Update on Endoscopic Treatment of Chronic Pancreatitis

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Endoscopic therapy has been increasingly recognized as the effective therapy in selected patients with chronic pancreatitis. Utility of endotherapy in various conditions occurring in chronic pancreatitis is discussed. Its efficacy, limitations, and alternatives are addressed. For the best management of these complex entities, a multidisciplinary approach involving expertise in all pancreatic specialties is essential to achieve the goal. (Korean J Intern Med 2009;24:169-179)

Keywords: Chronic pancreatitis; Endoscopic treatment

INTRODUCTION

In patients with chronic pancreatitis, characterized by progressive and irreversible pancreatic injury, the aims of endoscopic therapy are to alleviate outflow obstruction of the pancreatic duct (PD), thereby decreasing ductal hypertension; to drain fluid collections; to divert flow away from the fistula/leak; and to relieve pain. Among the available endoscopic modalities, endoscopic retrograde cholangiopancreatography (ERCP) is used to treat pancreatic strictures, pancreatic ductal stones, pseudocysts, PD fistulas/leaks, and bile duct strictures. Data are accumulating concerning the outcome following endoscopic therapy in chronic pancreatitis [1]. In a large series of 1000 patients with chronic pancreatitis who were treated endoscopically, with long-term follow-up, 65% of the patients with strictures and/or stones showed improvement in pain after endotherapy [2]. Endoscopic intervention consisted of PD stricture dilatation, stone extraction, or PD sphincterotomy. Endoscopic ultrasound (EUS) can be used to pseudocyst drainage, perform celiac plexus neurolysis or block to improve pain. Jejunal tube placement for enteral feeding may be used for gut rest and to decrease pancreas stimulation.

Pancreatic sphincterotomy

Pancreatic sphincterotomy can be performed with a needle-knife incision over a guiding pancreatic stent or with a pull-type sphincterotome passed over a guidewire. This can be used to treat manometrically documented or suspected pancreatic sphincter of Oddi dysfunction (SOD). However, most pancreatic sphincterotomies are performed as a part of pancreatic stone, stricture, or pseudocyst management, or combined pancreatobiliary sphincterotomy for SOD. After such sphincterotomy, a 3 Fr single pigtail plastic stent, 4 to 6 cm in length, is used to prevent post-procedure pancreatitis, unless a larger diameter stent is required for treatment of a simultaneous stricture. The small-diameter single pigtail stent generally passes into the gastrointestinal tract within 7-14 days without the need for a second endoscopic procedure for stent retrieval. Risks of pancreatic sphincterotomy include early complications of pancreatitis (2-7%), bleeding (0-3%), and perforations (<1%), and late complications of sphincter stenosis (up to 10%) [4].
Dilation and stenting of pancreatic strictures

Benign strictures of the main PD are generally due to inflammation or fibrosis around the main PD. Focal strictures of the pancreatic head or body can be approached by endoscopic dilation and/or stent placement. Cases in which the narrowing involves the sphincter per se are classified as SOD and are best diagnosed by manometry.

Patients with focal head/body strictures with upstream dilation are the best candidates for the endoscopic management of pancreatic stricture, whereas patients with complex strictures and associated stones, pseudocysts, inflammatory mass of the head, or diffuse ductal changes are poor candidates.

In most patients, pancreatic sphincterotomy (with or without a biliary sphincterotomy) via the major or minor papilla is performed to facilitate placement of accessories or stents. A guidewire must be maneuvered upstream to the narrowing before stenting or dilation of the stricture with a balloon or dilating catheter. High-grade strictures require dilation prior to insertion of the endoprosthesis (Fig. 1). This may be performed with graduated dilating catheters or hydrostatic balloon dilating catheters. PD strictures from chronic pancreatitis are often densely fibrotic, and thus simple balloon dilation alone does not generally result in a satisfactory long-term response. Therefore, one or more PD stents are placed through the strictures to chronically expand the lumen (Table 1). The goals of pancreatic stenting are 1) to adequately expand the narrowing so that it allows good flow long after the stent is removed, and 2) to predict the response to surgical drainage if necessary. In general, the diameter of the stent should not exceed the downstream duct diameter. Stent

Table 1. Result of pancreatic duct stenting in dominant pancreatic duct strictures (10 Series; 1988-2005)

| Number of patients | Technical success rate | Follow-up | Patients improved rate | Major complications | Mortality |
|--------------------|------------------------|-----------|-----------------------|---------------------|-----------|
| 525                | 91%                    | 34        | 62%                   | 18%                 | 1%        |
calibers range from 3 to 10 Fr are usually used. For pancreatitis prophylaxis, 3-5 Fr stents are usually used; stricture therapy usually requires single or multiple 7, 8.5, or 10 Fr stents.

