Partial Biliary Diversion May Promote Long-Term Relief of Pruritus and Native Liver Survival in Children with Cholestatic Liver Diseases

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Partial biliary diversion in children may ensure long term relief of severe pruritus in children with cholestatic liver disease

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Background/Aim. Rare cholestatic liver diseases may cause debilitating pruritus in children. Partial biliary diversion (PBD) may relieve pruritus and postpone liver transplantation which is the only other alternative when conservative treatment fails. The aim was to report long-term outcome after PBD in a population of 26 million people during a 25-year period.

Methods. This is an international, multicenter retrospective study reviewing medical journals. Complications were graded according to Clavien-Dindo classification system.

Results. 33 patients, 14 males, underwent PBD at median 1.5 (0.3-13) years at four pediatric surgical centers. Progressive familial intrahepatic cholestasis was the most common underlying condition. Initially, all patients got external diversion, either cholecystojejunostomy (25 patients) or button placed in the gallbladder or a jejunal conduit. Early complications occurred in nine (27%) patients, of which three were Clavien-Dindo grade 3. Long-term stoma related complications were common (55%). Twenty operations due to stoma problems have been done because of prolapse, stricture, and bleeding, and conversion to other forms of PBD. Thirteen children have undergone liver transplantation, and two are listed for transplantation due to inefficient effect of PBD on pruritus. Serum levels of bile acids in the first week after PBD construction were significantly lower in patients with relief of pruritus (13 (2-192) μmol/L) than in those with poor effect (148 (5-383) μmol/L; p=0.02) on pruritus.

Conclusion. PBD may ensure long-term satisfactory effect on intolerable pruritus in children with cholestatic liver disease. However, stoma related problems and reoperations are common.

Several rare liver diseases in children may cause debilitating pruritus. Progressive familial intrahepatic cholestasis (PFIC), a heterogenous group of autosomal recessive disorders, is the most common of the cholestatic disorders causing severe pruritus. Other liver diseases typically associated with severe itching include Alagille and Aagenaes syndromes. These congenital liver diseases may lead to end stage liver failure and need for liver transplantation. In some children, the pruritus is so debilitating that liver transplantation may be indicated even though most liver function parameters are satisfactory. To postpone liver transplantation due to extreme pruritus or the development of liver failure, various forms of partial biliary diversions (PBD) have been described (1, 2). Since PFIC, Alagille and Aagenaes syndromes are all rare conditions, experience with PBD is limited in individual centers. Consequently, most reports on PBD consist of small number of patients and have relatively short follow-up times (1, 3). The largest series to date includes 58 patients operated at 14 different centers in the United States, and in this series the main focus was to study the effect on postoperative liver function parameters (4). The present series report long-term results in all patients operated with PBD in the Nordic countries, representing a population of around 26 million people and covering a time period of 25 years. The main aims were to record effect of PBD on intractable pruritus and surgical complications.

1. Patients and Methods

1.1. Data collection

Clinical data were recorded through retrospective review of medical records. Patient demographics, laboratory and surgical data were collected in addition to latest follow-up data using a standardized data collection form which were mailed to all Nordic university pediatric surgical centers having performed PBD. Postoperative complications were graded according to the Clavien-Dindo classification system (5). Itching was graded from 1-3 where 1 denotes no itching, 2 moderate itching and 3 severe and troublesome itching.

1.2 Ethics

The study was approved by the institutional review boards and/or ethics committees at each centre.

1.3 Statistical analysis

Numerical data are presented as median [min-max] or mean (SD) as appropriate. Categorical data are given as frequencies and percentages. Mann-Whitney U-test or Student-t test were used to compare continuous variables and Chi-square to compare categorical data. A two-sided p-value less than 0,05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp. Released 2016.

