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Different techniques for biliary diversion in progressive familial intrahepatic cholestasis

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ABSTRACT

Background: Progressive familial intrahepatic cholestasis (PFIC) is a cholestatic liver disease of childhood. Pruritus resulting from increased bile salts in serum might not respond to medical treatment, and internal or external biliary drainage methods have been described. In this study, we aimed to evaluate different internal drainage techniques in patients with PFIC.

Patients and methods: Between 2009 and 2014, seven children (4 male, 3 female, 3 months–5 years old), (median 2 years of age) with PFIC were evaluated. The patients were reviewed according to age, gender, complaints, surgical technique, laboratory findings and outcome. In each two patients, cholecystoileocolonic anastomosis, cholecystojejunocolonic anastomosis and cholecystocolostomy were performed. Cholecysto-appendico-colonic anastomosis was the technique used in one patient.

Results: Jaundice and excessive pruritus were the main complaints. One of the patients with cholecystoileocolonic anastomosis died of comorbid pathologies (cirrhosis, adhesive obstruction and severe sepsis). Temporary rectal bleeding was observed in all the patients postoperatively. Regardless of the surgical technique, pruritus was dramatically decreased in all the patients in the postoperative period.

Conclusion: Regardless of the technique, internal biliary diversion methods are beneficial for the relief of pruritus in PFIC patients. Selection of the surgical method might vary depending on the surgeon's preference and the surgical anatomy of the gastrointestinal system of the patient.

Progressive familial intrahepatic cholestasis (PFIC) is an autosomal recessive liver disease characterized by intermittent attacks of cholestasis, which could start at any age and progress to hepatic failure [1]. Pruritus is a frequent symptom in cholestasis. It develops as a result of the increase of many substances in serum induced by failed bile excretion. Pruritus might not respond to medical treatment [2]. Surgical biliary diversion methods with internal or external drainage might be useful for resolving pruritus. Biliary drainage has been reported to delay the progressive course of the disease in many patients [3–5]. Biliary diversion might save time and even be therapeutic in patients for whom liver transplantation is necessary. In this study, we evaluated four internal drainage methods and their results in seven patients with PFIC.

1. Patients and methods

Between 2009 and 2014, seven PFIC patients (4 male, 3 female) from 3 months to 5 years of age (median 2 years) were evaluated. The patients were reviewed in terms of age, gender, complaints, the surgical technique and laboratory findings. All the patients received medical treatment consisting of ursodeoxycholic acid, a second-generation antihistamine and cholestyramine. In cases with grade 4 pruritus (severe pruritus with epidermal bleeding), medical treatment was determined to have failed, and these patients underwent surgery. The patients were operated on by three different surgeons, who had similar experience performing biliary diversion surgery.

Of the three surgeons who operated on the seven children included in this report, the first surgeon performed one cholecystojejunocolonic (CCJC), one cholecysto-appendico-colonic (CCAC) and one cholecystoileocolonic (CCIC) anastomosis. Another surgeon performed one CCJC, one cholecystocolostomy (CCCT) and one CCIC anastomosis. The last surgeon performed one CCCT. Pruritus was assessed from 0 to 4, according to the Whitington and Whitington scale [6]. ALT (alanine aminotransferase enzyme), AST (aspartate transaminase enzyme), GGT (gamma glutamyl transferase enzyme), ALP (alkaline phosphatase) and direct–indirect bilirubin levels were evaluated preoperatively and postoperatively. A CCIC anastomosis was performed in two patients. For CCIC anastomosis, a 10-cm long isoperistaltic ileal segment was divided from the ileum and placed behind the colon transmesocolically; the proximal end was anastomosed to the gallbladder, whereas the distal end was connected to the transverse colon as an end-to-side anastomosis (Fig. 1). A CCAC anastomosis was performed in one patient, and a CCJC anastomosis was performed in two patients. For the CCJC, a 10 cm long isoperistaltic jejunal segment was divided distal to 40 cm

