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ORIGINAL ARTICLE

Nasobiliary drainage prior to surgical biliary diversion in progressive familial intrahepatic cholestasis type II

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Abstract

Progressive familial intrahepatic cholestasis (PFIC) can cause intense pruritus that is refractory to medical therapy. Surgical biliary diversion techniques, including partial internal biliary diversion (PIBD), have been developed over the years to relieve pruritus without requiring liver transplantation. No clinical or genetic features can currently predict postoperative pruritus response. We present three PFIC type 2 (PIFC 2) patients who underwent transient endoscopic nasobiliary drainage (NBD) prior to PIBD surgery. Two patients repeatedly responded to NBD and presented with complete pruritus resolution after subsequent PIBD. NBD failed technically in the third patient, and PIBD was partially successful. Mild post-endoscopic biological pancreatitis occurred in 2/6 NBD procedures and resolved spontaneously. The only adverse effect observed within 7 years post-PIBD was very mild transient osmotic diarrhea.

Conclusion: Our limited data suggest that NBD is a safe and effective way to predict pruritus response before performing permanent biliary diversion surgery in PFIC patients.

What is Known:
- *Surgical biliary diversion techniques have been developed to relieve intractable pruritus in progressive familial intrahepatic cholestasis (PFIC).*
- *No clinical or genetic features can currently predict pruritus response to surgery.*

What is New:
- *Our data suggest that nasobiliary drainage could be a safe and effective tool to predict pruritus response to biliary diversion and avoid unnecessary surgery in PFIC patients.*

Keywords Biliary diversion · Nasobiliary drainage · Familial cholestasis · Pruritus · Bile acids

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Abbreviations

ERCP	Endoscopic retrograde cholangiopancreatography
MARS	Molecular adsorbents recirculating system
NBD	Nasobiliary drainage
PEBD	Partial external biliary diversion
PFIC	Progressive familial intrahepatic cholestasis
PIBD	Partial internal biliary diversion
TBA	Serum total bile acids

Introduction

Progressive familial intrahepatic cholestasis (PFIC) refers to a group of autosomal recessive disorders, which result in liver cholestasis caused by hepatocellular defects in the secretion of bile components. Patients may experience extremely intense pruritus despite medical therapy; this was originally an indication for liver transplantation [1, 2]. Over the years, various surgical techniques for biliary diversion have been developed to relieve pruritus without liver transplantation [3]. Among those surgical techniques, partial internal biliary diversion (PIBD) has shown very promising results and has the advantage of avoiding external stoma and related infections [4, 5]. Despite the efficacy and safety of this procedure, some patients do not respond to the surgery and there is currently no method for predicting response according to genotype or other clinical parameters. Ramachadran et al. observed pruritus improvement in seven out of ten PFIC 1 and PFIC 2 patients after PIBD [4]. Erginel et al. observed pruritus reduction in five out of six PFIC 1 and PFIC 2 patients after PIBD, and suggested that outcomes may be better in PFIC 1 patients after biliary diversion [5]. However, PIBD can be a useless permanent intervention in patients who do not show any post-operative pruritus improvement, with subsequent risk of osmotic diarrhea [4, 6]. Endoscopic nasobiliary drainage (NBD) is a reversible procedure, which may improve pruritus in various cholestatic diseases, including primary biliary cirrhosis or benign recurrent intrahepatic cholestasis [7, 8]. This procedure has proven to be safe even for long-term use, the principal adverse effect being post-endoscopic pancreatitis [7, 9]. It has already been suggested that NBD could be an efficient way to evaluate pruritus response to biliary drainage before performing a surgical procedure with permanent effects [10]. To our knowledge, no clinical case has been published to confirm this hypothesis.

We present three PFIC 2 patients who underwent NBD to evaluate their clinical response to biliary drainage prior to PIBD surgery. NBD was inconclusive in one patient, since no bile was ever drained by the catheter. The two other patients displayed full response to NBD and then underwent PIBD successfully, with complete resolution of pruritus.

Materials and methods

Inclusion criteria

Patients were retrospectively identified in the Pediatric Hepatology database of the Cliniques Universitaires Saint-Luc. The inclusion criteria were:(1) confirmed diagnosis of cholestatic liver disease and (2) NBD followed by surgical biliary diversion. No age restrictions were applied. We identified three patients diagnosed with PFIC 2 who underwent NBD prior to PIBD between 2011 and 2019.