In a prospective study, Weber et al. investigated clinical success rates in 19 patients after initial ERCP and relapse rates during a 2 year follow-up period [5]. The overall patient assessment of stent therapy revealed complete satisfaction in 17 of 19 patients. A relapse rate of approximately 30% was seen within 2 years after stent extraction, and relapse was treated by repeated stent therapy. At 5 year follow-up, another series reported pain relief in 65% of patients with ductal outflow obstruction due to dominant PD stricture that was treated by stent drainage [6]. Costamagna et al. studied 19 patients with severe chronic pancreatitis and with a single pancreatic stent through a refractory dominant stricture in the pancreatic head with the following protocol: (i) removal of the single pancreatic stent; (ii) balloon dilation of the stricture; (iii) insertion of the maximum number of stents allowed by the stricture tightness and PD diameter; and (iv) removal of the stents after 6-12 months [7]. They reported that the median number of stents placed through the major or minor papilla was three, with diameters ranging from 8.5 to 11.5 Fr and lengths ranging from 4 to 7 cm. Only one patient (5.5%) had persistent stricture after multiple stenting. During a mean follow-up of 38 months after removal, 84% of the patients were asymptomatic, and 10.5% had symptomatic stricture recurrence.

Benign stricture of the main PD is usually managed with placement of one or multiple plastic stents. There have been several trials using metal stents for benign strictures of the PD (Fig. 2). Eisendrath et al. inserted self-expandable, uncovered Wallstents (n=20) and partially or totally covered Wallstents (n=18) in patients with chronic pancreatitis associated with dominant stricture of the main PD [8]. The results using uncovered Wallstents were unsatisfactory because of frequent stent dysfunction caused by tissue ingrowth (65%) through the wire mesh. In cases using partially or totally covered stents, epithelial hyperplasia and stent migration were the major late complications. They concluded that self-expandable stents provided disappointing results. Park et al. used fully covered, self-expandable metal stents for refractory benign pancreatic stricture in 13 patients [9]. The stents were left in place for 2 months in nine of 13 patients. Early migration occurred in five patients (39%; 1 proximal and 4 distal). In all nine patients, the stents were successfully removed after 2 months, and patients were followed for a median period of 5 months (2-10 months). During the follow-up period, there was no pain relapse in any of the patients. However, further long-term randomized studies of the use of metal stents in benign lesions of the pancreas are required.

In a recent randomized trial comparing endoscopic transampullary drainage of the PD and operative pancreaticojejunostomy, complete or partial pain relief was achieved in 32% of the patients receiving endoscopic drainage as compared with 75% of the patients receiving surgical drainage ($p=0.007$) [10]. The rate of complications, length of hospital stay, and changes in pancreatic function were similar between the two treatment groups, but patients receiving endoscopic treatment required more procedures than those in the surgery group (median of 8 vs. 3, $p<0.001$). The investigators concluded that surgical drainage of the PD was more effective than endoscopic
treatment in patients with obstruction of the PD due to chronic pancreatitis.

Occasionally, PD strictures are very tight or angulated and may not be traversable with conventional dilators and catheters. Familiari et al. described the placement of a guidewire (used as a dilator) across these types of strictures for 24 hours [11]. They hypothesized that the guidewire, left in place across the stricture, in combination with its slight movements caused by breathing, facilitated noninvasive dilation of the stenosis and allowed subsequent mechanical dilation and stent insertion. We have had similar good outcomes in five patients.