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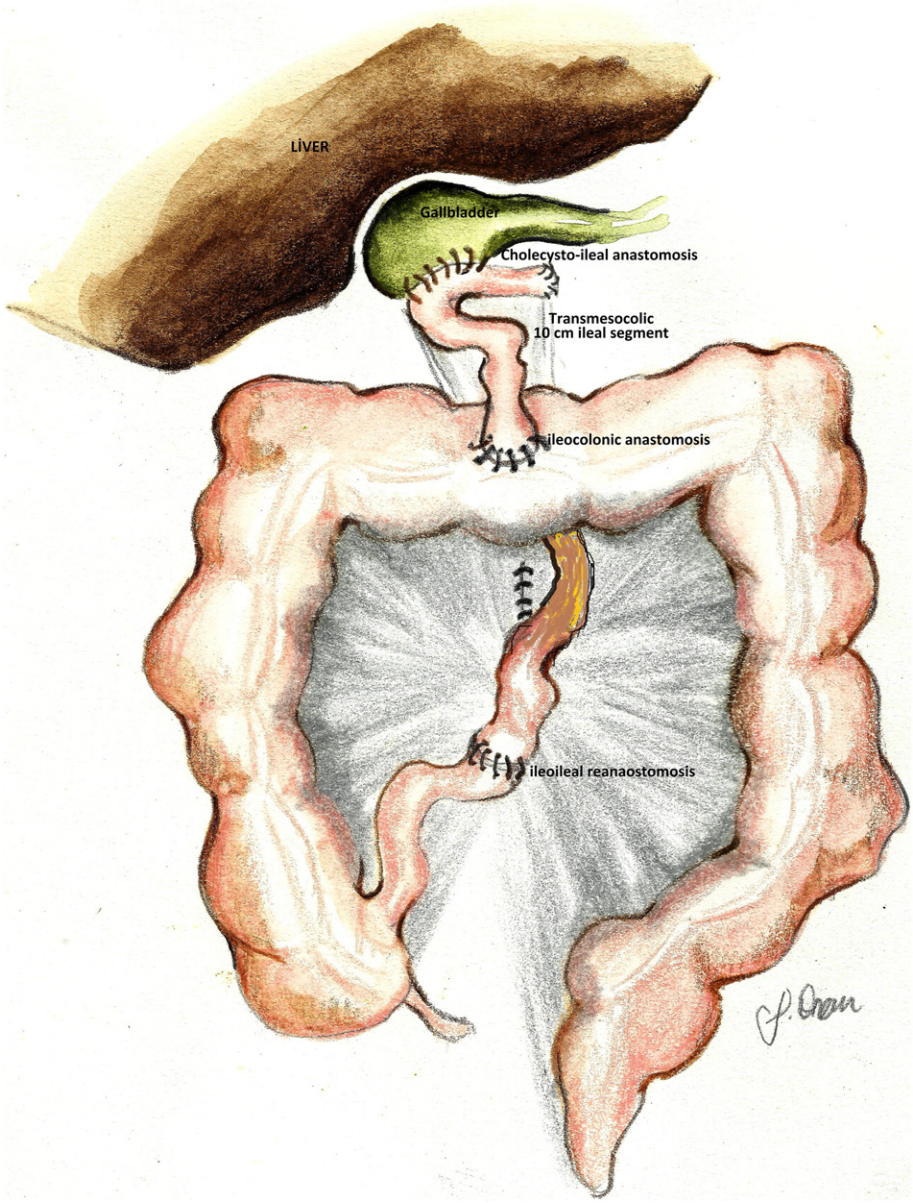

Fig. 1. Cholecystoileocolonic anastomosis.

