Original Article

Treatment of acute pancreatitis with early pancreatic stenting: a case series of 336 patients

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Background: Pancreatic duct (PD) obstruction and hypertension may play a central role in the onset and progression of acute pancreatitis (AP). However, only a few studies have reported using pancreatic stenting to relieve PD obstruction in the early phase of AP, with conflicting results. Whether pancreatic stenting is effective in the early phase of AP remains unknown. We conducted this experiment in order to study the therapeutic efficacy and safety of pancreatic stenting in the early stage of AP.

Methods: We conducted a retrospective analysis of 336 AP patients from 2011 to 2018 who underwent pancreatic stenting within 48 hours of admission.

Results: A total of 330 (98.2%) patients underwent successful pancreatic stenting, of whom 23 (7.0%) had severe AP, 178 (53.9%) had moderately severe AP, and 129 (39.1%) had mild AP. Visible PD obstructive material was observed in 94 (28.5%) patients. The mean oral refeeding time since admission and length of hospital stay were 3.5±2.7 and 7.4±6.7 days, respectively. Procedure-related adverse events, in-hospital mortality, and local complication rates were 0.3%, 0.3%, and 7.6%, respectively.

Conclusions: Early endoscopic pancreatic stenting in AP patients effectively shortened the fasting time and length of hospital stay and did not increase the risk of adverse events, death, or local complications. A further prospective randomized controlled clinical trial is currently underway to validate the safety and efficacy of this procedure.

Keywords: Pancreatic stenting; ERCP; acute pancreatitis (AP); endoscopy

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Introduction

Acute pancreatitis (AP) is one of the most common diseases of the digestive system, causing significant financial and healthcare burdens. In 2014, the incidence of AP in adults was 111.2 cases per 100,000 people and has continued to increase according to United States data (1,2). The overall mortality of AP varies from 1–5% and can be as high as 20–30% in patients with severe AP (1-3).

Two overlapping periods in AP have been identified that reflect different major manifestations and causes of death (4). The early phase is characterized by acute sterile inflammation of the pancreas that involves systemic disturbances in

more severe cases. In severe cases, systemic inflammatory response syndrome (SIRS) may develop, leading to multiple organ failure (MOF), which is the primary cause of death during this phase. Thus, management of AP in the early phase, as outlined in current guidelines (5-8), includes aggressive intravenous hydration, pain control, correction of electrolyte and metabolic abnormalities, and nutritional support. In the late phase, which typically develops after a few days, local complications emerge and become the principal issue of AP. The presence of infected necrosis results in a second mortality peak and requires invasive treatment interventions (9).

Endoscopic retrograde cholangiopancreatography (ERCP) is an important and minimally invasive procedure for treating biliary and pancreatic disorders. ERCP is only recommended for acute biliary pancreatitis (ABP) combined with cholangitis or persistent biliary obstruction in the early phase (10) or in the presence of pancreatic ductal disruption in the late phase of AP (11). In the early phase, ERCP is used for biliary drainage to rapidly remove any biliary obstruction. In the late phase it is used for pancreatic drainage to reduce leakage of pancreatic juice. Most studies accept that pancreatic duct (PD) obstruction and hypertension play a central role in the onset and progression of AP (12-14), but there have been few studies that have focused on the treatment of AP with pancreatic interventions to relieve PD obstruction in the early phase (15-17). Moreover, the results of those studies have been controversial. Thus, whether pancreatic stenting is effective in the early phase of acute pancreatitis remains unknown.

Coincidentally, during the endoscopic procedure for AP patients in the early phase, we have observed thick mucus or even solid whitish material blocking the PD. After we removed those materials and performed pancreatic stenting, patients' abdominal symptoms were noted to be significantly improved (18). Therefore, this article retrospectively analyzed a case series of patients who underwent pancreatic stenting in the early phase of AP to investigate the feasibility and safety of this strategy. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/gs-21-574).

