Pancreatology 19 (2019) 834–841

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Long-term outcomes of therapeutic ERCP in pediatric patients with pancreas divisum presenting with acute recurrent or chronic pancreatitis

Jun Wen [a, 1], Tao Li [b, 1], Lei Liu [a], Li-Ke Bie [a], Biao Gong [a, *]

[a] Digestive Endoscopy Center, Department of Gastroenterology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China
[b] Department of Gastroenterology, Changzheng Hospital, Second Military Medical University, Shanghai, China

ARTICLE INFO

Article history:
Received 6 January 2019
Received in revised form
2 August 2019
Accepted 7 August 2019
Available online 8 August 2019

Keywords:
Acute recurrent pancreatitis
Chronic pancreatitis
Endoscopic retrograde cholangiopancreatography
Pancreas divisum
Pediatrics

ABSTRACT

Objectives: The aim of this study was to evaluate the long-term outcomes of therapeutic endoscopic retrograde cholangiopancreatography (ERCP) for pediatric patients with pancreas divisum (PD) presenting with acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP).

Methods: Between May 2008 and August 2017, pediatric patients with PD who received endotherapy at Ruijin Hospital were identified and grouped according to clinical presentation, namely ARP and CP. Primary success was defined as patients' improvement in symptoms after index ERCPs, without further intervention or any analgesic.

Results: A total of 74 ERCPs were performed in 38 pediatric patients. The frequency of at least 1 genetic mutation identified in patients with ARP and CP was 44.4% and 68.4%, respectively. Patients with CP required more ERCPs than those with ARP (2.4 ± 1.7 vs. 1.1 ± 0.4, $P = 0.005$). The incidence of post-ERCP complications was 14.9%, including pancreatitis of 13.5% and hemorrhage of 1.4%. During a median follow-up duration of 41 months (range, 12–123 months), the frequency of pancreatitis episodes decreased significantly from 2.31 to 0.45 ($P < 0.0001$). The 25% recurrence and reintervention rates were estimated at 25 and 48 months, respectively, without significant difference between patients with ARP or CP. There was a nonsignificant trend towards a higher rate of primary success in patients with ARP than those with CP (92.9% vs. 69.6%, $P = 0.123$). After further endotherapy, 91.3% patients with CP improved clinically.

Conclusions: Therapeutic ERCP is an effective and safe intervention for pediatric patients with symptomatic PD. Patients presenting with CP seem to achieve improvement after additional ERCPs.

Introduction

Pancreas divisum (PD), as the most common congenital anomaly of the pancreas, occurs due to failed fusion of the ventral and dorsal duct system during embryonic development. As a result of the anatomic variant, the majority of the pancreas drains through the dorsal duct via the minor papilla [1]. PD is found in 2.6%–14% of the general population [2,3], whereas only a little portion of PD is of clinical significance and causes symptoms such as acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) [4–6]. A community-based study shows a significantly higher prevalence of PD in patients with ARP or CP than in controls in the community, indicating that PD acts as a predisposing factor for pancreatitis [2]. Meanwhile, PD is found to be an independent obstructive factor for ARP and CP in the pediatric population [7,8].

Therapeutic endoscopic retrograde cholangiopancreatography (ERCP) including minor papilla sphincterotomy, dorsal duct stent placement and minor papilla balloon dilation, has been frequently utilized in adults with symptomatic PD, with a response rate ranging from 31.3% to 95.7% varied by clinical presentation [9]. Although ERCP has been increasingly used in the pediatric

Abbreviations: PD, pancreas divisum; ARP, acute recurrent pancreatitis; CP, chronic pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography; EPS, endoscopic pancreatic sphincterotomy; PEP, post-ERCP pancreatitis; SD, standard deviation; CFTR, cystic fibrosis transmembrane conductance regulator; SPINK1, serine protease inhibitor Kazal-type 1; PRSS1, cationic trypsinogen; CTRC, chymotrypsin.

* Corresponding author. 197 Ruijin Er Road, Shanghai, 200025, China.
E-mail address: gbercp616@163.com (B. Gong).

[1] Jun Wen and Tao Li contributed equally to this article.

https://doi.org/10.1016/j.pan.2019.08.004
1424-3903/

population [10–12], data on endoscopic therapy for symptomatic PD are still scarce [7], possibly owing to the technical difficulty of performing intervention via the minor papilla in pediatric patients. As far as we know, there have been no studies focusing on long-term outcomes of therapeutic ERCP for pediatric PD.

Given their longer life expectancy, pediatric patients are likely to achieve a long-term improvement after endotherapy, which may be also accompanied with a higher risk of ERCP-related complications. Herein, we carry out this study to assess the rates of technical and clinical success, post-ERCP complications and long-term outcomes of therapeutic ERCP in pediatric patients with symptomatic PD according to their clinical presentation.

Methods

Patient selection

In January 2008, an electronic endoscopy database was established to collect demographic, diagnostic, therapeutic and endoscopic procedural details of patients who received ERCP at the Digestive Endoscopy Center of Ruijin Hospital, a tertiary referral center in Shanghai, China. Medical records of consecutive patients with symptomatic PD who underwent therapeutic ERCP at our center between May 2008 and August 2017 were obtained by retrieving the database. Patients aged 18 or below at the time of initial ERCP were identified. Patients who had received endoscopic or surgical intervention for pancreatic disease previously were excluded. During patients' hospitalization, imaging (MRCP or CT scan) and laboratory tests, including serum calcium, triglyceride, bilirubin, liver enzymes, γ-globulin, IgG4 and autoantibodies were performed to determine the etiology of ARP or CP. Patients with ARP or CP of any known causes other than PD were ruled out. Patients with choledocholithiasis or pancreaticobiliary maljunction were also excluded because these disorders might induce acute pancreatitis and affect the assessment of clinical outcomes. In addition, genetic tests were generally suggested for patients with unexplained ARP or CP, whereas whether to receive the test was at the discretion of patients themselves or their parents. We conducted a detailed chart review of patients who fulfilled the inclusion criteria. This study was approved by the Institutional Review Board of Ruijin Hospital.

We divided our patients into two groups according to their clinical presentation: (1) ARP: at least 2 attacks of abdominal pain together with increased serum amylase or lipase more than 3 times the upper limit of normal, without CP changes on imaging examination; and (2) CP: typical changes of CP on magnetic resonance cholangiopancreatography (MRCP) or pancreatography based on the definition and grading of the Cambridge classification [13].

