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Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Mesut Akarsu, MD, Full Professor, Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Dokuz Eylul University, Izmir 35320, Turkey. mesut.akarsu@deu.edu.tr

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Retrospective Study

Efficacy and safety of endoscopic retrograde cholangiopancreatography in recurrent pancreatitis of pediatric asparaginase-associated pancreatitis

Kai-Hua Yang, Jing-Qing Zeng, Sheng Ding, Tian-Ao Zhang, Wen-Yu Wang, Jia-Yu Zhang, Lan Wang, Jian Xiao, Biao Gong, Zhao-Hui Deng

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Kai-Hua Yang, Jing-Qing Zeng, Sheng Ding, Tian-Ao Zhang, Wen-Yu Wang, Jia-Yu Zhang, Lan Wang, Jian Xiao, Zhao-Hui Deng, Department of Gastroenterology, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200127, China

Biao Gong, Department of Gastroenterology, Shanghai Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200120, China

Corresponding author: Zhao-Hui Deng, PhD, Chief Physician, Department of Gastroenterology, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, No. 1678 Dongfang Road, Shanghai 200127, China. dzhrij@163.com

Abstract

BACKGROUND

Asparaginase (ASP) is an important drug in combined chemotherapy regimens for pediatric acute lymphoblastic leukemia (ALL); ASP-associated pancreatitis (AAP) is the main adverse reaction of ASP. Recurrent pancreatitis is a complication of AAP, for which medication is ineffective.

AIM

To evaluate the efficacy and safety of endoscopic retrograde cholangiopancreatography (ERCP) in treating recurrent pancreatitis due to AAP.

METHODS

From May 2018 to August 2021, ten children (five males and five females; age range: 4–13 years) with AAP were treated using ERCP due to recurrent pancreatitis. Clinical data of the ten children were collected, including their sex, age, weight, ALL risk grading, clinical symptoms at the onset of pancreatitis, time from the first pancreatitis onset to ERCP, ERCP operation status, and postoperative complications. The symptomatic relief, weight change, and number of pancreatitis onsets before and after ERCP were compared.

RESULTS

The preoperative symptoms were abdominal pain, vomiting, inability to eat, weight loss of 2–7 kg, and 2–9 pancreatitis onsets. After the operation, nine of ten patients did not develop pancreatitis, had no abdominal pain, could eat normally;

the remaining patient developed three pancreatitis onsets due to the continuous administration of ASP, but eating was not affected. The postoperative weight gain was 1.5–8 kg. There was one case of post ERCP pancreatitis and two cases of postoperative infections; all recovered after medication.

CONCLUSION

ERCP improved clinical symptoms and reduced the incidence of pancreatitis, and was shown to be a safe and effective method for improving the management of recurrent pancreatitis due to AAP.

Key Words: Acute lymphoblastic leukemia; Asparaginase; Endoscopic retrograde cholangiopancreatography; Pancreatic pseudocyst; Recurrent pancreatitis; Children

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Core Tip: Recurrent pancreatitis is a complication of asparaginase-associated pancreatitis (AAP), and medications do not prevent recurrence. This study was conducted to evaluate the efficacy and safety of endoscopic retrograde cholangiopancreatography (ERCP) in treating recurrent pancreatitis due to AAP. Our research found that ERCP improved clinical symptoms and reduced the incidence of pancreatitis, and was shown to be a safe and effective method for improving the management of recurrent pancreatitis due to AAP.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a malignant tumor with a high incidence in children. One of the key drugs in the combined chemotherapy regimen to treat ALL is asparaginase (ASP). ASP is important for inducing remission and achieving long-term disease-free survival, but it has a high probability of inducing ASP-associated pancreatitis (AAP). The overall incidence of AAP is 2%–18%, with 7%–66% of cases classified as severe; the mortality rate due to AAP is as high as 2% [1-5]. Asparaginase-induced pancreatitis is often seen as acute toxicity with lasting issues such as recurrent pancreatitis, causing patients to be at risk for progressing to chronic pancreatitis over time. This may affect children's eating, weight, and quality of life [6-11]. Recurrent pancreatitis is the main complication of AAP, wherein children are unable to eat normally and lose weight, thus seriously affecting their quality of life [6-11]. If pancreatitis repeatedly recurs in AAP, the effects of medications such as somatostatin and its analog octreotide are not efficacious for preventing recurrent pancreatitis, which is a difficulty in clinical treatment.