2. Results

2.1 Patients

In the Nordic countries, a total of 33 pediatric patients have undergone PBD until the end of December 2018, and the first patient was operated in 1992. These 33 children, 14 (42%) males, were operated at four university hospitals in Stockholm, Oslo, Helsinki, and Gothenburg, treating 16, 10, 4, and 3 patients, respectively. PFIC2 was the most common diagnosis (Table 1). In all operated children conservative treatment, including a combination of different drugs, had proven unsuccessful to relieve itching. Preoperative itching was in all patients graded as 3. The most commonly used drugs were cholestyramine (n=13), naltrexone (n=8), antihistamines (n=15), and rifampicine (n=20). Prior to biliary drainage median serum levels of bile acids were 339 (65-687) μmol/L, bilirubin 60 (3-577) μmol/L, and albumin 35 (29-37) g/L. Median age at the first PBD was 1.5 (0.25-13) years, and median Z-scores for weight and height were -1.1 (-3.3-0.4) and -2.0 (-4.0-1.6), respectively.

Survival. The median follow-up time is 10 (0.6-25.2) years. Three patients died during the follow-up. One died of complications after liver transplantation. Indication for liver transplantation for this patient was intolerable itching. One patient was operated due to adhesion ileus two years after PBD, got sepsis and died, whereas the third patient died of unknown cause.

2.2 Operative details and complications

Various operations were used for the initial PBD, but all patients underwent an external PBD. In 25 patients a short jejunal segment was used as biliary conduit where one end was sutured to the gallbladder and the other end of the segment constructed as an ostomy (cholecystojejunostomy). When a button was used for biliary drainage, the button was either placed in the gallbladder (n=7) or in a jejunal conduit sutured to the gallbladder (n=1). When a button was used for biliary drainage, the gallbladder or the conduit was sutured to the anterior abdominal wall. Only three operations were done laparoscopically, and in all three a button was put in the gallbladder.

Early (<30 days) complications after the initial biliary drainage operation were common and occurred in nine (27%) patients (Table 2). The majority of the early complications were minor, but three patients (9%) needed a reoperation during the first postoperative month. After the first month, complications related to the external diversions were common (55%). These included leakage and frequent need for change of stoma equipment, skin irritation, bleeding from the stoma, skin infection, and stricture.

Secondary surgical interventions were frequently performed, and some patients underwent multiple operations because of complications related to the PBD (Table 3). Indications for reoperations were mainly stoma related problems (leakage, problems to apply stoma equipment, bleeding, prolapse), patients' wish for removal of the external stoma or inadequate bile drainage with persistent severe itching. Six cholecystojejunostomies with excellent effect on itching were converted to internal diversions because of stoma related

problems by anastomosing the jejunal conduit to the ascending colon. Only two of these six patients continued to have satisfactory effect on itching with the internal diversion. Three underwent liver transplantation, and one patient had the internal diversion closed and a button placed in the conduit with excellent result on itching. Of the seven patients who initially got a button in the gallbladder for external PDB, three needed conversion to a cholecystojejunostomy due to poor bile flow and insufficient effect on itching. In two of these three patients, the symptoms relieved after conversion.

2.3. PBD survival

The PBDs have been in use for median 10 (0.6-25.2) years. Two patients died with the PBD in use, 14 and 24 months after cholecystojejunostomy. One of these had severe itching (grade 3) until death, whereas the other did not have any itching (grade 0). In another patient the cholecystojejunostomy closed spontaneously after a few months, and the patient is doing well.

At present 17 patients have some form of PBD; cholecystojejunostomy (N=9), button in conduit (N=3), button in gallbladder (N=3), or internal diversion (N=2). Ten patients are doing well without itching (grade 1) or deteriorating liver function, five have moderate itching (grade 2) and two severe itching (grade 3). Three patients with button either in the gallbladder or in a conduit, drain bile intermittently during the day. Two patients are on the waiting list for transplantation, and both have severe itching. A total of 13 patients have undergone liver transplantation due to inefficient relief of the PBD on itching. No patient underwent liver transplantation with good relief of pruritus of the PBD, but progression of liver disease.

