On demand pancreatic stenting in chronic pancreatitis might provide good palliation of pain

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Abstract

***Background and aim* : Chronic pancreatitis (CP)-related pain is a considerable problem in gastroenterology practice that frequently requires several endoscopic interventions. We aimed to investigate the efficacy of pancreatic duct stenting performed on demand, instead of at defined intervals, for the management of the CP-related pain.**

***Methods* : This study is a retrospective evaluation of thirteen years of data. Sixty-seven patients with CP who suffered from intractable pain were enrolled in the study. Pancreatic stenting was performed mainly with single stents according to the diameter of the pancreatic duct and width of the stricture or, less frequently, with multiple stents aiming to achieve stricture resolution. The subsequent endoscopic session was scheduled based on the patient's symptoms.**

***Results* : Overall, 65 of 67 patients underwent successful pancreatic cannulation (technical success rate 97%). Fifty-seven patients with a pancreatic stenting history were still undergoing follow-up. Of these patients, 26 patients still had pancreatic ductal stents; however, the stents were removed from 31 patients. Only 8 patients (25%) required further endoscopic or surgical intervention because of the re-emergence of pain after a median stent-free period of 17 months (3-127 months). One patient with a biliary stricture and one patient with a pancreatic mass underwent surgery. Pancreatic stents remained for a median length of 14 months (3-84 months). During the follow-up period, 55 of 65 patients became pain-free or had partial pain relief (clinical success rate 84%).**

***Conclusions* : On demand replacement of pancreatic stent is feasible in patients with CP and it might provide a good palliation of CP-related pain.** (Acta gastroenterol. belg., **2019**, 82, **401-406**).

Key words : Chronic pancreatitis, pancreatic stenting, endoscopic retrograde cholangiopancreatography

Introduction

Chronic pancreatitis (CP) involves a fibro-inflammatory process associated with progressive injury of the pancreatic parenchyma and results in the eventual loss of exocrine and endocrine functions (1). Although its clinical presentation depends on the degree of pancreatic dysfunction, abdominal pain is present in most patients independent of pancreatic injury (1,2).

The causes of the pain might stem from mechanical, inflammatory, malabsorptive and neurogenic changes in the pancreas (3). It is thought that ductal or parenchymal hypertension due to the presence of peripancreatic fibrosis, ischaemia and stricture or stone of the pancreatic duct play a major role in the pathogenesis of CP-related pain (3,4). Both the intensity and frequency of the pain attacks inevitably lead to a deterioration in the quality of life, repeated hospitalization, workforce loss and increased health care costs (5). Therefore, the primary goal of treatment is to achieve pain relief (5,6).

A working group for the international consensus guidelines recommended endoscopic treatment for the amelioration of pain, in addition to various medications and supportive therapy (7). Endoscopic retrograde cholangiopancreatography (ERCP) provides decompression of ductal and parenchymal hypertension through endoscopic pancreatic sphincterotomy, dilatation of pancreatic strictures, pancreatic stone extraction, and/or pancreatic duct stenting (8-10). Pancreatic duct stenting, a non-operative ductal decompression therapy in patients with pancreatic duct stones, strictures, or both, can provide efficient palliation of CP-related pain (8-10).

However, different options exist in terms of the persistency of pancreatic stents. Planned pancreatic stent exchange at 3- to 6-month intervals was recommended in some clinical trials (15,16). No consensus exists regarding how long pancreatic stents should be kept in place and when extraction or exchange of stents should be scheduled. We postulated that pancreatic stent extraction or exchange should be performed 'on demand' according to the patient's symptoms rather than at constant intervals. In here, we aimed to investigate retrospectively the efficacy of on-demand pancreatic stenting in CP patients suffering from intractable pain.

Materials and methods

This is a retrospective study in order to assess endoscopic interventions for the treatment of CP-related pain. Patients with painful CP admitted for endoscopic treatment to the Gastroenterology Department of the tertiary referral centre were reviewed during thirteen years of follow-up (2002-2015). All participants were required to have a score of 3 at least regarding the severity

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of CP based on the Cambridge classification, and pain was required to be the primary indication for endoscopic intervention (12). Patients who underwent pancreatic duct cannulation at least once with ERCP were included in the study. We excluded patients with a diagnosis of acute pancreatitis, asymptomatic CP, pancreaticobiliary neoplasms, Billroth II or Roux-en-Y anatomy, a medical history of pancreatic surgery or celiac ganglion blockage.