ERCP procedures

Written informed consent was obtained from the parent or guardian of each child before ERCP. All procedures were carried out by experienced endoscopists who were competent in performing ERCP on pediatric patients, with a standard duodenoscope (JF-240, JF-260, TJF-260; Olympus Optical, Tokyo, Japan). Therapeutic manipulations were performed on the basis of pancreatogram findings, including endoscopic pancreatic sphincterotomy (EPS), minor or major papilla balloon dilation, bougienage, stone extraction and dorsal duct stent placement (Fig. 1). The size and length of the inserted stent were determined by the diameter and the site of the stricture. Pancreatic stents were replaced at intervals of 3–6 months, or on demand (in the case of recurrent abdominal pain or pancreatitis). On the basis of the improvement in symptoms, resolution of previous stricture and patency degree of contrast medium or pancreatic juice outflow evaluated during the subsequent ERCP, endoscopists decided whether to exchange or remove the stent. The duration of stent in situ was defined as the period between stent placement and complete removal. All patients undergoing therapeutic ERCP at our center were hospitalized for observation of development of any post-ERCP complications and received tests of serum amylase 3 and 24 h after the procedure to monitor dynamic changes of amylase following ERCP.

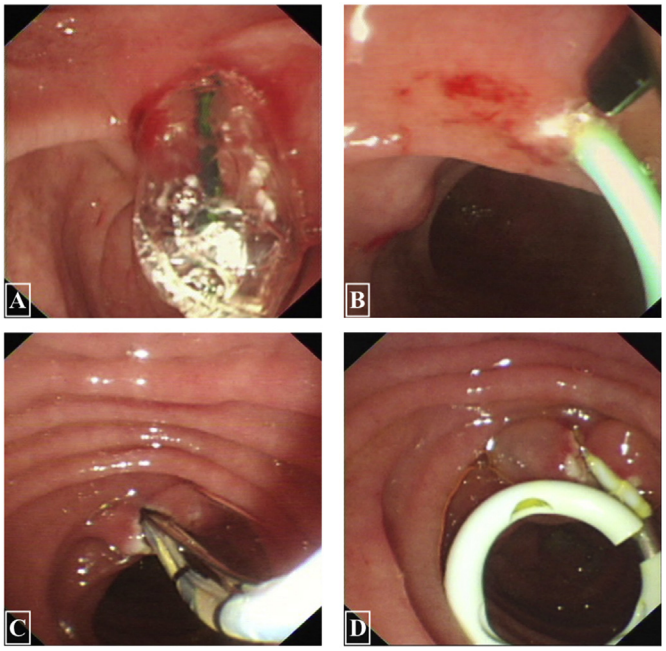

Fig. 1. (A) Endoscopic balloon dilation via the minor papilla. **(B)** Needle-knife sphincterotomy of the minor papilla following dorsal duct stent placement. **(C, D)** Endoscopic minor papilla sphincterotomy followed by dorsal duct stenting.

Follow-up

Follow-up was based on telephone contact in combination with face-to-face interview and reexamination during return visits to our outpatient department. A questionnaire was formulated by investigators to collect the following information: patients' present condition, episodes of pancreatitis or pain after initial ERCP, any further endoscopic or surgical intervention and usage of analgesics. In the case of patients who received repeated ERCPs at our center, the follow-up data was supplemented by the review of medical records. At the last follow-up (August 2018), patients' condition of symptoms was graded according to the following 5-point Likert scale: 1, cured; 2, better; 3, same; 4, worse; and 5, much worse. The duration of follow-up was defined as the period between the initial ERCP at our institution and the last follow-up contact.

Patients were considered to have achieved primary success if they reported resolution or improvement of symptoms (i.e. cured or better on Likert scale), without reintervention after index ERCPs, and without analgesic usage for pain control [14]. Given the necessity of additional procedures to replace pancreatic stents, the index ERCPs were defined as endoscopic interventions performed in the first year.

Definitions

The diagnosis of PD was confirmed by pancreatogram findings during ERCP procedure. When cannulation via the major papilla

reveals a short ventral duct without crossing the midline or complete absence of the ventral duct, PD should be considered. Subsequent cannulation through the minor papilla demonstrates the existence of a predominant dorsal duct. Anatomically, PD could be categorized into three variants: (1) Complete PD: no branch connects the ventral and dorsal ducts; (2) Incomplete PD: a tiny branch connects the two ducts; and (3) Ventral duct absent: isolated dorsal duct drains the entire pancreatic duct system via the minor papilla with complete absence of the ventral duct [6]. Technical success was defined as deep cannulation of the dorsal duct and completion of intended therapeutic maneuvers.

Post-ERCP complications were classified and graded according to the consensus criteria [15,16]. Post-ERCP pancreatitis (PEP) was defined as new or worsened abdominal pain with an elevated amylase at least 3 times the upper limit of normal at more than 24 h after the procedure, requiring admission or prolongation of planned hospitalization. Mild PEP was defined as the presence of PEP requiring hospitalization to 2–3 days. Moderate PEP required hospitalization of 4–10 days. Severe PEP required hospitalization for more than 10 days, or developed hemorrhagic pancreatitis or pseudocyst or phlegmon, or needed percutaneous or surgical intervention.

Statistical analysis

Statistical analyses were performed with the STATA 14.1 (Stata Corp, College Station, Texas, USA). Continuous variables were presented as mean ± standard deviation (SD) or median (range) and analyzed by the *t*-test or Wilcoxon rank-sum test. Categorical variables were expressed as frequency (percentage) and analyzed by the chi-square test or Fisher's exact test.

Paired *t*-test was used to examine the difference in the frequency of pancreatitis episodes before and after endotherapy. The rates of recurrence and reintervention during follow-up was estimated by the Kaplan-Meier method. The log-rank test was used for the comparison of recurrence and reintervention curves between the two groups.

Potential predictors of PEP and primary success were assessed by univariate analysis with the chi-square test or simple logistic regression where appropriate. Given that no significant variables except dorsal duct stent placement were identified in univariate analysis, we then used multiple logistic regression to determine the association between stenting and PEP after adjusting for potential confounders. A P value of less than 0.05 was considered statistically significant.