Bile acid levels at discharge were significantly lower in those who later did not need a liver transplantation (table 4). There was no significant difference in age at first PBD, levels of platelets, bilirubin, and ALT between those who had a favourable outcome after PBD and those who did not.

3. Discussion

The main finding of this multicenter study is that PBD may delay liver transplantation for many years in children with various rare cholestatic liver disorders causing intolerable itching. Furthermore, this study shows that PBD complications are common, and many patients will need reoperations because of PBD related problems.

Several papers during recent years have shown that PBD may relieve intractable pruritus in children with cholestatic liver disease. However, most of these studies report outcome from single center small series, typically including less than 20 patients, and follow-up time is usually only a few years (2) (6-8). Consequently, it is difficult to conclude on the long-term efficacy of PBD both in relation to effect on pruritus and liver function. In addition, several operative techniques are used for biliary diversion, and a poor functioning PBD may be replaced by another type PBD. Thus, the heterogeneity of the treatment complicates the assessment of outcome and complication rates even more. The first described and still most common operation for PBD is the cholecystojejunostomy when a jejunal conduit sutured to

the gallbladder is fashioned as an ostomy (9). Because the presence of an external stoma may be uncomfortable and is associated with multiple stoma-related complications, various forms of internal PBD have been proposed. Ileal exclusion is one alternative. In this technique around 15% of the terminal ileum is excluded from the enterohepatic circulation (10). Although initial results were promising, up to 50% recurrence rates were reported (11). Internal PBD may also be fashioned using a jejunal conduit from the gallbladder to the ascending colon or by a cholecystocolostomy where the transvers colon is anastomosed to the gallbladder and the mid-descending colon using a Roux-en-Y loop (2) (3). Recently, placing a button in the gallbladder has been presented, and the results of this technique in the literature are promising (12, 13). In the present study involving four different centers, the choice of techniques reflect the literature; the cholecystojejunostomy is the most commonly performed way of PBD, and various forms of internal PBD have been tried when problems related to the cholecystojejunostomy occurred. The use of buttons for PBD and especially by laparoscopic technique has only been performed in recent years.

PBD was first described to treat PFIC1. Later PBD has also been offered to patients with PFIC 2 and 3, as well as syndromes such as Alagille, Aagenaes and others (2). As in most series reporting results of PBD, the majority of the patients in this study have PFIC. Due to the relatively small number of patients with the different diagnosis, it was not possible to compare results of PBD between the various diagnosis groups. Importantly, relief of pruritus was obtained for patients with all of the different diagnoses, indicating that PBD should be an alternative for children with debilitating itching due to cholestatic liver disease unless their liver function for other reasons suggests that a liver transplantation is a better alternative.

Few series report early complications after PBD. In this series 9% experienced Clavien-Dindo grade 3b complications, meaning that the patients needed a surgical, endoscopic or radiological intervention under general anesthesia. In a small series from Phoenix, one out of four patients was operated during the first seven postoperative days because of bleeding from the jejunal anastomosis (14). In a series of 14 children, two were reoperated during the first postoperative week due to bleeding and wound dehiscence (1). Why such a relatively minor operation has such a high complication rate is not obvious. A plausible reason is that PBD is a very rarely performed operation, and few surgeons therefore gain experience with the technique.

We have found that stoma related problems were common and in particular related to cholecystojejunostomies. The patients reported leakage and difficulties finding appropriate stoma equipment. There are not many studies that have addressed stoma related complications after PBD. In a series of 14 patients getting a cholecystojejunostomy, 3/14 patients needed surgical correction of stoma prolapse or parastomal hernia, and one patients needed dilatation of the stoma (1). Matei and coworkers also reported problems with leakage from the ostomy (14). Prolapse has been reported in several previous reports and also in this present series. The patients with prolapse in this series were operated with shortening of the jejunal conduit with no recurrence of prolapse afterwards. Thus, it is important when establishing a cholecystojejunostomy to take caution to not make the conduit longer than necessary.

