JOP. J Pancreas (Online) 2007; 8(1 Suppl.):141-150.

CONFERENCE REPORT

Endoscopic Stenting in Benign Pancreatic Diseases

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Summary

The role of endoscopic therapy in the management of pancreatic diseases is continuously evolving; at present, most pathological conditions of the pancreas are successfully treated by endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS) or both. Endoscopic placement of stents has played and still plays a major role in the treatment of chronic pancreatitis, pseudocysts, pancreas divisum, main pancreatic duct injuries, pancreatic fistulae, complications of acute pancreatitis, recurrent idiopathic pancreatitis and in the prevention of post-ERCP pancreatitis. These stents are currently routinely placed to reduce intraductal hypertension, bypass obstructing stones, restore lumen patency in cases with dominant, symptomatic strictures, seal main pancreatic duct disruption, drain pseudocysts or fluid collections, treat symptomatic major or minor papilla sphincter stenosis, and prevent procedure-induced acute pancreatitis. The present review aims at updating and discussing techniques, indications and results of endoscopic pancreatic duct stent placement in acute and chronic inflammatory diseases of the pancreas.

The role of endoscopic therapy in the management of pancreatic diseases is continuously evolving; at present, most pathological conditions of the pancreas are successfully treated by endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS) or both. On the assumption that intraductal hypertension caused by obstructive lesions of the main pancreatic duct (MPD) is one cause of the pain often present in either chronic or acute pancreatic diseases, stent insertion beyond the obstruction to decompress the hypertension has a pivotal role in their therapeutic management.
Endoscopic placement of stents has played and still plays a major role in the treatment of chronic pancreatitis, pseudocysts, pancreas divisum, main pancreatic duct injuries, pancreatic fistulae, complications of acute pancreatitis, recurrent idiopathic pancreatitis, and in the prevention of post-ERCP pancreatitis. Stents are currently routinely placed to reduce intraductal hypertension, bypass obstructing stones, restore lumen patency in cases with dominant, symptomatic strictures, seal main pancreatic duct disruption, drain pseudocysts or fluid collections, treat symptomatic major or minor papilla sphincter stenosis, and prevent procedure-induced acute pancreatitis.
The present review aims at updating and discussing the role of endoscopic pancreatic duct stent placement in benign acute and chronic diseases of the pancreas.

Technique of Stent Placement and Drainage

Pancreatic Ductal System

The technique employed for placing pancreatic stents is similar to that used to

place stents in the biliary tract. Once the main or accessory pancreatic duct has been deeply cannulated, a hydrophilic 0.035 inch (for 5F, 7F, 10F stents) or 0.018 inch (for 3F stents or when the minor papilla is cannulated) guidewire is introduced into the duct and maneuvred if possible beyond the stricture or leakage. The stent is then introduced over the guidewire.

Pancreatic stents are generally made of polyethylene and are similar to biliary stents except for side holes along their length to allow flow from side branches. To prevent migration into the pancreatic duct, small-diameter stents have a J or 'pigtail' shape. For transpapillary stenting of a pseudocyst, a double pigtail stent should be used to prevent displacement outside the cyst cavity. Recently, an S-shaped stent with many side holes has been proposed for MPD stenting in chronic pancreatitis [1]; this stent is made of ethylene vinyl acetate, which is more flexible than that of polyethylene. The S-shape enables the stent to better adapt to the course of the MPD and reportedly achieves a better outcome in patients with chronic pancreatitis and upstream duct dilatation than in patients treated with the standard straight polyethylene stents.

The diameter of the stent should not exceed the size of a normal downstream duct, so 5F and 7F stents should be used in cases with non-dilated ducts while 10F and sometimes 11.5F can be used when the ducts are dilated, as in advanced chronic pancreatitis. Sometimes in advanced chronic disease, the stricture is too tight to place a stent across it; in these cases, the stricture must be dilated with a balloon or bouginage to permit insertion. In some cases, the Soehendra stent retriever (5F or 8F) can be used to dilate the stricture and allow insertion.

