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Endoscopic Treatment of Pain in Chronic Pancreatitis

Indications, Optimal Timing, and Technical Aspects

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Introduction

Chronic pancreatitis (CP) is characterized by progressive inflammation leading to permanent fibrotic changes and subsequent loss of endocrine and exocrine function. The predominant symptom of CP is severe abdominal pain, which can seriously impair quality of life, work productivity, and social functioning [1,2]. The nature and pathogenesis of pain in CP is complex and includes inflammation, changes in the peripheral and central nervous system, and cognitive and psychological aspects. Another important etiological factor is an increased pancreatic ductal pressure, resulting from ductal obstruction due to fibrosis or stones [3,4].

Achieving adequate pain relief is difficult and more than half of the patients continue to suffer from pain 10 years after the onset of symptoms [5]. Pain often leads to chronic use of opiates, which is associated with significant side effects and dependence. Along with medical treatment, ductal decompression is employed to alleviate pain in CP. Usually, a step-up approach is applied, with lifestyle changes and analgesics as first step, endoscopic therapy as second step, and surgical intervention as last resort. In this chapter, a detailed overview is provided with regard to indications, optimal timing, technical aspects, and outcome of endoscopic therapy for CP-associated pain.

Selecting the Right Patient for Endoscopic Therapy: Who and When?

Endoscopic therapy (ET) for CP-associated pain generally aims at either decompression of the pancreatic duct (PD) or inhibition of the afferent pancreatic pain signals. PD drainage can be achieved through sphincterotomy, lithotripsy and stone extraction, and/or dilation or stenting of strictures. However, technically successful ductal decompression does not always translate to clinical improvement, which implies the involvement of other pathogenic factors of CP-associated pain, and underscores the complex nature of the pain syndrome in these patients. A careful selection of patients that qualify for ET is therefore of major importance.

Factors Predictive of Clinical Success

Patients with CP who are most likely to benefit from endoscopic drainage have an obstructive stone in the head of the pancreas in the absence of a main pancreatic duct (MPD) stricture. Additional factors predictive of clinical success are short disease duration, non-severe pain, and absence or cessation of cigarette smoking and alcohol use [6]. Imaging modalities such as high-resolution computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasonography (EUS) can be used to establish the presence and extent of MPD dilation and obstructive stones. These techniques provide a detailed image of the ductal system, with important information on the location and extension of stricture(s), location and size of stones, and anatomical variations such as pancreas divisum. Secretin is used in secretin-enhanced MRCP (s-MRCP) or EUS (s-EUS) to stimulate the pancreas to exert its exocrine function, thereby increasing fluid secretion and causing transient ductal dilation. This technique can delineate the upstream anatomy of the MPD and the length of the strictures more clearly, and may help to identify strictures or obstructions that would have been missed without secretin stimulation. In patients with pancreas divisum, a dilated MPD after secretin administration is predictive of a beneficial effect from endoscopic therapy [7], but no such relation has been established for other CP patients. In severe CP, the MPD

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becomes rigid, rendering its response to secretin less pronounced as compared to patients without CP [8,9].

Optimal Timing and Treatment Choice

The management of pain in CP patients starts with lifestyle education. Patients should be counseled to quit drinking alcohol and stop smoking. Opioids are frequently used in the treatment of painful CP, but caution is advised since long-term use can be harmful and counterproductive as they may induce hypersensitivity to pain stimuli [10]. Also, patients are at risk for developing opioid dependency. Estimating the optimal timing for an intervention in CP, either endoscopically or surgically, is challenging. The guideline of the European Society of Gastrointestinal Endoscopy (ESGE) recommends ET and/or extracorporeal shock-wave lithotripsy (ESWL) as first-line therapy for patients with uncomplicated painful CP with an obstructed stone in the head or body of the pancreas. When ET and/or ESWL fails to improve pain, medical treatment with analgesics is recommended. Surgery should be considered in patients who fail to improve six to eight weeks after ET or in case of technical failure [11]. In contrast to the ESGE guideline, in the United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU), the timing of ET is positioned after failure of analgesics [6].

