ORIGINAL ARTICLE

Prevalence and Factors Associated with Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis in Children

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Abstract

Background Pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP).
Aim To assess the prevalence and factors associated with post-ERCP pancreatitis (PEP) in a Chinese pediatric population.
Methods Sixty-six children who underwent ERCP between March 2018 and March 2019 at Shanghai Children's Medical Center were retrospectively recruited for the study. Clinical data, including demographics, indications, comorbidities, and procedural data, were reviewed to identify the prevalence and factors associated with PEP.
Results Ninety-two ERCPs were performed on 66 pediatric patients aged from 8 months to 14 years. The indications for ERCP were chronic pancreatitis (49, 53.2%), pancreaticobiliary maljunction (19, 20.7%), pancreas divisum (19, 20.7%), and pancreatic pseudocyst (5, 5.4%). All ERCPs were performed for therapeutic purposes. PEP was identified in 19 (20.7%) patients; there were ten mild cases, eight moderate cases, and one severe case. The univariate analysis revealed that a history of chronic pancreatitis was negatively associated with PEP ($P = 0.033$), and sphincterotomy was positively associated with PEP ($P = 0.01$). The multivariate analysis showed that sphincterotomy was a risk factor for PEP ($P = 0.017$, OR 4.17; 95% CI, 1.29, 13.54).
Conclusions Our data revealed a high prevalence of PEP in a Chinese pediatric population. Chronic pancreatitis was a protective factor, and sphincterotomy was a risk factor for PEP development.

Abbreviations

CBD   Common bile duct
ERCP   Endoscopic retrograde cholangiopancreatography
PD   Pancreatic duct
PEP   Post-ERCP pancreatitis
SD   Standard deviation
SOD   Sphincter of Oddi dysfunction

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Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic technique that combines gastrointestinal endoscopy and fluoroscopy for the diagnosis and treatment of pancreatic and biliary diseases [1]. ERCP has been used routinely in adults for over 50 years [1]. The application of ERCP in children has been increasing in recent years, but it is still used conservatively based on insufficient experience, limited safety and effectiveness data, and limited operator qualification [2, 3]. Although ERCP allows minimally invasive access to the pancreatic and biliary duct, complications after the procedure occur in both adults and children [3, 4]. Post-ERCP pancreatitis (PEP) is recognized as the most common complication with varied prevalence in different studies [4–6]. The identification of risk factors for PEP is very important for the development of preventive strategies. For example, studies have shown that prophylactic pancreatic duct (PD) stent placement, the use of statins, and rectal

indomethacin administration could decrease the incidence and severity of PEP in high-risk adult patients [7–11].

Recent case series studies reported that the prevalence of PEP ranged from 1.2 to 10.9% in the pediatric population [12–16]. Various factors associated with PEP were identified in pediatric patients [12, 14]. It was reported that therapeutic procedures and the presence of chronic pancreatitis were risk factors for PEP in a study that included 343 ERCPs performed in 224 children [12]. Troendle et al. [14] showed that PD injection and pancreatic sphincterotomy were positively associated with PEP, whereas a history of chronic pancreatitis was negatively associated with PEP. The wide range in prevalence and various risk factors for PEP in pediatric populations may be due to differences in procedural indications and comorbidities between the study populations.

The prevalence and factors associated with PEP in European and North American pediatric patients have been reported in the literature. However, a similar study is currently lacking in the Chinese pediatric population. Here, we conducted a single-center retrospective study to investigate the PEP prevalence and associated factors in pediatric patients in China.

Materials and Methods

Study Cohort

A total of 66 children aged 8 months to 14 years who underwent ERCP between March 2018 and March 2019 at Shanghai Children's Medical Center were retrospectively recruited for the study. Clinical data, including demographics, indications, comorbidities, and procedural data, were collected and reviewed to identify the PEP prevalence and associated factors. This study was in compliance with the Helsinki Declaration and was approved by the Ethical Review Board of Shanghai Children's Medical Center. Written informed consent was obtained from the parents or legal guardians of all pediatric patients.

