

REVIEW ARTICLE

Endoscopic Treatment of Patients with Chronic Pancreatitis

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ABSTRACT

Relapsing chronic pancreatitis is often caused by elevated pressure within the pancreatic duct due to impaired pancreatic juice outflow in the presence of pancreatic duct stricture or stones formed by chronic pancreatic inflammation. Most of this condition is alcoholic, and patients should stop drinking as a treatment. Alleviating the impaired pancreatic juice outflow and decompressing the pancreatic duct constitute a reasonable treatment approach for relapsing pancreatitis. Methods available for pancreatic duct decompression include surgical procedure such as pancreatectomy or pancreaticojejunostomy, extracorporeal shock wave lithotripsy and endoscopic treatment (e.g., endoscopic pancreatic duct stenting). Endoscopic stenting has been increasingly used as a minimally invasive method of treating pancreatic duct stricture, but it involves several problems. If the pancreatic stones are large, a combination of this procedure and extracorporeal shock wave lithotripsy will allow easier stone removal and stenting. Differentiating the benign from malignant nature of the pancreatic duct stricture is important. Sufficient understanding of the accidental symptoms that accompany stent insertion is also necessary. In patients with intense pancreatic duct stricture, which makes stenting difficult; patients in which the stricture fails to alleviate even after successful stenting and thus requires stent replacement; and patients with large pancreatic stones that are difficult to eliminate by using extracorporeal shock wave lithotripsy, surgery is an essential treatment option that should be performed without delay. Pancreatic duct stenting is greatly useful in controlling and preventing symptoms of relapsing obstructive chronic pancreatitis, although it involves many issues related to indications, insertion period, form and diameter of the stent to be inserted, and medico-economic aspects.

INTRODUCTION

Relapsing pancreatitis is often attributable to elevated pressure inside the caudal pancreatic duct due to impaired pancreatic juice outflow in the presence of pancreatic duct stricture or stones formed by chronic pancreatic inflammation [1, 2]. Relapsing pancreatitis can also be accompanied by elevated pressure inside the caudal pancreatic duct that leads to a pancreatic cyst in the caudal pancreatic duct. Most of this condition is alcoholic, and patients must stop drinking as a treatment [1,2]. Alleviating the impaired pancreatic juice outflow and decompressing the pancreatic duct constitute a reasonable treatment approach for relapsing pancreatitis. Methods available for pancreatic duct decompression include surgery (pancreatectomy or pancreaticojejunostomy) and endoscopic pancreatic duct stenting. Cahen *et al.* [3] conducted a randomized control trial (RCT) comparing surgery with endoscopic stenting, reporting that surgery yielded better outcomes. However, symptoms that remain after surgery are not uncommon, with the reported long-term response rate to surgery being approximately

60% [4, 5]. Meanwhile, endoscopic stenting has become widespread as a minimally invasive treatment method [6]. The results of pancreatic stenting in past reports were favorable, with the success rate being 72–100% and the symptom alleviation rate being 65–87% [7-12]. However, indications, stent selection, stenting period, long-term usefulness, limitation, and safety of this procedure remain to be discussed further [13]. This paper discusses the current status of endoscopic treatment of relapsing pancreatitis.

ENDOSCOPIC TREATMENT OF PANCREATIC DUCTAL STONES

Pathophysiology

More than half of all patients with relapsing chronic pancreatitis have pancreatic stones [14, 15]. Pancreatic stones impair pancreatic juice outflow, elevating the pressure inside the pancreatic duct and thus causing pancreatic pain. Endoscopic removal of pancreatic stones is considered a rational treatment method for symptomatic chronic pancreatitis accompanied by stones because it reduces the pressure within the pancreatic duct and thereby relieves the pain. This therapy is indicated also in symptom-free cases if the patient is young or if pancreatic stone removal is expected to preserve pancreatic function.

Diagnosis

The presence of pancreatic stones can be easily diagnosed by computed tomography or magnetic resonance

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cholangiopancreatography. These modalities enable not only localization or size determination of pancreatic stones but also collection of information about the arrangement or stricture of the pancreatic duct. Distinction from pancreatic cancer is also important. Endoscopic retrograde cholangiopancreatography is performed for endoscopic pancreatic stone removal. Pancreatography is performed for assessment of the pancreatic duct arrangement, stone location, and presence/absence of pancreatic duct stricture. Pancreatic juice cytological findings are also important to rule out cancer [16].

