Journal of Pediatric Surgery xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Outcomes following partial external biliary diversion in patients with progressive familial intrahepatic cholestasis

Caroline Lemoine [a], Tanya Bhardwaj [a], Lee M. Bass [b], Riccardo A. Superina [a,*]

[a] Division of Transplant Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University, Chicago, IL, USA
[b] Division of Gastroenterology, Hepatology, and Nutrition, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University, Chicago, IL, USA

ARTICLE INFO

Article history:
Received 3 November 2016
Accepted 8 November 2016
Available online xxxx

Key words:
Progressive familial intrahepatic cholestasis (PFIC) C
Partial external biliary drainage
Bile acids
Liver transplantation

ABSTRACT

Background/purpose: PFIC is a family of bile acid (BA) transport disorders that may result in serious liver disease requiring transplantation. We reviewed our experience with PEBD as a method to improve liver function and avoid transplantation.
Methods: All patients with PFIC were reviewed. Outcomes included changes in serum BA, conversion to ileal bypass (IB), and survival without transplantation. Statistics were obtained using paired t-test and Wilcoxon test.
Results: Thirty-five patients with PFIC were identified. Data were available in 24. Twenty-four children (12 males) underwent PEBD: 10 PFIC-1, 13 PFIC-2, and one PFIC-3. BA levels decreased in PFIC-1 patients (1724 ± 3215 to 11 ± 6 μmol/L, $P = 0.03$) and in the single PFIC-3 patient (821 to 11.2 μmol/L), but not significantly in PFIC-2 patients (193 ± 99 to 141 ± 118 μmol/L, $P = 0.15$). Seven patients were converted to IB. There were no significant changes in BA levels following conversion. Five-year transplant-free survival was 100% in PFIC-1 and PFIC-3, but only 38% (5/13) in PFIC-2 ($P = 0.004$).
Conclusion: PEBD is an effective procedure to reduce total BA levels and improve symptoms in PFIC patients. However, it appears to be less efficacious in the PFIC-2 group. The higher BA levels could contribute to ongoing liver damage, and thus a higher transplant rate in PFIC-2 patients.
Level of evidence: Level IV.

Progressive familial intrahepatic cholestasis (PFIC) is a family of autosomal recessive disorders caused by genetic mutations that affect the transport of bile salts. There are 3 principal types of PFIC that are caused by distinct genetic mutations (PFIC 1, 2 and 3). The three disorders differ by age at presentation of jaundice, pruritus, and liver biopsy findings [1–4]. The common hallmark of all PFIC patients is the development of intracellular cholestasis with characteristic symptoms of pruritus and jaundice caused by the cutaneous and intrahepatic accumulation of bile acids (BA), respectively. Studies have shown that the sustained accumulation of BA in the liver leads to fibrosis and ultimately development of portal hypertension (PHT) and cirrhosis, eventually requiring liver transplantation (LT) [5].

The partial external biliary diversion (PEBD) was conceived as a possible therapeutic intervention in the 1980s [6]. This consisted of placing a free jejunal loop between the gallbladder and the skin. This allowed for the elimination of BA from the enterohepatic circulation, resulting in improvement of pruritus and cholestasis. It also often led to improvement in the histological appearance of the liver, presumably by decreasing the ongoing inflammation associated with the high intrahepatic BA concentration. PEBD has been shown to effectively reduce serum BA, ameliorate liver function tests and improve liver histology [7–12]. Complete normalization of liver function tests has been reported after PEBD in noncirrhotic patients and has also been shown to preclude the need for eventual liver transplantation [13,14].

In the mid-90s, Holland et al. described an alternative to PEBD consisting of an internal ileal bypass (IB) [15]. While this surgery offers some benefits compared to the PEBD (absence of stoma, and decreased electrolytes anomalies), studies have shown it has a lower long-term effectiveness, with up to 50% of patients developing recurrence of symptoms and increase in BA after one year [10]. PEBD therefore is recommended by many as the primary surgical intervention in the

Abbreviations: PFIC, Progressive familial intrahepatic cholestasis; PEBD, Partial external biliary diversion; IB, Internal bypass; BA, Bile acids; LT, Liver transplantation.

* Corresponding author at: Ann & Robert H. Lurie Children's Hospital of Chicago, 225 E. Chicago Avenue Box 57, Chicago, IL, 60611. Tel.: +1 312 227 4040; fax: +1 312 227 9387.
E-mail address: RSuperina@luriechildrens.org (R.A. Superina).

http://dx.doi.org/10.1016/j.jpedsurg.2016.11.021
0022-3468/

management of PFIC in patients without evidence of end-stage liver disease (ESLD).

The following represents our experience with PEBD in the PFIC population, its effectiveness for symptom control and liver function improvement, complications of the operation, and the requirement for rescue liver transplantation following a PEBD.

1. Methods

1.1. Patient selection

All patients with a diagnosis of PFIC who underwent a PEBD at our institution from January 1997 to February 2015 were reviewed retrospectively. The diagnosis of PFIC was made by clinical criteria, and confirmed through genetic testing and liver biopsy. All PFIC patients were first treated with ursodeoxycholic acid (UCDA), fat-soluble vitamins, and families received nutritional counseling [16]. When medical therapy failed at controlling symptoms of pruritus, PEBD was offered for noncirrhotic PFIC patients, regardless of their PFIC subtype. Patients with symptoms of ESLD (synthetic failure, ascites, bleeding from varices because of PHT) were referred for LT. The surgical intervention for PEBD was performed as previously described by interposing a 10–15 cm segment of jejunum anastomosed to the gallbladder and the abdominal wall, creating an external stoma [6]. Some patients who had undergone PEBD were converted to IB because of stoma-related complications or for personal preference. The ileocolonic anastomosis used to bypass the last 100 cm of distal ileum was performed as described in the literature [15]. Patients who developed ESLD despite PEBD were listed for LT.

