Journal of Pediatric Surgery (2007) **42**, 1324–1328

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Journal of Pediatric Surgery

www.elsevier.com/locate/jpedsurg

Kasai portoenterostomy: 12-year experience with a novel adjuvant therapy regimen

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Index words:
Biliary atresia;
Kasai portoenterostomy;
Corticosteroids

Abstract

Aim: The role of adjuvant therapy with corticosteroids and choleretics after Kasai portoenterostomy for biliary atresia (BA) remains uncertain. Experience with a novel postoperative adjuvant therapy regimen is reported.

Methods: Between 1994 and 2006, 71 infants with BA were referred. Four died from uncorrectable congenital heart disease/cardiorespiratory failure without undergoing portoenterostomy, 7 underwent primary liver transplantation (3 referred ≥19 weeks of age), and 60 underwent portoenterostomy at a median of 51 (10-104) days. Of these, 55 (92%) had type 3 BA and 6 had the BA splenic malformation syndrome. Fifty (83%) received the following adjuvant therapy beginning on postoperative day 5: oral dexamethasone 0.3 mg/kg bd for 5 days, 0.2 mg/kg bd for 5 days, and 0.1 mg/kg bd for 5 days together with oral ursodeoxycholic acid 5 mg/kg bd and phenobarbitone 5 mg/kg nocte, both of which were continued for 1 year. All infants received routine perioperative prophylactic antibiotics.

Results: Overall, 42 of 60 (70%) infants cleared their jaundice (bilirubin <20 μmol/L): 38 of 50 (76%) with the dexamethasone/ursodeoxycholic acid regimen compared with 4 of 10 (40%) not receiving this adjuvant treatment. There were 4 late deaths after portoenterostomy: 2 from associated congenital disorders and 2 after liver transplantation. Of the remaining 56 children, 39 (70%) are currently alive with their native liver at a median follow-up of 3.3 years and 17 are alive after liver transplantation. Surgical complications occurred in 3 after portoenterostomy: adhesive bowel obstruction (2) and an anastomotic leak. One infant had gastrointestinal bleeding that may have been related to dexamethasone, but this resolved with ranitidine. There were no perioperative septic complications.

Conclusion: In this series, adjuvant postoperative treatment with a short course of oral dexamethasone and longer-term ursodeoxycholic acid significantly improved the outcome after Kasai portoenterostomy.

Biliary atresia (BA) continues to remain the leading indication for pediatric liver transplantation. It is estimated that more than 70% of affected children will eventually require a liver transplant. About half of the annual budget of $77 million spent on pediatric liver transplantation in the United States is used to treat children with BA [1]. Improving the results of the Kasai portoenterostomy is a health care priority.

The potential benefit of adjuvant therapy with corticosteroids and choleretics after Kasai portoenterostomy for BA remains uncertain. Numerous small studies suggest that

Presented at the British Association of Paediatric Surgeons 53rd Annual International Congress, Stockholm, Sweden, July 2006.

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0022-3468/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.jpedsurg.2007.03.026

adjuvant treatment with corticosteroids and ursodeoxycholic acid improves the outcome of Kasai portoenterostomy, probably by ameliorating inflammatory and immunologic processes and by promoting choleresis [2-6]. While most institutions now use steroids postoperatively [7], there have been no published randomized controlled trials; and there is no consensus on the type of corticosteroid, its dose, timing of administration, and duration of therapy.

Kasai's own experience and other reports [5,8] prompted us to use adjuvant postoperative corticosteroids as part of our routine clinical management from 1994, and a regimen commonly used in the treatment of premature babies with lung disease was adopted. Experience with this novel postoperative adjuvant therapy regimen is reported.