Results

Patients

A total of 46 pediatric patients with symptomatic PD underwent therapeutic ERCPs at our center during the study period. Five patients were excluded due to the presence of choledocholithiasis (n = 1) and pancreaticobiliary maljunction (n = 4), and 3 patients were lost to follow-up. Therefore, 38 (82.6%) patients with available follow-up information were included in the final analysis. The baseline characteristics of 38 pediatric patients were summarized in Table 1. There were 14 (36.8%) patients with ARP and 24 (63.2%) patients with CP. The demographic data were comparable between the two groups. Patients suffered from recurrent episodes of pancreatitis or abdominal pain for a median period of 19 months (range, 1–84 months) before endotherapy. None of the patients with CP developed diabetes mellitus and none of them had a history of alcohol consumption. Complete and incomplete PD was found in 18 (47.4%) and 19 (50.0%) patients, respectively, and there was 1 (2.6%) patient with the absence of the ventral duct. There was no significant difference between the two groups regarding anatomic variations of PD (P = 0.173). Data on genetic testing for pancreatitis-related mutations were available in 73.7% (28/38) of our cohort, with 11 (39.3%) of the 28 patients tested for fewer than 3 genes (Table 1). At least 1 genetic mutation was found in 44.4% (4/9) and 68.4% (13/19) of patients with ARP and CP, respectively (P = 0.225). The most common mutation was in cystic fibrosis transmembrane conductance regulator (CFTR) in both the ARP and CP groups. One patient with CP was identified with mutations in serine protease inhibitor Kazal-type 1 (SPINK1) and CFTR. The frequency of cationic trypsinogen (PRSS1), CFTR, SPINK1 or chymotrypsin C (CTRC) mutations did not differ significantly between patients with ARP or CP.

ERCP procedures

The details of endoscopic findings and procedures were presented in Table 2. A total of 74 ERCPs were performed in the 38 pediatric patients, including once in 22 (57.9%) patients, twice in 8 (21.0%) patients, three times in 3 (7.9%) patients and more than three times in 5 (13.2%) patients. There was a significant difference in the average number of ERCP sessions needed between the ARP and CP groups (1.1 ± 0.4 vs. 2.4 ± 1.7, P = 0.005). EPS of the minor papilla was performed in 29 (39.2%) of 74 procedures. Those patients in whom EPS of the minor papilla was considered difficult or

Table 1
Baseline characteristics of 38 pediatric patients with symptomatic PD.

	Acute recurrent pancreatitis (n = 14)	Chronic pancreatitis (n = 24)	Overall (n = 38)	P value
Female, n (%)	9 (64.3)	14 (58.3)	23 (60.5)	1.000
Median age at initial ERCP (range), yr	11 (2–17)	10 (3–18)	10 (2–18)	0.981
Median symptom duration[a] (range), mo	25 (1–72)	18 (1–84)	19 (1–84)	0.553
Diabetes mellitus	0	0	0	–
Anatomic variations, n (%)				0.173
Complete PD	8 (57.1)	10 (41.7)	18 (47.4)	0.503
Incomplete PD	5 (35.7)	14 (58.3)	19 (50.0)	0.313
Ventral duct absent	1 (7.1)	0	1 (2.6)	0.368
Genetic mutations, positive/tested (%)	4/9 (44.4)	13/19 (68.4)	17/28 (60.7)	0.225
PRSS1	1/8 (12.5)	4/17 (23.5)	5/25 (20.0)	0.520
CFTR	2/6 (33.3)	5/16 (31.3)	7/22 (31.8)	1.000
SPINK1	1/6 (16.7)	4/14 (28.6)	5/20 (25.0)	0.573
CTRC	0/3 (0)	1/11 (9.1)	1/14 (7.1)	0.588

PD, pancreatic divisum; ERCP, endoscopic retrograde cholangiopancreatography; SD, standard deviation; PRSS1, cationic trypsinogen; CFTR, cystic fibrosis transmembrane conductance regulator; SPINK1, serine protease inhibitor Kazal-type 1; CTRC, chymotrypsin C.

[a] Symptom duration denotes the period between the first attack of pancreatitis or pain and the initial therapeutic ERCP.

Table 2
Therapeutic details and post-ERCP complications of 74 procedures in 38 pediatric patients with PD.

	Acute recurrent pancreatitis n (%)	Chronic pancreatitis n (%)	Overall n (%)	P value
ERCP sessions, patients (%)				
1 ERCP	12/14 (85.7)	10/24 (41.7)	22/38 (57.9)	0.016
2 ERCPs	2/14 (14.3)	6/24 (25.0)	8/38 (21.0)	0.684
3 ERCPs	0	3/24 (12.5)	3/38 (7.9)	0.283
≥4 ERCPs	0	5/24 (20.8)	5/38 (13.2)	0.137
Average ERCP sessions (SD)	1.1 (0.4)	2.4 (1.7)	1.9 (1.5)	0.005
Technical success	16/16 (100.0)	53/58 (91.4)	69/74 (93.2)	0.579
Therapeutic interventions				
EPS of the minor papilla	12 (75.0)	17 (29.3)	29 (39.2)	0.001
EPS of the major papilla	0	9 (15.5)	9 (12.2)	0.191
Minor papilla balloon dilation	0	4 (6.9)	4 (5.4)	0.571
Major papilla balloon dilation	0	2 (3.4)	2 (2.7)	1.000
Bougienage	3 (18.8)	15 (25.9)	18 (24.3)	0.746
Median diameter of bougies (range), Fr	7 (7)	7 (6–8.5)	7 (6–8.5)	0.703
Stone extraction	–	30 (51.7)	30 (40.5)	–
Dorsal duct stent placement	6 (37.5)	39 (67.2)	45 (60.8)	0.031
Median diameter of stents (range), Fr	5 (5–7)	7 (5–8.5)	7 (5–8.5)	0.049
Median length of stents (range), cm	7 (5–7)	7 (4–14)	7 (4–14)	0.846
Duration of stent in situ (range), mo	3 (0.5–7)	10 (2–37)	7.5 (0.5–37)	0.003
Post-ERCP complications				
Overall complications	1 (6.3)	10 (17.2)	11 (14.9)	0.437
Post-ERCP pancreatitis	1 (6.3)	9 (15.5)	10 (13.5)	0.680
Mild	0	9 (15.5)	9 (12.2)	0.191
Moderate	1 (6.3)	0	1 (1.4)	0.216
Moderate Hemorrhage	0	1 (1.7)	1 (1.4)	1.000