Demographic characteristics and medical data consisting of the aetiology of pancreatitis, pain pattern and severity, type and number of endoscopic procedures and complications of endoscopic treatment were recorded. Abdominal pain relief was an essential parameter used to describe the clinical success of endoscopic intervention. First, the pain was qualified as severe, moderate or mild with a continuous or intermittent pattern according to the patient's medical reports at study enrollment and at the end of follow-up. Then, the pain experienced before endoscopic therapy was compared to that after the endoscopic intervention. The 0-10 Numeric Rating Scale (NRS) was used in pain scoring (13). NRS scores ≤ 5 corresponded to mild, scores of 6-7 to moderate and scores ≥ 8 to severe pain in terms of pain-related interference with functioning.

All endoscopic interventions were performed by experienced endoscopists (a workload of at least 500 ERCPs annually) under consciousness sedation. Selective pancreatic cannulation was attempted via a wire-guided technique during the ERCP procedure. A pancreatic sphincterotome loaded over a guidewire was carefully directed to the pancreatic orifice at its usual 1-2 o'clock position on the major papilla. Minor papilla cannulation was attempted in cases of pancreas divisum. Blended current mode setting on 40W maximally (35-25W cutting and 5-15W coagulation, Olympus PSD 20) was used during sphincterotomy. Contrast medium was injected carefully through the papilla of Vater under fluoroscopic guidance as needed to determine the anatomic direction of the pancreatic duct in some patients or to eradicate pancreas divisum. Pre-cutting using a standard sphincterotome or needle-knife was performed when selective wire-guided pancreatic cannulation failed.

The findings of diagnostic ERCP, including pancreatic or biliary duct strictures/dilatation, pancreatic duct stones, pancreatic divisum and pancreatic pseudocyst were identified in detail. All patients had also computerized tomography and/or magnetic resonance imaging for evaluation of anatomic characteristics of hepatobiliary system. Therapeutic ERCP procedures comprising pancreatic sphincterotomy, pancreatic duct dilatation, pancreatic stone removal, and pancreatic stent placement were recorded in each session. Various types sphincterotomes, needle-knives, endoscopy catheters, balloon catheters and stents were used during the 13-year period.

Stones were removed using balloons, baskets or mechanical lithotripters. Lithotripsy through extracorporeal shock wave lithotripsy (ESWL) was applied only for pancreatic radio-opaque stones that were difficult to extract during ERCP sessions. ESWL was preferably performed after pancreatic stent placement and was occasionally conducted without a pancreatic stent when the guidewire could not pass beyond the pancreatic stone. A maximum of 5000 shocks were delivered for each ESWL session with an intensity of 9-12 kV at a frequency of 90-120 shocks per minute. The shock wave frequency and power were determined based on the characteristics of the stones and patient tolerance. This procedure was terminated when fragmentation or clearance of pancreatic stones was not established after at least two sessions.

When a stricture was confirmed, dilation was performed, followed by insertion of a stent. Dilatation was performed with a 4-8 mm balloon dilator or 5-7 Fr bougies according to characteristics of the stricture, and a 7 Fr Sohendra stent retriever was used for tight strictures. Pancreatic stenting was performed with a single stent ranging in size from 5F to 10F according to the diameter of the pancreatic duct and width of the stricture, or less frequently, multiple stents (based on the preference of the endoscopist) were used to achieve stricture resolution.

Patients with plastic stents had no set stent exchange dates. This procedure was scheduled according to the patient's symptoms. The subsequent ERCP session for pancreatic stent exchange was arranged when the patient began to suffer pain. When the contrast medium emptied rapidly from the pancreatic duct on a pancreatogram or when the stone extraction balloon inflated as to the diameter of the pancreatic duct and passed through the stricture easily during an ERCP session, the patient did not undergo stent placement, even in cases of a residual stricture. Otherwise, the pancreatic ductal stent was replaced. If a residual stone was present in the pancreatic duct, pancreatic stent exchange was performed.