1. Methods

Between June 1994 and June 2006, 71 infants with BA were referred to our unit. Four infants died without undergoing portoenterostomy: 2 from uncorrectable congenital heart disease and 2 from cardiorespiratory failure secondary to severe primary pulmonary hypertension and Down syndrome with associated congenital heart disease, respectively. Seven underwent primary liver transplantation: 3 were referred at age of at least 19 weeks (the parents of one of these declined Kasai portoenterostomy); 1 had short gut syndrome with only 42 cm of small bowel remaining after neonatal surgery for small bowel atresia and volvulus; and 3, aged 6, 11, and 12 weeks, were considered to have advanced cirrhosis at laparotomy and did not proceed to portoenterostomy. Five of these 11 infants who did not undergo a portoenterostomy had the BA splenic malformation syndrome (BASM) [9].

Sixty infants underwent a Kasai portoenterostomy at a median of 51 (10-104) days. Of these, 55 (92%) had type 3 BA, 4 had type 1, and 1 had type 2 (Japanese Society of Pediatric Surgeons classification) [10]. Six had the BASM. Portoenterostomy was performed using a standard technique [11] but *without* abdominal drainage. All operations were performed by a single surgeon (MDS).

1.1. Group 1

Fifty infants (83%) received the following adjuvant therapy:

- Oral dexamethasone 0.3 mg/kg twice daily for 5 days, 0.2 mg/kg twice daily for 5 days, and 0.1 mg/kg twice daily for 5 days, beginning on postoperative day 5
- Oral ursodeoxycholic acid 5 mg/kg twice daily and phenobarbitone 5 mg/kg nocte beginning with resumption of oral feeding (typically postoperative day 3) and continued until 1 year of age
- Oral ranitidine 1 mg/kg 3 times daily while taking steroids
- Perioperative prophylactic antibiotics: a 5-day course of intravenous amoxicillin (25 mg/kg 3 times daily) and gentamicin (2.5 mg/kg 3 times daily) beginning on induction of anesthesia followed by oral cephradine (25 mg/kg twice daily) for 4 weeks.

In addition, all infants received fat-soluble vitamin supplements and a commercially available formula feed rich in medium-chain triglycerides. None of the infants in this cohort received further steroid therapy.

1.2. Group 2

Ten infants (17%) participated in a double-blind, randomized, placebo-controlled, 2-center trial of adjuvant steroid therapy conducted between 2001 and 2004; and they did not receive dexamethasone or ursodeoxycholic acid. Instead, they received either oral prednisolone (2 mg/kg once daily) beginning on postoperative day 7 for a period of 2 weeks followed by a reduced dose of prednisolone (1 mg/kg once daily) for a further week (n = 5) or an oral placebo for 3 weeks (n = 5). Other medication was the same as in group 1. This study received Institutional Ethical Approval (project no. 00/023). Two infants in this group subsequently received a short course of prednisolone (2 mg/kg once daily) in conjunction with intravenous antibiotics for refractory cholangitis, but both eventually required a liver transplant.

A successful Kasai portoenterostomy was defined as complete resolution of biochemical jaundice (plasma bilirubin <20 μmol/L) within 6 months of surgery.

All survivors remain under active regular follow-up. Beyond the first few years, nutrition and growth are assessed at least annually together with the results of an abdominal ultrasound scan and biochemical liver function tests.

Results were compared between the 2 treatment groups using χ^2 analysis with Yates' correction, taking $P < .05$ as statistical significance. Surgical complications and possible adverse events from steroid therapy were recorded.

2. Results

Overall, 42 of 60 (70%) infants cleared their jaundice (bilirubin <20 μmol/L): 38 of 50 (76%) with the dexamethasone/ursodeoxycholic acid regimen (group 1) compared with 4 of 10 (40%) receiving alternative adjuvant medication (group 2) ($\chi^2 = 3.57$, $P = .06$). Table 1 shows that both groups consisted of similar patients except that the worse prognosis BASM patients were all in group 1. In group 2, 2 of the 5 infants who received prednisolone and 2 of the 5 who received placebo cleared their jaundice. A further infant from each group achieved a fall in plasma bilirubin to between 20 and 34 μmol/L (ie, less than 2 mg/dL), but both subsequently required a liver transplant; they are considered as having an unsuccessful Kasai portoenterostomy.

There were 4 late deaths after portoenterostomy, all in infants who failed to clear their jaundice: one with BASM