Methods

Patients

Patients with AP who underwent pancreatic stenting within 48 hours of admission to our center between October 5, 2011, and January 1, 2018, were retrospectively analyzed. Diagnostic criteria, grading criteria, and local complications of AP were defined according to the 2012 revision of the Atlanta classification and definitions (4). The computed tomography severity index (CTSI) was used according to Balthazar's CT grading standard (19). Patient screening was based on the following inclusion criteria: (I) the diagnosis of AP was confirmed according to the 2012 revision of the Atlanta classification and definitions (4); (II) patients were aged between 18 and 90 years; (III) patients voluntarily accepted pancreatic stenting for treatment of AP and signed informed consent. The following cases were excluded from this study: (I) AP in pregnancy; (II) recurrent pancreatitis after previous pancreatic stenting; (III) an acute episode of chronic pancreatitis; (IV) pancreatic stenting performed over 48 hours from admission.

Endoscopic procedure

The procedures were performed by one experienced endoscopist who had more than 10 years of experience, including more than 500 ERCP procedures each year and more than 500 PD cannulations. The endoscopic procedure was performed using an Olympus TJF-260V, JF-260V electronic duodenoscope, Olympus disposable high-frequency papillotomy (KD-V411M-720), COOK® band guidewire (ACRO-35-450), and a COOK® PD stent (outer diameter 5–7 Fr, length 4–12 cm). After patients were fasted for more than 12 hours, 10 mg of scopolamine butyrate and 75 mg of meperidine were intramuscularly injected 15 minutes before the procedure. The procedure was performed in the left supine position. After the duodenoscope reached the duodenum, a guidewire was softly inserted from the ampulla and verified along the direction of the PD under fluoroscopy. A sphincterotome was inserted into the PD for aspiration until pancreatic juice was observed to confirm the intrapancreatic position. A pancreatic stent with a 5-Fr caliber was placed into the main PD. If the patient had suspected biliary system disease, endoscopic retrograde cholangiography (ERC) and biliary drainage were performed simultaneously. Sphincterotomy was performed as necessary.

Patient management

All AP patients are treated as inpatients in China. After admission, fasting and infusion therapy were commenced. Consistent with the guidelines (5,20), patients requiring

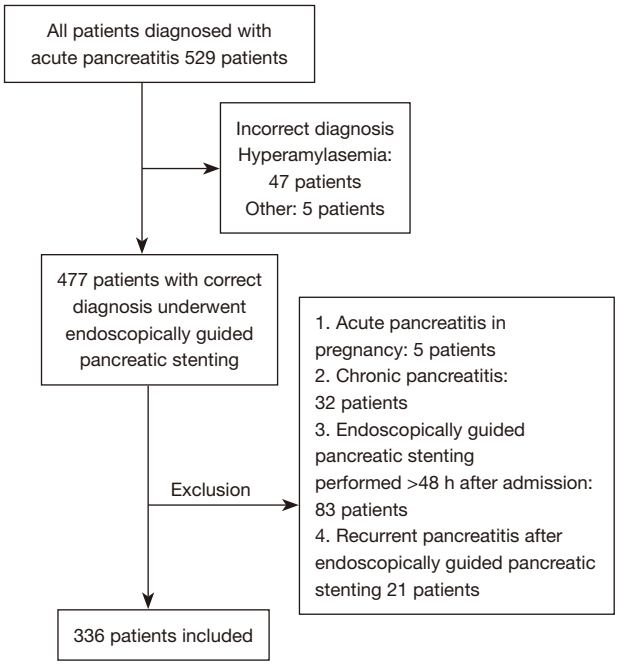

Figure 1 The screening process.

intensive care were transferred to the Intensive Care Unit (ICU) for appropriate treatment. The patient's condition was evaluated daily.