Endoscopic retrograde cholangiopancreatography (ERCP) is a minimally invasive method for diagnosing and treating recurrent pancreatitis, and its efficacy and safety have been confirmed [12-17]. As patients with ALL are special, research has seldom focused on procedures for the complication of ASP. This study aimed to evaluate the efficacy and safety of ERCP in treating recurrent pancreatitis due to AAP.

MATERIALS AND METHODS

General information

This study was approved by the Institutional Review Board of Shanghai Children's Medical Center (SCMCIRB-K2019005). All the participants' legal guardians provided written informed consent. From May 2018 to August 2021, ten children with AAP underwent ERCP due to recurrent pancreatitis that persisted for 3 mo and for which medication was ineffective. Their sex, age, ALL risk grading, clinical symptoms at the onset of pancreatitis, time from the first pancreatitis onset to ERCP, weight, ERCP operation status, and postoperative complications of ERCP were summarized. The status of symptomatic relief, number of pancreatitis onsets, and weight change before and after ERCP operation were compared. For all ten children, smoking, alcohol consumption, biliary pancreatitis, hyperlipidemia, hypercalcemia, tumor invasion, trauma, and autoimmune diseases were excluded.

Definitions

AAP was defined as acute pancreatitis after using ASP, and its diagnosis was based on a combination of clinical, biochemical (amylase, lipase), and imaging evidence. According to the diagnostic criteria put forward by the Toxicity Working Group established by the Ponte di Legno consortium in 2016, cases that meet two or more of the following

criteria can be diagnosed as having AAP[18,19]: (1) Acute pancreatitis-related abdominal pain; (2) blood amylase or blood lipase exceeding three times the upper limit of normal; and (3) imaging examination findings (ultrasonography, computed tomography, or magnetic resonance imaging) consistent with pancreatitis.

ERCP procedures

Prior to ERCP, each child's guardian signed a written informed consent for the procedure. All procedures were performed by the same experienced endoscopist, who had, incidentally, performed more than 30000 ERCPs. The children underwent ERCP in the prone position under general anesthesia using a standard pediatric duodenoscope (JF-240, Olympus, Tokyo, Japan), and vital signs were continuously monitored. Therapeutic maneuvers were selected during the operation according to the pancreatic imaging results, including endoscopic pancreatography sphincterotomy, placement of pancreatic duct stent, balloon dilation, and stone extraction. **Figure 1A** and **B** show the most common ERCP procedures of stone extraction and placement of pancreatic duct stent. The fluoroscopic view of the pancreatic duct is shown in **Figure 1C**. A fluoroscopic view of the pancreatic duct stricture dilation performed by balloon manipulation and huge pseudocyst is shown in **Figure 1D**. Post-ERCP complications were assessed by monitoring the child's blood amylase and lipase levels, using pancreatic ultrasound images, and assessing postoperative abdominal pain, fever, and bleeding 24 h after ERCP. Post-ERCP complications were treated using the conventional treatment in internal medicine, and further evaluation and treatment were required for children with severe disease. The discharge criteria were absence of fever and abdominal pain along with a return of blood amylase levels to normal. Patients who did not meet the discharge criteria were evaluated for treatment.

Follow-up and evaluation indicators

Follow-up time: All patients were followed up for an average of 1.2 years, the shortest follow-up time was 1 year and the longest was 1.5 years.