Endoscopic nasobiliary drainage

A catheter (size 5 French in children and 7 French in adults) was placed in the common bile duct by endoscopic retrograde cholangiopancreatography (ERCP) under general anesthesia (Fig. 1a). No sphincterotomy was performed. The position of the nasobiliary catheter was confirmed by contrast product injection through the catheter.

Partial internal biliary diversion surgery

Right subcostal laparotomy was performed to place a jejunal conduit of 25 cm between the gallbladder fundus and the transverse colon (Fig. 1b). Jejunal continuity was restored through jejunal termino-lateral anastomosis. Antibiotic prophylaxis with cefuroxime and metronidazole was administered to the patients for 4 days after surgery coupled with long-term fat-soluble vitamin supplementation.

Pruritus score

Pruritus was assessed according to the scale of Whitington et al., modified as follows: 0 = none; 1 = rubbing or mild scratching when undistracted; 2 = active scratching without evident skin abrasions; 3 = abrasions evident; 4 = cutaneous mutilation and scarring evident, impaired quality of life [11].

Results

Clinical case no. 1

The first patient was a Caucasian female diagnosed with PFIC 2 based on the presence of two compound heterozygous mutations identified in the *ABCB11* gene: c.1548T>G (p.Ile516Met) and c.1622T>C (p.Ile541Thr). She suffered from mild jaundice and intense pruritus since her first year of life. Pruritus caused her major sleep and concentration troubles. Various pharmaceutical interventions were unsuccessfully tested, including rifampicin, cholestyramine, ursodeoxycholic acid, phenobarbital, simvastatin, anti-

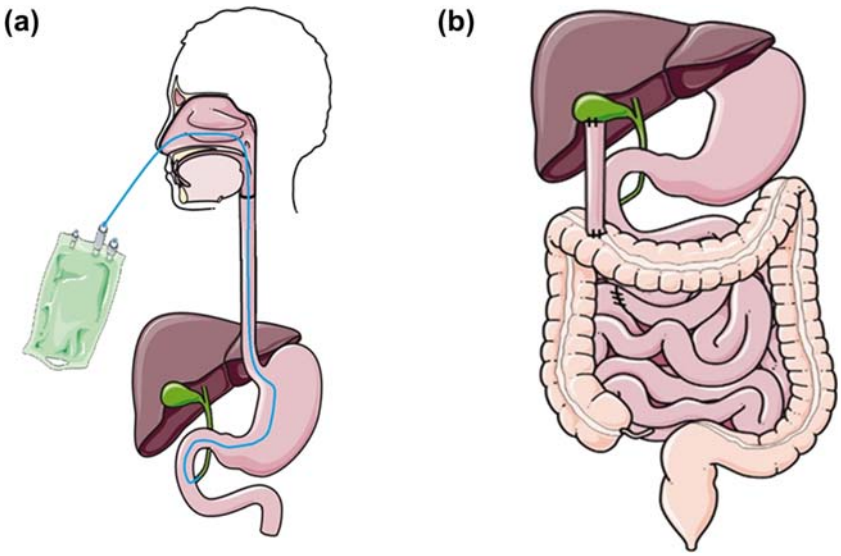

Fig. 1 **a** Nasobiliary drainage; **b** partial internal biliary diversion. Illustrations are modified from Servier Medical Art