ERCP Procedures

ERCP procedures were performed by an adult gastroenterologist with significant experience specifically with ERCP. (The physician had performed more than 30,000 ERCPs.) A pediatric endoscope (JF-240, Olympus, Tokyo, Japan) was typically used. The outer diameter and channel size of the JF-240 endoscope are 12.6 mm and 3.2 mm, respectively. It allows use of all ERCP accessories essential for a therapeutic procedure in our study patients. Indications for ERCP were dependent on clinical history, physical examination, laboratory tests (liver function, serum amylase, and lipase levels), abdominal ultrasound, computed tomography (CT),

magnetic resonance cholangiopancreatography (MRCP), and prior ERCP findings. Patients were hospitalized 2 days before ERCP. The ERCP procedures were performed with the patient in the prone position under general anesthesia, with continuous monitoring of vital functions. Iohexol (300 mg/30 mL) diluted 1:1 with sterile water was used for the cholangiography and pancreatography. Appropriate therapeutic procedures were performed, including endoscopic sphincterotomy (both biliary and pancreatic), pancreatic and biliary duct stenting, stricture dilation, and biliary or pancreatic stone extraction. Patients with pancreatic pseudocysts directly communicating with the main pancreatic duct had pancreatic duct stents placed during the ERCP for drainage of the pancreatic pseudocysts. The management of symptomatic pancreas divisum includes minor papillotomy, pancreatic duct dilatation, and pancreatic duct stent placement. Minor papillotomy was performed in all patients with symptomatic pancreas divisum undergoing their first ERCP procedure. Minor papillotomy was not performed repeatedly in patients who had undergone previous ERCP. Success of the procedure was defined as allowing adequate therapy for the prespecified indication. Serum amylase concentrations were measured by using a VITROS chemistry method (VITROS 250, Johnson & Johnson Ltd., NY, USA) at 24 h after the procedure. The reference range for the amylase level is 30–110 U/L. The patients who met discharge criteria (tolerated oral intake, had no complaints of pain, and had normal blood amylase levels) were discharged. Patients not meeting discharge criteria were admitted for further evaluation.

Diagnosis of PEP

PEP was diagnosed according to the 1991 consensus criteria statement and the revised Atlanta classification for the diagnosis of acute pancreatitis [17, 18]. PEP was defined as new or increased abdominal pain typical of acute pancreatitis and at least a threefold elevation in serum amylase levels 24 h after the procedure, resulting in hospitalization (or prolongation of existing hospitalization) of at least two nights, or evidence of pancreatic inflammation on abdominal imaging [17, 18]. The severity of pancreatitis was classified according to Cotton's criteria as follows: mild if additional hospitalization for 1–3 days was required; moderate if additional hospitalization for 4–10 days was required; and severe if hospitalization for more than 10 days was needed, as well as in cases of hemorrhagic pancreatitis, phlegmon, or pseudocysts [17]. After the ERCP procedure, increased hospital stays that were caused by medical issues other than PEP were excluded in the severity classification. ERCP procedural data of patients not complicated by pancreatitis were also collected and reviewed to identify factors associated with PEP.

Statistical Analysis

All data were entered into a customized database and then analyzed by R software 3.5.1 (The R Foundation, Vienna, Austria). For patients who underwent more than one ERCP, each individual ERCP procedure was assumed to be a statistically independent observation. Quantitative data were summarized as the mean $\pm$ standard deviation (SD) or number with percentage, where appropriate. The Chi-square test was used to evaluate the differences in general characteristics between patients with PEP and those without PEP. Multivariate binary logistic regression analysis was conducted. Sex and PD stent placement were analyzed in the final model. Chronic pancreatitis was not included in the multivariate analysis due to a high correlation with pancreatic pseudocysts, which could have caused collinearity problems. Statistical significance was considered when the two-sided P value was < 0.05.