With regard to the choice between endoscopic and surgical drainage, data from retrospective studies suggest that surgery results in better outcomes of pain relief and endocrine pancreatic function. Furthermore, improved pain relief can be achieved in patients who do not use opioids prior to surgery and had less than five endoscopic treatment procedures preoperatively [12]. In a prospective randomized controlled trial comparing endoscopic and surgical PD drainage in patients with severe CP, surgical treatment was associated with higher rates of complete or partial pain relief, as compared to ET (75% vs. 32%) [13]. The long-term outcome after seven years showed persistent superiority of surgery with regard to pain relief (80% vs. 38%), and the need of additional drainage procedures after initial PD decompression. Nine patients (47%) who initially underwent endoscopic drainage had to undergo surgery due failure of endoscopic drainage [14]. Although this study evidently showed that endoscopic drainage is inferior to surgery, these results cannot be extrapolated to all CP patients as only those with advanced disease were included (with a combination of large/multiple stones and strictures), most of them being opioid-dependent.

There is evidence that ductal decompression at an early disease stage may prevent loss of pancreatic function and irreversible damage. Studies have shown that a short disease duration prior to ET is a predictive factor for long-term pain relief [15–17]. Besides, there is evidence that pancreatic insufficiency develops early in the disease course of obstructive pancreatitis, with permanent insufficiency developing after several weeks [18]. Therefore the Dutch Pancreatitis Study Group has conducted the ESCAPE trial, a randomized controlled trial comparing early surgery to a step-up approach in patients with non-opioid-dependent CP, with the Izbicki pain score as primary outcome. It revealed that early surgery resulted in a larger decrease in Izbicki pain score (−26 vs. −16; $P = 0.04$). However, in a substantial number of endoscopically treated patients, there were protocol deviations rendering endotherapy not up to current standard. Furthermore, at the time of the trial direct panceatoscopy with electrohydraulic lithotripsy (EHL) was not part of the treatment armentarium [19]. Overall, it is still feasible that ET is particularly beneficial for early CP with less complex pathology, but this needs further investigation.

It is important to note that ET and surgery should be seen as complementary rather than competing treatments. Some patients, for example those with an enlarged pancreatic head, are better candidates for surgery, requiring a head resection rather than ductal drainage only. If pain relief after ET is not satisfactory, surgery should be considered as the next treatment step in order to prevent disease progression and improve long-term quality of life, and possibly better preservation of pancreatic function [20].

Treatment of Pancreatic Duct Stones

Obstruction of the PD can be caused by strictures, intraductal stones or, in the majority of cases, by a combination of both. As pancreatic stones are usually hard and impacted in the PD, ET is often challenging, especially when combined with ductal strictures.

Extracorporeal Shock-wave Lithotripsy

Technical Aspects

ESWL is the current cornerstone of treatment of stone-predominant symptomatic CP. Although small stones (<5 mm) can usually be extracted during endoscopic retrograde cholangiopancreatography (ERCP) with a basket or balloon after pancreatic sphincterotomy, the majority of the stones are large, hard, and impacted, requiring fragmentation prior to endoscopic removal [21]. The clinical guideline of the ESGE recommends ESWL as first step, immediately followed by endoscopic extraction of stone fragments, as treatment for patients with uncomplicated painful CP and stones of 5 mm or larger obstructing the PD [11].

ESWL of pancreatic stones requires careful targeting of the stone with specialized equipment that consists of a strong electromagnetic lithotripter and a fluoroscopic targeting system. Therefore, the procedure is often only executed in expert centers. The procedure is usually performed under general anesthesia or deep conscious sedation as treatment is lengthy (on average one to two hours) and can be painful. Multiple sessions are often required to complete fragmentation and are usually carried out within a few days, during which time the patient remains admitted to the hospital.

After ESWL, ET is performed to extract fragmented stones and to evaluate the presence of MPD strictures [21]. ESWL without subsequent ERCP may be indicated in patients with small radiopaque stones located in the head of the pancreas, and absence of MPD strictures [6,11]. In case a pancreatic stone is not clearly visible on X-ray, endoscopic pancreatic sphincterotomy may be required prior to ESWL for deployment of an endoprosthesis to facilitate targeting during ESWL. Other indications for endoprosthesis placement prior to or between ESWL treatment sessions are to facilitate pancreatic drainage and to prevent impaction of fragmented stones. ESWL is contraindicated in patients with coagulation disorders or pacemakers or defibrillators, pregnant women, and when calcified aneurysms are in the shock-wave path.