The optimum duration of stent placement, stent number and diameter, and degree of balloon dilation are not well known. Michael et al. attempted to identify endoprosthesis- or patient-related risk factors for pancreatic stent occlusion in patients with chronic pancreatitis [12]. However, the clinical and laboratory data did not reliably indicate clogging. Therefore, they recommended stent removal or exchange within 3 months in high-risk patients. Alternatively, some centers leave stents in situ until symptoms recur. Patients with chronic pancreatitis have elevated risk for pancreatic cancer. Endoscopists must maintain a high index of suspicion of underlying cancer whenever treatment of a PD stricture is performed and should obtain appropriate tissue samples [13].

The early complications of stent placement (bleeding and pancreatitis) are similar to those of sphincterotomy. Late complications are mainly related to stent migration and occlusion, which present with pain, pancreatitis, or infection [14]. In addition, PD stents may produce ductal changes, including strictures or focal areas of chronic pancreatitis [15,16]. However, these changes may improve with time.

**Removal of pancreatic duct stones**

Obstructing pancreatic stones may contribute to abdominal pain or acute pancreatitis in patients with chronic pancreatitis. Approximately 10-25% of pancreatic stones can be removed effectively by standard techniques, with a balloon and/or basket [17]. The best candidates for endoscopic removal of PD stones are main duct stones of the head or body with upstream main PD dilation (Fig. 3). Patients with extensive stones of the whole gland or side branch duct stones without main PD dilatation are poor candidates for endoscopic removal of PD stones.

Simple stone extraction can be achieved by various techniques, including balloon or basket sweep. Larger stones usually require lithotripsy via extracorporeal shockwave lithotripsy (ESWL) followed by balloon or basket sweep, mechanical lithotripsy, intracorporeal lithotripsy with a pulse-dye laser or electrohydraulic lithotripsy (EHL), or surgery [18].

ESWL has been used to facilitate the removal of PD stones during therapeutic endoscopy (Fig. 4, Table 2). Patients frequently require several ESWL sessions to achieve stone clearance from the duct [19]. Some investigators have reported high success rates of stone clearance with ESWL, whereas others have had less impressive results [20,21]. In a nonrandomized study, Dumonceau et al. compared pain relief in 55 patients with painful calcified chronic pancreatitis after ESWL alone (n=26) and after ESWL combined with endoscopic drainage of the main PD (n=29) [22]. After one month, diameter of main pancreatic duct was significantly decreased. The number of pain episodes during the year after treatment decreased markedly in both groups, and the difference between both groups was not significant. Two years after treatment, the rates of pain relapse were 38% in the ESWL group and 45% in the ESWL plus endoscopy
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The presence of obstructive calcifications in the head of the pancreas was the only factor independently associated with the absence of pain relapse. There was no procedure-related mortality, and only one procedure-related complication (a pseudocyst treated successfully by endoscopy) was seen. Treatment costs per patient in the ESWL plus endoscopy group were about threefold the costs in the ESWL alone group. The investigators concluded that ESWL alone is a safe and effective preferred treatment for selected patients with painful calcified chronic pancreatitis. Intraductal lithotripsy guided by endoscopy has also been used to fragment PD stones. In a large series of patients, pain relief was achieved in 70-80% of patients after stone removal, and the pain relapse rate was approximately 30% over 2 years [2].

Surgical removal of PD stones can also be achieved. In one randomized trial of endoscopic and surgical therapies, surgery was superior for long-term pain reduction in patients with painful obstructive chronic pancreatitis, and endotherapy without conjunctive ESWL appeared to be a suboptimal approach for PD stone therapy [23]. Generally, endotherapy is preferable as it is less invasive, and surgery

**Figure 4.** Extracorporeal shockwave lithotripsy (ESWL) to facilitate the removal of pancreatic duct stones. (A) Huge calcified stone is seen in the pancreas. (B) Fragmented Pancreatic duct stones are seen after ESWL. (C) Fragmented stones are removed with forceps. (D) Dilated main pancreatic duct is seen after complete removal of stones.

| Table 2. Clinical results of endoscopy and ESWL for pancreatic duct stones (11 Series; 1992-2005) |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Number of patients | Complete or partial pain relief | Overall increase in body weight | Exocrine function | Endocrine function | Need for surgery | Mean follow-up (month) |
|-------------------|---------------------------------|-------------------------------|------------------|------------------|-----------------|------------------------|
| 1041              | 79%                             | 61.8%                         | 55.6%            | 32.5%            | 16.5%           | 7.9%                   | 31.7%                  |
is considered a second-line therapy for patients in whom endoscopic therapy fails. Improvements in pain (77-100% and 54-86%, respectively) have been reported in some short-term and long-term follow-ups, to 5 years [24,25]. In the author’s experience, approximately 50% of patients have pain relapse within a 5 year follow-up period. This may be caused by new stone formation or underlying ongoing pancreatitis.