ERCP, endoscopic retrograde cholangiopancreatography; PD, pancreatic divisum; SD, standard deviation.
This table is designed on the number of procedures.

hazardous, were managed by bougienage (n = 4) or balloon dilation (n = 4) via the minor papilla combined with dorsal duct stent placement in order to relieve intraductal pressure and improve dorsal duct drainage. Besides, bougienage was used for pancreatic duct stricture in 11 cases, for difficult stone extraction in 3 cases. In the case of incomplete PD, EPS and balloon dilation via the major papilla was performed in 9 and 2 cases, respectively. Dorsal duct stent placement was performed more frequently in patients with CP than in those with ARP (67.2% vs. 37.5%, P = 0.031). Patients with CP underwent stenting for a significantly longer duration (median, 10 months; range, 2–37 months) compared with patients with ARP (median, 3 months; range, 0.5–7 months; P = 0.003). Moreover, 4 (16.7%) of the 24 patients with CP received two-stent insertion at the same time.

The changes of CP on pancreatography were graded as moderate in 4 (16.7%) patients and marked in 20 (83.3%) patients according to the Cambridge classification. Of the 58 procedures performed in the 24 patients with CP, dorsal duct dilation was observed in 55 (94.8%) procedures, with dorsal duct stricture in 17 (29.3%) and pancreatic duct stones in 33 (56.9%). Stones were extracted successfully in 30 (90.9%) of 33 procedures.

Overall, technical success was achieved in 93.2% (69/74). All failed ERCPs occurred in patients of the CP group because of unsuccessful minor papilla cannulation (n = 2) and failed pancreatic duct stone extraction (n = 3). Cannulation via the minor papilla succeeded in the second attempt in one child, whereas another child's parents refused to receive repeated ERCP and then underwent surgical intervention. All of the 3 cases with initially failed stone extraction received extracorporeal shock wave lithotripsy (ESWL) and underwent successful stone removal in subsequent endotherapy.

Post-ERCP complications

The overall incidence of ERCP-related complications was 14.9% (11/74), including PEP of 13.5% (10/74) and moderate hemorrhage of 1.4% (1/74) (Table 2). The occurrence of post-ERCP complications did not differ between patients with ARP and CP. All patients with PEP improved following conservative management. One patient developed hemorrhage one day after ERCP and was treated by endoscopic submucosal epinephrine injection into the sphincterotomy site. No ERCP-related severe complications or mortality occurred during the study period.

In univariate analysis, dorsal duct stenting was associated with an increased rate of PEP (P = 0.042). After adjusting for sex, age, clinical presentation (i.e. ARP or CP), technical success, EPS and stone extraction, stenting was not a significant risk factor for PEP (odds ratio [OR], 7.99; 95% confidence interval [CI], 0.80–79.55; P = 0.076).

Long-term outcomes

The median follow-up duration was 44 months (range, 12–123 months) (Table 3). One (2.6%) patient in the CP group underwent pancreaticojejunostomy after failed cannulation of the minor papilla. The patient receiving surgery reported an improvement in symptoms (i.e. better) at the end of follow-up. Given the purpose of our study, the patient with surgical intervention was not included in the analysis of long-term outcomes of therapeutic ERCP. During the follow-up period, 20 (54.1%) of 37 patients with technically successful endotherapy had no further episodes of pancreatitis or pain after index ERCPs, including 8 with ARP and 12 with CP. The remaining 17 (45.9%) patients experienced recurrence of pancreatitis or pain after a median period of 16 months (range, 3–69 months). Of the 17 patients with symptom relapse, 10 (58.8%) were treated conservatively without further intervention and 7 (41.2%) required further endoscopic intervention after a median period of 27 months (range, 6–69 months) (Table 4). Reinterventions were needed more often in the CP group (26.1%) than in the ARP group (7.1%), without reaching statistical significance (P = 0.217). In addition, three patients with CP used pancreatic enzymes on demand (e.g. a diet with high volume of fat) for nutritional management, not for the treatment of pain. None of these patients necessitated analgesics for pain control, and there was no

Table 3
Follow-up period and long-term outcomes of 37 pediatric patients with technically successful endotherapy.

	Acute recurrent pancreatitis (n = 14)	Chronic pancreatitis (n = 23)	Overall (n = 37)	P value
Median follow-up period (range), mo	34 (12–85)	57 (19–123)	41 (12–123)	0.117
Long-term outcomes, n (%)				
Symptom relapse	6 (42.9)	11 (47.8)	17 (45.9)	1.000
Requirement for further endotherapy	1 (7.1)	6 (26.1)	7 (18.9)	0.217
5-point Likert scale				0.894
1. cured	10 (71.4)	13 (56.5)	23 (62.2)	
2. better	4 (28.6)	8 (34.8)	12 (32.4)	
3. same	0	1 (4.4)	1 (2.7)	
4. worse	0	1 (4.4)	1 (2.7)	
5. much worse	0	0	0	
Response rate, n (%)				
Primary success	13 (92.9)	16 (69.6)	29 (78.4)	0.123
Improvement after further endotherapy	1/1 (100.0)	5/6 (83.3)	6/7 (85.7)	1.000
Overall clinical improvement	14 (100.0)	21 (91.3)	35 (94.6)	0.517

ERCP, endoscopic retrograde cholangiopancreatography.

Table 4
Pediatric patients with further endoscopic or surgical interventions during follow-up period.