Other concomitant therapeutic approaches such as drainage of a pancreatic pseudocyst or stenting of the biliary duct stricture were noted. Biliary duct stenting was performed using a 10 Fr plastic stent. These stents were changed 3-4 times per year. If a patient required re-stenting at the end of the year, biliary-digestive surgery was offered. All post-interventional complications including pancreatitis, bleeding, pancreatic leakage, stent migration and broken stents were recorded.

Surgical or repeat endotherapy options were offered to patients with a resurgence of pain after they had been stent-free. Repeat endotherapy was considered if patients had contraindications to surgery or refused the operation. Except for this indication, surgery was performed for intractable pain despite the presence of stents and or a pancreatic or biliary cancer.

The technical success of ERCP was defined as the completion of the targeted endoscopic procedure. Clinical success was defined as relief or disappearance of pain and reduction of the requirement of narcotic analgesics or hospitalization after endoscopic treatment. If surgical intervention was necessary or no improvement in the

intensity of pain was achieved, the procedure was considered a failure.

Patients with a pancreatic stent and patients who had their stents removed were monitored at regular intervals, and their symptoms and biochemical parameters were assessed during this period. In recent years, patients underwent follow-up visits at 3 and 6 months and then yearly after stent removal. Patients living in the same city were called for inspection at our unit. Those living outside the city were contacted by telephone. If the patient was not admitted or was not contacted by telephone by the primary referring physicians, the patient was called by telephone at the time of data collection.

Statistical analysis

The mean, standard deviation (SD), and range were used to summarize the data for continuous variables, and percentages were used for categorical variables. Fisher's exact test or the $\chi 2$ test were used to identify associations between categorical variables. The effectiveness of the interventions was analysed by the intention-to-treat (ITT) principle. Statistical significance between the groups was determined by one-way analysis of variance. A P-value < 0.05 was considered statistically significant. The statistical analysis was conducted using SPSS version 19.0 (SPSS, Chicago, IL, USA).

Results

Sixty-seven patients (19 women and 48 men) with a mean age of 36.4 ± 15 years (range 15-69) were enrolled in the study. Thirteen patients (19%) had alcoholic pancreatitis; familial pancreatitis was diagnosed in 4 patients (6%) due to their family history. The aetiology of CP was idiopathic in the majority of the patients (35 patients, 52%) (Table1). All patients received pancreatic enzyme substitution, and seventeen diabetic patients were treated with insulin or oral antidiabetic drugs.

Fifty-eight patients (86%) underwent pancreatic cannulation and sphincterotomy during the first ERCP session. Pancreatic cannulation was performed in the second ERCP session in seven patients (10%) ; however, it could not be implemented in two patients. Cannulation and sphincterotomy of the minor papilla were performed in 16 patients (23%) due to pancreas divisum.

Table 1. — **Baseline characteristics of patients**

Characteristics	Value
Number of patients	67
Age, years (median±SD)	36.4 ± 15
Gender (F/M)	19/48
Etiologies of CP, n (%)	
İdiopathic	35 (52)
Alcohol	13 (19)
Heredity	4 (6)
Others	15 (23)

All patients exhibited pancreatic ductal dilation with a mean duct diameter of 11 mm (range 8-15 mm). Fifty-seven patients (87%) had pancreatic ductal strictures. Among these patients, ductal stricture in the tail (proximal pancreatic duct stricture) was found in 11 patients, while multiple strictures throughout the pancreatic duct were observed in 46 patients. Twenty-eight patients had stones located in the main pancreatic duct. Pancreatic pseudocysts were found in 14 patients (20%), while biliary strictures other than pancreatic ductal strictures were present in 11 patients (16%) (Table 2).

