholic acid, antibiotic administration, and vitamin supplements are examples of such agents.[9,15,16]

Our current study reviews the outcome of patients with biliary atresia who treated with high dose methylprednisolone administered before and after operation.

Patients and Methods

A prospective study on infants with biliary atresia was conducted at Namazi hospital affiliated to Shiraz University of Medical Sciences, southern Iran. All patients with biliary atresia younger than 90 days old were evaluated during April 1999-December 2005. The patients with age beyond 90 days, major congenital heart anomalies, biliary hypoplasia, inspissated bile syndrome, and TORCH syndrome were excluded from the study. Having informed the parents regarding the different aspects of the protocols, verbal consents were obtained. The protocol was approved by the ethics committee in Shiraz University of Medical Sciences. All the patients were managed by portoenterostomy and antireflux operation as described by Nakajo et.al.[17]

The following parameters were recorded: date of birth, sex, birth weight, age at the diagnosis, age at the time of Kasai operation, the need for reoperation, timing and dose of steroid therapy before and after operation, existence of jaundice and acholic stool, serum bilirubin, liver enzyme levels, platelet count, the interval between the operation and the jaundice-free state, and the findings in favor of cholangitis. In addition, the patients' general condition, size of liver and spleen, signs of portal hypertension, ascites or biliary cirrhosis, were recorded as well.

Considering steroid therapy, the patients were assigned every other month into the case (study) group and control (standard) group. The study group (G I) received high-dose intravenous methylprednisolone for 3 successive days before operation: 10, 8, and 6 mg/kg/day, respectively. Thereafter, the drug was continued after operation for 6 successive days as follows: 10, 8, 6, 5, 4, and 3 mg/kg/day to be followed by 2 mg/kg/day for four weeks. The control group (G II) received intravenous methylprednisolone 2 mg/k/day immediately after operation that was continued for four weeks. The other aspects of management including bowel preparation and postoperative drug administration in both groups were similar. According to clinical and paraclinical indices, the patients were labeled as jaundice-free if the level of bilirubin declined to less than 2 mg/dl in 3 months. The patients, who developed fever (with or without acholic stool), rise in bilirubin and/or a positive blood culture, were considered as having cholangitis. In this situation, they would receive not only broad-spectrum antibiotics, but high-dose intravenous methylprednisolone (10 mg /k/day for 1 week). Should there be no improvement, re-operation would be planned for curetting the site of portoenterostomy. Ultrasonography of abdomen and hepatobiliary scintigraphy were performed during the follow-up period. Data were then analyzed using SPSS software version 11.5 (LEAD Technologies, Inc, USA). The tests used for comparison between the two groups were Chi square, Fisher exact and Student's *t* tests. P value less than 0.05 was considered significant.

Results

During the 6-year-period of the study, 72 patients with biliary atresia were treated (45 females, 27 males). The patients were assigned every other month to G I (30 patients) and GII (42 patients). The operation was performed before the 75 days of age in 80% of the patients in G I and 70% of the patients in G II.

The mean serum bilirubin level on presentation was 15.51mg/dl (SD ±6.447mg/dl) in G I and 16.32 mg/dl (SD ±7.212 mg/dl) in G II. Remarkable decline (<2mg%) in serum bilirubin level within 90 days after operation was observed in 26 of 30 patients (86%) in G I compared with 15% (7 of 42 patients) in G II ($p<0.0001$). However, the other quantitative values such as liver enzymes levels and platelet count were not significantly different in both groups ($P>0.05$). Furthermore, 6 patients (20%)

in G I developed cholangitis during the follow-up period, while this complication occurred in 24 (57%) patients in G II (P<0.005). Seven patients (23%) in G I needed re-operation, while eight patients (13%) in G II needed re-operation (P>0.05). Twenty-six patients (86%) in G I had a conjugated bilirubin level less than 2 mg/dl within 90 days of surgery, in contrast to seven patients (17%) in GI (P<0.005).

Follow-up ultrasonography of abdomen was performed in 35% of all the patients in G I, which revealed almost normal liver and spleen size and echotexture accompanied by normal intra hepatic ducts diameter. On the contrary, only 5 of the 11 patients (45%) in G II undergoing ultrasonography of abdomen had normal findings. In the remaining six patients some abnormalities such as dilated intra-hepatic bile ducts, hepatosplenomegaly, and abnormal echo texture of liver parenchyma were reported.

Follow-up Scintigraphy was performed in five patients in G I and 11 patients in G II. All the five patients in GI had good bile flow excretion, while only 3 of the 11 patients (31.25%) in G II showed normal excretion. In other words, eight patients (72%) in G II had poor bile flow excretion. However, 7% (2 of 30 patients) in G I had jaundice and were generally ill.

There was a significant difference in the 3-year survival rate between G I and G II [(24 patients (80%) in GI *v* 13 patients (30%) in G II (p<0.05)] (table 1). The mortality related to biliary atresia (because of hepatic failure, severe cholangitis, and septicemia) was significantly higher in G II compared with G I [12 patients (29%) in G II *v* one patient (3.3%) in GI (P<0.005)]. The death non-related to biliary atresia, mainly because of severe congenital cardiac anomalies, occurred in three patients in G I and in one patient in G II.