Patient no.	Sex	Age, years	Group	Initial endoscopic findings	Initial therapeutic interventions	Symptom relief[a], months	Indication for further ERCP	Further interventions	Overall ERCPs	The last therapy	Follow-up period, months
1	M	8	CP	Dorsal duct dilation, Pancreatic stone	EPS of the minor papilla, Bougienage (7-Fr), Stone extraction, Dorsal duct stent (7-Fr)	26	Attacks[b]	Minor papilla balloon dilation, Major papilla balloon dilation, Bougienage (8.5-Fr), Stone extraction, Dorsal duct stents (7-Fr×2)	7	2013/02	123
2	M	4	CP	Dorsal duct dilation, Dorsal duct stricture, Pancreatic stone	EPS of the minor papilla, Stone extraction, Dorsal duct stent (5-Fr)	48	Attacks	Bougienage (8.5-Fr), Stone extraction, Dorsal duct stent (7-Fr)	5	2012/07	121
3	M	6	CP	Dorsal duct dilation, Pancreatic stone	EPS of the major papilla, Bougienage (8.5-Fr), Stone extraction, Dorsal duct stent (8.5-Fr)	27	Attacks	EPS of the minor papilla, Bougienage (8.5-Fr), Dorsal duct stents (7-Fr, 8.5-Fr)	5	2012/01	112
4	F	5	CP	Dorsal duct dilation, Dorsal duct stricture	EPS of the minor papilla, Bougienage (7-Fr), Dorsal duct stent (5-Fr)	69	Pain[c]	Dorsal duct stent (7-Fr)	5	2015/06	107
5	F	16	ARP	Without imaging changes of chronic pancreatitis	EPS of the minor papilla	26	Attacks	Dorsal duct stent (7-Fr)	2	2014/01	81
6	F	15	CP	Dorsal duct dilation, Dorsal duct stricture, Pancreatic stone	EPS of the minor papilla, Stone extraction, Dorsal duct stents (7-Fr, 8.5Fr)	39	Attacks	Stone extraction, Dorsal duct stents (7-Fr×2)	5	2017/08	57
7	F	13	CP	Dorsal duct dilation	EPS of the minor papilla, Bougienage (6-Fr), Dorsal duct stent (5-Fr)	6	Pain	Dorsal duct stent (7-Fr)	2	2017/07	19
8	F	10	CP	MRCP findings: Dorsal duct dilation, Pancreatic stone	Failed cannulation via the minor papilla	–	–	Pancreaticojejunostomy	1	2013/01	77

ERCP, endoscopic retrograde cholangiopancreatography; CP, chronic pancreatitis; ARP, acute recurrent pancreatitis; EPS, endoscopic pancreatic sphincterotomy; MRCP, magnetic resonance cholangiopancreatography.
[a] Symptom relief denotes the period between the initial ERCP and a relapse of pancreatitis or pain which necessitates further endoscopic intervention.
[b] Attacks denote an acute pancreatitis relapse.
[c] Pain denotes recurrent episodes of abdominal pain without elevated pancreatic enzyme.

pancreaticobiliary malignancy or procedure-related death.

The scores of 5-point Likert scale were presented in Table 3. Of the 30 patients without reintervention, 20 (66.7%) reported complete resolution of symptoms (i.e. cured), 9 (30.0%) improved (i.e. better), and the condition of 1 (3.3%) remained the same. In addition, 6 (85.7%) of the 7 patients with further endoscopic intervention reported an improvement in symptoms (i.e. cured or better) at the end of follow-up, whereas 1 (14.3%) still complained of persistent mild-to-moderate pain (i.e. worse). Overall, the average number of pancreatitis episodes per year before and after index ERCPs was 2.31 (95% CI, 1.86–2.75) and 0.45 (95% CI, 0.27–0.63), respectively ($P < 0.0001$). A significant reduction in the frequency of pancreatitis attacks after endotherapy was observed in both ARP and CP groups ($P = 0.0006$ and $P < 0.0001$, respectively) (Fig. 2). Meanwhile, the mean diameter of the dorsal duct dilation in patients with CP improved significantly from 6.31 mm (95% CI, 5.16–7.46) to 5.18 mm (95% CI, 4.48–5.89) ($P < 0.05$) after therapeutic ERCP. But on the other hand, stent-related dorsal duct dilation was observed in one patient with ARP after 7-month stenting and the dilation improved slightly after stent removal.

At the last follow-up, 29 (78.4%) of the 37 patients with technically successful endotherapy achieved primary success, with 20

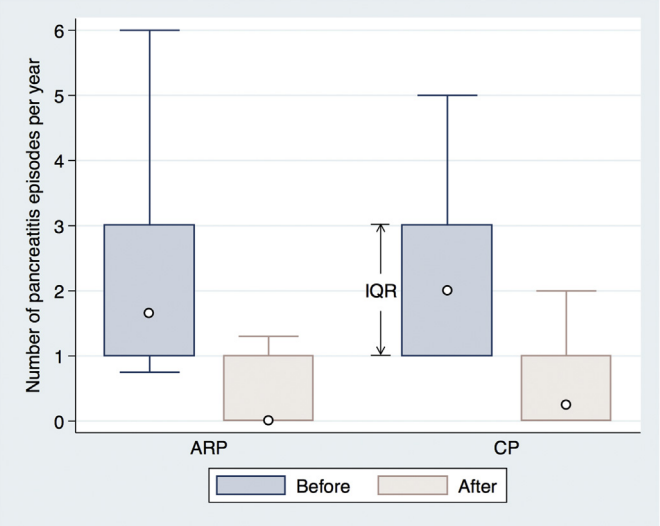

Fig. 2. The number of pancreatitis episodes per year before and after endotherapy in 37 pediatric patients with technically successful ERCP according to clinical presentation. Error bars denote minimum and maximum. ARP, acute recurrent pancreatitis; CP, chronic pancreatitis; IQR, interquartile range; ○, median.

(54.1%) free of symptom. Compared to patients with ARP, patients with CP had a poorer response to initial endotherapy (69.6% vs. 92.9%), whereas this difference was not statistically significant (P = 0.123) (Table 3). The overall clinical improvement was observed in 91.3% (21/23) patients with CP after additional ERCPs.

Of the 37 patients with technically successful ERCP, the 25% and 50% recurrence rates after initial endotherapy were estimated at 25 and 48 months, respectively (Fig. 3). On the other hand, the 25% reintervention rate was estimated at 48 months following initial ERCP (Fig. 4). The log-rank test revealed no significant difference between the two groups regarding the recurrence curve (P = 0.676) or reintervention curve (P = 0.397).