Results

Baseline Characteristics

As shown in Table 1, a total of 92 ERCPs were performed in 66 pediatric patients at our center during the study period. The mean age of the children was 7.1 ± 4.3 years (ranging from 8 months to 14 years). Thirty patients (45.4%) had undergone previous ERCP. CT or MRCP was performed on all patients to confirm the indications prior to ERCP, and the indications for ERCP were chronic pancreatitis with repeated attacks of pancreatitis (49, 53.2%), pancreaticobiliary maljunction complicated with recurrent retrograde cholangitis or pancreatitis (19, 20.7%), pancreas divisum concomitant with recurrent pancreatitis (19, 20.7%), and pancreatic pseudocyst with a cyst larger than 6 cm that did not shrink after 1 month of conservative medical treatment (5, 5.4%). Patients with chronic pancreatitis undergoing ERCP had pancreatic ductal dilatation and/or diffuse calcification that was confirmed by CT, MRCP, or prior ERCP. All ERCP procedures were performed for therapeutic purposes, and the ERCP success rate was 100%. Sphincterotomy was performed in 39 cases, including pancreatic sphincterotomy (20, 21.7%), minor papillotomy (8, 8.7%), and biliary sphincterotomy (11, 12.0%). PD stricture dilation was performed in 64 (69.6%) cases, and common bile duct (CBD) stricture dilation was performed in 15 (16.3) cases. PD stents and CBD stents were placed in 54 (58.7%) and ten (10.9%) cases, respectively. Endoscopic nasopancreatic drainage and endoscopic nasobiliary drainage were performed in 14 (15.2%) and three (2.2%) patients, respectively. Stone extraction was performed by balloon manipulation and basket catheter in 13 (14.1%) and 12 (13.0%) patients,

Table 1 Baseline characteristics of children undergoing ERCP

	No.	%
Demographics ($n=66$)		
Female	35	53.0
Age		
0–3 y	18	27.3
3–6 y	18	27.3
6–14 y	30	45.4
Patients undergoing prior ERCP[a]	30	45.4
Procedural indication ($n=92$)[b]		
Chronic pancreatitis	49	53.2
Pancreaticobiliary maljunction	19	20.7
Pancreas divisum	19	20.7
Pancreatic pseudocyst	5	5.4
ERCP procedural characteristics ($n=92$)		
Diagnostic	0	0
Therapeutic	92	100
Sphincterotomy		
Pancreatic sphincterotomy	20	21.7
Minor papillotomy	8	8.7
Biliary sphincterotomy	11	12.0
PD/CBD stricture dilation		
PD stricture or dilation	64	69.6
CBD stricture or dilation	15	16.3
PD stent placement	54	58.7
CBD stent placement	14	15.2
Endoscopic nasopancreatic drainage	10	10.9
Endoscopic nasobiliary drainage	2	2.2
Stone extraction		
Balloon manipulation	13	14.1
Stone basket catheter	12	13.0
Attempts for successful cannulation		
1	73	79.3
2–5	18	19.6
>5	1	1.1
Duration for successful cannulation		
<2 min	73	79.3
2–5 min	18	19.6
5–10 min	1	1.1
Imaging		
Pancreatogram	86	93.5
Cholangiogram	20	21.7
Contrast agent dose		
≤5 mL	79	85.9
>5 mL	4	4.3

ERCP endoscopic retrograde cholangiopancreatography; *PD* pancreatic duct; *CBD* common bile duct

[a]Including prior ERCP performed in other centers based on the medical history. [b]Chronic pancreatitis with relapsing pancreatitis, pancreaticobiliary maljunction complicated with recurrent retrograde cholangitis or pancreatitis, pancreas divisum concomitant with recurrent pancreatitis, and pancreatic pseudocyst with a cyst larger than 6 cm that did not shrink after 1 month of conservative medical treatment

respectively. The number of cannulation attempts to successful cannulation in most ERCPs (73, 79.3%) was 1 time with duration less than 2 min. Pancreatogram and cholangiogram were undertaken in 86 (93.5%) and 20 (21.7%) patients, and the majority of patients (79, 85.9%) received a contrast agent dose of less than 5 mL.