1.2. Data collection

Data collection was performed and included the following information: patient demographics (age, sex, PFIC subtype), age at surgery, type of diversion, surgical complications, serum BA levels before and after PEBD, outcome data (conversion from PEBD to IB, reason for conversion, serum BA levels before and after conversion), and LT-related data (age at transplant, reason for liver transplant, transplant-free survival).

The study was approved by our institutional review board (IRB 2014–15,699).

1.3. Statistical analysis

Patients were divided by PFIC subtype for data analysis. Statistics were obtained using the Wilcoxon signed rank test (results significant at $P \leq 0.05$). Kaplan–Meier survival curves were generated to assess transplant-free survival in all patients.

2. Results

2.1. Demographics and PFIC subtypes

A total of 35 patients with PFIC were identified, but complete data were available in only 24 patients. Those were included in this study. All 24 patients (12 males) were noncirrhotic and underwent a PEBD and included: PFIC-1 (n = 10), PFIC-2 (n = 13), PFIC-3 (n = 1).

Patients were excluded from this study for the following reasons: either they did not undergo a diversion procedure (n = 6). In one other, the child underwent an IB as primary procedure because of parental choice. There was incomplete/missing data relative to diversion procedure in 4 patients born in the 1980s. Two patients had a diversion procedure, but the date and the outcome of the diversion surgery could not be retrieved from past medical charts. A further two patients were excluded because it was not known whether they even had diversion after going through past medical paper charts. Figs. 1 and 2 present the selection and distribution of patients, including PFIC subtypes, and excluded patients.

2.2. PEBD results

The median age at the time of diversion surgery was 1.3 (range 0.2–8.7) years. Fig. 3 shows change of BA levels before and after PEBD. Median BA levels decreased significantly in PFIC-1 patients (1724 ± 3215 μmol/L to 11 ± 6 μmol/L, $P = 0.03$) and in the only PFIC-3 patient (821 μmol/L to 11 μmol/L). The median levels also decreased in the PFIC-2 group, but did not reach statistical significance (193 ± 99 μmol/L to 141 ± 118 μmol/L, $P = 0.15$, Wilcoxon signed rank test).

2.3. Conversion from partial external biliary drainage to internal bypass

Seven patients (7/24 patients, 29%) were eventually converted from PEBD to IB. There were 2 patients in the PEBD-PFIC-1 group (2/10 patients, 20%), 4 patients with PEBD-PFIC-2 (4/13 patients, 31%), and the only PFIC-3 patient included in the study. Two patients were converted to IB for electrolyte imbalances in preparation for liver transplant listing because of worsening liver function. Those 2 patients were therefore excluded from the further PEBD to IB conversion subgroup analysis (n = 5). They were both PFIC-2 patients.

The majority of patients undergoing conversion were female (4/5 patients, 80%). Median age at the time of conversion was 13 (range 5.2–18.8) years. Median time from PEBD to IB conversion was 12 years (range 4.5–14.9 years). Overall, median BA levels increased following conversion (6.70 ± 1.6 μmol/L to 12.2 ± 30.2 μmol/L; $P = 0.13$). Reason to perform conversion was patient preference (cosmetic) in all 5 patients. Two suffered from recurrence of the pruritus within a month of conversion but considered this more tolerable than the presence of a stoma. In one girl with recurrent pruritus, serum BA levels did go up from 6.5 to 73.8 μmol/L but liver function remained stable. Parastomal hernia, stoma prolapse, or stricture, were not reported. There were no significant changes in mean BA levels following conversion.

2.4. Liver transplantation following partial external biliary drainage

Eight patients ultimately required a liver transplant (33%). The reason to perform LT was high PEBD stoma output and dangerous electrolyte disorders (n = 2), progression of liver disease to PHT/cirrhosis (n = 4), and persistent severe growth failure (n = 2). The median age at transplant was 2.6 years (range 0.9–12.6 years). Median time between PEBD and transplant was 1.6 year (range 0.5–3.1 years). All patients who underwent a LT were PFIC-2 subtype (8/13 PFIC-2 patients, 62%).

There was a statistically significant difference in the five-year transplant-free survival based on PFIC subtype. All PFIC-1 and PFIC-3 patients (11/11) that underwent a PEBD had a 100% transplant-free survival rate, but only 38% (5/13) of the PFIC-2 patients ($P = 0.002$) remained transplant-free (Fig. 4).

3. Discussion

In this 18-year review of PFIC patient treatment at a single institution, PEBD was highly effective at reducing BA levels, particularly in patients with PFIC-1 and -3 subtypes. The procedure was associated with a low complication rate with no stomal prolapse, parastomal hernia, stoma stricture, or intestinal obstruction, although these have all been previously reported. No ascending cholangitis occurred, despite the increased risk associated with an external stoma [9,17,18].

IB does not appear to be as effective as PEBD, with recurrence of symptoms in about half the patients at one year because of ileal adaptation [10]. However, in our study population, there was no significant change in BA after conversion to IB. Almost a third of our patients was converted to IB. The majority of those patients were female teenagers.

Please cite this article as: Lemoine C, et al, Outcomes following partial external biliary diversion in patients with progressive familial intrahepatic cholestasis, J Pediatr Surg (2016), http://dx.doi.org/10.1016/j.jpedsurg.2016.11.021