Table 2. — **Findings on ERCP and interventions**

Findings & Intervention	Value
Findings on ERCP, n (%)	
Pancreatic ductal stricture	57 (85)
Pancreatic stone	28 (43)
Pancreas divisium	16 (24)
Biliary stricture	11 (16)
Interventions, n (%)	
Single pancreatic stent	50 (76)
Multiple pancreatic stents	10 (15)
5 Fr pancreatic stent	7 (12)
7 Fr pancreatic stent	41 (68)
10 Fr pancreatic stent	12 (20)
Pancreatic balloon dilatation	27 (41)
ESWL	28 (43)

Pancreatic stents were inserted in 60 patients ; of those, a single plastic stent was placed in 50 patients, two stents were placed in 8 patients, and three stents were placed in 2 patients. Regarding stent size, 7 Fr stents were used in 41 patients (68%), 10 Fr stents were used in 12 patients (20%), and 5 Fr stents were used in 7 patients (12%). Balloon dilatation for pancreatic duct strictures was performed on 27 patients. Eleven patients received both pancreatic and biliary stents (Table 2). Pancreatic stents remained in the patients for a median length of 14 months (3-84 months). At this stage of the study, some patients still have pancreatic ductal stents, and endoscopic re-interventions have been performed from two to seven times in all patients.

Of the 28 patients with a pancreatic stone, stone extraction was achieved in 21 patients; 17 patients required subsequent stenting procedures, while the remaining patients did not require additional procedures (Figure 1). On average, one (range: 1-4) ESWL session was performed on 16 selected patients. After the treatment with ESWL, complete clearance, partial clearance or no clearance of stones occurred in 10, 4 and 2 patients, respectively. All of these patients underwent ERCP after ESWL to remove whole stones or fragments of stones (Figure 2). No ESWL-related complications occurred.

Five patients experienced post-ERCP pancreatitis, which was the most common complication after ERCP (Table 3). Haemorrhage after papillotomy was observed in one patient. Perforation of the duodenal wall and then abscess formation occurred in two patients. In 6 patients, the proximal stent migration was corrected by pulling

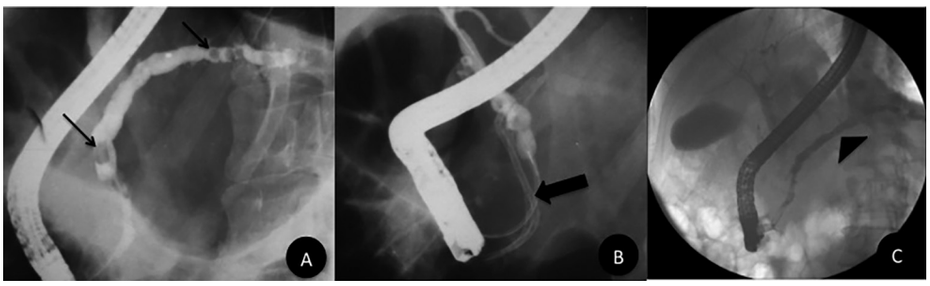

Figure 1. — Endoscopic retrograde cholangiopancreatography images show multiple stones (A, arrow) in a dilated pancreatic duct, multiple pancreatic stents (B, thick arrow), and improved structure of the pancreatic duct after stone removal (C, arrow head).

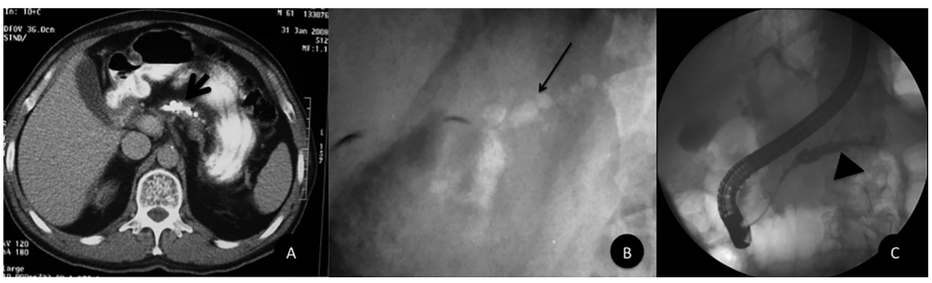

Figure 2. — Computed tomography scans in the axial plane show atrophied pancreatic parenchyma and calcifications (A, thick arrow). Round, uniform and well-circumscribed radio-opacities in pancreatic regions are visible on an abdominal radiograph (B, arrow). An endoscopic retrograde cholangiopancreatography image shows improvement in the structure of the pancreatic duct after extracorporeal shock wave lithotripsy combined with basket-assisted stone extraction (C, arrow head).