histamines, and zinc. Liver transplantation was considered but never performed due to normal liver function and histology. In another attempt to relieve pruritus, Molecular Adsorbents Recirculating System (MARS—also termed albumin dialysis) was tried at the age of 24 years. The first attempt (two cycles in 2 days) improved her pruritus (score 4 decreased to 2), but its intensity returned to baseline (score 4) 15 days after the first dialysis. One month later, a second MARS attempt (three cycles in 3 days) only mildly improved pruritus (score 4 decreased to 3) for a few days. Seven months later, ERCP-guided NBD was performed in this patient. At the time, she had normal total serum bilirubin levels and gamma-GT, with elevated serum total bile acids (TBA) (93.7 μmol/L; normal value < 10 μmol/L). Her liver transaminases and liver function were normal. A few hours after the procedure, the pruritus drastically decreased (score 4 decreased to 0), and TBA levels normalized to 5.0 μmol/L after 24 h. The patient developed mild biological post-endoscopic pancreatitis, which resolved without any treatment. The catheter spontaneously dislodged from the biliary tree after 3 days, leading to pruritus recurrence. A second NBD was performed 1 month later to assess reproducibility. Pruritus markedly improved again (score 4 decreased to 1), and TBA levels decreased from 90.0 to 14.0 μmol/L. Post-endoscopic pancreatitis did not occur. Three months later, at 25 years of age, she underwent PIBD surgery. At the time, her liver transaminases and liver histology were still completely normal (Metavir score F0). The pruritus resolved completely a few hours after surgery (score 4 decreased to 0), and TBA levels decreased from 282.0 μmol/L before surgery to 40.7 μmol/L 3 days after surgery (Table 1). Two weeks after surgery, TBA levels were 103 μmol/L and pruritus was still absent. Two months after surgery, she complained about mild osmotic diarrhea, with excellent response to cholestyramine therapy and rapid resolution. Three years after surgery, she experienced transient pruritus (score 2) during a constipation episode, which spontaneously resolved after a few weeks. Seven years after surgery, she is still free of pruritus and does not present any adverse effects due to the surgery. Her liver function and enzymes remain normal, with normal bilirubinemia and improved TBA levels (11.9 μmol/L).

Clinical case no. 2

The second patient was a Caucasian male diagnosed with PFIC 2 at the age of 6 months. The following compound heterozygous mutations were identified in the *ABCB11* gene: c.2178+1G>A and c.389+8G>A. His major symptoms during childhood were pruritus and failure to thrive. Around the age of 12 years, the pruritus became severely debilitating, despite medical therapy with rifampicin, cholestyramine, and ursodeoxycholic acid. Liver transplantation was not formally indicated, since his liver function was normal, and liver biopsy showed only very mild fibrosis (Metavir score F0-F1). He first underwent NBD at 27 years of age. At the time, he had total bilirubin levels of 1.6 mg/dL (normal value 1.2 mg/dL), with normal gamma-GT, and elevated TBA levels (178.0 μmol/L). His liver transaminases were slightly elevated (AST 60 U/L and ALT 54 U/L; normal values < 40 U/L). A few hours after the procedure, the pruritus completely resolved (score 4 to 0), TBA levels decreased slightly to 140.0 μmol/L, and liver transaminases almost completely normalized (AST 42 U/L and ALT 31 U/L). The nasobiliary catheter remained for 6 days, and pruritus recurred 4 days after catheter removal. Two more NBDs were performed in this patient, 2 months and 4 months after the first attempt. Both procedures completely abrogated the patient's pruritus (scores 4 decreased to 0), until a few days after the removal of the catheter. None of the three NBD procedures caused post-ERCP pancreatitis. Four months later, at 28 years of age, he underwent PIBD surgery. The

Table 1 Serum TBA levels and pruritus scores before and after PIBD. Last follow-up was 7 years after the surgery for patient 1, 1 month after the surgery for patient 2, and 6 months after the surgery for patient 3. Normal TBA levels < 10 μmol/L. *PIBD*, partial internal biliary diversion; *TBA*, serum total bile acids

	Pre-PIBD		3 days post-PIBD		15 days post-PIBD		Last follow-up	
	TBA (μmol/L)	Pruritus score	TBA (μmol/L)	Pruritus score	TBA (μmol/L)	Pruritus score	TBA (μmol/L)	Pruritus score
Patient 1	282	4	40.7	0	103	0	11.9	0
Patient 2	314.4	4	220.9	0	382.5	0	304.6	0
Patient 3	402	4	267	0	635.8	3	533	1–2

pruritus resolved completely a few hours after surgery (score 4 decreased to 0), and TBA levels decreased from 314.4 to 220.9 μmol/L 3 days after surgery (Table 1). Two weeks after surgery, TBA levels returned to 382.5 μmol/L without pruritus recurrence. One month after surgery, the patient was well and free of pruritus. TBA levels were 304.6 μmol/L.