Prevalence and Severity of PEP

PEP was identified in 19 (20.7%) of the 92 ERCPs; there were ten mild cases, eight moderate cases, and one severe case of PEP (Table 2). The mean age of the patients who developed PEP was 7.7 ± 3.7 (range 3–14 years). As shown in Table 3, the indications were chronic pancreatitis (7, 36.8%), pancreaticobiliary maljunction (6, 31.6%), pancreas divisum (3, 15.8%), and pancreatic pseudocyst (3, 15.8%). Ten mild cases had their discharges delayed for 2–3 nights,

seven moderate cases had their discharges delayed for 4–7 nights, and the severe case had their discharges delayed for 13 nights. The mean serum amylase level 24 h after the procedure among the patients who developed PEP was 744.5 ± 538.4 U/L (range 312–2400 U/L).

Risk Factors for PEP

The results of the univariate analysis of preprocedural factors showed that there were no significant differences in age, sex, or previous ERCP between children with PEP and those without PEP (Table 4). We found that a history of chronic pancreatitis was negatively associated with PEP ($P = 0.033$). The serum bilirubin level of all patients was in the normal range (data not shown). The univariate analysis of procedural characteristics revealed that patients undergoing sphincterotomy were at a high risk of developing PEP ($P = 0.01$). The number of cases with prior ERCP who underwent sphincterotomy during an index ERCP was 17, and six cases developed PEP. Prior ERCP has little impact on the incidence of PEP in patients who underwent sphincterotomy (6/17 vs 7/21, $P = 0.986$). There were no significant differences in endoscopic nasopancreatic drainage, endoscopic nasobiliary drainage, biliary stent placement, doses of contrast agent, or cannulation attempts and duration to successful cannulation between patients with PEP and those without PEP (Tables 4 and 5). Multivariate analysis showed that sphincterotomy

Table 2 Prevalence and severity of PEP

	No.	%
Severity of PEP		
Mild	10	10.9
Moderate	8	8.7
Severe	1	1.1
Fatal	0	0
Total	19	20.7

PEP post-ERCP pancreatitis

Table 3 Clinical characteristics of patients experienced with PEP ($n = 19$)

Patient	Sex	Age	Indication	Resultant hospitalization	Serum amylase[a]
21	Female	3	Pancreas divisum	Discharge delayed 2 nights	312
3	Male	9	Chronic pancreatitis	Discharge delayed 3 nights	497
17	Male	12	Pancreaticobiliary maljunction	Discharge delayed 3 nights	376
23	Female	6	Chronic pancreatitis	Discharge delayed 3 nights	1010
37	Female	10	Pancreas divisum	Discharge delayed 3 nights	749
51	Male	10	Pancreas divisum	Discharge delayed 3 nights	422
56	Female	3	Pancreaticobiliary maljunction	Discharge delayed 3 nights	610
69	Female	10	Pancreas divisum	Discharge delayed 3 nights	893
85	Female	3	Chronic pancreatitis	Discharge delayed 3 nights	345
21	Female	11	Chronic pancreatitis	Discharge delayed 3 nights	352
11	Male	6	Pancreatic pseudocyst	Discharge delayed 4 nights	2400
76	Female	11	Pancreaticobiliary maljunction	Discharge delayed 4 nights	466
83	Male	14	Pancreas divisum	Discharge delayed 4 nights	1101
43	Female	4	Chronic pancreatitis	Discharge delayed 4 nights	506
62	Female	4	Chronic pancreatitis	Discharge delayed 4 nights	562
33	Female	6	Pancreas divisum	Discharge delayed 5 nights	770
6	Male	6	Pancreatic pseudocyst	Discharge delayed 7 nights	1766
71	Male	10	Pancreatic pseudocyst	Discharge delayed 7 nights	409
90	Female	3	Pancreaticobiliary maljunction	Discharge delayed 13 nights	600

PEP post-ERCP pancreatitis

[a]Level at 24 h after the procedure (U/L)