Pretreatment

Endoscopic pancreatic sphincterotomy is performed to enable easier pancreatic stone removal. This procedure is intended also to prevent stone impaction leading to post-extracorporeal shock wave lithotripsy. In patients of pancreatic divisum, an approach via the accessory papilla is made, and the accessory papilla is incised. Many such patients are complicated by pancreatic duct stricture, and removal of pancreatic stones is simplified by dilatation of the stricture site using a dilating balloon catheter, dilating catheter, or Soehendra stent retriever. In patients of negative for stones on radiography, extracorporeal shock wave lithotripsy is performed with insertion of a transnasal endoscopic pancreatic duct drainage tube. Meanwhile, in patients of positive for stones on radiography, overlapping with the vertebrae is sometimes difficult to check, and insertion of a pancreatic or bile duct stent as a marker of extracorporeal shock wave lithotripsy will increase the success rate of extracorporeal shock wave lithotripsy [16].

Uncombined Endoscopic Pancreatic Stone Removal

Good candidates for uncombined endoscopic pancreatic stone removal are those with three or fewer stones, those with stones at the pancreatic head or body, those free of pancreatic duct stricture closer to the duodenum than the pancreatic stones, and those with pancreatic stones 5 mm or smaller without impaction [17]. A basket or dilating balloon catheter is used for stone removal.

Endoscopic Pancreatic Stone Removal Combined with Extracorporeal Shock Wave Lithotripsy

If extracorporeal shock wave lithotripsy is performed before endoscopy treatment, multiple stones, large stones (5 mm or bigger), stones located within the stricture site, and impacted stones can also be removed endoscopically [18-24]. The success rate of endoscopic pancreatic stone removal without extracorporeal shock wave lithotripsy is reportedly less than 10% [25]. In approximately 90% of all patients with pancreatic stones, lithotripsy can be completed in fewer than three sessions of extracorporeal shock wave lithotripsy [13, 26], with reported extracorporeal shock wave lithotripsy and pancreatic stone removal success rates of 75–100% and 37.5–100%, respectively [2, 21]. In a large-scale study of endoscopic treatment combined with extracorporeal shock wave lithotripsy, favorable pain relief was achieved in 60–80% of all cases [26-28]. Endoscopic pancreatic stone removal combined with extracorporeal

shock wave lithotripsy is recommended for patients with relapsing chronic pancreatitis with pancreatic stones. However, depending on the size and number of stones, even uncombined endoscopic pancreatic stone removal or uncombined extracorporeal shock wave lithotripsy also allows for a safety treatment.

Difficult Cases of Extracorporeal Shock Wave Lithotripsy

Pancreatic duct endoscopy-guided laser or electrohydraulic lithotripsy is an alternative treatment option for patients with unsuccessful extracorporeal shock wave lithotripsy. However, the procedure involves technical difficulties [29-31]. In the past, a videoscopy or fiberscopy had been used in pancreatic duct endoscopy-guided electrohydraulic lithotripsy. In 2011, however, the Spy Glass System (Boston Scientific, Boston, Massachusetts, US) became available for use, allowing electrohydraulic lithotripsy to be performed relatively simpler [32]. The 10-Fr plastic tube (Spy Scope) can be manipulated in four directions. While water is supplied from the water supply orifice and observation is made via the 0.8mm optical fiber, a 1.9-Fr electrohydraulic lithotripsy probe is inserted through this tube to crush pancreatic stones under endoscopic guidance. The pancreatic stones can be crushed if they can be viewed from the front, but they cannot be crushed if the stones are located, for example, at the curved point of the pancreatic duct. The crushed pancreatic stones are then removed by using, for example, basket forceps.

Complications

Ecchymosis has been reported as the most frequent complication that arise from extracorporeal shock wave lithotripsy (18.5%) [26]. Other complications reported include pain due to pancreatic stone impaction, pancreatitis, and gastric submucosal hematoma, many of which can be managed with conservative treatment. Complication that arises from endoscopic pancreatic stone removal includes guidewire-related pancreatic duct injury, basket impaction, pancreatic stones due to insufficient stone removal, and pancreatitis, although only few severe cases have been reported.

TREATMENT OF PANCREATIC STRICTURE WITH PLASTIC STENT

Problems

The treatment goal for intense pancreatic duct stricture associated with chronic pancreatitis is to dilate the stenotic site sufficiently so that the impaired pancreatic juice outflow can be alleviated. However, advancing the guidewire beyond the stenotic area is sometimes difficult because of conditions such as tortuous or curved pancreatic duct, and pancreatic stone impaction, thus requiring this procedure to be combined with extracorporeal shock wave lithotripsy in many patients. Furthermore, pancreatic duct stricture and pancreatic cancer should be distinguished from each other. Although the reported outcomes are

favorable (stent insertion success rate, 85–98%; pain relief, 65–95%) [29], the questions of how long the plastic stent needs to be kept inserted to alleviate stricture and when to withdraw the plastic stent remains to be answered.