Clinical case no. 3

The third patient was a Caucasian male diagnosed with PFIC 2 at the age of 3 months (homozygous mutation C1810-3C>G in the *ABCB11* gene). Because of intense pruritus refractory to medical therapy, it was decided to try biliary diversion. He underwent NBD at the age of 2 years and 9 months. At the time, total bilirubin levels were 2 mg/dL, gamma-GT levels were normal, and TBA levels were elevated (414 μmol/L). His liver transaminases were elevated (AST 213 U/L and ALT 177 U/L). Liver histopathology showed marked fibrosis with occasional nodules (Metavir score F3-F4). A 5-French catheter introduced in the common bile duct never drained any bile and was removed 17 h later because of increased lipase levels. Biological pancreatitis resolved spontaneously a few days after catheter removal. TBA levels were unchanged (402 μmol/L, 24 h after the procedure). No pruritus improvement was noticed during NBD, but the procedure was considered inconclusive, as no bile was ever drained. No further NBD was attempted, and the patient underwent PIBD 1 month later. Pruritus markedly improved following surgery (score 4 decreased to 0,) and TBA levels decreased to 267 μmol/L after 48 h. Five days post-surgery, total bilirubin decreased to 1.4 mg/dl and transaminases were improved (AST 58 U/L and ALT 47 U/L). Fifteen days after surgery, pruritus recurred (score 0 increased to 3) during an episode of constipation with enlargement of the jejunal conduit used for the diversion (TBA levels, 635.8 μmol/L). The pruritus fully responded to laxative therapy. Six months after surgery, the patient complained about mild pruritus (score 1–2). His TBA levels were 533 μmol/L with total bilirubin at 1.7 mg/dl and elevated transaminases (AST 135 U/L and ALT 114 U/L). Liver histology was stable.

Discussion

Our experience suggests that NBD is a safe way to predict pruritus response to PIBD in PFIC 2 patients. We observed two mild transient occurrences of post-endoscopic pancreatitis over the six NBD procedures, with rapid and spontaneous resolution. When performed after successful NBD, PIBD drastically improved the quality of life of our patients. The only adverse effect observed up to 7 years post-surgery was very mild osmotic diarrhea, which was easily treated with cholestyramine.

Biliary diversion techniques were originally developed to improve pruritus through interruption of biliary enterohepatic circulation [11, 12]. Bile acids are normally excreted by the liver in the bile, and then mostly reabsorbed in the small intestine to return to the liver through the hepatic portal circulation. In cholestatic disease, it was hypothesized that pruritus resulted from intradermal bile acid accumulation secondary to elevated serum TBA levels [4]. Enterohepatic cycle interruption through biliary diversion would lead to an excretion of bile acids, with progressive depletion of the total bile acids pool and pruritus improvement. Unexpectedly, a correlation between pruritus and TBA levels was never demonstrated [13]. Kremer et al. reported that TBA levels can rise back to baseline values during NBD without associated recurrence of pruritus [13]. In the same study, MARS strongly decreased pruritus severity, while TBA levels were not significantly reduced. In our experience, complete pruritus resolution occurred after biliary diversion through NBD or PIBD, even with moderate reduction in TBA levels. We also observed that TBA levels could rise back to baseline values after biliary diversion without pruritus recurrence. Regarding MARS, one of our patients underwent several cycles on two occasions. As already suggested for cholestatic disease, the decrease in pruritus experienced after dialysis was only transient [14]. In our patient, pruritus relief was stronger following NBD compared to MARS [13]. An alternative hypothesis suggesting how biliary diversion reduces pruritus involves the lysophospholipase autotaxin (ATX) as a potential mediator of cholestatic pruritus [15]. It was observed that pruritus and serum ATX reduction are directly correlated following NBD and MARS [13]. Since no ATX was detected in the bile, it was hypothesized that an ATX-inducing factor exists in the bile and is removed from the enterohepatic

circulation by the biliary diversion [13]. This mechanism could explain the rapid resolution of pruritus that we observed in our patients after NBD and PIBD. However, the ATX-inducing factor remains to be identified and the physiopathology of pruritus in cholestatic diseases is still not completely understood.