How long stents are best left in place is not yet known. Pancreatic stents have been left in place for six months and long-term therapy requires multiple stent exchange. However, the duration of a single stent placement depends on the stent diameter: the larger the diameter, the longer the stent can be left in place.

Pseudocyst and Fluid Collections

When the endoscopic approach is used, a prior evaluation of the wall thickness of the pseudocyst and intra-cystic fluid density by contrast-enhanced CT scanning or magnetic resonance imaging (MRI) are mandatory. With a CT scan, it is possible to evaluate the distance between the cystic lesion and the upper gastrointestinal tract wall, which does not exceed 10 mm, and the density of the intracystic fluid collection; however, the technique may underestimate the degree of pancreatic necrosis associated with peripancreatic fluid collections. MRI shows fluid superbly well on T2-weighted images and is superior to a CT scan in the identification of possible communication between the cyst and the pancreatic ductal system. The endoscopic approach involves the identification of the area of maximum bulge induced by the pseudocyst on the mucosa of either the stomach or the duodenum with the use of a side-viewing endoscope, needle localization of the tract for cautery, entry into the pseudocyst cavity using a needle-knife papillotome with radiologic verification by contrast injection, dilation of the opening by using a balloon dilator over the previously seated guidewire to a diameter of 8 to 10 mm, and insertion of one or two 8.5F or 10F, double pigtail biliary stents to drain the cavity [2]. One end of the stent is allowed to deploy within the cyst and the other pigtail end in the gastrointestinal tract lumen. Straight stents are unsuitable because of their tendency to migrate. The temptation to greatly extend the small opening with the needle-knife or a standard papillotome must be avoided because this involves a high risk of hemorrhage. To enlarge the needle-knife opening, a cystoenterostome may be used instead of a balloon; the cautery device is inserted into the opening over the guidewire and a 10 mm-diameter fistula between the cyst cavity and the stomach/duodenal wall is achieved within 48 hours, with a significant reduced risk of bleeding and perforation [3].

By using endoscopic ultrasonography (EUS), it is possible to identify both cystic cavities

which do not create an obvious bulge and the most favorable site of puncture, to accurately define the characteristics of the intracystic fluid and to minimize the risk of bleeding by avoidance of wall varices and other vascular structures. The echoendoscope can be used only to localize the collection in relationship to surrounding structures and endoscopic landmarks or to directly drain the pseudocyst [4].
Stents are left in place until there is radiological evidence that the pseudocyst has resolved, typically after 1 to 4 months.