Plastic Stent Types / Insertion Methods

Plastic stents with varying diameters (5, 7, 8.5, and 10 Fr) and sizes have been supplied by manufacturers. The PS is either straight or S shaped. A stent appropriate for a given case is selected according to the intensity/location of the pancreatic duct stricture, pancreatic duct form, and the approach used (major or minor papillary approach). Recently, a type of Plastic stent for pancreatic duct made of a stent combined with a pusher as a single unit has been marketed (Advanix Pancreatic Stent, Boston Scientific) and utilized in the prevention of stent migration. The plastic stent is kept inserted either as a single stent or as multiple stents.

Duration of Plastic Stent Placement

The mean plastic stent patency period is 2–12 months [33, 34]. Once the plastic stent becomes obstructed, acute pancreatitis (suppurative pancreatic ductitis in some cases) can develop as a complication [33, 34]; hence, during long-term insertion, plastic stent needs to be renewed appropriately. If the stricture is alleviated, plastic stent withdrawal is possible, but complete alleviation of stricture is observed in 10% of all cases or fewer [7]. In most cases, plastic stent withdrawal is performed while some extent of stricture remains.

Timing for Plastic Stent Removal

In a study on plastic stent withdrawal upon confirmation of alleviated stricture through pancreatography, the median total plastic stent insertion period for the withdrawn cases was 23 months and the percentage of cases that required plastic stent reinsertion for pain relapse within 1 year after withdrawal was 30% [36]. In a study on periodical renewal of the plastic stent at intervals of two months and withdrawal of the plastic stent at six months after first insertion, the pain relapse rate at one year after plastic stent withdrawal was 48% [10]. Thus, the therapeutic efficacy with any of these insertion methods was not sufficient.

Treatment of Pancreatic Duct Stricture with Multiple Plastic Stents

In a previous study, multiple plastic stents were inserted in patients in whom stricture could not be resolved by conventional plastic stent treatment [37]. According to the report, stricture was alleviated in 18 of 19 patients when two to four plastic stents (8.5 to 11.5 Fr) were kept inserted for 6–12 months. Follow-up for a mean period of three years revealed re-stricture with symptoms in only two patients (10.5%), thus indicating that this method may be more useful than the conventional method that uses one plastic stent.

Complications Caused by Plastic Stent

Plastic stent-related complications occurred in 6–39% of all cases, with mild pancreatitis being the major complication. Stent migration and pancreatic abscesses were also reported [29].

TREATMENT OF PANCREATIC DUCT STRICTURE BY USING A METALLIC STENT

Uncovered Metallic Stent or Covered Metallic Stent?

Recently, the use of metallic stents has expanded to include cases of pancreatic duct stricture such as benign bile duct stricture. The first report on metallic stent insertion in patients with pancreatic duct stricture compared between the uncovered metallic stent and the covered metallic stent [38]. When uncovered metallic stent was inserted in 20 patients, the symptoms alleviated for a while in all patients, but pain relapsed within two years in 85% of the patients, with hyperplastic re-stricture formation within the metallic stent in 55%. Thus, the author concluded that clinical use of uncovered metallic stent is undesirable. By contrast, when covered metallic stent was inserted in 18 patients (partially covered metallic stent in nine patients and fully covered metallic stent in nine patients), symptoms alleviated for a while in all of the patients, but pain relapsed in 75% of the 16 followed-up patients. Hyperplasia within the metallic stent (noted earlier after uncovered metallic stent insertion) was absent in the fully covered metallic stent insertion group, but metallic stent dislocation was observed in 50% of the patients.

Short-Term Insertion Method

Okushima *et al.* [39] reported the results of short-term insertion (two days to one week) of a fully polyurethane membrane-covered Diamond Stent (Boston Scientific) in three intractable patients. Although the insertion period was short, the metallic stent exerted sufficient dilating and stricture-alleviating effects by the time of withdrawal, and all of the patients had remained free of relapse when followed up 1.5–2.1 years after withdrawal, thus suggesting the effectiveness of short-term insertion of a large-diameter metallic stent.

Preventive Measures for Metallic Stent Dislocation

As a preventive measure for metallic stent dislocation, a VIABIL Stent fitted with an anchor fin (ConMed) was kept inserted for three months in six patients who were difficult to treat with a plastic stent [40]. In that study, metallic stent dislocation was not observed in any case, but pain relapsed in three patients (60%) within four months after metallic stent withdrawal. In a study that involved insertion of a Niti-S Pancreatic Stent, a bumpy stent (TaeWoong Medical) designed to prevent dislocation by changing the metallic stent cell size and the dilating power among the different parts for a period of three months in 32 cases [41], metallic stent dislocation was absent in all the patients and the symptoms and stricture were alleviated in all patients at the time of metallic stent withdrawal. The follow-up period after metallic stent withdrawal was short

(mean, five months; range, three to seven months), but the pain relapse rate was only 16%. Thus, long-term results are awaited with much expectation.

