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Title: Treatment and follow-up of late onset intra hepatic bile duct stones in congenital dilation of biliary duct: Impact of double-balloon enteroscopy

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Abstract

Purpose: The postoperative course after surgery for congenital dilation of the bile duct (CDBD) has some complications. Intrahepatic bile duct (IHBD) stones were known as a late complication. We report on the treatment and long-term follow-up of postoperative IHBD stones in our department.

Method: Patients who underwent CDBD surgery at age 15 years or younger in our department were identified. Those followed up for 5 years or more were enrolled. Annual blood chemistry tests and abdominal ultrasonography were performed. Each patient's surgical procedure, IHBD stone diagnosis, treatments, and outcomes were retrospectively assessed.

Results: Fifty-one patients were analyzed. The median age at the last visit was 24 years (range 7-45 years), and the median age at CDBD surgery was 3 years. Eight patients (16%) developed late-onset IHBD stones. The median age at onset was 25 years, and the median duration after surgery was 20 years. The initial treatment was double-balloon enteroscopy (DBE) in 4 cases, which resulted in stone removal in 3 of the 4 patients (75%).

Conclusion: Since CDBD may cause late-onset IHBD stones, continuous follow-up is required even in adulthood. In this study, DBE was effective and minimally invasive, and it is recommended as the initial treatment.

Key words: 1. CDBD 2. IHBD 3.DBE 4. PTCD 5. Roux en Y

Introduction

Congenital dilation of the bile duct (CDBD) is an anomaly involving cystic dilatation of the biliary tree. It increases the risk of biliary carcinoma in adults, and is usually accompanied by pancreaticobiliary maljunction. In 1969, Babbitt [1] described the reflux of pancreatic enzymes into the biliary tree. Therefore, cyst resection with biliary diversion is accepted as the standard procedure for CDBD. While CDBD has a good prognosis, some postoperative complications have been reported during follow-up, including intrahepatic bile duct (IHBD) stones, cholangitis, and cholangiocarcinoma.

IHBD stones are a known remote complication after CDBD surgery, and can be caused by anastomotic stenosis, cholestasis in the hepaticojejunostomy limb, and IHBD stenosis [2]. Patients with cholangitis may potentially have cholestasis, and in cases of postoperative cholangitis, bile flow obstruction may lead to bile stone formation. [3,4].

Endoscopic retrograde cholangiopancreatography (ERCP) is the standard method for removing bile stones. Although ERCP is successful in about 90% of patients [5], the success rate is lower in patients with a Roux-en-Y anastomosis [6,7]. For cases of IHBD stones in the context of CDBD, the most common therapeutic choices are percutaneous transhepatic cholangiodrainage (PTCD) or surgery because it is difficult to advance the endoscope to the site of jejunojejunostomy through the Roux-en-Y limb.

Technological developments in endoscopy have made it possible to perform double-balloon enteroscopy (DBE), a novel diagnostic and therapeutic modality reported by Yamamoto et al.[8] DBE is feasible in

patients with altered gastrointestinal anatomy, and it may be considered when pancreaticobiliary diseases occur in patients undergoing Roux-en-Y reconstruction [9]. DBE is a minimally invasive and safe treatment method for bile stones, and is capable of reaching the anastomosis after Roux-en-Y for CDBD [10]. We have used DBE for treatment of IHBD stones since 2017.

Long-term surveillance remains essential in patients who have undergone CDBD, but the optimal therapeutic approach for IHBD stones is controversial. There have been a few previous reports on late-onset IHBD stones that developed after surgery more than 5 years and their management. Therefore, we report here on the treatment including DBE and long-term follow-up of CDBD patients in our department.

Methods

Patients

Patients who met the following inclusion criteria were identified: underwent CDBD surgery at age 15 years or younger, followed in our department, and had a last visit between August 2019 and January 2021 as a study period. Patients who were followed up for 5 years or more were included in the analysis as late-onset IHBD stones. All patients had undergone total resection of the extrahepatic bile ducts and bile duct reconstruction by Roux-en-Y hepaticojejunostomy or jejunum interposition between 1978 and 2015. Annual blood chemistry tests and abdominal ultrasonography were performed routinely. During the study period, 51 patients were treated in our department after CDBD surgery. Patient charts were retrospectively

reviewed for surgical procedure, IHBD stone diagnosis, treatments, and outcomes.

The diagnosis of IHBD stones was initially made by abdominal ultrasonography and then by magnetic resonance cholangiopancreatography (MRCP) as confirmation. IHBD stones were treated by surgery, PTCD, and/or DBE.

Surgical treatment

For surgical treatment, the abdomen was opened and the hepaticojejunostomy was dissected, and then the IHBD stones were manually removed with a forceps or spoon. In addition, peripheral stones were crushed and removed with a cholangioscope and forceps through the channel and/or side of the scope that was applied intraoperatively. After the stones were removed, a hepaticojejunal anastomosis was reconstructed.