The first PBDs to be performed were external diversion, typically a cholecystojejunostomy. Due to the increasing awareness of complications associated with these stomas, internal PBDs were proposed as an alternative. There are variations in how internal diversions are performed. In our and several other series an isolated jejunal loop was anastomosed to the gallbladder fundus and the ascending colon. Using this technique in 12 children, a study from India with a median observation time of 30 months, reported that pruritus resolved in nine children with a significant reduction in bile acids (2). However, there are reports showing less good results after internal diversion with recurrence rate up to 50 % of the patients (11). To reduce the recurrence rate of pruritus, Diao and coworkers presented a new technique using an antireflux Y-loop for the cholecystocolostomy in 20 children with a 85% success rate and median 54 months follow-up (3). In our series, six children underwent internal PBD, but it was only successful in one third of the patients. Notably, all these patients had good effect of the external PDB suggesting that internal diversion may not work even though an external PDB has good results. An important observation from this study is that reversing the internal PDB may have a favorable outcome and postpone the need for liver transplantation.

To place a button in the gallbladder for either continuous or intermittent draining of bile is an appealing alternative for PBD (12, 13). In the literature, the results from this technique are good. In our series, 4/7 patients getting a button in the gallbladder needed a reoperation due to insufficient effect on pruritus. In all, bile drainage and symptoms improved after revision to a cholecystojejunostomy. It is difficult to explain why drainage through a button is insufficient when a cholecystojejunostomy is effective. In one of our patients, contrast studies were performed, but could not demonstrate any obstruction to bile flow. It is an important finding from this study that insufficient effect of a button in the gallbladder does not necessarily mean that PBD is ineffective, but that another form of PBD should be tried. At the same time, for those who get sufficient biliary drainage from the button, this form of PBD is often very well tolerated.

Since the effectiveness of PBD on relieving pruritus due to cholestatic liver disease is so unpredictable, a predictor for success would be of great help. Unfortunately, we could not find that age, preoperative levels of bilirubin, ALT, platelets, albumin (results not shown) or INR (results not shown) were different in patients with and without a favorable outcome of PBD. Interestingly, we found that levels of serum bile acids at discharge after PBD were significantly lower in those who did not need a liver transplantation later. Our data indicate that an early decrease in biliary acid levels in the first week after PBD is a significant prognostic factor for a favorable long term outcome.

PBD in the Nordic countries has only been performed in the four centers taking part in this study. In Denmark no child has undergone PBD (personal communication). Thus, there seems to be a significantly different use of PBD in the Nordic countries. Since our populations are so similar, one would expect the various cholestatic liver diseases had approximately the same incidence. One explanation for the differing use of PBD could be that some pediatric hepatologists refer these patients to liver transplantation instead of PBD. A recent publication showed that quality of life was similar in pediatric patients undergoing liver

transplantation and PBD (15). However, in this publication one did not take into account the long term side effects of immunosuppressive treatment. Based on this and other reports, we would argue that PBD should be the first surgical treatment of choice for patients with intractable pruritus because of cholestatic liver disease since the operation has fewer major complications than liver transplantation, and there is no need for immunosuppression. Furthermore, a liver transplantation may be done later if the PBD is unsuccessful.

The strength of this study is that it involves results after PBD from several countries and centers. The records of all patients in the Nordic countries operated with PBD have been included. Furthermore, the follow-up time is long for many of the patients. The retrospective nature of the study is a limitation, and for some patients not all data were possible to retrieve in retrospect. Lastly, there is not a precise diagnosis for all patients, particularly for those treated in the early years of the study, and no precise grading of itching could be performed in retrospect.

This study shows a significant early complication rate and frequent need for further surgical procedures after PBD. No comparable long term registration of surgical complications has to our knowledge been published previously. Our findings suggest that these operations should be centralized enabling some centers to get experience with the method. It is also important that surgeons treating these patients are aware of common complications and that patients and parents are informed appropriately.