Table 4 Univariate analysis of factors associated with PEP development

	No PEP (%)	PEP (%)	P
Demographics (n = 66)	52	14	
Female	25 (48.1)	10 (71.4)	0.183
Age 0–3 y	13 (25.0)	4 (28.6)	0.964
Patients who underwent prior ERCP	23 (44.2)	7 (50.0)	0.745
ERCP characteristics (n = 92)	73	19	
Chronic pancreatitis	43 (59.0)	6 (31.6)	0.033*
Pancreas divisum	13 (17.8)	6 (31.6)	0.21
Pancreatic pseudocyst	2 (2.7)	3 (15.8)	0.058
Pancreaticobiliary maljunction	15 (20.5)	4 (21.0)	1
Sphincterotomy	26 (35.6)	13 (68.4)	0.01*
PD/CBD stone	55 (75.3)	16 (84.2)	0.547
Stone extraction	18 (24.7)	7 (36.8)	0.288
PD/CBD stricture dilation	63 (86.3)	16 (84.2)	0.727
PD drainage	58 (79.5)	14 (73.7)	0.707
Pancreatogram	67 (91.8)	19 (100)	1
Contrast agent dose (> 5 mL)	2 (2.9)	2 (10.5)	0.257

PD pancreatic duct; *CBD* common bile duct; *PEP* post-ERCP pancreatitis

*Statistically significant

Table 5 Impact of number of cannulation attempts and duration to successful cannulation on the risk of PEP

	No PEP (n = 73) (%)	PEP (n = 19) (%)	P
Attempts for successful cannulation[a]			
1	59 (80.8)	14 (73.7)	0.494
2–5	14 (19.2)	4 (21.1)	0.854
> 5	0 (0)	1	0.207
Duration for successful cannulation[b]			
< 2 min	59 (80.8)	14 (73.7)	0.494
2–5 min	14 (19.2)	4 (21.1)	0.854
5–10 min	0 (0)	1	0.207

PEP post-ERCP pancreatitis

[a]An attempt is defined as each continuous contact with the papilla, loosing contact and repositioning counted as a new attempt. Successful cannulation is defined as deep pancreatic cannulation with the guide wire or cannula well inside the pancreatic duct. [b]The duration time is counted starting from the initial contact with the papilla and ended with the deep cannulation

was a predictor of PEP in our study cohort (P = 0.017, OR 4.17; 95% CI, 1.29, 13.54, Table 6).

Table 6 Multivariate analysis of factors associated with PEP development

	β	P	OR (95% CI)
Female	− 1.14	0.064	0.32 (0.09, 1.07)
Sphincterotomy	1.43	0.017*	4.17 (1.29, 13.54)
PD stent placement	0.29	0.648	1.33 (0.39, 4.60)

*Statistically significant

PD pancreatic duct; *PEP* post-ERCP pancreatitis; *OR* odds ratio; *CI* confidence interval

Discussion

In this study, we retrospectively reviewed a total of 92 ERCPs performed on pediatric patients treated at Shanghai Children's Medical Center, China. The prevalence of PEP was 20.7%, which was higher than that reported from previous studies in both children and adults [5, 12–16]. An early study including 343 ERCPs performed in 224 children reported an overall PEP incidence of 5.0%, including both patients with and without chronic pancreatitis [12]. A PEP rate of 7.4% was reported from a study that included 54 ERCPs performed on 31 children [8]. Troendle et al. [14] identified a PEP prevalence of 10.9% in 432 ERCPs performed on 313 pediatric patients. A recent study that included 856 ERCPs in 626 pediatric patients [16] reported a low incidence of PEP (1.2%). Two major reasons may account for the high incidence of PEP identified in our study population: patient selection and procedural purpose. First, the majority of patients in our study suffered from pancreatic diseases, such as pancreatic pseudocysts and chronic pancreatitis. Li et al. [19] reported a similar PEP rate (17/110, 15.5%) in children and adolescents with chronic pancreatitis. The main indications for ERCP in several previous studies reporting a low PEP rate in pediatric patients were biliary diseases, including choledocholithiasis, cholangitis, or biliary stricture [12, 14]. It has been reported that pediatric patients with biliary diseases have a low risk of PEP development [14]. Nevertheless, previous large studies in pediatric pancreatitis patients reported low rates of PEP [20, 21]. It has been reported that PEP occurred in only seven of 231 ERCPs (7/231, 3.0%), performed in 167 children; the most common indication was chronic or recurrent pancreatitis (106/167, 63.4%) [20]. Agarwal et al. [21] showed that procedure-related adverse events were seen in eight (8/172, 4.7%) patients with pancreatic diseases undergoing ERCP. Second, all ERCPs from our study were therapeutic interventions, such as PD stricture dilation, PD stone extraction, and sphincterotomy. It has been previously shown that pediatric patients undergoing ERCP for diagnosis only were less likely to develop PEP [12]. However, a previous study including 294 endoscopic sphincterotomies among 198