Observation indicators: The primary observation indicators, including the number of acute pancreatitis onsets, symptoms related to acute pancreatitis such as abdominal pain, vomiting, normal eating habits, and body weight were evaluated every 3 mo. Those with pancreatic pseudocyst underwent reexaminations by B-ultrasonography.

The secondary observations were post-ERCP complications[20]. Post-ERCP pancreatitis (PEP), bleeding, infection, and perforation are the most common complications. PEP was defined as new or worsening abdominal pain with elevated blood amylase three times above the normal value and lasting longer than 24 h. Bleeding was defined as bleeding foci or persistent oozing of blood that was visible to the naked eye during the operation and vomiting of blood, blood in stool, or black stool with a progressive decrease in hemoglobin after the operation. Infection was defined as a postoperative temperature greater than 38°C and lasting for more than 24 h. Perforation was characterized by sudden abdominal pain and signs related to peritonitis during or after the operation. This included signs such as subdiaphragmatic free gas and retroperitoneal gas on imaging.

RESULTS

Basic clinical information

Among the ten children, there were five males and five females (age range: 4–13 years). There were nine cases at moderate risk and one case at low risk. All ten children showed recurrent abdominal pain and vomiting and were unable to eat. Among them, seven were fed through nasal jejunal tubes. The number of pancreatitis onsets before the operation was equal to or greater than two times. The weight loss before the operation was 2–7 kg. The time from the first AAP onset to ERCP was 3–8 mo (**Table 1**).

Status of ERCP operation

There were five cases of pseudocyst (5/10, 50%), six cases of pancreatic duct stones (6/10, 60%), and four cases of pancreatic duct stenosis (4/10, 40%). A total of seven cases (7/10, 70%) underwent pancreatic duct stent implantation; eight cases (8/10, 80%) underwent sphincterotomy; and five cases (5/10, 50%) had balloon manipulation. In total, two patients underwent ERCP operations twice for stent removal, while the remaining eight patients underwent only one operation (**Table 2**).

Status after ERCP

Among the five cases of pseudocyst, the cyst disappeared in four cases; no changes were observed in the cyst in one case even following the operation, but no pancreatitis occurred. After ERCP was performed, one patient developed three pancreatitis onsets due to continuous administration of ASP, but eating was not affected. The remaining nine patients did not develop pancreatitis after the operation and could eat normally. Weights increased by 1.5–8 kg across all patients.

After ERCP, one case developed mild pancreatitis, which recovered after medication. Moreover, two children developed postoperative infections but recovered after receiving anti-infective treatment (**Table 3**).

Table 1 Preoperative data of ten children

Case	Sex	Age (yr)	Risk grading	Interval between first AAP onset and ERCP (mo)	Clinical features	Nasal jejunal tube	Number of AAP onsets (times)	Weight loss (kg)
1	Female	4	Medium	4	Abdominal pain, vomiting, inability to eat	Yes	6	2
2	Male	10	Medium	3	Abdominal pain, vomiting, inability to eat	Yes	4	6
3	Male	12	Medium	3	Abdominal pain, vomiting, inability to eat	Yes	7	7
4	Male	6	Low	6	Abdominal pain, vomiting, inability to eat	Yes	9	4
5	Female	13	Medium	3	Abdominal pain, vomiting, inability to eat	Yes	5	2
6	Male	4	Medium	3	Abdominal pain, vomiting, inability to eat	No	5	3
7	Female	4	Medium	6	Abdominal pain, vomiting, inability to eat	Yes	9	3
8	Male	7	Medium	3	Abdominal pain, inability to eat	Yes	2	7
9	Female	7	Medium	8	Abdominal pain, vomiting, inability to eat	No	9	3
10	Female	4	Medium	4	Abdominal pain, vomiting, inability to eat	No	5	3

AAP: Asparaginase-associated pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 2 Status of endoscopic retrograde cholangiopancreatography operation