**Biliary obstruction in chronic pancreatitis**

Distal common bile duct stricture has been reported in at least 35% of patients with chronic pancreatitis [26-28]. These strictures result from a fibrotic inflammatory restriction or compression by a pseudocyst. The anatomical relationship of the common bile duct with the head of the pancreas is an important factor influencing the nature of the stenosis in chronic pancreatitis [29]. Common bile duct stricture occurs as a consequence of recurrent acute inflammatory episodes, which may ultimately result in periductal fibrotic stricture [30]. This is seen more commonly in advanced chronic pancreatitis in calcific variants with calcifications [31,32].

Jaundice occurs in 30-50% of stricture patients and may be transient, recurrent, or persistent [30,33]. Transient jaundice is typically seen during acute exacerbation and recedes with resolution of the inflammatory process [34]. The most commonly used laboratory test is the determination of an elevated alkaline phosphatase (ALP) level [27]. A persistent increase of ALP, greater than twofold for more than 1 month, has been proposed as a specific marker of bile duct stricture [35]. We favor no treatment unless the ALP is ≥2× normal with ductal dilation.

Most studies have shown that cholestasis can be effectively resolved in the short-term setting by ERCP plastic biliary stenting [36,37]. Before attempting endoscopic treatment, it is necessary to ensure that the bile duct stricture is not the result of pancreatic cancer. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is required to exclude the possibility of cancer. The risk for pancreatic cancer is increased in patients with chronic pancreatitis, although the magnitude of the increase is uncertain [38,39].

Chronic obstruction of the common bile duct may cause hepatic fibrosis and secondary biliary cirrhosis [40,41]. Hemmel et al. studied liver biopsy specimens from 11 patients with chronic stenosis of the common bile duct attributable to chronic pancreatitis [41]. All patients had undergone liver biopsy before and after the insertion of biliary drainage. Patients without restenosis showed improvement of hepatic fibrosis after biliary drainage. In our experience, these strictures do not commonly resolve, and long-term stenting, or preferably surgical bypass, is needed. Preliminary experience with the placement of 4-8 cm, 10 Fr plastic stents has suggested better long-term patency. Fully coated metal stents placed at ERCP are being evaluated for treatment of these strictures. To be successful, it is essential that these stents be removable after 6-24 months in situ and cause no ductal injury. Van Berkel et al. reported that the use of self-expanding metal stents for long-term stenting of benign biliary strictures due to chronic pancreatitis was safe and that it provided successful and prolonged biliary drainage in a selected group of patients in whom surgical intervention was not possible or desirable [42]. Larger, prospective, randomized, long-term studies are required to confirm these results.

Figure 5. Disruption of the main pancreatic duct. (A) Partial pancreatic duct disruption. (B) Complete pancreatic duct disruption.
Pancreatic duct leaks

PD disruptions or leaks can occur from a blowout upstream of obstructing strictures or stones in chronic pancreatitis [43-45]. Disruption of the main pancreatic duct (MPD) may be partial or complete (Fig. 5). On ERCP, partial disruption appears as fluid collection communicating directly with the MPD. Complete disruption consists of MPD transection, leading to pancreatic ascites, pleural effusions, pseudocyst formation, and internal and external pancreatic fistulas. PD leaks can often be treated with endoscopic placement of transpapillary stents. Varadarajulu et al. performed a study in 97 patients with PD disruptions to identify predictors of outcome after endoscopic transpapillary stent insertion, and univariate analysis showed that endoscopic therapy was successful in closing the leak in approximately 60% of the patients [46]. Factors associated with a better outcome included partial disruption, successful bridging of the disruption with a stent, and longer duration of stent placement (approximately 6 weeks). On multivariate analysis, partial pancreatic disruption and a stent bridging the disruption were correlated with a successful outcome. There have been no comparative studies of surgical, medical, or endoscopic therapy for the treatment of PD leaks.