Oral refeeding starting with a soft diet was allowed for those patients who had relief of symptoms such as nausea, bloating, and abdominal pain (numeric rating scale (NRS) pain score ≤2) and when their serum amylase decreased to less than three times the upper limit of normal. For patients with moderately severe or severe AP, an enhanced CT was performed once a week during hospitalization to assess local complications. Additional interventions were performed for patients with late phase local complications who were symptomatic, had rapid enlargement of local collections, or had systemic illness due to infected local complications that did not improve with medical management. The intervention method depended on the patient's condition and site of the local complications. Patients were discharged when they could completely tolerate oral feeding without symptomatic complications. The PD stent was removed after 1–2 months.

Primary endpoints

Oral refeeding time and length of hospital stay were the primary endpoints. Time to oral soft diet tolerance since admission without symptom recurrence was recorded as the oral refeeding time.

Other endpoints

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score, white blood cell count (WBC), serum amylase on admission and 48 hours after admission, adverse events due to the procedure, local complications, the need for additional interventions due to local complications, and mortality were recorded.

Ethical aspects

This study was conducted in accordance with the ethical standards set out in the Helsinki Declaration (as revised in 2013) and was approved by the Medical Research Ethics Review Committee of the General Hospital of Ningxia Medical University (No. 2019-466) and informed consent was taken from all the patients. This study was registered as a single-center, retrospective case series (ChiCTR1900025500) at chictr.org.cn.

Statistical analysis

All data were analyzed using SPSS 22.0 software (IBM Corp., Armonk, New York, USA). Results are expressed as mean ± SD or number and proportions. The chi-square test or Fisher's exact test were used to compare discrete variables, and *t*-tests or ANOVA were used to compare quantitative variables. Pairwise comparison among the different severities of AP was routinely performed. No special treatment was performed for missing variables.we conducted sensitivity analysis omitting one study at a time to investigate the information of each study on the results. A P value <0.05 was considered statistically significant.

Results

Figure 1 shows the screening process. A total of 336 cases met the inclusion and exclusion criteria, of which 330 (98.2%) underwent successful pancreatic stenting. The causes of failure were four cases of severe duodenal edema and two cases of suspected pancreatic malformation. Of the 330 patients, 23 (7.0%) had severe AP, 178 (53.9%) had moderately severe AP, and 129 (39.1%) had mild AP. *Table 1* shows the general demographic information of the 330 patients. During the endoscopic procedure,

Table 1 General demographic information according to the severity of AP

Variable	Mild AP (n=129)	Moderately severe AP (n=178)	Severe AP (n=23)	P value
Male	72 (55.8)	92 (51.7)	14 (60.9)	0.631
Age, years	56.7±16.3	59.0±17.0	62.5±14.9	0.225
Referral patient	88 (68.2)	112 (62.9)	18 (78.3)	0.276
Diabetes mellitus	14 (10.9)	23 (12.9)	3 (13)	0.866
Causes				
Gallstone	112 (86.8)	140 (78.7)	21 (91.3)	
Hyperlipidemia	6 (4.7)	17 (9.6)	1 (4.3)	
Idiopathic	6 (4.7)	15 (8.4)	0 (0)	
Alcohol misuse	2 (1.6)	1 (0.6)	0 (0)	
Choledochocele	2 (1.6)	0 (0)	1 (4.3)	
Tumor	0 (0)	3 (1.7)	0 (0)	
Dysmorphia	0 (0)	2 (1.1)	0 (0)	
Trauma	1 (0.8)	0 (0)	0 (0)	
Onset/admission interval, days	2.4±2.9	2.3±2.1	3.2±2.7	0.249
CTSI				<0.001
0–3	120 (93.0)	92 (51.7)	5 (21.7)	
4–6	0 (0)	72 (40.4)	10 (43.5)	
7–10	0 (0)	5 (2.8)	4 (17.4)	
Absence	9 (7.0)	9 (5.1)	4 (17.4)	
APACHE II score	5.6±2.8	7.9±3.6	16.7±5.6	<0.001
Acute organ failure	–	78 (44.0)	23 (100.0)	<0.001
Respiratory	–	71 (40.0)	21 (91.0)	<0.001
Renal	–	10 (6.0)	13 (57.0)	<0.001
Cardiovascular	–	6 (3.0)	13 (57.0)	<0.001
Multiple	–	8 (4.0)	15 (65.0)	<0.001
Admission/endoscopic procedure, hours	13.2±11.1	13.2±11.2	13.9±13.5	0.964