Case	Presence of pseudocyst and its size (mm)	Pancreatic duct stenosis	Pancreatic duct stones	ERCP operation mode	ERCP operation times
1	40 × 15	No	Yes	EPS+ERPD	2
2	/	No	Yes	EPS+balloon manipulation	1
3	81 × 41	Yes	No	Balloon manipulation +ERPD	1
4	/	Yes	Yes	EPS+ERPD	2
5	68 × 40	Yes	No	Balloon manipulation+EPS+ERPD	1
6	16 × 12	No	No	EST	1
7	/	No	Yes	Balloon manipulation+ERPD	1
8	48 × 40	Yes	No	Balloon manipulation+EPS+ERPD	1
9	/	No	Yes	EPS	1
10	/	No	Yes	EPS+ERPD	1

EPS: Endoscopic pancreatography sphincterotomy; EST: Endoscopic sphincterotomy; ERPD: Endoscopic retrograde pancreatic drainage; ERCP: Endoscopic retrograde cholangiopancreatography.

DISCUSSION

AAP is a serious adverse reaction to ASP and is the most common reason for interruption of ASP treatment[21-23]. AAP is defined as an acute inflammatory process within the pancreatic parenchyma following ASP treatment. The diagnosis is based on the presence of at least two of the following three criteria: Abdominal pain suggestive of pancreatitis, serum amylase or lipase three or more times the upper-normal level, and characteristic imaging findings suggestive of pancreatitis. The underlying pathophysiology is not fully understood, but is thought to involve the reduction of protein synthesis, especially in organs with high protein turnover, such as the liver and pancreas, and results from systemic

Table 3 Follow-up data of the seven children

Case	Ultrasonography for pseudocyst	After ERCP acute pancreatitis onsets (times)	Clinical symptoms	Postoperative complications	Weight gain/yr (kg)
1	At 6 mo after the operation, no pseudocyst was found by ultrasonography	0	Abdominal pain disappeared, able to eat	No	5
2	/	0	Abdominal pain disappeared, able to eat	Postoperative pancreatitis	5
3	At 3 mo after the operation, no pseudocyst was found by ultrasonography	0	Abdominal pain disappeared, able to eat	Infection	8
4	/	0	Abdominal pain disappeared, able to eat	Infection	7
5	At 4 mo after the operation, ultrasonography revealed that the pseudocyst had disappeared	0	Abdominal pain disappeared, able to eat	No	3
6	There was still a 16 mm × 12 mm pseudocyst	0	Abdominal pain disappeared, able to eat	No	7
7	/	0	Abdominal pain disappeared, able to eat	No	1.5
8	At 2 mo after the operation, no pseudocyst was found by ultrasonography	0	Abdominal pain disappeared, able to eat	No	2
9	/	3	Abdominal pain, but did not affect eating	No	2
10	/	0	Abdominal pain disappeared, able to eat	No	3

ERCP: Endoscopic retrograde cholangiopancreatography.

