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Surgical treatment for intractable cholangitis with intrahepatic biliary cysts followed by Kasai operation in biliary atresia: a retrospective cohort study

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Purpose: Intrahepatic biliary cysts (IBCs) after Kasai portoenterostomy (KPE) are associated with intractable recurrent cholangitis. This study aimed to investigate the feasibility of its use as well as indication for surgical management of IBCs in pediatric patients.
Methods: We retrospectively reviewed the medical records and imaging studies of patients who underwent KPE for biliary atresia from 2010 to 2020.
Results: An imaging study identified IBCs in 28 of 129 patients who underwent KPE with biliary atresia (21.7%). Among them, 5 patients were subjected to surgical treatment for intractable cholangitis. The median time from KPE to the development of IBCs was 1.7 years. Four out of 5 patients had IBCs confined to the left lateral lobe, and in one patient, the IBCs were in the hepatic hilum. All 5 patients experienced more than one cholangitis. Although they received intravenous antibiotic treatment and percutaneous transhepatic cholangiodrainage as treatment, they were intractable. Three patients underwent hepatectomy, and 2 underwent cystojejunostomy. There was no recurrence of cholangitis during the median follow-up period of 2.9 years.
Conclusion: Surgical treatment for IBCs after KPE could be considered a safe and effective surgical procedure for children if appropriate indications are applied.
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Key Words: Biliary atresia, Cholangitis, Hepatic portoenterostomy, Pediatrics

INTRODUCTION

The development of intrahepatic biliary cysts (IBCs) or bile lakes following Kasai portoenterostomy (KPE), has an estimated incidence of 6%–25% [1-4]. Several mechanisms have been hypothesized with regard to the formation of IBCs after KPE for the management of biliary atresia (BA), but bile stasis commonly occurs in the damaged bile duct, causing repeated cholangitis [3,5-7]. This condition has a poor prognosis and is associated with an increased risk of liver transplantation (LT) [3-5]. However, its optimal treatment remains under debate. Percutaneous transhepatic cholangiodrainage (PTCD) and continuous use of antibiotics as a treatment strategy for intractable recurrent cholangitis caused by IBCs has limited

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efficacy due to repeated hospitalization and poor quality of life. In this study, we aimed to verify the effectiveness of surgical management in patients with intractable cholangitis caused by IBCs in whom the liver function was maintained. In addition, we established criteria for implementing surgical treatment for the management of IBCs.

METHODS

We performed KPE on 129 patients with BA from 2010 to 2020 and routinely followed them up at 3-month intervals for 1 year at the outpatient clinic; the interval was adjusted according to individual patient conditions. Patients with IBC underwent MRI or CT to confirm liver stiffness. The indications for surgical treatment were as follows: (1) the focus of fever was cholangitis; (2) patients with recurrent cholangitis caused by IBCs who did not respond to conventional treatment; and (3) patients with Pediatric End-stage Liver Disease (PELD) or Model for End-stage Liver Disease (MELD) scores of <10 and without ascites or portal hypertension who were not eligible for LT. Based on clinical records, we conducted a retrospective review of the treatment courses, complications, and outcomes of patients who underwent KPE before and after surgical treatment for intractable cholangitis. The value of total serum bilirubin was periodically checked after surgery, and persistent jaundice was defined as a value observed higher than 2.0 mg/dL. Postoperative complications were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) ver. 5.0. All procedures involving human participants in this study were conducted in accordance with the ethical standards of the Institutional Review Board of Asan Medical Center Children's Hospital (No. 2020-1409), which approved the study. The patient information was anonymized, and patient consent was waived.