Stent Placement in Chronic Pancreatitis

In chronic pancreatitis the MPD may be partially occluded by strictures or stones; the rise of intraductal pressure in the ductal segment above the obstruction causes dilation and obstructive pain. Pancreatic intraductal hypertension occurs regardless of the etiology and whether or not the MPD is dilated; ductal and interstitial hypertension, together with reduced acinar blood flow, may further contribute to the formation of fibrosis and progression towards more severe damage [5]. Removing the barriers to the outflow of the pancreatic juice may relieve chronic pain or exacerbate the chronic pancreatitis. Obstruction-related reduced outflow of pancreatic juice into the duodenum may also cause maldigestion of nutrients even in cases with still conserved pancreatic enzyme secretion, or worsening of maldigestion already present in advanced cases.
Although pancreatic ductal strictures can be treated by catheter or balloon dilation alone, a stent has usually has to be inserted because stricture relapse is commonplace. The insertion of a stent beyond the ductal blockage achieves lasting relief of the intraductal hypertension and subsequent pain and possible maldigestion, also restoring the lumen patency, by dilating the stricture. If a 10F stent or larger is used, the patient generally requires sphincterotomy of both the pancreatic and the biliary segments of the sphincter, followed by stricture dilation.
The presence of both obstruction and ductal dilation is vital for predicting which patients are most likely to benefit from stricture therapy; the best candidates for stenting are those with a distal stricture and upstream dilation.
Most investigators consider endoscopic management to be the preferred interventional approach for chronic pancreatitis in patients selected on the basis of anatomical changes caused by the disease; endoscopic treatment is generally safe, minimally invasive, can be repeated and does not interfere with eventual surgery [6]. Other investigators, however, found surgery superior to endotherapy for long-term pain reduction. Dite *et al*. [7], in a prospective randomized trial comparing endoscopic and surgical therapy for chronic, painful, obstructive pancreatitis, reported complete resolution of pain at the five-year follow-up in 37% of patients after surgery and in 14% of those after endotherapy; short-term results were similar in the two groups.
The technical success of endoscopic stricture manipulation can range from 80 to 100% of patients with or without prior pancreatic sphincterotomy. In chronic pancreatitis patients with dominant stricture, pain relief was obtained in 52-95% of cases over a follow-up ranging from 8 to 72 months [8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21]. Stenting was also associated with weight gain and fewer hospital visits. Good clinical outcomes were related to cessation of alcohol consumption and/or smoking [16]. Early complications were reported in about 17% of cases and were related mainly to pancreatic and/or biliary sphincterotomy, stent clogging (juice infection) and inward migration.
It is not clear how long stents should best be left in place. On the average, although the plastic 10F stents are thought to remain clinically patent for a year, they are generally removed and replaced every 6-9 months. In fact, stent dysfunction leading to pancreatitis, recurrent pain or infection can occur before the scheduled exchange time in about half the cases; therefore, repeated stent exchange is required in the long term. This may make it

difficult to ensure compliance with long-term stenting treatment.
Despite encouraging medium- and long-term results, duct stricture may persist or recur after removal of a stent so definitive removal seems impracticable in a subset of patients, because of the recurrence of pain. In an intention-to-treat analysis, a German multicenter study on long-term outcomes in 1,000 patients with chronic pancreatitis after pancreatic stenting reported unsatisfactory results in 35%; 16% of these patients continued with endotherapy and 24% opted for surgery [13].
A multiple stenting approach was proposed by Costamagna *et al*. [22] in a subset of patients with refractory dominant MPD strictures; they reported lasting stricture dilation in 84% of their patients at a 38-month follow-up. Although placing a mean of three stents within pancreatic strictures may be difficult, this approach appears feasible and safe and could, in fact, dramatically reduce the need for surgery in the majority of patients with chronic obstructive pancreatitis.
Self-expandible metal stents have been proposed for patients with relapsing dominant strictures to achieve long-term stent patency and avoid the need for stent exchange [23]. The success rate of stent placement was 100% and patients enjoyed immediate relief of symptoms and reduction of duct diameter; however, during follow-up, these patients had high occlusion rates of the stent from mucosal hyperplasia, and it became impossible to remove the stent, so this approach has, in fact, been abandoned.