Discussion

Biliary atresia is a disease with uncertain pathogenesis, most commonly presenting at neonatal age. Currently, though no proved theory has been proposed, it appears that many etiologies such as occult viral infections and abnormal bile duct formation (without mesodermal support) result in bile leakage and ultimately intense inflammatory reaction. Genetic predisposition, immunologic, inflammatory, and obstructive pathways are also possible explanations.[1,18] With the introduction of portoenterostomy by Kasai in 1959, the survival rate in this fatal disease increased dramatically.[3,6] Since that time this surgical procedure has relatively remained unchanged, though modifications for conduction of bile and prevention of cholangitis have been performed. However, their efficacy has not yet been proved. Intussusceptions-type antireflux valve in Roux-en-Y loop is one of these modifications introduced by Nakajo et al.[17,19,20] As shown by Toyosak, extensive dissection at porta hepatis may improve the bile drainage in long term.[21] All of our patients were operated on by extensive dissection. And we did not have mortality during operation.

Acute cholangitis is the most likely complication that may occur after the surgery. Management of this condition includes intravenous broad-spectrum antibiotic therapy, short-term pulse steroid therapy, and in some patients re-operation.[15,22,23] In patients with poor response to Kasai portoenterostomy, liver transplantation may be beneficial in infants and young children.[7] However, it may be more logical to change the disease process rather than subjecting the patients to a major surgery.

During the last decade, new therapeutic trends have focused on controlling the possible destructive immunologic process that can affect the biliary system.[1,11,12] Corticosteroids have been administered because of their immunosuppressive effects since mid-1990s in conjugation with broad-spectrum antibiotics to manage the postoperative cholangitis.[8,24] Having considered the anti-inflammatory and immunosuppressive effects of corticosteroids, it is reasonable to use them for re-establishing the bile flow following portoenterostomy. Karrer and Lilly used short-term high-dose prednisolone to increase bile excretion after portoenterostomy.[11] Dillon et al, who administered immunosuppressive dose of methylprednisolone after portoenterostomy; succeeded in reducing the need for liver transplantation.[10] In another study, when administration of methylprednisolone was limited following portoenterostomy, most of the patients required liver transplantation.[14]

Muraji and Higashimoto administered methylprednisolone with the initial dose of 4mg/kg/day, and tapered that over 1-2 weeks to 2.5mg/kg/day postoperatively. They reported

Table 1: comparison of some variable in GI and G II

Variable/Group	No of patients in G I (%)	No of patients in G II (%)	P value
Bilirubin< 2mg in 90 days	26 (86%)	7 (15%)	<0.0001
Cholangitis	6 (20%)	24 (57%)	<0.005
3-year survival	24 (80%)	13 (30%)	<0.05
Death related to biliary atresia	1 (3.3%)	12 (29%)	<0.005

amelioration of intrahepatic periportal inflammation. Using this protocol, 77% of the 13 patients became jaundice-free compared with the 29% of the 17 patients in non-steroid subject groups.[19] In a similar study by Kobashi et al, they reported the positive impact of steroids on elimination of jaundice in patients with biliary atresia.[13]

The effectiveness of high-dose steroid, ursodeoxycholic acid, and long term intravenous antibiotic in accelerating the elimination of jaundice was reported by Meyer et al. In this study, 11 of 40 patients (29%) in the steroid group and 3 of the 11 (21%) patients in control group became asymptomatic within 3-4 months after the surgery.[25] Most recently, Escobar et al evaluated the effect of corticosteroid therapy on the outcome of patients with biliary atresia. Similar to the previous reports, significant effect of steroids in reducing serum bilirubin levels was shown in that study. However, in their review, steroid therapy had no effect on the rate of cholangitis, the need for hepatic transplantation, and overall survival.[26]

Corticosteroids have been only used postoperatively in all previous clinical studies. As it is predictable, any surgical intervention induces the infiltration of inflammatory cells and also chemokine expression at the sites of the procedure. In an experimental study performed recently by Hsieh et al, in rats with cholestasis it was found that pretreatment with glucocorticoids suppressed chemokine expression and inflammatory cell infiltration with subsequent minimal hepatic damage.[27]

In the present study, to suppress the inflammatory response to surgical intervention, high dose of methylprednisolone was administered in three successive days before operation. This policy of high dose steroid therapy was continued postoperatively for 6 successive days. Thereafter the patients received a maintenance dose of 2 mg/Kg/day for a period of 4 weeks. Our study proved that pre-operative use of high dose steroid in these patients not only is safe, but also has a positive impact on elimination of jaundice compared with the patients in G II.

In our study the rate and severity of cholangitis were much lower in G I compared with G II. The clinical success of this new therapeutic trend can be claimed by the relatively high number of patients in good health condition some years after operation. Twenty-four patients (80%) in G I are still alive and doing well several years after portoenterostomy in contrast to 30% in G II.

Although our study suggests the efficacy of peri-operative steroids in comparison with the standard protocol, a multi-center, prospective trial of high dose glucocorticoid therapy before and after operative management of biliary atresia is deemed necessary.

Conflict of Interest: None declared

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