RESULTS

In our study, 28 out of 129 patients (21.7%) who underwent KPE developed IBCs, 5 of which required surgical treatment due to intractable cholangitis. The characteristics of the IBCs and patients are shown in Table 1. The median time to the onset of IBCs after KPE was 1.7 years (range, 0.2–12.3 years). Of the 5 patients, 3 had multiple cystic lesions, 1 had beaded cystic lesions, and 1 had solitary cystic lesions. All 5 patients had at least 1 cholangitis, and PTCD was administered to 4 patients who were refractory to intravenous antibiotic treatment. The other patient underwent immediate surgical treatment without PTCD. The degree of hepatic fibrosis in patients varied from mild to early liver cirrhosis on liver elastography and MRI. In case 4, collateral vessels and narrowing of the portal vein caused by liver fibrosis were confirmed. No patients with ascites were observed due to portal hypertension. Surgical drainage

Table 1. Characteristics of IBCs in patients after Kasai operation

Case No.	Sex	Age at Kasai (day)	Time to IBC onset after Kasai	Location of IBCs	No. of IBCs	Maximum size of IBCs (cm)	Cholangitis episodes	PTCD	Hepatic fibrosis	Ascites/ varices	PELD or MELD score
1	Male	70	7.0 yr	LLS, S4, S8	Beaded	1.2	>10	Failed	Moderate	–/–	8.0
2	Female	60	1.7 yr	LLS	Multiple	2	5	Failed	Mild	–/–	6.2
3	Female	20	2.1 mo	LLS	Multiple	4.2	8	Failed	Severe	–/+	2.8
4	Female	81	10.1 mo	Hepatic hilum	Multiple	1.8	1	Failed	Early LC	–/–	1.0
5	Female	60	12.3 yr	LLS	Single	2.0	>10	NA	Mild	–/–	9.0

IBC, intrahepatic biliary cyst; PTCD, percutaneous transhepatic cholangiodrainage; PELD, Pediatric End-stage Liver Disease; MELD, Model for End-stage Liver Disease; LLS, left lateral segmentectomy; NA, not applicable.

Table 2. Surgical drainage and outcomes

Case No.	Surgical drainage methods	Bilirubin at surgical drainage (μmol/L)	Bilirubin at 3 mo (μmol/L)	Follow-up (yr)	Outcomes
1	LL	1.2	0.5	5.4	SNL
2	LLS	3.9	0.4	6.5	SNL
3	LL	0.5	0.4	2.9	SNL
4	S3 PH, cystojejunostomy	0.7	0.5	2.2	SNL
5	S4 PH, cystojejunostomy	1.6	0.7	0.2	SNL

LL, left lobectomy; LLS, left lateral segmentectomy; SNL, survival of the native liver; PH, partial hepatectomy.

was performed according to each patient's condition, and the results are shown in Table 2. We performed lobectomy in cases 1–3 and bile drainage through cystojejunostomy in cases 4 and 5. Cases 1 and 2 received left lobectomy, and case 3 underwent left lateral segmentectomy considering remnant liver function. The median follow-up period was 2.9 years (range, 0.8–5.4 years), and neither persistent jaundice nor hospitalization for recurrent cholangitis was noted. Six months after undergoing cystojejunostomy, case 5 developed an ileus with CTCAE ver. 5.0 grade 3. The patient underwent adhesiolysis to address the condition. The remaining patients had no serious complications. To date, all patients have maintained survival with the native liver.

DISCUSSION

IBCs worsen the function of native liver and are a significant complication affecting the survival of patients undergoing KPE for BA [8,9]. Although these lesions indicate poor prognosis, the exact incidence of this association is not well known. The incidence of IBC is approximately 6%–25% [1-4]. We investigated the IBC of postoperative BA patients using periodic MRIs. In this study, the incidence of IBC was 28 in 129 patients (21.7%), which is also comparable to the results of previous studies.

