SUPPLEMENT

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Nasobiliary Drainage for Benign Recurrent Intrahepatic Cholestasis in Patients Refractory to Standard Therapy

Abstract

Purpose: Benign recurrent intrahepatic cholestasis (BRIC) is characterized by episodic cholestasis and pruritus without anatomical obstruction. The aim of this study was to evaluate the safety and efficacy of nasobiliary drainage (NBD) in patients with BRIC refractory to medical therapy and to determine whether the use of NBD prolongs the episode duration.

Methods: This was a multicenter retrospective study consisting of 33 patients suffering from BRIC. All patients were administered medical treatment and 16 patients who were refractory to standard medical therapies improved on treatment with temporary endoscopic NBD. Duration of treatment response and associated complications were analyzed.

Results: Sixteen patients (43% females) underwent 25 NBD procedures. The median duration of NBD was 17 days. There were significant improvements in total and direct bilirubin and alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma-glutamyl transpeptidase on the 3rd day of NBD. Longer clinical remission was monitored in the NBD group. Post-endoscopic retrograde cholangiopancreatography pancreatitis was observed in one of 16 cases.

Conclusion: NBD effectively eliminates BRIC in all patients and improves biomarkers of cholestasis. It can be suggested that patients with attacks of BRIC can be treated with temporary endoscopic NBD; however, the results of this study should be confirmed by prospective studies in the future.

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Cholestasis is a liver disease caused by impaired bile secretion and often associated with secondary to intracellular accumulation of bile acids in the hepatocytes [1]. Benign recurrent intrahepatic cholestasis (BRIC) is an autosomal recessive liver disease characterized by intermittent episodes of cholestasis and pruritus without an anatomical obstruction [2].

The disease may appear at any age, but it usually commences before the second decade (11 – 14 years) and most of the cases resolve spontaneously. Cholestatic episodes are sometimes triggered by infections [3-5]. The attacks can last from weeks to months and cholestasis gradually becomes permanent [6]. During the attacks, patients usually present with a conjugated hyperbilirubinemia, malaise, anorexia, pruritus, weight loss and malabsorption. They are completely asymptomatic for months to years between symptomatic periods, but during exacerbations, they may suffer from unbearable itching with the inability to work and suicidal ideation. Although BRIC is considered benign in nature with no development of liver cirrhosis, some research reports that it occasionally leads to progressive liver disease [7, 8]. In this regard, it has been suggested that patients with BRIC need a regular follow-up. Challenging laboratory findings in BRIC include episodic increase in serum bilirubin and bile acids and typically normal or low serum gamma-glutamyl transpeptidase (GGT) activity. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) is usually only mildly elevated but may occasionally be markedly elevated.

Generally, medical treatment for BRIC is ineffective and includes corticosteroids, phenobarbital, cholestyramine, ursodeoxycholic acid (UDCA), rifampin [9] and a decreased fat diet [8]. UDCA represents the first-line medical treatment [10]. Rifampicin has been reported to prevent cholestatic episodes [11]. Bijleveld *et al.* proposed that an increase in serum lithocholates contributes to cholestasis (being cholestatic itself) [8]; therefore, treatment with cholestyramine and reduction of intestinal bacteria may reduce these secondary bile acids in the serum. Another treatment modality is intermittent albumin plasmapheresis used during cholestasis [12].

There have been some cases of endoscopic nasobiliary drainage (NBD) with complete, rapidly-developing and long-term remission in BRIC [13, 14]. Obstructive jaundice, cholangitis and post-operative bile leaks are some indications for which NBD has been used with success [15]. To summarize, NBD is performed during endoscopic retrograde cholangiopancreatography (ERCP), first by introducing a nasobiliary catheter, with a diameter of 6 to 7 Fr, into the

common bile duct to drain bile through its external end, followed by passing the latter out of the nose and connecting to a bag for free, continuous drainage. The catheter in place should be irrigated with sterile saline to ensure its patency.