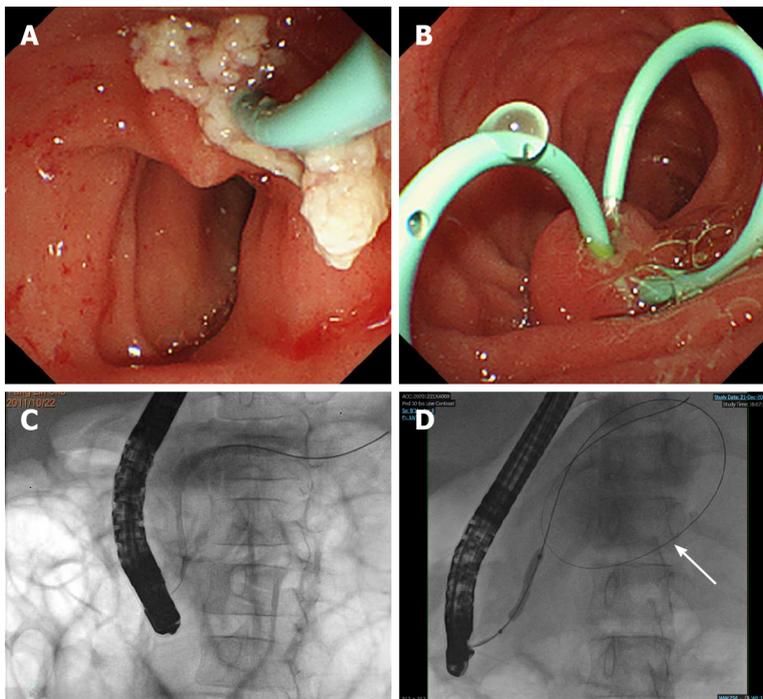
depletion of asparagine[19,24]. The Ponte di Legno consortium classified AAP into three grades according to the degree of pancreatic injury[19]. On the basis of severe pancreatitis, repeated pancreatitis is a high-risk factor for chronic pancreatitis. In addition, recurrent onsets of pancreatitis lead to children's inability to eat normally during chemotherapy, causing inadequate nutrition. Combined with the impact of chemotherapy drugs, this results in weight loss and insufficient immunity, seriously impacting children's quality of life.

In our study, ten children with AAP experienced recurrent pancreatitis presenting as abdominal pain, vomiting, inability to eat normally, and weight loss. Although seven patients had been placed on nasal jejunal tube feeding, their weight was still below the ideal due to recurrent pancreatitis. Therefore, once recurrent pancreatitis appears in AAP, intervention is necessary as early as possible to improve the quality of life of children and prevent chronic pancreatitis in the long term. However, most human clinical studies have focused on how to treat acute pancreatitis rather than relapsing pancreatitis.

ERCP is an endoscopic technique that combines gastrointestinal endoscopy and fluoroscopy for the diagnosis and treatment of pancreatic and biliary diseases. The application of ERCP in children has been increasing in recent years and its efficacy and safety have been demonstrated in operations such as sphincterotomy, papillary dilation, and pancreatic duct stenting. ERCP can safely be performed in children with a pooled complication rate of approximately 1.2-10.9%, paralleling that observed with adults[25,26].

Recurrent pancreatitis is a therapeutic indication for ERCP. Our study was comprised of ten children with recurrent pancreatitis related to ASP. Five had pancreatic pseudocyst, four had pancreatic duct stenosis, and six had pancreatic duct stones, suggesting that pseudocyst and pancreatic duct lesions were the root causes of recurrent pancreatitis and might even be the pathological basis of chronic pancreatitis. For pseudocyst and pancreatic duct lesions, medication is ineffective. ERCP is a minimally invasive treatment for biliary and pancreatic diseases in children, and symptomatic pancreatic pseudocyst and pancreatic duct diseases (stenosis and stones) are indications for ERCP[27-29]. Through pancreatic duct stent implantation, dilatation, and sphincterotomy, four cases of pseudocyst were resolved. Pseudocyst remained in one case, but no pancreatitis occurred; therefore, an observation strategy was maintained for natural absorption. A total of nine cases did not develop pancreatitis after the operation and the patients could, therefore, eat normally. Pancreatitis was observed in one case three times due to continuous use of ASP; however, the abdominal pain was mild and did not affect eating. The patient recovered after medication. All ten children gained weight after the operation. Two of the children developed an infection but recovered after anti-infective treatment. This supports ERCP as an effective and safe intervention for AAP with recurrent pancreatitis.