In univariate analysis, none of the potential variables, including sex, age, symptom duration before endotherapy, clinical presentation, the presence of genetic mutations, ERCP findings (i.e. dorsal duct dilation, stricture or stone), EPS and dorsal duct stenting, were significant predictors of primary success. The OR of primary success

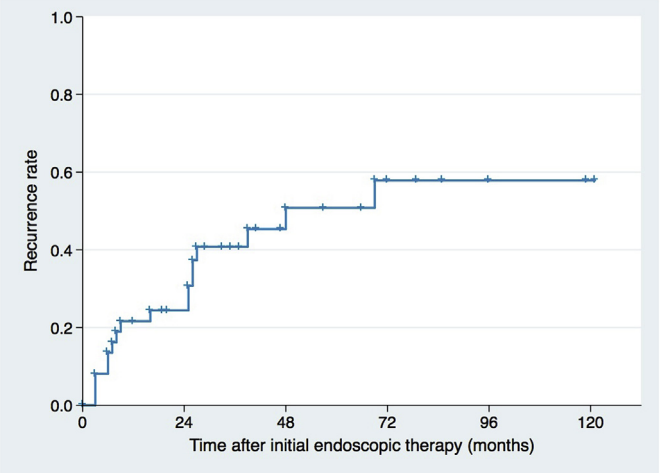

Fig. 3. The cumulative incidence of symptom recurrence in 37 pediatric patients with technically successful ERCP.

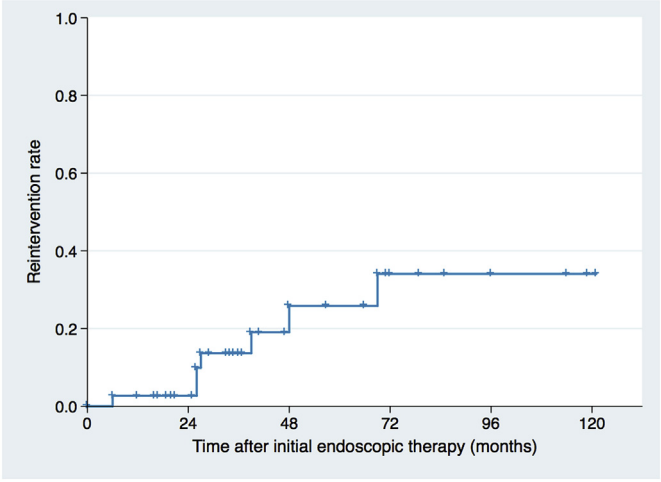

Fig. 4. The cumulative incidence of reintervention in 37 pediatric patients with technically successful ERCP.

for patients with PRSS1, CFTR, SPINK1 and any genetic mutation was 1.33 (95% CI, 0.12–14.90; P = 0.815), 0.63 (95% CI, 0.08–4.96; P = 0.656), 1.00 (95% CI, 0.08–12.56; P = 1.000) and 0.72 (95% CI, 0.11–4.82; P = 0.737), respectively.

Discussion

Our group previously reported that the efficacy and safety of therapeutic ERCP for symptomatic PD in adult patients was similar to younger patients [17]. Herein we described detailed endoscopic findings and therapeutic maneuvers in pediatric patients with PD and evaluated the long-term outcomes grouped according to their clinical presentation. Despite the small sample size, this is the first study to report the long-term follow-up results of endoscopic therapy for symptomatic PD in the pediatric population.

In the present study, the overall post-ERCP complications occurred in 14.9% (11/74) procedures, with PEP being the most common (10/74, 13.5%). The incidence of PEP in this study is comparable to the rate of 9.9% observed in our former study [17] and 10.6% in one larger series of endotherapy for adult patients with PD [14]. Compared with the PEP rate of 4.3%–7.7% reported in previous pediatric studies [10,11,18–20], the incidence of PEP in our study appeared to be higher, probably because a large proportion of ERCP procedures performed in those studies were for biliary indications. The evidence to support this explanation is that similar PEP rates were observed in pediatric studies concerning ERCP for CP (with or without PD) reported by Li et al. (15.5%) and Iqbal et al. (14.9%) [21,22]. In addition, diagnostic and therapeutic interventions including pancreatic duct cannulation, injection and EPS, were performed frequently in the present study. All of these manipulations were identified as procedure-related risk factors for PEP in both pediatric and adult studies [23–25]. Moreover, previous pancreatitis were recognized as patient-related predictors of PEP in previous adult literature [25]. In the present study, all of the 38 patients experienced episodes of pancreatitis previously.

In univariate analysis, only dorsal duct stenting showed an association with a higher PEP rate (P = 0.042), whereas it failed to remain statistical significance after a correction for multiple variables (P = 0.076). Similar finding has been noted in two pediatric studies, in which pancreatic stent placement (for therapeutic or prophylactic purpose) was found to be associated with increased rates of PEP [22,24]. However, most of the existing studies demonstrated that pancreatic stent placement significantly

reduced the risk of PEP in adult patients [26,27]. Prophylactic pancreatic stenting has been recommended for the prevention of PEP in high-risk patients [25]. This apparent inconsistency between pediatric and adult patients may be due to the age-related difference in pathophysiologic characteristics, which necessitating further study to investigate this phenomenon.

Previous studies indicated that therapeutic ERCP was an effective treatment for adults with symptomatic PD [5,28]. However, the definition of clinical improvement after endotherapy varied in available studies, with the response rates reported in the range of 31.3%–95.7% [9]. In the present study, we defined the primary success according to the description given by Borak et al. [14], which was based on patients' improvement in symptoms together with the requirement for reinterventions or analgesic medication. Our study showed that 78.4% pediatric patients with PD achieved clinical improvement after their index ERCPs, similar to the rate of 72.3%–81.3% reported in previous adult studies [29–31]. Moreover, the follow-up results of our study revealed a significant decrease in the frequency of pancreatitis attacks after endotherapy in both ARP and CP groups (Fig. 2). Therefore, endoscopic therapy should be considered as an effective intervention in pediatric patients with symptomatic PD.

The literature concerning the efficacy of therapeutic ERCP for symptomatic PD in the adult population mostly grouped patients by clinical presentation and showed that patients with ARP would respond better to endotherapy than those with CP [5,14,28,32]. A recent meta-analysis of existing adult studies showed that the pooled response rate in the ARP group was 76%, whereas the rate in the CP group was 52% [9]. CP was identified as an independent predictor of clinical failure in one of the largest series involving 113 adults with PD [14]. In the present study, the rates of primary success did not significantly differ between pediatric patients with ARP and CP (92.9% vs. 69.6%, $P = 0.123$). The reason for this disagreement may be attributed to the relatively small sample size in our pediatric study, limiting the power to reach statistical significance. Another potential factor may be the effectiveness of additional ERCPs in pediatric patients with CP in this study. We observed a significantly more ERCP sessions required in the CP group than in the ARP group (2.4 ± 1.7 vs. 1.1 ± 0.4, $P = 0.005$) per patient. In addition, the utility of therapeutic ERCP was found to be similar in patients with ARP and CP (with multiple predisposing factors) in a large cohort of pediatric pancreatitis [33].