Only a few studies to date have reported the use of NBD in BRIC. There have been small case series suggesting efficacies of NBD in BRIC. Due to the low number of patients with BRIC, it is difficult to perform randomized controlled trials to examine the effect of different treatment options. Clinical experience and results of case reports are cornerstones in the evaluation and treatment of these patients; hence, this multicenter retrospective study with a larger sample size was performed to enhance knowledge on use and benefits of NBD in BRIC with failed medical therapy. To our knowledge, this is the largest study on patients with BRIC undergoing NBD.

Materials and Methods

Study Design and Patients

The present study included 33 consecutive patients with BRIC who were referred and admitted to the gastroenterology units of Baskent University Adana Hospital, Baskent University Konya Hospital and Mustafa Kemal University Faculty of Medicine Hospital, Turkey, between January 2009 and December 2014. Data about the patients from these three academic medical centers were retrospectively analyzed. Out of 33 patients with mean age of 23.42 ± 6.23 years, 16 were female and 17 were male. All the patients had a thorough clinical examination, routine hematological, biochemical, serological investigations and abdominal ultrasonography (USG).

Eligibility criteria

Diagnosis was based on the following diagnostic criteria for BRIC: (a) at least two episodes of jaundice separated by a symptom-free interval lasting several months to years; (b) laboratory results suggestive of intrahepatic cholestasis; (c) severe pruritus secondary to cholestasis; (d) liver histology demonstrating centrilobular cholestasis; (e) normal intrahepatic and extrahepatic bile ducts confirmed by cholangiography; and, (f) absence of factors known to be associated with cholestasis, (i.e., drugs, pregnancy) [14].

Because of the recurrent character of jaundice, diagnosis of BRIC can be only confirmed after exclusion of other possible congenital or acquired causes of intrahepatic cholestasis with liver biopsy [12]. Liver biopsy was recommended for all admitted patients, but it was performed on 21 patients.

TABLE 1. Demographic and clinical features of patients with benign recurrent intrahepatic cholestasis

	Medical Therapy (n = 17)	Nasobiliary Drainage (n = 16)	P value
Age (year)	24.4±5.7 (15 – 34)	22.3±6.7 (14 – 36)	NS
Gender (male/female)	8/9	9/7	NS
Time from the first exacerbation (months)	57.0±17.2 (48 – 110)	52.7±44.3 (3 – 168)	NS
Total number of exacerbations	4.8±1.7 (3 – 8)	3.8±3.1 (1 – 10)	NS
Pre-treatment	1.4±0.8 (1 – 4)	3.1±2.2 (1 – 7)	0.012
Post-treatment	3.2±1.2 (2 – 6)	0.6±0.0 (0 – 3)	<0.001
Medications			
Ursodeoxycholic acid	17	16	NS
Cholestyramine	17	16	NS
Rifampicin	10	5	NS
Hydroxyzine HCl	17	16	NS
Sertraline	6	4	NS
Plasmapheresis	3	6	NS
Liver biopsies			
Canalicular cholestasis			
with no fibrosis	2	4	NS
with severe fibrosis	5	4	NS
Intra-acinar cholestasis with porto-portal fibrosis	2	4	NS
Laboratory findings			
Total bilirubin (0.2 – 1.05 mg/dL)	23.6±4.2	23.7±3.2	NS
Direct bilirubin (0.01 – 0.30 mg/dL)	21.7±5.8	20.6±8.2	NS
Aspartate aminotransferase (5 – 35 IU/L)	77.1±8.0	93.2±9.5	NS
Alanine aminotransferase (7 – 49 IU/L)	72.1±41.5	83.1±30.4	NS
Alkaline phosphatase (25 – 100 IU/L)	284.3±23.4	377.1±24.9	0.010
Gamma-glutamyl transpeptidase (7 – 40 IU/L)	25.5±1.6	39.8±3.3	0.002
Blood urea nitrogen (BUN) (mg/dL)	17.3±1.0	17.1±1.2	NS
Creatinine (0.5 – 1.1 mg/dL)	0.8±0.1	1.0±0.1	NS
Total protein (6.4 – 8.3 g/dL)	6.4±0.1	6.4±0.1	NS
Albumin (3.2 – 5.0 g/dL)	3.7±0.2	3.7±0.3	NS
White blood cell count (4000 – 10000/μL)	7987.7±328.2	8745.8±423.4	NS
Platelet count (130000 – 400000/μL)	186352.9±14033.0	193562.5±10657.5	NS
PT% (70 – 130)	64.8±4.4	65.3±5.8	NS
INR (0.85 – 1.20)	1.3±0.0	1.4±0.0	NS