Pancreatic duct stones (PDS) are stones formed in the main pancreatic duct and pancreatic duct branches. They are a manifestation of protein embolism or mineralization (caused by calcium carbonate or protein in the pancreas precipitating in the pancreatic ducts) and are characteristic pathological changes of chronic pancreatitis. PDS and pancreatitis are mutually causal. Recurrent pancreatitis leads to increased secretion of pancreatic juice and the activation and concen-



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Figure 1 Endoscopic retrograde cholangiopancreatography procedures. A: Endoscopic view of stone extraction; B: Endoscopic view showing that two pancreatic stents were placed after stone extraction; C: Fluoroscopic view of endoscopic retrograde cholangiopancreatography showing the dilated and tortuous pancreatic duct; D: Fluoroscopic view of pancreatic duct stricture dilation performed by balloon manipulation. White arrow shows the guide wire coiled inside the pseudocyst.

tration of a large amount of trypsinogen in the pancreatic ducts, leading to the formation of pancreatic stones. PDS block the pancreatic ducts, causing stenosis or dilation of the pancreatic ducts and subsequent recurrent pancreatitis[30]. In this study, six children were found to have PDS during the ERCP operation, and the cause of their formation might be related to the recurrence of pancreatitis after using ASP.

Approximately 23% of AAP episodes resulted in pancreatic pseudocyst, a markedly higher proportion than reported in a case series of pancreatitis due to all etiologies, which ranged from 2% to 16%[31]. Pancreatic pseudocyst is a common complication of pancreatitis that can manifest with abdominal symptoms of pain, nausea, and vomiting; it can also present without any clinical symptoms. Approximately 20%–60% of pancreatic pseudocysts naturally resolve within 6–12 wk[32,33]; therefore, ERCP is not the first treatment choice. When pancreatic pseudocysts are symptomatic, endoscopic intervention should be the therapy of first choice. In this study, the five cases of pseudocysts presented with recurrent pancreatitis. We observed these for at least 3 mo during which time the pseudocysts were still not absorbed. Furthermore, the children lost weight while waiting for the pseudocysts to be naturally absorbed. Therefore, once pancreatic pseudocysts with recurrent pancreatitis are present, we recommend ERCP treatment as early as possible.

In one case (case 9), where AAP recurred even after the ASP dosage was reduced by half, ERCP operation was performed to enable subsequent ASP treatment. After the operation, the child continued to receive three injections of ASP. Although there were still onsets of pancreatitis, compared with that before the operation, the number of onsets was reduced, degree of abdominal pain was alleviated, and eating was not affected. We believe that the implantation of a pancreatic duct stent is the key to ensuring successful chemotherapy with ASP. Meta-analysis data of many clinical reports show that stent placement could effectively relieve the symptoms of abdominal pain, with immediate relief rates of 65%–95% and sustained relief rates of 32%–68%[34]. Moreover, pancreatic duct stents could prevent post-ERCP pancreatitis in high-risk patients. Therefore, in the majority of patients (seven out of ten) in the study, a pancreatic duct stent was implanted, effectively relieving abdominal pain and, in the ninth case, protecting the pancreas from the damage caused by repeated ASP use. Repeated use of ASP in severe AAP is not typically recommended because up to 63% of children had a second recurrence of pancreatitis[5]. Based on our experience of using ERCP treatment in the ninth case, we believe that ERCP can be attempted in children with AAP prior to resuming the use of ASP to ensure that patients can complete their ASP treatment course, thereby improving the event-free survival rate in cases of ALL where children's ASP therapy is interrupted. To our knowledge, the efficacy and safety of ERCP in recurrent pancreatitis of ASP in children has not been reported to date. This is the largest number reported in China, with further detail than has previously been reported.

There are several limitations in the present study. First, this was a single-center and retrospective study with potential biases in inclusion criteria. Second, the sample size is notably limited due to the technically demanding and less commonly available nature of the ERCP procedure in most hospitals. The prevalent approach for cases of recurrent pancreatitis post-AAP prioritizes fluid replacement therapy, nutrition, and pain management. Additionally, it is important to note that ERCP is still in the process of development and refinement, especially concerning its application

for children with leukemia. Third, there was no control group in our study. Fourth, due to the underdeveloped nature of the rural area from which the patients originated, access to hospital resources is limited. This limitation could potentially contribute to the onset of pancreatitis, abdominal pain, vomiting, and weight gain among the patients. Finally, our study has a relatively short follow-up duration, averaging 1.2 years. This shorter duration may also impact the results of ERCP in AAP.