PTCD

The hepatic duct was punctured under ultrasound guidance and the guide wire was advanced to perform PTCD. The anastomosis was dilated with a balloon catheter, and the size of the PTCD tubes was increased up to 12 French. A cholangioscope was inserted through the PTCD site and lithotripsy was performed on the basket with a balloon catheter.

DBE

DBE was performed using a double-balloon endoscope (EI-580BT; Fujifilm, Tokyo, Japan), a flexible overtube with balloons, and a controller to inflate or deflate the balloons under sedation. The basic structure of the DBE endoscope is the same as that of ordinary endoscopes except that the DBE scope has an air

channel for the balloon. The balloons were inflated until its diameter almost equaled that of the intestinal lumen so that it provided an effective grip and made it feasible to advance scope to the Roux-en-Y limb [11].

Analysis

Results are expressed as medians with ranges. Incidence were calculated using the Kaplan-Meier method. Data were analyzed using the JMP Ver.11 software package (SAS, Cary, NC, USA). Student's t-test was used for comparisons. P values less than 0.05 were considered statistically significant. This study was approved by our hospital's institutional review board (approval number 19493).

Results

Patient demographics

Of the 51 patients included in this study, 40 were females and 11 were males. The median age at the last visit was 24 years (range 7–45 years) and the median age at the original operation was 3 years (range 0–15 years). In 47 patients the bile duct was reconstructed by Roux-en-Y hepaticojejunostomy, and the jejunal interposition method was used in 4 patients. Forty-three patients underwent surgery at our department and 8 underwent surgery at other hospitals. The type of bile duct dilatation was cystic in 25 patients, cylindrical in 6, and fusiform in 2; it could not be classified in 17 patients, and there was no dilatation in one patient. The characteristics of the patients are shown in **Table 1.**

IHBD stone formation

The median duration of postoperative follow-up was 21 years (range 5–42 years). Among 8 patients (16%) who developed late-onset IHBD stones, the median age at onset was 25 years (range 13–39 years) and the median interval between CDBD surgery and the onset of IHBD stones was 20 years (range 9–36 years). The incidence among patients who underwent surgery in our department was 14% (6 of 43 patients). The incidence in only our department was almost same as the overall incidence. The Kaplan-Meier incidence is plotted in Fig. 1.

Treatments

For initial therapy of IHBD stones, 2 patients received PTCD, 2 underwent re-hepaticojejunostomy, and 4 were treated with DBE. A treatment summary is shown in Table 2. In 7 of 8 patients, IHBD stones were ultimately removed with one or more types of treatment. Bile stones were not removed completely in Patient No. 1 because they were present throughout the peripheral bile ducts of the entire liver. In this patient, re-anastomosis was performed 19 years after the initial treatment of IHBD stones because intrahepatic stones remained, but the treatment was only palliative because stones were present extensively throughout the liver (Fig 2). Surgical treatment (Patient No. 1) resulted in a severe complication (hepatic artery injury), but there were no severe complications with PTCD or DBE. There was no mortality.

DBE

DBE resulted in successful IHBD stone removal in 3 of 4 patients (75%). A summary of DBE treatment is

shown in Table 3. In Patient No. 6, DBE was unable to reach the anastomosis through the Roux-en-Y limb, and surgical treatment became necessary. One patient (Patient No.5) developed recurrent IHBD stones about 2 years after complete stone removal by DBE, but these were successfully removed, again by DBE. In Patient No. 8, DBE retrograde cholangiography revealed IHBD stones. Balloon dilatation of the anastomosis stenosis and lithotomy were performed with a balloon catheter and a crusher catheter (Fig. 3). The mean duration of admission in patients who underwent successful DBE (n=4 including 2nd DBE in patient no. 5) was 16 days, which was significantly shorter than the 33-day mean for the other methods ($p=0.012$).

Discussion

In our series, 8 patients developed IHBD stones as a late complication. Late-onset IHBD stones were identified about 10 to 40 years after the original operation. IHBD stones after CDBD can be caused by anastomotic stenosis and IHBD stenosis [2,12]. Other studies detected IHBD stones as postoperative complications in approximately 5% of patients [2,3]. In our series, the incidence of bile stones was 16%, which was higher than in previous reports. This was presumably because in our series the mean follow-up duration of 20 years was longer than that of 8–12 years in the prior studies. Most IHBD stones form later than 10 years after the initial operation. In this study, the incidence at 12 and 20 years were 5% and 11%, respectively, according to Kaplan-Meier analysis (Fig. 3). The cumulative incidence might be higher than

the incidence before 10 years post-surgery, although this is uncertain because our study included cases with a short observation period. Additionally, we experienced a patient in whom the complete removal of IHBD stones was unsuccessful because they were present throughout the peripheral hepatic ducts. Therefore, bile stones should be detected until they are localized within the anastomotic area.