Sample Collection and Laboratory Analysis

Venous blood from all study subjects was collected in no-additives-containing tubes. The serum was separated by low-speed centrifugation (4°C, 1200 g, 15 minutes). Grossly hemolyzed or lipemic specimens were not used. Serum total bilirubin (TB) and direct bilirubin (DB), blood urea nitrogen (BUN), creatinine, total protein, albumin, electrolytes, cholesterol, calcium, phosphorus, uric acid, copper, alkaline phosphatase (ALP), GGT, ALT and AST were measured in an Abbott AEROSET autoanalyzer using Abbott kits (Abbott Laboratories, Abbott Park, IL, USA).

Ceruloplasmin and alpha-1 antitrypsin levels were measured with rate nephelometry (Boehring nephelometer; Hoechst UK, Hounslow). Copper levels were quantified by means of electrothermal atomic absorption spectrophotometry (ETAAS, Zeeman 3030, Perkin Elmer, Oherlingen, Germany).

Serologic tests for viral hepatitis (HAV, HBV and HCV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), anti-nuclear antibody (ANA) and anti-liver kidney microsome-1 antibody (anti-LKM-1) were performed.

Therapeutics

All patients received UDCA 500 mg four times daily, cholestamine 3-4 g three times daily and an antihistaminic tablet (Hidroksizin HCl) as a first-line therapy (as shown in Table 1). All patients received this standard treatment for at least three months. The drugs were then discontinued and rifampicin 300 mg per day was started. Moreover, plasmapheresis was performed in nine cases (three cases in the medical therapy group; six cases in the NBD group).

BRIC refractory to medical therapy was defined as persistent pruritus, high serum bilirubin levels, and high liver enzymes except for GGT despite treatment for one month. Sixteen patients, who were unresponsive to medical treatment, were treated with endoscopic NBD. The study participants gave informed consent for insertion of an NBD catheter to drain bile during ERCP. Each repeated NBD procedure was considered a separate case and therefore, the number of cases exceeded that of the patients. Exclusion criteria for NBD group were as follows: taking an anticoagulant/antiplatelet drugs or showing hemorrhagic diathesis, having contrast medium allergy, having previous gastric operation, being pregnant and declining to give informed consent.

Nasobiliary Drainage

ERCP was performed by using a ED-3440 T or ED 3585 T duodenoscopy (Pentax Medical Systems Corp, Tokyo, Japan) when the patients were under conscious sedation with midazolam and diprivan. The common bile duct was selectively deep-seated and the adequate position of the cannula was verified by aspirating some amount of bile. To avoid cholangio-venous reflux, contrast agents were not infused for positioning the cannula whenever possible. All patients, other than those who were using anticoagulants or antiplatelets, having bleeding diathesis or taking prophylactic rectal nonsteroidal anti-inflammatory drugs (NSAIDs), underwent endoscopic sphincterotomy (EST) in the primary session. Rectal NSAIDs have been strongly recommended by recent meta-analyses for patients at high risk for post-ERCP pancreatitis (PEP) [16-18].

A 7 Fr nasobiliary catheter was placed into the left or right hepatic duct by using a 0.035-inch guide wire (Hydragewire 5605; Boston Scientific Corp, Natick, MA). The catheter was 255 cm long, tapered and pigtail tipped, with 9 side holes from the tip and with an alpha loop in the duodenal portion (Dispomedica, Hamburg, Germany).

All patients were subjected to pre-discharge abdominal plain film to rule out stent dislodgement. The definitions and grading systems established by the 2010bb workshop of the American Society of Gastrointestinal Endoscopy workshop were used to register procedural adverse events [19].