Treatment of chronic pancreatitis due to pancreas divisum

Opening the minor papilla by sphincterotomy and the combined sphincterotomy/stenting technique has been shown to eliminate recurrent pancreatitis in 75% of patients with chronic pancreatitis and to improve pain in approximately 50% of those with pain syndrome. Vitale et al. evaluated the long-term efficacy of endoscopic stenting in 24 patients with chronic pancreatitis due to pancreas divisum, who were followed for a mean period of 59.6 months [47]. The mean pain score and number of hospital admissions decreased significantly after stent placement. Pain medication usage decreased in 58% of the patients, remained the same in 21%, and increased in 13%. The authors concluded that endoscopic stenting of the PD is a safe and effective first-line treatment for patients with pancreatitis secondary to pancreas divisum.

Endoscopic jejunal tube placement for enteral feeding

In patients with unrelenting pain from chronic pancreatitis, gut rest by either enteral feeding (preferred) or parenteral nutrition can be recommended. By feeding the gut beyond the ligament of Treitz, enteral feeding causes negligible stimulation of the pancreas and is associated with improved immune function, reduced infections, and lower pain scores. Short-term feeding can be accomplished with a nasojejunal tube. For longer-term feeding in patients with frequent vomiting, a combination gastrostomy and jejunostomy tube is often used. However, patients who vomit up their jejunostomy tube require a direct jejunostomy tube placed laparoscopically or endoscopically.

Celiac nerve block and neurolysis

Celiac plexus block or neurolysis can be performed to improve pain in patients with chronic pancreatitis. Celiac plexus block involves injection of a steroid (triamcinolone) and an anesthetic agent (bupivacaine) into the celiac plexus, and celiac plexus neurolysis involves injection of a neurolytic agent (absolute alcohol) into the celiac plexus to ablate or destroy the ganglia, thereby interrupting pain transmission. EUS can be used in patients with a suboptimal response to medical management. In general, EUS-guided celiac plexus block improves pain in about 50% of patients for a period of 3-6 months. Younger patients (<45 years old) and those with previous pancreatic surgery were less likely to respond to EUS-guided celiac plexus block [48].

Complications of celiac plexus block or neurolysis are infrequent and mostly self-limiting. The most common side effects are transient diarrhea and hypotension, which may occur in 30-40% of patients. Sympathetic blockade can manifest as diarrhea and hypotension because of the relatively unopposed visceral parasympathetic activity. In most patients, diarrhea is mild and self-limiting, lasting for less than 48 hours. Major complications, including retroperitoneal bleeding and peripancreatic abscess, have been reported infrequently. It is advisable to administer antibiotic prophylaxis (against mouth flora) to patients undergoing celiac plexus block. Antibiotics may not be necessary when alcohol is used, owing to the inherent bactericidal properties of alcohol. However, ethanol causes a dense desmoplastic reaction, making any future pancreatic surgery more difficult. Therefore, we avoid alcohol neurolysis for chronic pancreatitis, because these patients may require future surgery. As celiac block is of clinical benefit in only ~50% of patients, we use EUS-guided block when EUS is being performed for diagnostic reasons or in patients who would benefit from a vacation from pain or pain medications.
Pancreatic pseudocysts

Pancreatic pseudocysts (PPs), arising from duct disruption in areas of inflammation or necrosis, develop in approximately 20-40% of patients with chronic pancreatitis. Pseudocysts may be located within or outside the pancreas, may be single or multiple, may occur with or without persistent connection to the ductal system duct, and may be symptomatic or asymptomatic. The treatments of choice are surgery, external drainage, and endoscopic cyst-enteric drainage, as well as conservative treatment for selected candidates. Intervention is indicated for PPs that are symptomatic, in a phase of growth, or complicated (infected, hemorrhage, biliary, or bowel obstruction), or in those occurring together with chronic pancreatitis and when malignancy cannot be unequivocally excluded [49]. Many factors such as the amount of necrosis, suspicion of main PD disruption, the size of the pseudocyst, bulging on the gut lumen, ductal communication, coagulopathy /portal hypertension, tolerance to multiple procedures, and symptoms can affect PPs management. Symptomatic and large pseudocysts (>7 cm) generally require drainage by endoscopic, surgical, or percutaneous approaches [50]. Percutaneous drainage is preferred for fluid collection outside the pancreas without associated necrosis (low probability of persistent ductal disruption).