Data are shown as n (%) or the mean ± SD.

simultaneous bile duct drainage was performed in 306 (92.7%) patients, and sphincterotomy was performed in 168 (50.9%) patients. Visible whitish material was endoscopically removed from the PD in 94 (28.5%) patients (*Figure 2*). The baseline characteristics were similar among patients of different severity, except for the CTSI and APACHE II severity indicator scores and the acute organ failure rate (*Figure 3*).

Oral refeeding time and length of hospital stay

A total of 226 (68.5%) patients resumed an oral diet within 3 days of admission. The mean oral refeeding time since admission and length of hospital stay were 3.5±2.7 and 7.4±6.7 days, respectively. With regard to the different severity of AP, the mean oral refeeding time was 2.8±1.4 days for mild AP patients and 4.1±3.2 days for moderate and

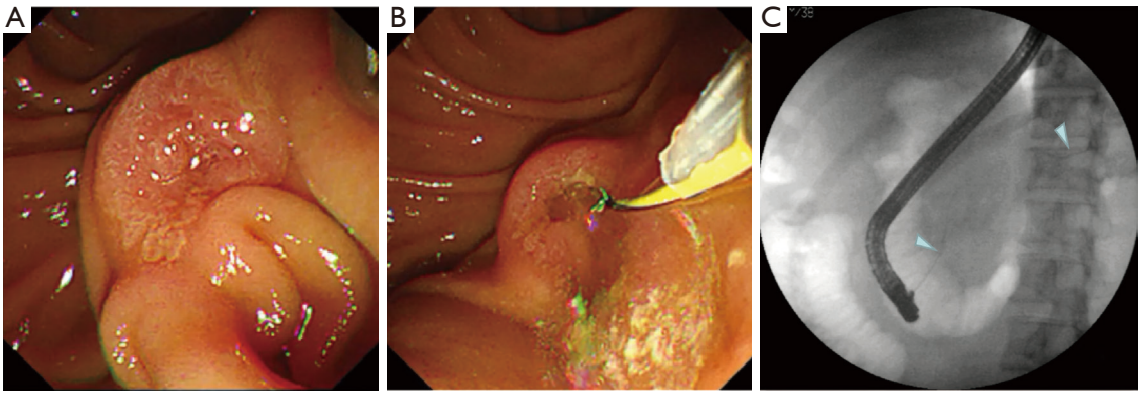

Figure 2 The presence of PD obstructive materials during the endoscopic procedure of a patient with severe AP. (A) Duodenal papilla; (B) after PD cannulation and suction, a large amount of obstructive whitish material is observed; (C) fluoroscopic imaging shows the guidewire (arrows) traveling along the direction of the PD. PD, pancreatic duct; AP, acute pancreatitis.

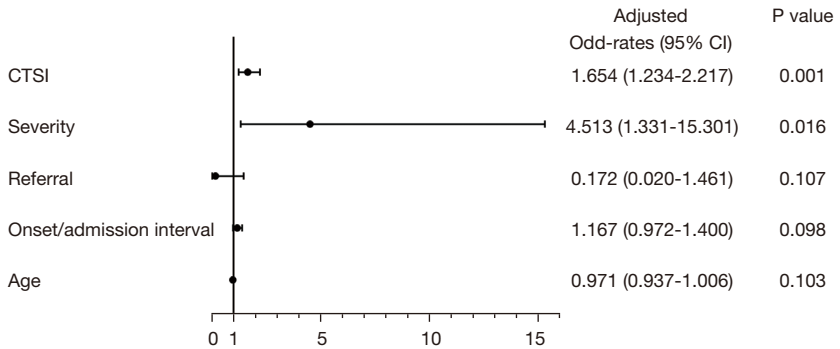

Figure 3 Risk factors of additional intervention in multivariate analysis. Hosmer-Lemeshow test, χ^2=1.271, P value =0.996.