All adverse events associated with the NBD procedure were recorded. The following criteria agreed in the literature were used to define PEP [16, 20]: (i) newly developed or worsening abdominal discomfort with clinical features compatible with acute pancreatitis; (ii) determination of serum amylase or lipase levels that were $\geq 3X$ the upper limit of normal 24 hours' post-procedure; and, (iii) a delay in patient discharge by at least 2 days. Severe PEP was indicated by presence of pancreatic necrosis or pseudocyst, or the need for additional endoscopic, percutaneous or surgical procedures. Patients not meeting these criteria were considered to have mild PEP.

The bile output from the catheter was recorded and measured on days 1, 2, 3 and 7. At least three measurements of serum TB, DB, ALP, AST, GGT and ALP were performed: pre-procedural (day 0) and at post-procedure (days 3 and 7). Two surrogate markers were used to assess efficacy of bile duct drainage: the rate of decrement in parameters of cholestasis (TB, DB, ALP, AST, GGT, and ALP) and efficacy of elimination of jaundice.

The rate of decrement in each parameter was determined by the following formula:

$$[(\text{Day 0} - \text{Day 3}) / \text{Day 0}] \times 100$$

in which Day 0 and Day 3 represent the values of each parameter on day 0 and day 3, respectively. The success rate in jaundice relief was defined as the proportion of patients having values on day 3 lower than those on day 0.

Duration of NBD was also recorded. Duration of a BRIC episode after NBD catheter removal was also analyzed to determine the effect of NBD on BRIC. The follow-up interval for individual patients was determined according to their clinical need. In both the medical treatment and NBD groups, serum TB, DB, AST, ALT, GGT and ALP levels were measured on the starting day (0th day), on day 3 and in weeks 1, 2, 3, 4, 12, 24, 48, 72, 96 and 144.

This study was approved by Mustafa Kemal University Medical Faculty institutional review board and ethics committee. In accordance with the Helsinki Declaration, the written informed consent from all the participants was obtained at inclusion.

Statically analysis

All parametric results were expressed as mean±standard deviation (SD). Statistical Package Program for Social Sciences (SPSS, version 20 for Windows; SPSS Inc., Chicago, Illinois, USA) was used for all statistical calculations. Normal (Gaussian) distributions of the continuous variables were evaluated by using One Sample Kolmogorov Smirnov test. Categorical variables were compared with the X² test. Comparisons between the groups were made with Student's t-test or Mann-Whitney U test, as appropriate. Wilcoxon signed-rank test was used for the comparison of continuous data. Correlations between the variables were evaluated by Pearson or Spearman correlation as appropriate. Differences were considered statistically significant at $P < 0.05$.

Results

Demographic, clinical, biochemical and histological characteristics of the patients at the beginning of the study are presented in Table 1. There was not a significant difference in the abovementioned characteristics between medical therapy and NBD groups at baseline. Two patients were brothers and had a family history of liver disease. None of the patients had a history of exposure to toxins or drugs. On physical examination, all patients were icteric and most of them had diffuse excoriations all around their bodies caused by severe

TABLE 2. Bile Output on days after nasobiliary drainage

	Bile output (mL)	P value
1 st day	387.8±29.9	0.004 (between 1 st and 3 rd days)
2 nd day	376.5±20.3	0.078 (between 1 st and 2 nd days)
3 rd day	360.3±22.8	0.008 (between 2 nd and 3 rd days)
7 th day	367.8±26.4	0.019 (between 1 st and 7 th days)

itching. There were not any signs of cirrhosis on physical examination.

Biochemically, all the patients had hyperbilirubinemia with DB dominance and elevated AST, and ALP. In addition, serum GGT was normal. BUN, creatinine, total protein, and albumin levels were all normal. Serologic tests for HAV, HBV, HCV, CMV and EBV were all negative. The patients were also negative for ANA and anti-LKM-1. The diagnoses of Wilson disease and alpha-1 antitrypsin deficiency were excluded by normal plasma levels of copper, ceruloplasmin and alpha-1 antitrypsin.