from the ligament of Treitz. The proximal end was anastomosed to the gallbladder in an end-to-end fashion whereas the distal end was connected to the transverse colon as an end-to-side anastomosis. For the CCAC anastomosis, the appendix base was separated from the cecum, and the appendicular vessels were protected. A 1.5 cm-long incision was made on the gallbladder. The distal tip of the appendix was anastomosed to the gallbladder. The proximal tip of the appendix was anastomosed to the transverse colon in an end-to-side fashion. To protect the appendico-colonic anastomosis, a 1.5 cm long subserosal tunnel was created on the tenia of the colon (Fig. 2). In two patients, anastomosis was performed with the CCCT technique. The colon was separated from the splenic flexura, its mesentery was freed and the 10 cm-long colon segment was anastomosed to the gallbladder as a Roux-en-Y bypass. Colocolic anastomosis was performed on the antimesenteric side of the proximal colon in an end-to-side fashion, and thus the continuity of the colon was ensured (Fig. 3). The protocol for the postoperative follow-up consisted of evaluation of bilirubin and liver enzymes for the first month after surgery and then every three months.

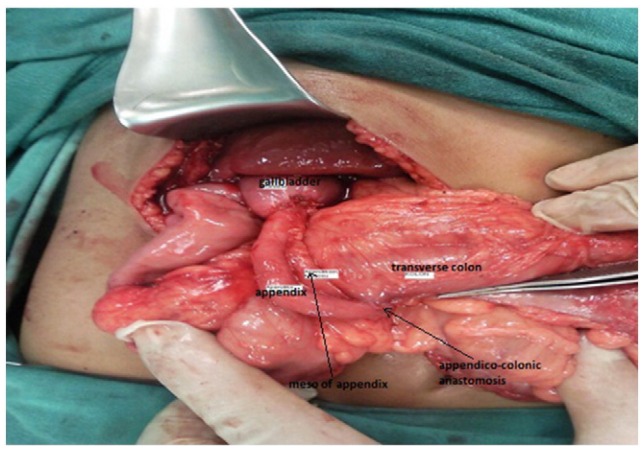

Fig. 2. Cholecysto-appendico-colonic anastomosis.

Fig. 3. Cholecystocolostomy.

2. Results

The primary complaints of all the patients were jaundice and excessive pruritus. (All the patients had grade 4 pruritus, which caused epidermal bleeding.) The pruritus conditions did not respond to medical treatment. The preoperative bilirubin, ALT, AST, and ALP levels of all the patients were found to be high whereas their GGT values were found to be within normal limits. Postoperatively, the patients were followed for 3 months to 6 years (a median follow-up of 2 years). Although the postoperative bilirubin and liver enzymes decreased, they remained above normal limits, and the difference between the preoperative and postoperative levels was not statistically significant (Table 1). One patient with a CCJC underwent liver transplantation two years after the procedure. This patient is still alive and healthy. One patient with a CCJC was admitted with cirrhosis, severe sepsis and adhesive intestinal obstruction six months after the diversion. Although the adhesions were released and an ileostomy was performed, severe sepsis induced by delayed admission and advanced cirrhosis resulted in the death of the patient. This patient had a PFIC resulting from neonatal giant cell hepatitis. One patient is on the waiting list for liver transplantation. The liver functions of the other patients remain normal, and these patients are not on the transplant waiting list. Postoperative hematochezia was present in all the patients; however, it regressed between the 3rd and 5th postoperative day. Regardless of the surgical technique and the postoperative liver functions, pruritus regressed significantly in all the patients. The ultimate pruritus level was grade 0–1 (no itching to mild itching). None of the patients had signs and symptoms of fat malabsorption.

3. Discussion

Progressive familial intrahepatic cholestasis (PFIC) is a disorder with cholestasis, and it progresses to cirrhosis in the first decade of life.

Table 1
Preoperative and postoperative biochemical parameters.