severe AP patients. The mean length of hospital stay was 5.4±2.4 days for mild AP patients and 8.8±8.2 days for moderate and severe AP patients. Both values were significantly greater in those patients with an increased severity of AP and the presence of visible PD obstructive materials (*Table 2*). However, there was no significant difference in the average oral refeeding time and length of hospitalization between patients with or without either simultaneous bile duct drainage or sphincterotomy (*Table 2*).

Adverse events

One 76-year-old female patient (0.3%) developed intermittent hematemesis 3 hours after the endoscopic procedure. She had a pacemaker implanted for malignant arrhythmia 8 years before the onset of AP and a long-term oral aspirin history. Examination confirmed she had common bile duct and gallbladder stones. Multiple superficial gastric erosions and stale clots were found during the procedure. Biliary drainage and 5Fr-6-cm pancreatic stenting were performed without either sphincterotomy or stone extraction. The upper gastrointestinal bleeding was stopped by intravenous hemostatic medicines. No other bleeding or duodenal perforations relating to the endoscopic procedure occurred.

Mortality

One patient (0.3%) died in the acute phase during hospitalization. This patient had severe multiple organ failure on admission combined with bile duct stones and acute cholangitis. On admission, he had a modified Marshall score of 5 and an APACHE II score of 26. He underwent an emergency endoscopic procedure after admission. The sediment-like stones in the bile duct were removed during the procedure, and a 5Fr-6-cm PD stent was

Table 2 Oral refeeding time and length of hospital stay according to the severity of AP, whether there were visible obstructive materials in the PD, and whether sphincterotomy or bile duct drainage were performed simultaneously

Variable	Oral refeeding time (days), overall 3.5±2.7		Length of hospital stay (days), overall 7.4±6.7	
	Average value	P value	Average value	P value
Severity of AP		<0.001**		<0.001**
Mild AP (n=129)	2.8±1.4		5.4±2.4	
Moderately severe AP (n=178)	3.8±2.6		8.0±5.0	
Severe AP (n=23)	7.7±6.8		20.0±23.3	
Obstructive materials in PD		0.020*		0.017*
Yes (n=94)	4.1±3.3		8.9±10.2	
No (n=236)	3.3±2.4		6.8±4.6	
Endoscopic sphincterotomy		0.201		0.069
Yes (n=168)	3.4±2.7		6.7±8.0	
No (n=162)	3.8±2.7		8.1±5.1	
Simultaneous bile duct drainage		0.335		0.342
Yes (n=306)	3.5±2.7		7.3±6.9	
No (n=24)	4.1±2.9		8.7±4.6	

Data are shown as the mean ± SD. *, P<0.05; **, Pairwise comparison P<0.05.

Table 3 Analysis of the clinical features of patients after treatment according to the severity of AP

Variable	Mild AP (n=129)	Moderately severe AP (n=178)	Severe AP (n=23)	P value
In-hospital death	0 (0)	0 (0)	1 (4.3)	0.070
Automatic discharge	0 (0)	1 (0.6)	7 (30.4)*	<0.001
Local complications	0 (0)*	20 (11.2)	5 (21.7)	<0.001
Infected necrosis	0 (0)*	13 (7.3)	4 (17.4)	<0.001
Additional intervention	0 (0)	11 (6.2)	5 (21.7)	<0.001**

Data are shown as n (%). *, only the marked group differs from the other two groups according to pairwise comparison; **, all groups differ from each other according to pairwise comparison.

smoothly placed. Organ failure was aggravated 8 hours after admission, and the patient died after resuscitation attempts. Eight patients (2.4%) were automatically discharged (*Table 3*), and four patients (1.2%) died of severe organ failure within 1 week of automatic discharge.