Abdominal USG did not show an abnormality. There were neither gallstones nor intrahepatic or extrahepatic bile duct obstructions. The spleen was in normal size and there was no ascites or other abdominal abnormality. Bile ducts were also normal on ERCP. The bile output on day 1 was higher than that on day 7 ($p = 0.019$; Table 2) and it decreased significantly after day 3 ($p = 0.004$).

Liver biopsies revealed canalicular cholestasis without fibrosis in two patients in the medical therapy group and four patients in the NBD group, canalicular cholestasis with severe fibrosis in five patients in the medical therapy group and four patients in the NBD group and intra-acinar cholestasis with porto-portal fibrosis in two patients in the medical therapy group and four patients in the NBD group (Table 1). There was no significant difference in histological features between the groups ($p = 0.477$). The mean number of episodes, the mean duration of NBD ($p = 0.470$; $p = 0.162$ respectively) and biochemical features on liver biopsies were similar. The mean dwell time of drainage was significantly longer in the patients having canalicular cholestasis with severe fibrosis than in those having canalicular cholestasis without fibrosis ($p = 0.034$).

When TB levels had dropped to 10 mg/dL, the NBD catheter was removed (this is termed the dwell time) to eliminate the risk of catheter infection. The median duration of NBD was 17 days (mean 19; range 14–30 days). The mean number of NBDs was 1 (1 – 3). There was no significant difference in the number of episodes (pre- and post-treatment)

between the two groups, but there was a significant difference in both the pre- and post-treatment number of episodes ($p=0.012$; $p<0.001$, respectively) (Table 1). The number of pre-treatment episodes was higher, but the number of post-treatment episodes was lower in the NBD group than in the medical therapy group. NBD administration significantly decreased the number of episodes (the median number of episodes decreased from two to zero; $p<0.001$). In contrast, medical therapy significantly increased the number of episodes (the median number of episodes increased from one to three; $p<0.001$). All BRIC patients healed quickly (pruritus disappeared within 24 h of initiating drainage) and pruritus completely disappeared after alleviation of TBS levels by less than 10 mg/dL following 14 – 30 days of NBD. All were on a regular follow up for three years and did not suffer from another attack.

Effect of NBD on serum biochemistry tests

The effect of NBD administration on liver function tests is shown in Table 3. On the first day of NBD administration, TB, DB, AST, ALT and ALP increased insignificantly; however, there was a significant reduction in serum GGT on the first day of NBD ($p=0.011$). NBD significantly reduced serum TB (23.7 ± 3.2 vs. 16.6 ± 3.3 ; $p<0.001$), DB (20.6 ± 8.2 vs. 14.0 ± 3.1 ; $p<0.001$), ALT (83.1 ± 30.4 vs. 71.5 ± 22.7 ; $p=0.001$), AST (77.5 ± 33.4 vs. 69.9 ± 28.2 ; $p=0.035$), ALP (346.6 ± 67.3 vs. 301.4 ± 63.0 ; $p=0.002$), and GGT (41.0 ± 8.5 vs. 34.1 ± 9.07 ; $p=0.028$) on the 3rd day of NBD administration.

Correlation analysis

Correlation analysis in the total of 16 NBD administrated BRIC patients revealed positive correlations between dwell time of drainage and daily bile output (all $p<0.05$; Table 4). The correlation became stronger across time. The strongest correlation was noted between dwell time of drainage and bile output on day 7. Correlation analysis between dwell time of drainage and parameters of coagulation showed that dwell time of drainage was strongly and negatively correlated with platelet count ($r=-0.710$; $p=0.002$). A positive correlation was noted between the number of NBDs and pretreatment GGT levels ($r=0.525$; $p=0.037$), but the number of NBDs was not correlated with the results of other liver function tests.

Adverse events of NBD

A summary of adverse events associated with NBD is shown in Table 5. The rate of total adverse events was 18.2%. Minor

adverse events such as rhinorrhea, hoarseness, difficulty in face washing, difficulty in taking medicine, constant worry about the catheter and fatigue were observed in 10 out of 16 cases (62.5%). All minor adverse events resolved completely with appropriate medical management. In one case, PEP developed. There was no mortality associated with NBD. The most frequently encountered adverse event associated with NBD was sore throat (6 cases; 37.5%).