Table 3. — **Complications related ERCP**

Complications	Number of patient
Pancreatitis	5
Hemorrhage	1
Duodenal perforation	2
Stent migration	6

Table 4. — **Overall success**

	Number of patients (%)
Technical success	65 (97)
Clinical success	55 (84)
Requirement of further endoscopic intervention	6 (19)
Requirement of surgery	2 (6)

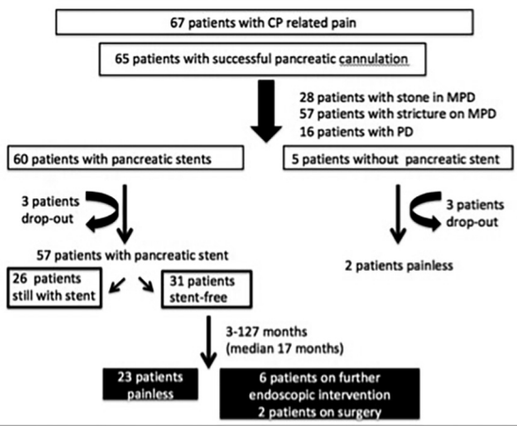

Figure 3. — Follow-up and current condition of chronic pancreatitis patients

the stent distally with an extraction balloon or biopsy forceps. No ESWL- or ERCP-related mortality occurred.

Overall, 65 of 67 patients underwent successful pancreatic cannulation (technical success rate 97%) (Table 4). Five patients received endoscopic intervention but not pancreatic stenting. In contrast, sixty patients underwent pancreatic stent placement. Six patients were lost to follow-up. Fifty-seven patients, who had a history of pancreatic stenting, are still undergoing follow-up. Of these patients, 26 still had pancreatic ductal stents, while the stents were removed from 31 patients. Only 8 patients (25%) required further endoscopic or surgical intervention due to the re-emergence of pain after a median stent-free period of 17 months (3-127 months). Endoscopic treatment was performed for all but two patients. One patient with a biliary stricture and one patient with a pancreatic mass underwent surgery (Figure 3). During the follow-up period, 55 of 65 patients became pain-free or had partial pain relief (clinical success rate 84%) (Table 4).

Discussion

CP frequently causes persistent abdominal pain (13). It is hypothesized that pancreatic ductal strictures and stones lead to ductal hypertension and painful distension

(13). In a large, multicentre study of endoscopic therapy for CP, main pancreatic duct obstruction was caused by strictures (47%), stones (18%), or a combination of both (32%) (14). In our series, fifty-seven patients (87%) had pancreatic ductal strictures, and 28 patients (43%) had a pancreatic ductal stone.

Interventional endoscopic and surgical therapy aiming to drain the pancreatic duct may improve pain control (15). Well-established endoscopic therapy for CP includes pancreatic sphincterotomy, balloon dilatation of strictures, stone removal, and long-term stent placement (16,17). Some improvements in endoscopic approaches have occurred in recent years. These changes include large pancreatic stents instead of thin stents, multiple stents instead of a single stent, utilization of ESWL in addition to several experimental implementations consisting of self-expendable metal stents and lithotripsy through pancreatoscopy (17-19).

Our approaches for endoscopic treatment of CP-related pain are different from conventional methods. We first perform a pancreatic sphincterotomy, followed by endoscopic dilation of the pancreatic stricture, pancreatic stone removal and then pancreatic stent placement. All procedures consisted of stepwise interventions that were part of a standard endoscopic therapy of CP. The pancreatic stent was left in the patient for as long as possible. Unless the patient had a stent-related complication or recurrent pain, the pancreatic stent was not removed or exchanged. Pancreatic stents remained in place for a median of 14 months were well tolerated by our patients. These stents were removed when pancreatic ductal strictures were improved based on ERCP images and/or when the patient was asymptomatic. This sequence was both technically and clinically successful in the vast majority of the cases (97% and 84%, respectively). In our retrospective study, even when a thin, single pancreatic stent was placed, removal was scheduled based on the patient's CP-related symptoms rather than a specified interval. Moreover, a substantial portion of patients did not require any intervention after the stent-free period. We noted promising results when the pancreatic stents remained in place for a prolonged period of time (longer than 12 months), and pancreatic stenting on demand appeared to be efficient for pain control.