In this study, the duration between the original surgery and IHBD stone development was ranged from 9 to 36 years. Therefore, follow-up should at least include this period. Continuous follow-up is required even in adulthood, and pediatric surgery plays an important role if the patient does not transition to an adult service. Follow-up should be performed on an individual basis, but routine work-ups are important to prevent missed follow-up visits. CDBD patients should undergo ultrasound examination and lab tests at least once a year, even if their postoperative course is uneventful.

Routine work-ups are important for the early detection of not only bile stones, but also malignancy. No cholangiocarcinoma developed in our series. The incidence of bile duct malignancy after CDBD surgery was reported to be 2% [13], with a higher rate in adults than pediatric patients [14]. Furthermore, the risk of malignancy was reported to increase more than 15 years after cyst excision [15]. Long-term follow-up to detect malignancy is critical.

The optimal therapeutic procedure to treat bile duct stones remains controversial. The surgical approach has been the gold standard. However, it is invasive and requires a long hospital stay. In this series, we experienced one case of hepatic artery rupture. For these reasons, surgical treatment should be reserved for

cases in which other methods have failed.

Another viable method is PTCD, which was used to treat 2 patients in this study. Stone extraction via PTCD was first performed using percutaneous transhepatic anastomosis balloon dilatation or percutaneous transhepatic choledochoscopic lithotomy [16]. To achieve percutaneous access for the choledochoscope, the bile ducts must be punctured by dilation of the access channel has to be performed for up to a couple of weeks [17,18] The stones can be removed either by pushing them forward into the Roux-en-Y limb over a previously dilated papilla or by extraction over the PTCD fistula. The procedure does carry a risk of major hemorrhage. Stone extraction via the percutaneous access can cause injuries to the liver due to the fact that the stones often have sharp edges. Therefore, a stable percutaneous fistula should ideally be established by dilation over a period of up to 2 or 3 weeks. While PTCD is less invasive than surgery, neither surgery nor PTCD is recommended as initial treatment due to long hospital stays, invasiveness, and risk of severe complications.

ERCP is commonly used to remove bile duct stones in individuals with normal anatomy. However, it is difficult to reach the hepaticojejunostomy through the Roux-en-Y reconstruction using a regular endoscope. DBE, which was first reported in 2001 [8], has made it possible to reach the hepaticojejunostomy via the leg of the Roux-en-Y reconstruction, and to perform successful therapeutic procedures involving the anastomotic stricture using balloon catheter dilation in adult. However, DBE seems to be more difficult in pediatric than adult patients because the intestinal wall in the former is thin and the intestinal lumen is

narrow. In our study, it was difficult to apply DBE in pediatric cases in patient No. 6. A recent study described the application of DBE in pediatric patients with IHBD stones after Roux-en-Y reconstruction, and reported that the rate of major complications in pediatric patients was not significantly higher than that in adults [19,20]. Moreover, DBE can be performed repeatedly. In our patients, multiple DBEs eventually led to the removal of bile stones. Since DBE is minimally invasive and requires only a short hospital stay, it should be used as initial treatment rather than surgery or PTCD.

Our study had several limitations. Since it included patients whose initial surgeries were many years ago, it was not always possible to collect data on surgical procedure or type of CDBD. Data on the incidence of late-onset IHBD stones are unreliable long after initial surgery because there are many censored cases in Kaplan-Meier analysis. Also, since DBE was developed more recently than the other procedures, its long-term efficacy and associated complications require further study.

Conclusions

Since CDBD may cause late IHBD stones, continuous follow-up is required even in adulthood, and pediatric surgery is likely to play a major role. Once IHBD stones are extensive, they cannot be removed; thus, it is necessary to detect them early. DBE is effective and is less invasive than PTCD and surgery; it should be tried first.

Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required

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Figure legends

Fig. 1 Incidence of late onset IHBD stone. The Kaplan-Meier incidence is plotted. Interval means the period (years) between CDBD surgery and the initial diagnosis of IHBD stone.

Fig. 2 Surgical treatment (Patient No. 1). (a) MRCP before surgical treatment. (b)hepaticojejunostomy. The anastomosis was opened (black arrow). The injured hepatic artery was over the anastomosis (white arrow) (c) Cholangioscope showed bile stone (black arrow) and balloon (white arrow) for stone removal. (d) Intraoperative cholangiography. Stone filled hepatic ducts

Fig. 3 DBE treatment (Patient No. 8). (a) Guidewire was cannulated into anastomosis (black arrow). (b)The anastomosis was dilated with a balloon. (c) A crusher catheter and crushed stones. (d) Cholangiography and stone (black arrow).