On the other hand, patients with CP in this study underwent dorsal duct stent placement more frequently than those with ARP and for a significantly longer duration (median, 10 months; range, 2–37 months) (Table 2). Similar results were observed in previous pediatric studies. Li et al. [21] reported the follow-up results of endoscopic management of 42 children with CP (with 7 PD). Each patient received an average of 2.6 ERCPs (range, 1–7). A total of 33 patients underwent pancreatic stenting for an average of 10 months (range, 0.3–54 months). The overall clinical success was reported to be 71.4% (30/42). Oracz et al. [34] reported 223 procedures of pancreatic duct stenting performed in 72 children with CP (with 27 PD). The median interval between stent replacements was 4.5 months (range, 1–24 months). A significant difference in the median number of pancreatitis episodes per year was observed before and after endotherapy (1.75 vs. 0.23, $P < 0.05$). In our opinion, patients with PD and CP have morphologic changes of the pancreatic duct and irreversible fibrotic destruction of the pancreas, contributing to the need for more procedures to ensure a durable resolution of ductal stricture or minor papilla stenosis. Our study showed a significant improvement of the dorsal duct dilation in patients with CP after endotherapy. As a result, we deem it reasonable to perform additional ERCPs to achieve a long-term remission. However, when it comes to patients with ARP, we have to focus on the stent-induced ductal changes, similar to previous reports [35,36], which have emphasized the need for limiting the duration of stent placement to avoid severe morphologic changes associated with stenting.

Our study indicated that approximately a half (45.9%) of patients suffered a symptom relapse after a median period of 16 months (range, 3–69 months). The Kaplan-Meier method estimated that 25% patients experienced recurrent pancreatitis or pain at 25 months after initial ERCP (Fig. 3). The duration of patients free of symptom in the present study was apparently shorter than that (25% recurrence at 50 months) reported in one study involving 24 adults with PD and ARP [35]. This difference may be due to a large proportion of patients with CP in our study, which was commonly considered a predictor of lower primary success [5,14,28,32]. Although the estimated recurrent rate in this study seemed to be high, there was still a significant decrease in the average number of pancreatitis episodes per year, from 2.31 to 0.45 after therapeutic ERCP ($P < 0.0001$). In addition, less than half (41.2%, 7/17) of patients with symptom relapse required repeated endoscopic intervention. We observed a trend towards a higher reintervention rate in the CP group than in the ARP group (26.1% vs. 7.1%), without reaching statistical significance ($P = 0.217$). The reintervention rate in our study is comparable with the rate of 27.7% reported by Attwell et al. [31]. Similarly, they recognized CP as a nonsignificant predictor of reintervention (CP, 33% vs. ARP, 19%; $P = 0.11$).

The association of symptomatic PD with genetic mutations has been investigated in previous studies [7,8,37,38]. A higher prevalence of CFTR mutations in patients with symptomatic PD identified in our study was similar to the results reported in both adult and pediatric literatures [7,37]. There was no significant association between patients with or without any genetic mutations and clinical improvement. However, it should be noted that only 28 (73.7%) of 38 patients underwent genetic testing and 39.3% (11/28) of them were screened for fewer than 3 genes. Thus, it is still necessary to conduct further research on the potential relation between genetic factors in children with symptomatic PD and long-term outcomes of endotherapy.

The major limitation of this study is its retrospective nature, which may be accompanied with the recall bias. Clinical information of patients included in this study was retrieved from an established electronic endoscopy database. Besides telephone contact, follow-up data could be supplemented by reexamination and face-to-face interview during return visits. Hence, the data could be considered relatively complete and objective. Another limitation of this study is the small sample size, thereby restricting the ability to identify potential factors for PEP and clinical success. In addition, our study showed that nearly half of patients experienced recurrence with a post-ERCP complication rate of 14.9%, with emphasis on careful patient selection and an appropriate treatment strategy to improve long-term outcomes and minimize the risk of associated complications. Given the relative low volume of pediatric ERCPs at a single center, further multicenter prospective cohort studies are required to verify our findings and determine predictors of a better response.

In conclusion, therapeutic ERCP is an effective intervention for symptomatic PD in pediatric patients, with an acceptable rate of post-ERCP complications. In addition, patients with CP require more procedures than those with ARP, whereas they are likely to have nonsignificant difference in clinical improvement. Patients with PD and CP may benefit from repeated ERCPs in long term.

Conflicts of interest

All authors declare no conflict of interests for this article.

Acknowledgements

The authors would like to sincerely thank all the staff in the Digestive Endoscopy Center, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, for their important contribution to this study.