pediatric patients reported that PEP occurred in 17 (5.7%) procedures [22]. In addition, Green et al. [23] reported that no instances of PEP were observed in 23 therapeutic procedures, including sphincterotomy, stent placement, stone removal, and dilation. Thus, future studies enrolling a large pediatric cohort are needed to further explore the roles of the indication and procedural purpose in PEP development.

Both preprocedural and procedural factors have been associated with the incidence of PEP [5]. Preprocedural factors include age, sex, serum bilirubin level, undergoing prior ERCP, and procedural indications, whereas others, such as PD stent placement, pancreatic sphincterotomy, and precut sphincterotomy, are related to the procedure [5]. We showed that young age, female sex, and prior ERCP were not related to the development of PEP in our study cohort. The role of chronic pancreatitis in PEP occurrence is controversial in the literature [24, 25]. Some studies have shown that patients with chronic pancreatitis have a protective effect, related to pancreatic atrophy and decreased exocrine function that was associated with a reduced incidence of PEP [24]. Troendle et al. [14] showed that a history of chronic pancreatitis was negatively associated with PEP in children. In contrast, other studies reported that the incidence of PEP was increased in both adults and pediatric patients with chronic pancreatitis [12, 25]. Here, we showed that chronic pancreatitis was negatively associated with PEP development in our pediatric patients. For other preprocedural factors, the serum bilirubin level of all patients was in the normal range, and suspected sphincter of Oddi dysfunction (SOD) was not observed. In addition, evaluation of the association of pancreatic pseudocysts with PEP development was limited by the fact that only five such patients were included in this series.

For procedural factors, PD stent placement is considered a protective factor that has been associated with reduced PEP incidence in adults [26]. However, it has been reported that PD stent placement was associated with a significantly increased rate of PEP in pediatric patients undergoing PD injection compared with those who had no attempt at stent placement [14]. Additionally, a previous study showed that PD stent placement increased the likelihood of developing PEP in children with chronic pancreatitis [12]. Our data showed that the rate of PEP was similar for children with PD stent placement, children without PD stent placement, and patients undergoing endoscopic nasopancreatic or nasobiliary drainage. The univariate analysis showed that sphincterotomy was a risk factor for the development of PEP, which was consistent with previous studies in both adults and children [5, 14]. Although other factors, such as balloon manipulation and PD injection, have been identified as risk factors for PEP in children [12, 14], they were not related to PEP development in our study population. A previous study showed that pancreatograms were a risk factor for PEP [27]. However, our data indicated that pancreatograms were not related to the incidence of PEP. Furthermore, endoscopist experience has been linked to procedural success and overall adverse event rates of ERCP [24, 28]. Endoscopist experience was not a factor for PEP development in our cohort, as all procedures were performed by the same experienced adult gastroenterologist who had performed more than 30,000 ERCPs. The number of cannulation attempts to successful cannulation in most ERCPs (73, 79.3%) was 1 time with duration less than 2 min. There was no statistical difference in cannulation attempts and duration to successful cannulation between patients with PEP and those without PEP.

There are several limitations in the present study. First, this was a single-center, pilot, retrospective study with a limited number of ERCP cases. Second, the majority of patients undergoing ERCPs in our study suffered from pancreatic diseases, limiting the ability of this study to evaluate the association of biliary diseases with PEP. Third, all ERCPs were performed for therapeutic purposes, and the association of diagnostic procedures with PEP development remains undetermined.

In summary, the prevalence of PEP was 20.7% in our studied Chinese pediatric population. Chronic pancreatitis was negatively associated with PEP, and sphincterotomy was a risk factor for PEP. Given the increasing applications of ERCP in children, more studies are needed to further investigate the safety and effectiveness of ERCP in pediatric patients.

Compliance with Ethical Standards

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