Discussion

BRIC represents a difficult-to-treat condition with limited treatment options, which are not uniformly efficacious. Patients for whom medical therapy has failed are candidates for invasive procedures, including NBD. There is a scarcity of studies exploring effects of NBD on BRIC, with the existing studies being limited to a few case series. The present study is distinct from other previous research in that it provides the largest retrospective multicenter dataset to date on the utility of NBD in BRIC. While confirming the already known benefits of NBD, thanks to its longer follow-up time, this study also addresses some unknown points and uncertainties regarding the use of NBD.

In this study, the dwell time of drainage was higher in the patients having canalicular cholestasis with severe fibrosis than in those without fibrosis. Daily bile output significantly decreased on day 3 after NBD. The median dwell time of drainage was 17 days. Compared with the medical therapy group, NBD group had a lower number of episodes (post-treatment). On day 3 after NBD administration, TB, DB, AST, ALT, GGT and ALP significantly decreased. The dwell time of drainage was positively correlated with daily bile output and negatively correlated with platelet count. The most frequently encountered adverse event associated with NBD was sore throat.

BRIC is a rare form of hereditary cholestasis syndrome characterized by repeated self-limited episodes of pruritus and jaundice. The classical form of BRIC was first described in 1959 by Summerskill and Walshe [6]. It is due to mutations in the FIC-1 gene [21] and a P-type ATPase. BRIC type 1 is caused by mutations in ATP8B1, and type 2 is caused by mutations in ABCB11, encoding BSEP [21, 22]. These genes are also associated with progressive familial intrahepatic cholestasis 1 (PFIC-I) [22]. BRIC type 2 is caused by mutations in ABCB11. BRIC must be differentiated from PFIC due to their similarity [23]. PFIC is a liver disease which is also characterized by cholestasis with normal GGT activity and starts in infancy, but progresses to cirrhosis, liver failure, and death unless a liver transplantation is performed [24]. It

should be postulated that there is a progression from BRIC to more severe PFIC which leads to liver insufficiency and cirrhosis [23, 24]. Liver transplantation is generally not considered because of the episodic and non-progressive nature of BRIC, although pruritus can be severe enough for the patient to seek liver transplantation.

BRIC is a physical and psychological challenge. A definitive medical treatment for BRIC is still unavailable. At present, the treatment aims to give symptomatic relief, shorten cholestatic attacks and prevent relapses. There are conflicting reports regarding the use of cholestyramine (bind to BS in the intestine and reduce their re-absorption), UDCA, and opioid antagonists (reduce the pruritogenic effect of endogenous opioids). One report suggested that cholestyramine therapy shortened the duration of icteric phase and that UDCA ameliorated the symptoms of pruritus [25]. Some recent reports have shown a beneficial role of rifampicin in remission of cholestasis [9]. Folvik *et al.* reported that both rifampicin and plasmapheresis represent important therapeutic options for acute cholestatic attacks in patients with BRIC [26]. Plasmapheresis has shown an effect on duration and severity of cholestatic attacks in BRIC1, particularly if treatment is started early during the attacks. A probable mechanism is a reduction of circulating cholestatogenic factors and bilirubin [27; however, another report has suggested that no treatment was successful in shortening the duration of symptoms [12]. In addition to this, surgical treatment of BRIC remains controversial [23]. In PFIC, surgical external biliary diversion or ileal exclusion or internal bypass techniques have been employed successfully [13, 28]. Although these techniques may also be effective in BRIC, its permanent character makes it less suitable to be used in an episodic disorder [10].