References

[1] Quest L, Lombard M. Pancreas divisum: opinio divisa. Gut 2000;47:317–9.
[2] Gonoi W, Akai H, Hagiwara K, et al. Pancreas divisum as a predisposing factor for chronic and recurrent idiopathic pancreatitis: initial in vivo survey. Gut 2011;60:1103–8.
[3] Fogel EL, Toth TG, Lehman GA, et al. Does endoscopic therapy favorably affect the outcome of patients who have recurrent acute pancreatitis and pancreas divisum? Pancreas 2007;34:21–45.
[4] Brugge WR. Endoscopic approach to the diagnosis and treatment of pancreatic disease. Curr Opin Gastroenterol 2013;29:559–65.
[5] Liao Z, Gao R, Wang W, et al. A systematic review on endoscopic detection rate, endotherapy, and surgery for pancreas divisum. Endoscopy 2009;41:439–44.
[6] Klein SD, Affronti JP. Pancreas divisum, an evidence-based review: part I, pathophysiology. Gastrointest Endosc 2004;60:419–25.
[7] Lin TK, Abu-El-Haija M, Nathan JD, et al. Pancreas divisum in pediatric acute recurrent and chronic pancreatitis: report from INSPPIRE. J Clin Gastroenterol 2019;53:e232–8 .
[8] Kumar S, Ooi CY, Werlin S, et al. Risk factors associated with pediatric acute recurrent and chronic pancreatitis: lessons from INSPPIRE. JAMA Pediatr 2016;170:562–9.
[9] Michailidis L, Aslam B, Grigorian A, et al. The efficacy of endoscopic therapy for pancreas divisum: a meta-analysis. Ann Gastroenterol 2017;30:550–8.
[10] Cho JM, Jeong IS, Kim HJ, et al. Early adverse events and long-term outcomes of endoscopic sphincterotomy in a pediatric population: a single-center experience. Endoscopy 2017;49:438–46.
[11] Giefer MJ, Kozarek RA. Technical outcomes and complications of pediatric ERCP. Surg Endosc 2015;29:3543–50.
[12] Agarwal J, Reddy DN, Talukdar R, et al. ERCP in the management of pancreatic diseases in children. Gastrointest Endosc 2014;79:271–8.
[13] Sarner M, Cotton PB. Classification of pancreatitis. Gut 1984;25:756–9.
[14] Borak GD, Romagnuolo J, Alsolaiman M, et al. Long-term clinical outcomes after endoscopic minor papilla therapy in symptomatic patients with pancreas divisum. Pancreas 2009;38:903–6.
[15] Cotton PB, Lehman G, Vennes J, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc 1991;37:383–93.
[16] Chandrasekhara V, Khashab MA, Muthusamy VR, et al. Adverse events associated with ERCP. Gastrointest Endosc 2017;85:32–47.
[17] Lu Y, Xu B, Chen L, et al. Endoscopic intervention through endoscopic retrograde cholangiopancreatography in the management of symptomatic pancreas divisum: a long-term follow-up study. Gut Liver 2016;10:476–82.
[18] Usatin D, Fernandes M, Allen IE, et al. Complications of endoscopic retrograde cholangiopancreatography in pediatric patients; a systematic literature review and meta-analysis. J Pediatr 2016;179:160–5. e3.
[19] Troendle DM, Barth BA. ERCP can Be safely and effectively performed by a pediatric gastroenterologist for choledocholithiasis in a pediatric facility. J Pediatr Gastroenterol Nutr 2013;57:655–8.
[20] Halvorson L, Halsey K, Darwin P, et al. The safety and efficacy of therapeutic ERCP in the pediatric population performed by adult gastroenterologists. Dig Dis Sci 2013;58:3611–9.
[21] Li ZS, Wang W, Liao Z, et al. A long-term follow-up study on endoscopic management of children and adolescents with chronic pancreatitis. Am J Gastroenterol 2010;105:1884–92.
[22] Iqbal CW, Baron TH, Moir CR, et al. Post-ercp pancreatitis in pediatric patients. J Pediatr Gastroenterol Nutr 2009;49:430–4.
[23] Rosen JD, Lane RS, Martinez JM, et al. Success and safety of endoscopic retrograde cholangiopancreatography in children. J Pediatr Surg 2017;52:1148–51.
[24] Troendle DM, Abraham O, Huang R, et al. Factors associated with post-ERCP pancreatitis and the effect of pancreatic duct stenting in a pediatric population. Gastrointest Endosc 2015;81:1408–16.
[25] Dumonceau JM, Andriulli A, Elmunzer BJ, et al. Prophylaxis of post-ERCP pancreatitis: european society of gastrointestinal endoscopy (ESGE) guideline - updated june 2014. Endoscopy 2014;46:799–815.
[26] Mazaki T, Mado K, Masuda H, et al. Prophylactic pancreatic stent placement and post-ERCP pancreatitis: an updated meta-analysis. J Gastroenterol 2014;49:343–55.
[27] Choudhary A, Bechtold ML, Arif M, et al. Pancreatic stents for prophylaxis against post-ERCP pancreatitis: a meta-analysis and systematic review. Gastrointest Endosc 2011;73:275–82.
[28] Kanth R, Samji NS, Inaganti A, et al. Endotherapy in symptomatic pancreas divisum: a systematic review. Pancreatology 2014;14:244–50.
[29] Yamamoto N, Isayama H, Sasahira N, et al. Endoscopic minor papilla balloon dilation for the treatment of symptomatic pancreas divisum. Pancreas 2014;43:927–30.
[30] Rustagi T, Golioto M. Diagnosis and therapy of pancreas divisum by ERCP: a single center experience. J Dig Dis 2013;14:93–9.
[31] Attwell A, Borak G, Hawes R, et al. Endoscopic pancreatic sphincterotomy for pancreas divisum by using a needle-knife or standard pull-type technique: safety and reintervention rates. Gastrointest Endosc 2006;64:705–11.
[32] Chacko LN, Chen YK, Shah RJ. Clinical outcomes and nonendoscopic interventions after minor papilla endotherapy in patients with symptomatic pancreas divisum. Gastrointest Endosc 2008;68:667–73.
[33] Troendle DM, Fishman DS, Barth BA, et al. Therapeutic endoscopic retrograde cholangiopancreatography in pediatric patients with acute recurrent and chronic pancreatitis: data from the INSPPIRE (INternational study group of pediatric pancreatitis: in search for a cuRE) study. Pancreas 2017;46:764–9.
[34] Oracz G, Pertkiewicz J, Kierkus J, et al. Efficiency of pancreatic duct stenting therapy in children with chronic pancreatitis. Gastrointest Endosc 2014;80:1022–9.
[35] Heyries L, Barthet M, Delvasto C, et al. Long-term results of endoscopic management of pancreas divisum with recurrent acute pancreatitis. Gastrointest Endosc 2002;55:376–81.
[36] Ertan A. Long-term results after endoscopic pancreatic stent placement without pancreatic papillotomy in acute recurrent pancreatitis due to pancreas divisum. Gastrointest Endosc 2000;52:9–14.
[37] Bertin C, Pelletier AL, Vullierme MP, et al. Pancreas divisum is not a cause of pancreatitis by itself but acts as a partner of genetic mutations. Am J Gastroenterol 2012;107:311–7.
[38] Garg PK, Khajuria R, Kabra M, et al. Association of SPINK1 gene mutation and CFTR gene polymorphisms in patients with pancreas divisum presenting with idiopathic pancreatitis. J Clin Gastroenterol 2009;43:848–52.