Stent Placement in Pancreas Divisum

Pancreas divisum is present in about 7% of the population; it occurs when the ventral and dorsal ducts of the gland fail to fuse during embryological development. This anatomical variant is asymptomatic in the majority of cases but, in some cases, it may cause pancreatic pain due to functional obstruction at the level of the minor papilla or recurrent episodes of acute pancreatitis; persistence of the obstruction over time may lead to chronic obstructive pancreatitis. Kamisawa *et al*. reported acute recurrent pancreatitis and chronic pancreatitis associated with pancreas divisum in 17.1% and 28.6% of their patients, respectively [24].
Endoscopic therapy with minor papilla sphincterotomy and/or stent placement appears to be the treatment of choice at present. Critical issues concerning endotherapy in pancreas divisum are patient selection, difficulty of papillary cannulation, technique for endotherapy (minor papilla sphincterotomy, dorsal duct stenting, or both), stent-induced duct injury, and risks of post-ERCP pancreatitis. Patients with acute recurrent pancreatitis are the best candidates for endotherapy as. in this group, the predicted sustained response rate was about 75%; the response rate in patients with chronic pancreatitis is 40-60%, whereas patients with recurrent or chronic abdominal pain respond poorly (20-40%) [25].
The minor papilla is often difficult to visualize, but its orifice can be easily identified by spraying methylene blue over the duodenal mucosa in the papillary area or injecting it directly into the ventral duct, in cases with incomplete pancreas divisum [26], by EUS [27] or by enhancing pancreatic secretion with i.v. secretin [28].
Endotheraphy of pancreas divisum includes minor papilla sphincterotomy and dorsal duct stenting with 5F, 7F and 10F stents, depending on the level of obstruction and degree of dilation. Dorsal duct stenting without sphincterotomy was adopted by McCarthy *et al*. [29], Lans *et a*l. [30] and Ertan [31], who reported satisfactory long-term results in 89%, 90% and 76% of cases, respectively. However, Heyries *at al*. reported more favorable long-term results with minor papilla sphincterotomy than with stenting [32]; they also observed fewer complications after sphincterotomy (25%) than after stenting (44%).
Of course, stenting is the only option in cases with dorsal duct strictures proximal to the papillary orifice. A strategy of empiric 3-6-month dorsal duct stenting may be adopted in patients with recurrent pain or pancreatitis

with a non-dilated dorsal duct or normal minor papilla motor function, investigated by manometry or MRCP and a secretin test in order to decide whether sphincterotomy would be appropriate. This approach in patients with non-pathological duct morphology, however, could lead to ductal changes consistent with chronic pancreatitis in about one-third of cases.

Stent Placement for Pseudocyst Drainage

Pseudocysts complicate acute and chronic pancreatitis in up to 20% of cases; approximately 50% of pseudocysts regress spontaneously within 6 to 12 weeks. Pseudocysts which are symptomatic, become larger on follow-up imaging or are associated with complications, require a drainage procedure. The pseudocyst communicates directly with the MPD in up to 40-66% of cases [33].

Transmural drainage is the preferred approach for resolving a pseudocyst and is the only way to drain it when the cystic cavity does not communicate with the main pancreatic duct. The success rate for achieving drainage varies with the selection criteria and ranges from 36 [34] to 90% [35]; technical success was associated with location of the pseudocyst in the head or body rather than the tail of the pancreas, when the transmural thickness was less than 10 mm as measured by CT scan or EUS, and when the pseudocyst complicated chronic rather than acute necrotizing pancreatitis. Procedure-related complications have been reported in up to 12.7% of cases and included bleeding (11.4%), perforation (2.2%), and sepsis secondary to infection of necrosis within the pseudocyst (12.7%) [36]. The presence of necrotic debris or loculations within the pseudocyst increases the risk of post-procedure infection and necessitates nasocystic lavage with saline or antibiotics. It is important, therefore, to create sufficient communication between the cyst cavity and the gastric or duodenal lumen to minimize the potential for secondary infection of otherwise poorly drained content of a pseudocyst. The complication rate has been reported to be reduced whith the use of ultrasound-guided drainage; a recent survey done by the American Society for Gastrointestinal Endoscopy (ASGE) showed that there was no statistically significant difference in the compliactions rates when compared to the use of EUS before the procedure, and EUS-guided drainage [36]. Available long-term results show that about 15% of patients need repeated endoscopic drainage of recurrent collections during a median follow-up of 21 months [3].

Pseudocysts with ductal communication can only be resolved by duct drainage [37]. This can be achieved during ERCP using a trans-papillary approach, thus avoiding the usual risks (bleeding and perforation) of endoscopic cysto-gastrostomy or cysto-duodenostomy, especially when endoscopic ultrasound guidance is not available. Trans-papillary 5F, 7F or 10F stents can be placed beyond the strictured segment of the MPD but not in the pseudocyst in cases with duct strictures downstream of the pseudocyst, or they can be placed directly directly into the pseudocyst cavity if no MPD strictures are found [38] or into the MPD bridging the communication between the duct and the cyst cavity. When the stent is placed directly in the pseudocyst cavity, a double pigtail stent is preferred to avoid the risk of displacement. Stents should be routinely changed every 6-8 weeks to avoid clogging and the risk of infection or pancreatitis.