The mechanism of this intrahepatic cholestasis of BRIC is that a decrease in bile flow in the absence of an overt bile duct obstruction results in the accumulation of bile constituents in the liver and blood [29]. Stapelbroek *et al.* [13] recently reported on intermittent NBD, showing normalization of phosphatidylcholine and bile salts within 24 h of initiating drainage. They found that the relative amounts of phospholipids and bile salts in bile collected during NBD appeared to be normal, but that the phospholipids, other than phosphatidylcholine, increased (especially sphingomyelin). For the first time, they proposed that temporary endoscopic NBD should be considered in cholestatic BRIC patients. They also reported a complete disappearance of pruritus and normalization of TB levels, following 11–21 days of NBD and that the duration of treatment response lasted for 8–12 months [13].

In the present study, 16 young patients with BRIC, presenting with cholestatic jaundice and pruritus, normal GGT activity, no obstruction of extrahepatic bile ducts and initially no signs of liver damage were reviewed. First-line medical therapy was administered to all the patients and plasmapheresis was also performed in six of 16 patients, but none of them recovered. Endoscopic NBD elicited a faster, complete, and long-lasting remission in these patients. All patients in the present study benefitted from NBD, showing significant improvement in pruritus and cholestasis parameters. These observations are consistent with previous reports and suggest that exacerbations of BRIC can be effectively treated with NBD.

Hegade *et al.* [30] reported that NBD duration should be guided by the patient tolerance of the catheter and drainage benefit for their pruritus; however, BRIC patients generally require 7–10 days of drainage at most; even so, in the current study, NBD was administered for a longer time (median 17 days and range 14–30 days) to ensure complete resolution of hyperbilirubinemia. The NBD removal time in this study is consistent with that reported by Appleby *et al.* [31] who found that the mean length of drainage was 19 days. They carried out long-term NBD in one BRIC patient with nutritional failure and reduction in quality of life secondary to pruritus for eight weeks.

BRIC patients experience episodes and are known to remain in spontaneous remission for months to years in between attacks [26]. In the present study, the maximum number of NBD treatments was three and more than one NBD treatment was required for seven of 16 patients (43%). All were on a regular follow-up for three years and none of the patients suffered from another attack. Another finding of this study was that dwell time of drainage was strongly correlated with daily bile output, especially on day 7. In their retrospective study, Hegade *et al.* [30] also reported that the duration of NBD response was not associated with the duration of drainage and bile output per day. They noted that the median duration of treatment response in eight BRIC patients was 459 days. It is worth noting that, clinically, both duration and the number of NBD treatments of BRIC patients with canalicular cholestasis with severe fibrosis were the highest in terms of liver biopsy.

In the present study, NBD was observed to have a favourable effect on liver biochemical parameters as reported in previous case reports [14], but unlike prior reports, there was a significant improvement in GGT levels on day 1 after NBD. Following NBD, a rapid biochemical and clinical response was seen during the first 3 days. A potential cause of

this difference may be the number of BRIC patients. This is the largest study to date and should therefore yield more reliable results. Moreover, all parameters, except for GGT, remained unchanged on the 1st day of NBD; the activity of GGT was attenuated by NBD, so GGT may be a premonitory marker for relief.

NBD may be associated with adverse events: 18.2% of our patients had adverse events, the majority of which were sore throats. PEP was observed in one of 16 patients (6.2%). This rate was lower than the one shown by Hegade *et al.* [30], who reported a PEP rate of 31%. Although the gauge of the NBD catheters in the current study was the same as that of the catheters used by Hegade *et al.* (7 Fr), the PEP rate was higher in their study. It may be that they did not use routine prophylactic rectal NSAIDs.

This large retrospective study confirms the effectiveness of NBD in treating BRIC patients refractory to medical therapy, and provides further evidence that NBD is effective in prolonging the duration between episodes. In addition, NBD had a favourable effect on liver function tests. However, it is an invasive procedure and some complications can be attributed to it and it is recommended that all of the patients undergoing NBD receive prophylaxis for PEP. Nevertheless, the present study showed that NBD is an outstanding and efficient rescue treatment option for BRIC patients refractory to medical therapy. This procedure should be seriously considered as a treatment option in suitable BRIC patients to prevent or delay PFIC. If prospective studies are performed to confirm the findings of this study, this treatment option should become widely used in the future.

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