In the literature, many publications indicate that the size of the stent should be at least as large as the diameter of the pancreatic duct and should traverse the stenosis, but it should be short enough to minimize ductal changes (18-20). Use of a 10 Fr plastic stent was associated with a decreased hospital admission rate in some analyses (21-25). Conversely, other trials using small calibre plastic stents to avoid blockage of side branches found that these stents also resulted in efficient pain control and ductal patency (26-28). Some researchers have suggested that even if the pancreatic stenosis remains, the pain will not recur when adequate drainage is provided (28,29). Therefore, criteria for adequate patency of the MPD and stent removal are described. These criteria consist of adequate outflow of contrast medium into the duodenum within 1 to 2 minutes after ductal filling upstream from the stricture and immediately after stent removal as well as extraction of ductal debris and easy passage of a 6 Fr catheter through the stricture (23, 27, 29). The concept of multiple plastic stent placement instead of a single stent for CP-related pain was advocated by Costamagna and associates (30). Larger or multiple stents lead to longer patency inarguably. Selection of calibres and lengths of the stents were not highlighted in the present study because this was a retrospective study. During our study period, which includes many years, stents were chosen according to preference of the endoscopist and based on the current literature. All endoscopist chose the stents according to the nature of stricture and dilatation of the duct in our clinic and preferred the largest ones as possible as.

Pancreatic stents are prone to occlusion in CP patients. The frequency and interval of stent exchange is still a subject for debate. Neither scheduled exchanges at 3- to 6-month intervals, nor 'on demand' periods have been found to be superior in the literature. Smits and colleagues performed ERCP and pancreatic stent placement every 3 months during a 34-month follow-up period (21). Weber and colleagues reported that of 17 patients who underwent pancreatic stenting at a 3-month interval, 57% remained completely pain-free (no relapse) at the end of 5 years (31). The European Society of Gastrointestinal Endoscopy (ESGE) guidelines state that pancreatic ductal strictures can be treated by placing a single 10 Fr stent with stent exchange planned at 1 year (19). Multiple plastic stents should be deployed in a stricture that persists at 1 year after single stent placement (19).

In our study, the re-intervention rate due to proximal plastic stent migration was only 9.2%. Stent occlusion caused stent exchanges at least twice and up to seven times in our study. Re-stenting was performed until the pancreatic ductal stricture was resolved.

Many CP patients experience relapses of pain after stent removal and require repeat stenting or surgery. In our study, after a median stent-free follow-up period of 17 months (3-127 months), 8 patients (25%) required further interventions, 6 patients underwent an endoscopic procedure, and 2 patients underwent surgery. This stent-free period was longer and the number of the patients who required new intervention was less than those reported in the literature (28). These findings reflect the benefits of both the appropriate timing of stent removal and leaving pancreatic stents in place as long as possible.

According to Dumonceau and associates, the safety and efficacy profile of ESWL is very good in CP patients (18). ESWL alone or combined with ERCP can be considered an appropriate intervention to manage pancreatic stones (32). Our study showed that ESWL produced favourable results for the clearance of pancreatic stones when incorporated into endotherapy.

There are some limitations in our study. First, due to the retrospective nature of the study, we were not able

to exact data to generate an objective pain score during follow-up; we defined partial and total relief of pain as clinical success. Additionally, we did not assess the quality of life score or endocrine and exocrine function. Second, we did not have comparison groups, such as patients undergoing on-demand stent exchange versus those with regular stent exchange intervals. Third, abdominal pain could have intensified due pancreatic pseudocyst in14 patients and biliary strictures in 11 patients apart from chronic pancreatitis, but pain **etiology** cannot be differentiated in these cases.

In summary, endoscopic therapy is a cornerstone of CP-related pain management. We observed that pancreatic stents might remain in place for as long as possible and be exchanged on demand according to the patient's symptoms. These findings should be corroborated in a larger series with long-term observations.

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