Features predictive of a successful trans-papillary approach are MPD dilation upstream of the ductal stricture when the stent is placed across the stricture, and a non-dilated pancreatic duct when the stent is placed to bridge the communication of the cyst with the pancreatic duct. Placing a stent in the pseudocyst in a case with non-dilated MPD is associated with a higher risk of pancreatitis.

Collective data regarding the endoscopic treatment of psudocysts seem to indicate that it is associated with slightly higher complication and recurrence rates but a significantly lower mortality rate when compared to open surgery [35].

Stent Placement in Pancreatic Fistulas

Fistulas can occur as a consequence of partial or complete rupture of the pancreatic duct caused by trauma, pancreatic surgery or complicating severe acute pancreatitis. During an attack of acute severe pancreatitis, ERCP found a pancreatic duct leak in 37% of cases and this was significantly associated with a higher incidence of necrosis and longer hospital stay [39]; the early recognition and treatment of such leaks is likely to improve outcomes.

At present, the diagnostic approach to pancreatic fistulas and suspected pancreatic duct leaks should be MRCP with secretin stimulation, leaving ERCP and EUS only for therapeutic purposes, once the lesion has been identified and staged. Before planning endoscopic treatment of fistulas or duct leaks, several points must be clarified: the location of the lesion within the pancreatic ductal system, the presence and type of pancreatic duct strictures downstream of the lesion, whether pancreatic duct disruption is complete or incomplete, whether there is any communication with a fluid collection and its anatomical characteristics.

Fifteen years ago, Kozarek *et al*. reported that bridging a pancreatic duct leakage by trans-papillary stent placement was effective for both internal and external pancreatic fistulas [40]. Transpapillary stenting of the MPD has now become the 'gold standard' for the treatment of fistulas and duct leaks, with success rates ranging from 55 [41] to 100% [42] and higher than 80% in most series. Telford *et al*. reported that the position of the bridging stent was the only variable related to a good outcome (92%) while stents placed at the level of the leakage or distal to it were more often associated with approximately 50% of failures [43]. A partially disrupted MPD, the location of the disruption at the level of the body of the pancreas, the stent positioned to bridge the disruption and a longer duration of stent therapy were identified as predictors of a favorable outcome in the endoscopic management of duct disruption on a large series of patients [41]. The stent should be left in place for four to six weeks. A shorter period of stenting may involve a higher rate of failure [43] while a longer period may increase the risk of stent occlusion and stent-induced alterations in ductal morphology.

Stent Placement in Smoldering Pancreatitis and Idiopathic Recurrent Pancreatitis

'Smoldering' pancreatitis refers to a syndrome in which patients recovering from acute pancreatitis suffer from unremitting abdominal pain, intolerance to food, persistently elevated serum levels of pancreatic enzymes and persisting inflammatory changes in and around the pancreas at imaging studies. Functional obstruction of the papillary orifice, induced by edema or sphincter spasm, and inflammation-related fibrotic strictures of the MPD may account for the unremitting course in a subset of patients with smoldering pancreatitis. In these cases, insertion of a stent into the MPD provided permanent relief of pain in 91% of patients within a mean of nine days (range 3-20 days) and discontinuation of parenteral nutrition within a mean of 15 days (range 7-39 days); the stents were left in place for a mean of seven weeks (range 2-19 weeks) [44].