There are several hypotheses regarding the development of IBCs in patients who undergo KPE for BA as follows: (1) The fibro-obliterative process of BA in the intrahepatic lobular spaces results in damage to the biliary epithelium [3]; (2) progressive inflammation leads to intrahepatic biliary obstruction [6]; and (3) ductal plate malformation is considered a factor in the development of IBCs [7]. These pathologic changes cause insufficient bile drainage that results in biliary stasis and cholangitis, which gradually progress to hepatic fibrosis and cirrhosis. Tainaka et al. [10] histologically demonstrated that bile stasis in the intrahepatic bile ducts forms calculi within the bile ducts. Calculi then repeatedly cause cholangitis and form IBCs by fusing with the damaged bile ducts.

Some studies have reported a close relationship between IBCs and cholangitis [3,5-7]. Cholangitis, often accompanied by fever without other infectious causes, is a frequent complication with various symptoms after KPE for BA. Its incidence during the first postoperative year ranges from 40% to 93% and gradually decreases as the bile flow and stasis of bile improve after a successful surgery [11-13]. In addition, cholangitis caused by IBCs is intractable even with PTCD and prolonged antibiotics, and the rate of recurrent cholangitis in patients with multiple intrahepatic cysts is as high as 93.8% [4,14,15]. Ginstrom et al. [15] reported that the annual frequency of cholangitis episodes in patients with IBCs was more than 5 times higher than that in patients without IBCs. In addition, an increase in the occurrence of cholangitis had a detrimental effect on native liver survivors. Intractable cholangitis associated with IBC results in the obstruction of bile flow and subsequent deterioration of hepatic function and cirrhosis [13,16]. Persistent hepatic dysfunction is related to various physiological problems, such as decreased synthetic function and malabsorption of nutrients, further leading to growth retardation.

IBCs have been managed by conservative treatments such as PTCD and prolonged intravenous antibiotics. PTCD is effective in treating single cysts, but not in the management of multiple cysts [14,17]. We inserted PTCD in 4 patients with multiple IBCs, and a very small amount of bile was drained in each patient, and cholangitis was not controlled by the procedure. Previous studies have also reported that patients with multiple IBCs do not respond to conventional treatment and show a poor prognosis [1,4]. In case 5 with a single IBC, surgical treatment for IBC was planned immediately without PTCD. Magnetic resonance cholangiography revealed the corresponding biliary dilatation and IBC was not associated with portojejunostomy. We suggest that the cyst was noncommunicating, and the IBC would not disappear or regress after a recommunication extending from the cyst to the intestine following PTCD. Moreover, older children with IBCs with late onset symptoms tend to resist these conventional treatment modalities [18]. Unless IBC is managed effectively, LT will inevitably be considered due to permanent liver injury in the long term [9]. If cystic dilatation was confined to the left lateral segment or the remnant liver function of the dominant lobe was maintained, transplantation was not considered.

LT may be considered in patients with multiple IBCs because the therapeutic effect of PTCD is insufficient. However, if the liver function is still well maintained, that is, if the

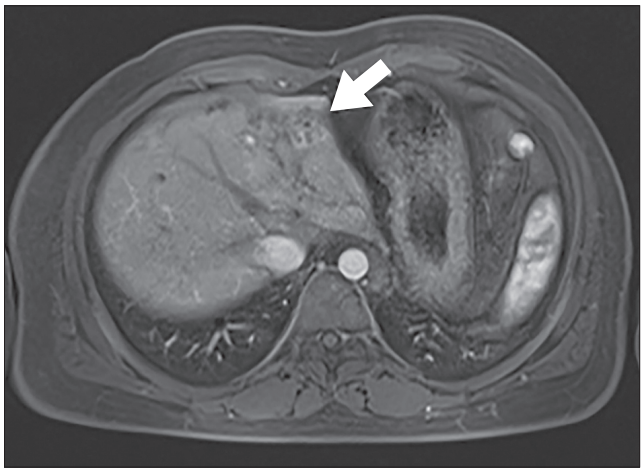

Fig. 1. Preoperative MRI of case 1. Multiple intrahepatic bile cysts were in the left lobe of the liver (arrow).