Complications

The most important concern in the insertion of a covered metallic stent in the pancreatic duct is the onset of acute pancreatitis due to obstruction of its branch. To date, however, no case of serious pancreatitis has been reported. When a covered metallic stent, which is larger in diameter than a plastic stent, is inserted, an inflammatory change called "stent-induced ductal change" due to stimulation by the stent tip can occur [42].

TREATMENT USING ENDOSCOPIC ULTRASOUND

Endoscopic Ultrasound-Guided Drainage of the Main Pancreatic Duct

In cases for which transpapillary pancreatic duct stenting is not possible for reasons such as intense stricture, postoperative state, divisum, and large stones, puncture drainage of the pancreatic duct with a dilated caudal segment via the digestive tract is performed under endoscopic ultrasonography guidance. This procedure, however, is indicated for only a small number of cases [29].

Transpapillary Rendezvous Approach

If the pancreatic duct with a dilated caudal segment can be punctured with a guide wire via the digestive tract under endoscopic ultrasonography and if the guide wire can be further advanced beyond the stenosed site of the pancreatic duct, the guide wire is left inserted and only the scope is changed with a JF, to enable a transpapillary approach.

Transluminal Approach

With the transluminal approach, the pancreatic duct with a dilated caudal segment is punctured via the digestive tract under endoscopic ultrasonography guidance and the guide wire is inserted in the pancreatic duct. Then, the puncture route needs to be dilated. However, this dilating process is quite difficult because of the problem related to the puncture angle or the presence of fibrotic pancreatic tissue.

Results

The symptom disappearance rate with this approach was 69% but decreased to 20% when assessed 450 days later [43]. The procedure success rate was 68–73%, and the complication rate was 5–43% [43-47].

Complications

Perforation, bleeding, pancreatitis, fever, and pain were observed as complications [53-57]. Migration and stent obstruction occurred at a high incidence (20–55%) [53]. This procedure should be implemented at high-volume centers.

ENDOSCOPIC VS SURGICAL DRAINAGE OF THE PANCREATIC DUCT IN PATIENTS WITH CHRONIC PANCREATITIS

Current Status

Because surgery has been reported to involve a high incidence of complications (18–53%) and high mortality

rate (0–5%) [29] and because patients tend to select noninvasive treatment, surgical pancreatic duct drainage for treatment of relapsing obstructive chronic pancreatitis is often selected for patients who fail to respond to endoscopic treatment. It is indicated for symptomatic cases where pancreatic duct stricture is intense or the presence of large pancreatic stones makes endoscopic treatment difficult. The operative procedure usually used for this purpose is side-to-side pancreatojejunostomy.

Randomized Controlled Trial

In an RCT comparing endoscopic treatment with surgery, the early pain relief effect only slightly differed, but the pain relief effect five years after treatment was smaller in the endoscopic treatment group [9]. In this RCT, endoscopic treatment was not combined with extracorporeal shock wave lithotripsy and patients who received stent replacement were excluded from the analysis.

In other RCTs, the percentage of patients who required additional drainage was higher in the endoscopic treatment group than in the surgery group when rated at the acute and chronic stages after treatment [3,47]. Furthermore, endoscopic treatment was converted to surgery in as many as 47% of all cases in the endoscopic treatment group [47]. The endoscopic treatment success rate in that study was lower than usual, suggesting the possibility of some biases related to the skill level of the endoscopy physician (surgeon factor) or the percentage of treatment difficult cases (patient's factor).

Perspectives for the Future

An RCT comparing extracorporeal shock wave lithotripsy - combined endoscopic treatment (permitting stent renewal) with surgery is desirable. If the outcome differs between these two treatment methods, surgery may be beneficial from the medico-economic point of view.

Chronic pancreatitis can be considered a high-risk factor for pancreatic cancer, but a report suggested that surgery for chronic pancreatitis could reduce the incidence of the complication of pancreatic cancer [47].

CONCLUSIONS

Relapsing pancreatitis is often attributable to impaired pancreatic juice outflow due to pancreatic duct stricture or stones. Thus, endoscopic stenting often succeeds in improving pancreatic juice outflow. In patients that are difficult to treat, it is essential to consider performing surgery at early stages. If symptoms are alleviated, nutrition is also improved, improving patient quality of life. Attention is required to prevent the aggravation of diabetes. Furthermore, considering that alcohol is often a cause for chronic pancreatitis, there may be a vicious cycle of symptom alleviation leading to resumption of drinking, discontinuation of hospital visit, and then critical care unit visit upon relapse of the disease. Therefore, encouraging the patient to stop drinking is also important.

Conflict of Interest

The authors have declared no conflicts of interest.

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