Today the etiology of acute pancreatitis remains undefined in 2-30% of cases, despite a careful diagnostic work-up including imaging techniques for pancreatic morphology (CT scan, MRCP, EUS), functional investigation of the sphincter of Oddi (manometry, secretin test), and tests for gene mutations and autoimmune disorders. In these cases the term 'idiopathic pancreatitis' is generally adopted and the failure to identify the cause predisposes to further recurrences. Despite the absence of morphofunctional alterations, however, it is generally believed that biliary sludge, microlithiasis or unrecognized transient sphincter of Oddi dysfunction (type 2) plays a causal role. In a therapeutic protocol study adopted at our institution, we found that the placement of a 5F or 7F stent into the MPD in cases with

pancreatitis still recurring after biliary sphincterotomy served to identify those patients with residual hypertension of the pancreatic segment of the sphincter of Oddi who benefit from pancreatic sphincterotomy, as documented during a 27-month follow-up. In these patients with a non-dilated MPD, stents were routinely changed every three months. This empiric approach can be suggested for patients with recurrent pancreatitis but no evidence of morphofunctional abnormalities, presenting at least two or three acute attacks over one year, in whom three- to six-month stenting can provide a reliable basis for deciding on pancreatic sphincterotomy [45].

Jacob *et al*. [46] reported the results of a prospective randomized nonblinded trial evaluating the effectiveness of pancreatic stent placement in preventing attacks of pancreatitis in patients with idiopathic recurrent pancreatitis over a five-year period. The stent group received three stents in one year while the control group underwent selective pancreatic duct opacification without stenting. Pancreatitis recurred in 53% of the control group and in 11% in the stent group. The authors concluded that unrecognized intermittent pancreatic duct sphincter dysfunction or relative outlet obstruction might be a cause of recurrent pancreatitis which could be prevented by stent placement. However, long-term stenting of the pancreatic duct may in itself cause ductal damage, so only short-term stenting in patients with frequent episodes of pancreatitis is justifiable.

Complications of Stent Placement

Several complications have been reported after pancreatic duct stent placement in benign diseases, ranging from 5 to 39%. These include inward or outward migration of the stent, occlusion and anatomic changes of the pancreatic duct [47, 48]. The latter limits the long-term use of stents in the treatment of benign disorders especially when pancreatic ducts are non-dilated. Changes of MPD morphology consistent with chronic pancreatitis have been reported after stent placement in 36-83% of patients; ductal changes of the pancreatogram appear as early as three months and do not seem to revert to normal in some cases after removal of the stent. Pancreatic stents placed in dogs were found to induce (within eight weeks) both radiological and histological changes of chronic pancreatitis in the ductal segment treated with the stent [49].

Although the mechanism by which changes are induced is not known, there is evidence that stenting the pancreatic duct leads to the formation of intraductal plugs in as little as three weeks even though pancreatograms may remain normal. These protein precipitates have the same composition as plugs removed from patients with chronic pancreatitis. Moreover, the conventional plastic stent does not provide enough side openings for unencumbered drainage at all sites where secondary ducts join the MPD; this obstruction and the pancreatic duct compression along the whole length of the stent induce a fibrotic reaction. A new pancreatic stent design with a wing shape has now been tested in dogs and have given encouraging results since this model permits an adequate flow of pancreatic juice even alongside the stent and does not compress the duct over its entire circumference, thus avoiding the risk of impaired drainage of pancreatic juice and mechanical trauma to the duct [50].

Conclusion

In the last 20 years, endotherapy of pancreatic disorders has evolved from an experimental therapy tested in a few centers for some pathological conditions in selected cases, due to the fear of severe complications, to being the ‘gold standard’ approach for most acute and chronic inflammatory disorders involving the gland. Because of the high level of technical skill required and the small numbers of patients who need this approach, pancreatic endotherapy should ideally only be carried out in selected centers where a multidisciplinary team is available.

Keywords Abnormalities; Cholangiopancreatography, Endoscopic Retrograde; Pancreas; Pancreatic Diseases; Pancreatic Pseudocyst; Pancreatitis, Chronic; Sphincterotomy, Endoscopic; Stents

Abbreviations MPD: main pancreatic duct

Conflict of interest The author has no potential conflicts of interest

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Document URL: http://www.joplink.net/prev/200701/28.html

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