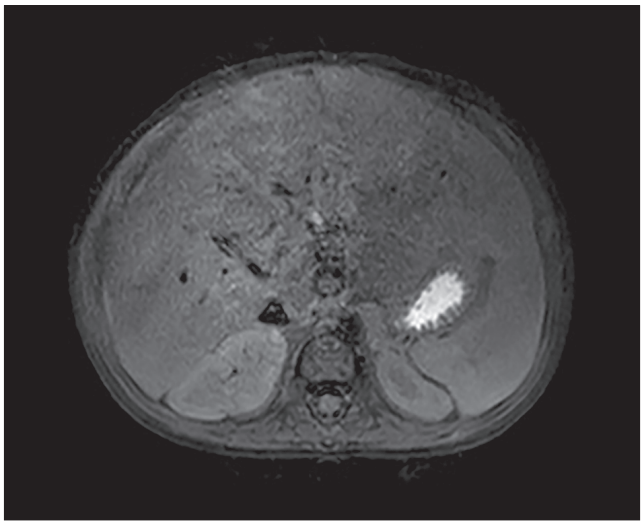

Fig. 2. MRI of case 4. 1 year after the Kasai portoenterostomy. Multiple cysts in the hepatic hilum were found.

PELD or MELD score is not high enough to receive LT, it is better to avoid excessive surgery. Two cases of lobectomy or cystojejunostomy as surgical treatments for intractable IBCs have been reported [19-21]. Despite several studies on the process and effect of IBCs in BA, the effectiveness of surgical treatment remains to be elucidated. Therefore, in this study, we carefully selected patients and surgical methods by considering various factors to determine the patients indicated for surgical treatment. We first selected patients with low PELD/MELD score (PELD/MELD score <10) as subjects for surgery and in whom we could expect survival of the native liver (SNL) if only cholangitis was resolved [22-25]. The method of surgical treatment for IBCs was determined according to the dominant lobe for liver function and the location of the IBCs. When the left lobe was a nondominant lobe and the main IBCs were located, we performed left lobectomy or left lateral segmentectomy according to the remnant liver function of patients (cases 1–3) (Fig. 1). When IBCs were in the dominant lobe or hilum, a cystojejunostomy was performed (cases 4 and 5) (Fig. 2). Further, IBCs in the right lobe, are considered more complicated. Cystenterostomy is difficult to perform when the lesion is on the right lobe, compared to when it is on the left lobe due to portojejunostomy, and liver resection may affect remnant liver function. Thus, further studies are warranted in the future considering the factors associated with successful surgical outcomes in the management of IBCs.

Considering the MELD/PELD score and the location of IBCs, patients who underwent surgical treatment had normalized bilirubin levels within 3months. No patient experienced jaundice during the follow-up period, and SNL was well-maintained, which is satisfactory in terms of life. Bu et al. [4] reported that among 39 patients with PTCD, the cysts disappeared only in 1 patient, and the mean interval between cyst detection and death was 3.75 months in patients with multiple IBCs. In cases with limited cystic changes and preserved remnant liver functional reserve, as noted in our study, surgical treatment may be considered as a potential alternative before proceeding to LT.

Although the sample size for surgical treatment is limited, further studies with larger cohorts are necessary to validate these findings.

In conclusion, IBCs are a common complication in patients with postoperative BA. Recurrent cholangitis, poor biliary drainage, and pathological changes in the intrahepatic biliary structure contribute to the development of multiple IBCs. Intractable cholangitis caused by multiple IBCs or poor biliary drainage persistently worsens liver function that may require LT. Surgical management of IBCs could be useful as a safe and effective procedure for IBCs of BA treatment in children if the surgery is selectively applied considering MELD/PELD scores and the location of lesions. Furthermore, it could be expected to improve the patients' quality of life by establishing a strategy to extend SNL. This study suggests that surgical intervention can be a viable option under certain conditions; however, further research is needed to confirm these findings in larger populations.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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