Local complications and additional interventions

Twenty-five (7.6%) patients developed late phase local complications, all of whom had moderately severe or severe AP. Seventeen had infected necrosis (5.2%), five had walled-off necrosis, and there was one case of spleen infarction. The proportion of local complications and infected necrosis was relatively higher in severe AP patients, but there was no significant difference between the severe and moderately severe AP patients (*Table 3*). Of the patients with local complications, 16 (4.8%) required additional interventions to treat local complications. The proportion of additional intervention requirements was significantly higher in patients with an increased severity of AP (*Table 3*).

APACHE II score, WBC count, and serum amylase

The APACHE II scores, WBC count, and serum amylase

Table 4 APACHE II score, WBC count, and serum amylase index of patients on admission and 48 hours after hospital admission

Variable	On admission	48 h after admission	P value
WBC ($\times 10^9$/L)	12.9±5.8	9.6±4.1	<0.001
APACHE II	7.5±4.2	5.0±3.3	<0.001
Amylase (U/L)	1,115.2±1,071.2	222.0±285.3	<0.001

Data are shown as the mean ± SD.

were significantly decreased 48 hours after admission compared with admission levels (*Table 4*), regardless of the severity of AP.

Discussion

Intra-acinar activation of proteolytic enzymes is recognized as the primary catalyst for the development of AP, which ultimately leads to an autodigestive injury to the pancreas (21). A similar cascade of events occurs once AP commences that is independent of the initiating event or mechanism. Several events are known to induce AP with varying degrees of certainty. However, the pathogenesis of AP is still not fully understood. PD obstruction is one of the widely accepted earliest events, which leads to the blockage of pancreatic enzyme secretion while synthesis continues (14,22). This breakdown in the synthesis-secretion coupling of pancreatic digestive enzymes causes the newly synthesized digestive enzymes to accumulate within the gland, leak out of the acinar cells through the basolateral membrane to the interstitial space, or even enter the systemic circulation. PD obstruction and hypertension have been implicated in acute biliary pancreatitis (23,24), ethanol-induced pancreatitis (24-26), iatrogenic pancreatitis (27), and diet-induced pancreatitis (28). In addition, increased PD pressure has been associated with more severe pancreatitis (29). However, PD obstruction is difficult to confirm from clinical evidence since it may appear as a "micro-obstruction" such as edema or spasm around the ampulla and PD. In this study, visible intra-PD obstructive materials were directly observed under endoscopy and were outwardly similar to the protein plug seen in chronic pancreatitis (30). However, these obstructive materials are likely to differ from the protein plug since patients with an acute episode of chronic pancreatitis were excluded from this study. The specific composition and formation mechanism of these blockage materials needs further study.

We set oral refeeding time and length of hospital stay as the primary outcomes because implementing the stenting technique in the early phase of AP resulted in rapid relief of abdominal symptoms that shortened fasting times and hospital stays. Moreover, our recorded oral refeeding time represents the following observations: (I) patients experienced relief from abdominal symptoms; (II) serum amylase decreased to less than three times the upper limit of normal; and (III) there was no symptom recurrence after commencement of an oral diet. As Eastern and Western countries have different hospitalization systems, we compared our results with early oral refeeding studies in Eastern countries. The reported mean oral refeeding time was 6.75 days (31) for mild AP patients and 10.5 days (32) for moderate and severe AP patients treated by conservative management. However, in the present study, patients achieved an average oral refeeding time as early as 2.8 days for mild AP patients and 4.1 days for moderate and severe AP patients. The average amylase was also decreased to less than three times the upper limit of normal within 48 hours of admission, which also facilitated early refeeding (see *Table 4*). Similarly, in equivalent conservative treatment studies, the average length of hospital stay was 10.4 days (31) for mild AP patients and 15.7 days (32) for moderate and severe AP patients, whereas our hospitalization period was relatively shorter (5.4 days for mild AP patients and 8.8 days for moderate and severe AP patients). However, the lack of a control group is the main disadvantage of this study, which will be addressed in our ongoing research. There were no significant differences in the average oral refeeding time and length of hospitalization between patients with or without simultaneous bile duct drainage and sphincterotomy, which suggests early oral refeeding and early discharge were not affected by those interventions. Our results indicated that visible PD obstructive materials existed in nearly 30% of patients, and their presence was associated with prolonged hospitalization and fasting times. On the one hand, PD obstruction in AP may appear as "micro-obstructions" such as outlet edema, spasm, or small size debris as previously discussed, which would not have been visible. On the other hand, bulky obstructive materials in PD may predict a more prolonged AP course.