The first surgical technique for biliary diversion developed to treat pruritus was partial external biliary diversion (PEBD). Whitington et al. demonstrated that PEBD not only showed excellent results on pruritus but that histological cholestasis and portal fibrosis resolution were observed a few years after surgery [11]. Those results were corroborated by Arnell et al., who observed successive reductions in histological cholestasis and then fibrosis after PEBD in 12 PFIC patients [16]. Moreover, Schukfeh et al. reported no progression of biochemical cholestasis in 13 out of 17 PFIC patients who underwent PEBD surgery without liver cirrhosis [17]. One year after surgery, those patients had reduced TBA and total bilirubin levels, with stable liver transaminases. On the contrary, all seven cirrhotic patients who underwent PEBD needed subsequent liver transplantation within 1 year after PEBD [17]. Over the years, PEBD has become a fistline therapy in PFIC types 1 and 2 in the absence of established cirrhosis [18]. PEBD and PIBD are both partial biliary diversion techniques, with very similar physio-pathological outcomes. In our first patient, biochemical cholestasis did not progress in 7 years of follow-up post-PIBD. In the future, PIBD could become an indication not only for the relief of severe refractory pruritus in PFIC but also for the slowing down of the progression of cholestasis and fibrosis in early disease stages.

PIBD has the advantage of avoiding external stoma and related complications but increases the concentration of bile acids in the colon. This might cause bile acid diarrhea, which usually responds well to cholestyramine therapy. Previous publications suggested that patients with colorectal cancers might have higher fecal bile acid levels than controls [19]. To our knowledge, no study has ever demonstrated that patients suffering from bile acid malabsorption are at higher risk for developing colorectal cancer. In the general population, the fraction of bile acids that are not reabsorbed by enterocytes, and thereby end up in the feces, represents approximately 5% of the total bile acid pool [20]. Due to BSEP mutations, the concentration of bile acids in the bile is very low in PFIC 2 patients (< 1% of normal) [21]. In this context, it is very unlikely that PFIC 2 patients who underwent PIBD would be at higher risk of colorectal cancer, as compared to the general population. Nonetheless, further research will be needed to investigate the potential risk of colorectal cancer related to PIBD in cholestatic patients.

In PFIC type 2 patients who underwent PEBD, common missense mutations (patients heterozygous or homozygous for p.Asp482Gly and/or p.Glu297Gly BSEP mutations) had been suggested to predict a better outcome compared to other BSEP mutations [22–24]. Our two patients who underwent successful NBD did not carry common missense BSEP mutations and still presented with good clinical outcomes following PIBD surgery. No correlation between PFIC genotype and post-surgical outcomes has been demonstrated to date in PIBD, but NBD could be a useful tool to help predict clinical outcomes after biliary diversion procedures.

The principal limitation of our work is the small number of participants. Of our three patients, two underwent successful NBD, and the procedure was inconclusive in the third patient. We observed that the two patients who responded to NBD underwent successful PIBD, but we cannot state that NBD failure leads to unsuccessful PIBD. In the same way, the number of patients that we present is too small to conclude that effective NBD will always lead to pruritus resolution after PIBD. Nonetheless, our results are encouraging and highlight NBD as a promising tool for predicting PIBD outcomes. It is also important to note that the successful NBD procedures that we describe were performed on two adult patients. Successful NBD and PIBD have already been described in pediatric patients, but the technical challenge of performing NBD in pediatric patients will have to be considered in future research [4, 25].

In conclusion, our limited experience suggests that NBD is an excellent way to test pruritus response to biliary diversion before performing permanent biliary diversion surgery in PFIC patients. Further research will have to be conducted to corroborate our data and to extend PIBD indication from refractory pruritus to disease progression in the absence of cirrhosis.

Authors' contributions GJ contributed to study conception and design, to data collection and analysis, drafted the manuscript and approved the final manuscript. XS contributed to study conception and design and to material preparation, revised the manuscript and approved the final manuscript. IS contributed to study conception and design and to material preparation, revised the manuscript and approved the final manuscript. FS contributed to study conception and design and to material preparation, revised the manuscript and approved the final manuscript. CDM contributed to study conception and design and to material preparation, revised the manuscript and approved the final manuscript. RR contributed to study conception and design and to material preparation, revised the manuscript and approved the final manuscript. ES contributed to study conception and design and to material preparation, revised the manuscript and approved the final manuscript.

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Compliance with ethical standards These procedures were considered as standard medical care and did not require prior ethical committee approval.

Conflict of interest The authors declare that they have no conflicts of interest.

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