The best candidates for endoscopic treatment of PPs are those in which the cyst is bulging into the stomach or duodenum, with an intact pancreas on abdominal CT or ERCP and cysts arising from side branches. Poor candidates for endoscopic treatment are PPs with organizing necrosis, ductal disconnection, or immature fluid collection. An endoscopic approach is used when a significant bulge is noted against the lumen of the stomach or duodenum (Fig. 6) and the distance between the gut wall and the pseudocyst is less than 1 cm, with no intervening major vascular structures. This entails the creation of a fistulous tract between the PPs and the gastric lumen (cystogastrostomy) or the duodenal lumen (cystoduodenostomy). A nasocystic catheter or a stent can be placed for continuous drainage. The choice of a nasocystic catheter or stent for

Figure 6. Endoscopic approach through the bulge in the lumen of the stomach or duodenum. (A) A pseudocyst bulging into gastric wall. (B) Cyst puncture using cystotome resulting initial pus drainage. (C) Transmural (10-mm) balloon dilation. (D) Placement of one 7 Fr. double pigtail stent. (E) Two 7-Fr. double pigtail stents placed into the cyst. (F) Fluoroscopic view showing two double pig tail stents in place.
drainage depends on the appearance of the cyst contents. A chronic cyst with clear liquid contents can be drained with one or more stents. On the other hand, an infected cyst may be aided by irrigation with a nasocystic catheter. Arvanitakis et al. treated patients with chronic pancreatitis with apparently complete disruption of the MPD by stent placement into the PPs or peripancreatic fluid collection [51]. Stent removal resulted in fluid reaccumulation, as the duct disruption persisted, and the investigators recommended long-term stenting. The authors, however, prefer definitive surgical diversion. Transpapillary drainage can also be performed when the pseudocyst connects to the MPD above the stricture. Hookey et al. published a comparative study on transmural and transpapillary drainage in 116 patients with PPs [52]. The drainage technique was transmural in 15 patients, transmural in 60, and both in 41. Successful resolution of symptoms and collection occurred in 87.9% of the cases. No significant differences were observed related to drainage technique or drainage site. In a summary of eight series from the literature, involving 311 patients, stent placement was technically successful in 80% of the cases, with complications in 17% and death in 1%. Recurrences were seen in 10% and 20%, as observed in surgical series, and resulted from persistent main duct disruption as noted above.

A web-based survey was sent to 3054 endoscopists belonging to the American Society for Gastrointestinal Endoscopy, and 266 (8.7%) responded. Among these, 198 reported performing pseudocyst drainage [53]. Drainage was most commonly done by the transgastric route. The number of stents placed ranged from 1 to 5, and these remained in place for 2-30 weeks. A CT was used before drainage by 95% of all respondents. EUS imaging was used before drainage by 72 (70%) of 103 US endoscopists, compared with 56 (59%) of 95 international endoscopists. EUS-guided drainage was used by 56% of US endoscopists and 43% of international endoscopists.

In conclusion, endoscopic transmural drainage is the best technique for bulging PPs, whereas EUS-guided drainage is required for non-bulging pancreatic collection and in patients with portal hypertension (Table 3). For patients with PPs due to complete disruption of the MPD, surgical resection or diversion is preferred.

### SUMMARY

Endoscopic management of chronic pancreatitis has continued to evolve over the last decade. Enhanced techniques, better patient selection for specific techniques, and more comprehensive comparisons with surgery have been reported. A team approach to these often difficult cases is recommended.

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### Table 3. Result of endoscopic therapy of pseudocysts (15 Series; 1985-2002)

| Number of patients | Initial resolution | Recurrence rate | Complications | Mortality |
|--------------------|--------------------|-----------------|---------------|-----------|
| 632                | 87%                | 15%             | 16%           | 0.3%      |
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