Effectiveness and Safety

Two large meta-analyses have shown that ESWL is an effective technique for clearance of the MPD and to decrease CP-related abdominal pain [22,23]. Successful fragmentation of pancreatic stones is reported in 37.5–100% and generally requires one to four sessions [22,23]. Successful fragmentation is more often achieved in the case of a solitary stone in the absence of MPD stricture [24–26]. According to the most recent meta-analysis, complete ductal clearance is achieved in 71% of patients, and partial clearance in 22% [23]. Pain relapse occurs more frequently in patients without complete stone removal and/or with a MPD stricture [26,27]. Furthermore, in patients with a pain relapse, approximately 40% have stone recurrence [28].

ESWL is a relatively safe procedure, with pancreatitis being the most common complication, occurring in 4% [23].

Pancreatoscopy-guided Lithotripsy

Technical Aspects

Peroral pancreatoscopy (POP) with lithotripsy of PD stones is a relatively new technique in which calculi are fragmented under direct endoscopic visualization. The first therapeutic POP was described by Howell in 1999, who performed EHL under direct vision using the mother–baby technique [29]. However, wide clinical acceptance was not achieved, as the technique was hampered by the need for two operators to control the two scopes simultaneously, and cumbersome fragility of the baby scope with high repair costs and poor maneuverability. The introduction of a digital single-operator cholangiopancreatoscope in 2007 (SpyGlass Legacy, Boston Scientific, Natick, MA, USA) has overcome these limitations. Although the image quality of the first system with a fiberoptic probe was moderate, its upgrade to a single-operator video cholangioscope (SpyGlass DS, Boston Scientific) in 2015 resulted in higher resolution imaging with a wider view. The current system consists of a disposable 10-Fr delivery catheter with fourway deflection capabilities, and dedicated separate irrigation and succinate channels. The scope has a large accessory channel (1.2 mm) through which a guidewire, biopsy forceps, or electrohydraulic or laser lithotripsy device can be introduced.

Intraductal lithotripsy can be achieved by EHL or laser lithotripsy (LL). With EHL, shock-wave pulses are generated via a bipolar probe in aqueous medium. Fragmentation of nearby stones is achieved by absorption of these high-frequency hydraulic shock waves. To prevent damage to the ductal wall or perforation, direct visualization is necessary to position the probe close to the stone and away from the wall (Figure 37.1).

In LL, laser light at a particular wavelength is aimed directly at the stone to induce fragmentation. There are currently two systems available. First, the neodymium:yttrium–aluminum–garnet (Nd:YAG) laser system fragments stones by formation of plasma on the surface of the stone. The infrared light energy is then absorbed, which produces a forceful shock wave. The holmium:YAG laser system directly transmits light energy from the laser to the stone and surrounding fluids. With its longer wavelength, a direct flash on the surface of the stone results in fragmentation. Fragments are then removed by a

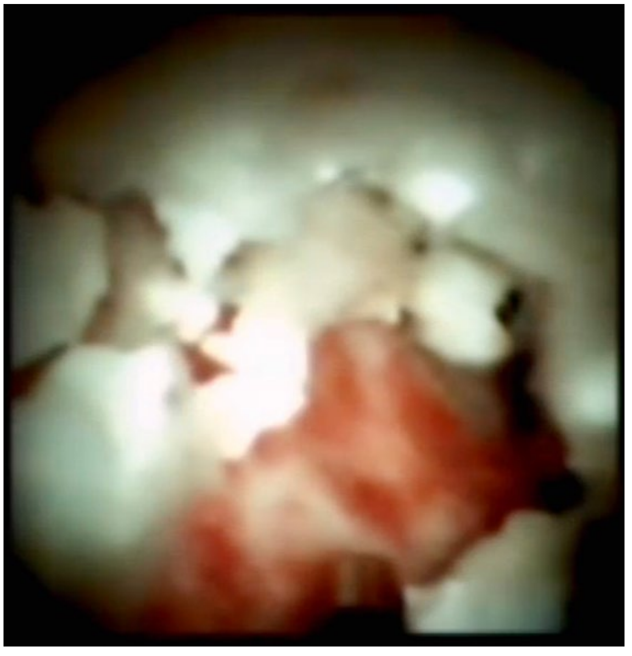

Figure 37.1 Fragmentation of an intraductal stone in the PD using EHL. *Source:* courtesy of P.M.C. Stassen, P.J.F. de Jonge, J.W. Poley, D.L. Cahen, and M.J. Bruno.

vapor bubble that is created by water absorption of the laser energy.