CONCLUSION

In summary, for AAP complicated by recurrent pancreatitis with pancreatic pseudocyst and pancreatic duct lesions (stones, pancreatic duct stenosis, or dilatation), ERCP appears to be an effective and safe intervention. Furthermore, ERCP seems to have a protective effect against pancreatic injury caused by repeated use of ASP. As a consequence, these patients can rapidly resume chemotherapy, which improves their outcome with regard to the underlying malignant disease.

ARTICLE HIGHLIGHTS

Research background

Asparaginase (ASP) is an important drug in combined chemotherapy regimens for pediatric acute lymphoblastic leukemia (ALL); ASP-associated pancreatitis (AAP) is the main adverse reaction of ASP. Recurrent pancreatitis is a complication of AAP, for which medication is ineffective.

Research motivation

As repeated occurrence of AAP limits the application of chemotherapy regimens for ALL, an effective, less invasive, and safe treatment strategy for AAP is desirable.

Research objectives

To evaluate the efficacy and safety of endoscopic retrograde cholangiopancreatography (ERCP) in treating recurrent pancreatitis due to AAP.

Research methods

From May 2018 to August 2021, ten children (five males and five females; age range: 4–13 years) with AAP were treated using ERCP due to recurrent pancreatitis. Clinical data of the ten children were collected, including their sex, age, weight, ALL risk grading, clinical symptoms at the onset of pancreatitis, time from the first pancreatitis onset to ERCP, ERCP operation status, and postoperative complications. The symptomatic relief, weight change, and number of pancreatitis onsets before and after ERCP were compared.

Research results

The preoperative symptoms were abdominal pain, vomiting, inability to eat, weight loss of 2–7 kg, and 2–9 pancreatitis onsets. After the operation, nine of ten patients did not develop pancreatitis, had no abdominal pain, could eat normally; the remaining patient developed three pancreatitis onsets due to continuous administration of ASP, but eating was not affected. The postoperative weight gain was 1.5–8 kg. There was one case of postoperative pancreatitis and two cases of postoperative infections; all recovered after medication.

Research conclusions

ERCP could improve clinical symptoms and reduce the incidence of pancreatitis, and was shown to be a safe and effective method for improving the management of recurrent pancreatitis of AAP.

Research perspectives

Based on our experience of using ERCP in treating recurrent pancreatitis due to AAP, we believe that ERCP can be attempted in children with AAP prior to resuming the use of ASP to ensure that patients can complete their ASP treatment course, thereby improving the event-free survival rate in cases of ALL where children's ASP therapy is interrupted.

FOOTNOTES

Author contributions: Yang KH, Zeng JQ, Ding S contributed equally to this work and share first authorship; Gong B and Deng ZH designed the study; Yang KH, Ding S, Zhang TA, Wang WY, Zhang JY, Wang L, Jian X acquired, analyzed, and interpreted the data; Yang KH and Zeng JQ drafted the manuscript; Deng ZH edited the manuscript; All authors contributed to the article and approved the submitted version.

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Country/Territory of origin: China

ORCID number: Kai-Hua Yang 0000-0002-1389-9137; Jing-Qing Zeng 0000-0002-7064-6662; Sheng Ding 0009-0007-8730-0979; Tian-Ao Zhang 0000-0002-8939-2244; Wen-Yu Wang 0000-0003-4118-1218; Jia-Yu Zhang 0000-0002-4553-2583; Lan Wang 0009-0004-4040-1623; Jian Xiao 0000-0002-3942-1924; Biao Gong 0000-0002-3645-2493; Zhao-Hui Deng 0000-0003-0780-9657.

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