Table 1. Diagnoses in 33 children undergoing partial biliary diversion due to intolerable itching caused by cholestatic liver diseases. Pre-operative levels of bile acids and bilirubin and grade of itching are listed for all patients and at latest follow-up for patients having their native liver.

Diagnosis[1]	**N**	**Years at first PBD[2]**	**Preop BA[3]**	**BA**	**Preop Bi[4]**	**Pres**
PFIC1	4	0,65 (0,5-0,9)	205 (195-457)	267 (248-310)	216 (41-536)	20 (6
PFIC2	19	1,6 (0,8-13)	350 (3-383)	92 (2-316)	69 (3-338)	13 (3
PFIC3	1	5,8	124		12	
Aageneas	1	7,9	531	11	28	7
Alagille	2	1,7 (1-2,2)	298 (121-475)	107	65 (48-82)	48
Unknown	6	1,7 (0,3-12,4)	254 (65-542)	6 (5-8)	24 (6-107)	2 (0,3

[1]PFIC1: Progressive familial intrahepatic cholestasis, type 1; PFIC2 Progressive familial intrahepatic cholestasis, type 2; PFIC3: Progressive familial intrahepatic cholestasis, type 3; Aagenes syndrom; Alagille syndrome; unknown diagnosis [2]PBD – Partial biliary diversion; [3]BA –Serum levels of biliary acids (□mol/L); [4] Bi: Serum levels of Bilirubin (□mol/L); [5]Tx: Percentage of patients who underwent or are listed for liver transplantation [6] Itching at last follow-up; 1: no itching; 2 moderate itching; 3 severe and troublesome itching. Median, minimum and maximum values are given. Only data from patients with their native liver are included.

Table 2. Early (<30 days) postoperative complications after partial biliary drainage in 33 children. Complications are graded according to the Clavien-Dindo classification system. Some patients had more than one complication. * CJJ: Cholecystojejunostomy; BC: Button in gallbladder; BJ: Button in jejunal conduit

	N	Procedure*
Patients with complications	9	
Grade 1 (total number of complications)		
Leakage from stoma	2	CJJ
Pain	1	BC
Grade 2 (total number of complications)		
Infection around button	3	BC
Infection around stoma	1	CJJ
Abscess at port site	1	BC
Suspected infection around insertion of epidural catheter	1	BJ
Grade 3b (total number of complications)		
Bowel prolapse	1	CJJ
Bleeding and leakage	1	CJJ
Revised because of inefficient drainage	1	BC

Table 3. Secondary surgical intervensions after initial partial biliary drainage in 33 children. Some patients had more than one operation. CCJ: Cholecystojejunostomy, BC: Button in gallbladder; BJ: Button in jejunal conduit

Type of operation	**N**
Revision of CCJ due to prolapse, bleeding, leakage, stricture, perforation	9
Conversion from CCJ to internal diversion	6
Revision from BC to CCJ	4
Internal diversion converted to BJ	1
BC converted to BJ	1
Ligation of common bile and total biliary diversion with jejunostomy for partial biliary return	1

Table 4. Levels of liver function parameters and patient characteristics in patients who did and did not need a liver transplantation. *The two patients waiting for liver transplantation are grouped together with those who have been transplanted. Median values, min and max are listed for liver function parameters

	No transplant	**Transplant***	**P**
Age at first biliary diversion	1,5 (0,3-13) yrs	1,5 (0,5-6,5) yrs	0,70
Preoperative Bilirubin	66 (3-577) μmol/L	54 (10-338) μmol/L	0,86
Preoperative ALT	6 (1-173) μmol/L	8 (1-265) μmol/L	0,59
Preoperative platelets	363 (184-882) μmol/L	432 (170-922) μmol/L	0,62
Preoperative bile acids	334 (65-687) μmol/L	345 (121-560) μmol/L	0,33
Bile acids at discharge after first biliary diversion	13 (2-192) μmol/L	148 (5-383) μmol/L	0,02

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