	Preoperative (mean ± S.E.)	Postoperative (mean ± S.E.)
Total bilirubin (mg/dl)	14.16 ± 5.03	7.63 ± 3.83
Direct bilirubin (mg/dl)	12.55 ± 4.27	6.45 ± 3.17
AST (U/L)	369 ± 170	202 ± 84
ALT (U/L)	213 ± 97	113 ± 44
GGT (U/L)	27 ± 3	30 ± 4
ALP (U/L)	295 ± 75	255 ± 48

Intermittent hepatitis, hepatomegalia, growth retardation, hyperbilirubinemia and pruritus are the main symptoms [7]. Pruritus is the most prominent symptom. In cholestatic patients, pruritus is induced by the stimulation of nonmyelinated subepidermal free nerve ends because of increased serum bile acids [2]. Although many medical agents have been used for treatment, medical treatment typically fails and surgical alternatives and liver transplantation might be necessary [1,7]. Recently, internal and external biliary diversion techniques have been performed as an alternative treatment to liver transplantation to increase the quality of life of the patients [8]. Anastomosis of the biliary tract to the intestines or to the skin disrupts the enterohepatic circulation and decreases the accumulation of excess bile salts in serum and changes the biliary acid composition and regulates cholestasis, delays progression to cirrhosis, decreases pruritus and improves the biochemical parameters. Biliary diversion extends the time interval before liver transplantation, and external and internal diversion techniques have been utilized for this purpose [8].

There are many published studies of external drainage in PFIC patients, such as a study by Ekinci et al. reporting patients with PFIC and failed medical treatment, whose pruritus was decreased and quality of life was increased by biliary drainage with partial external diversion [3]. However, stoma-associated complications, the need for revision, postoperative cholangitis and dehydration are disadvantages for the external drainage techniques [1,9,10]. Recently, internal drainage methods have been proposed, as in our study of different techniques. Bustorff-Silva et al. defined CCJC anastomosis in 2007 [4]. In a series of 12 cases by Ramachandran et al., the jejunal loop was used as conduit for internal biliary diversion; it was reported that pruritus resolved in nine of the patients and the serum biliary acids decreased [5]. Another study suggests the use of a cholecystojejunocolostomy [11]. Stoma-associated complications are resolved with internal diversion methods. In our series of seven cases, the following different techniques were performed for internal biliary diversion: cholecystojejunocolonic, cholecysto-appendico-colonic, cholecystoileocolonic and cholecystocolonic anastomosis. Pruritus decreased significantly, regardless of the surgical method used.

Liu reported a Roux-en Y cholecystocolonic bypass to be safe and applicable in an experimental study with rabbits [12]. In a series with 20 patients by Diao et al., laparoscopic cholecystocolostomy was performed, and the results were found to be more successful than the results of previously reported external diversion methods. This achievement was associated with a low average patient age [10]. The same surgical procedure (cholecystocolostomy) was performed on two of our patients with open surgery. None of our patients showed complications, and their pruritus regressed whereas their biochemical parameters improved. The median age of our seven cases was one year of age, which was found to be near the median age in the series by Diao. Because successful biliary diversion performed in the early stages of life would decrease the progression of liver damage, we hypothesize that the young of patient age would affect the success of the surgery.

Cholecystoappendicostomy, which is a modified Mitrofanoff procedure, is defined as an internal biliary diversion method [13]. In one of our patients, we performed a cholecysto-appendico-colonic anastomosis using the appendix as a conduit for internal drainage. No problems were encountered, and the patient's pruritus decreased significantly. We suggest that this method is a reasonable choice in patients whose appendix is mobile enough to be placed between the gallbladder and the transverse colon.

Biliary diversion is an alternative and/or time saving procedure to liver transplantation in patients with PFIC, particularly for those with excessive pruritus. Internal drainage techniques have lower complication rates, and provide a better quality of life. Long-term surgical problems might have a fatal outcome in cases complicated by liver failure. The technique for internal drainage depends on the gastrointestinal anatomy of the patient and/or the surgeon's preference and experience.

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