The use of early ERCP is controversial in AP due to ERCP-related adverse events, which can increase morbidity and mortality (8). However, more experienced endoscopists have lower complication rates (33) and higher success rates (34) than those who perform fewer procedures. For instance, a previous study has reported that endoscopic intervention on patients with severe AP in the intensive

care unit without fluoroscopy had a success rate of 100% and an ERCP-related adverse event rate of 0 (35). All the procedures in the present study were performed by one experienced endoscopist who had completed more than 500 PD cannulations. Consequently, the ERCP success rate was high, and ERCP-related adverse events were rare. However, performing endoscopic interventions in patients with AP and concomitant duodenal and papillary edema is still technically challenging. Only a few studies have discussed early pancreatic ductal interventions, but these have shown diametrically opposed outcomes (15-17). Fejes *et al.* (16,17) performed pancreatic duct stenting within 72 hours of pain onset with a success rate of 94.7–100% and low overall complication and mortality rates (overall complication rate 7–9.86%, mortality rate 0%). In contrast, Karjula *et al.* (15) performed pancreatic duct stenting in acute necrotizing pancreatitis on an average of 4.6 days from onset with a success rate of less than 50% and an infection rate as high as 100%. In theory, PD stents facilitate the drainage of pancreatic juices through the papilla, thus helping to remove the enzymatic substrate that causes the explosive cascade of events that can worsen the situation (36). It could be judged the occurrence of pancreatic cysts and pancreatic pseudotumors by pancreatic CT, and judged whether there would be stent failure in combination with pancreatic edema and pancreatic deformities. Stenting prevents pancreatic juices from leaking out from the disruption, thus promoting the healing of the ductal disruption and consequent pancreatic collections. In the present study, the in-hospital mortality rate was 0.3%, and local complications occurred in 6.7% of patients, corroborating the above theory. Similarly, we did not find that pancreatic stenting increased the infection risk. As all patients underwent pancreatic stenting within 48 hours of admission, we compared the WBC count, APACHE II scores, and serum amylase levels at admission and 48 hours after admission. In particular, the APACHE II system appears to provide superior performance in predicting the severity of AP during the early phase (37). After the patients received pancreatic stenting, those indicators were significantly decreased regardless of the severity of AP, suggesting pancreatic stenting facilitated the control of the inflammatory response in early phase AP.

In summary, early endoscopic pancreatic stenting within 48 hours of admission in patients with AP effectively shortens the fasting time and length of hospital stay. Meanwhile, it does not appear to increase the risk of adverse events, death, or local complications. Since this research reflects an initial clinical investigation of the feasibility of early pancreatic stenting in treating AP, the main limitation of this study is the lack of matched control cases. A further prospective randomized controlled clinical trial is currently underway to validate the safety and efficacy of this procedure.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/gs-21-574

Data Sharing Statement: Available at https://dx.doi.org/10.21037/gs-21-574

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/gs-21-574). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the ethical standards set out in the Helsinki Declaration (as revised in 2013). The study was approved by the ethics committee of General Hospital of Ningxia Medical University (No. 2019-466) and informed consent was taken from all the patients.

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