Effectiveness and Safety

Pancreatoscopy with intraductal lithotripsy is currently considered second-line therapy for MPD stones, after unsuccessful ESWL and ERCP. Although mainly from retrospective data, the literature shows promising results for stone removal in patients with calcified CP. Success rates for ductal clearance range between 43 and 100%, which is comparable to ESWL [30–32]. Higher success rates seem to be obtained for stones located in the head or the neck of the pancreas [31,33]. Also, clinical success, defined as pain reduction, less opiate usage and/or reduced hospitalizations, is achieved in 74–95% of patients [31–34]. To date, no prospective study has evaluated the differences in efficiency or safety of EHL and LL.

Adverse event rates for pancreatoscopy vary between 0 and 13.5% [30], again with pancreatitis as most common complication [32,33].

Figure 37.2 Pancreatic stricture in the head of the pancreas without outflow of contrast medium into the duodenum. *Source:* courtesy of P.M.C. Stassen, P.J.F. de Jonge, J.W. Poley, D.L. Cahen, and M.J. Bruno.

Treatment of Pancreatic Duct Strictures

PD strictures can be single or multiple and are classified as dominant or nondominant. The definition of a dominant PD stricture, as defined by the HaPanEU guideline, is a stricture in the head of the pancreas with an upstream MPD dilatation of 6 mm or more in diameter or a stricture that prevents outflow of contrast into the duodenum (Figure 37.2). Treatment of a dominant stricture, usually consisting of both stricture dilation and stenting, should be considered if it is located in the head and associated with pain [6].

Technical Aspects

To provide good access to the PD, a selective pancreatic sphincterotomy should be performed. A sphincterotomy can be performed using the pull-sphincterotomy or needle-knife technique over a stent that was placed at a previous occasion. It is important to note that the sphincterotomy should be large enough to allow insertion of instruments and to prevent post-sphincterotomy stenosis. In patients with CP, cannulation of the PD can be difficult due to active inflammation and accompanying edema of the papilla. The majority of the strictures can be passed with a regular guidewire, but sometimes a thinner guidewire may be required to enable dilation with a balloon or graduated dilating catheter. For very tight strictures that cannot be passed with a dilation balloon catheter, a Soehendra dilating catheter can be advanced (screwed) through the stricture over a nonmetallic guidewire.

After cannulation and, if needed dilation, a stent can be placed. For pancreatic drainage, different stents are available. The choice of stent depends on the stricture diameter and location and shape and diameter of the MPD. The diameter of plastic stents ranges from 3 to 11.5 Fr. Small-diameter stents are associated with risk of occlusion and pain relapse. Therefore, the stent diameter should be as large as possible, or multiple smaller-sized stents may be inserted side by side. The ESGE guideline recommends inserting a single 10-Fr plastic stent [11]. In the pancreas, straight polyethylene stents are most widely used, with S-shaped or wing-shaped stents as alternatives, as they have a lower migration risk [35–37].

Also, fully covered self-expandable metal stents (FC-SEMS) have been successfully deployed across pancreatic strictures, in particular in patients with a refractory MPD stricture [38]. Compared to plastic stents, they provide a larger maximum radial force and have a longer patency, which may result in more effective stricture dilation. A drawback is the risk of migration, in particular proximal into the MPD [39]. The use of biodegradable self-expandable stents has been reported to overcome this issue, but they are not yet routinely used in clinical practice [40].

The optimal duration of stent therapy remains a matter of debate. Some studies have suggested that prolonged stent therapy leads to intraductal damage and tailoring and limiting the duration of stent therapy could overcome this [41–44]. On the other hand, prolonged stent therapy might have the advantage of improving stricture dilation and thereby reduce the risk of pain recurrence.

Stent exchanges may be performed in case of symptoms ("on demand") or at regular intervals. The HaPanEu guideline recommends that stent exchange should be performed within one year for single plastic stents, even if the patient is asymptomatic. For refractory strictures (i.e. persistent symptomatic strictures after one year of stenting), they recommend placement of multiple stents [6]. A more aggressive approach is also being used, with stent exchanges every few months, to increase the number of stents up to the limit the PD can accommodate. The advantage of stent exchanges on a regular basis is prevention of pain relapse due to stent clogging [45,46], and frequent evaluation of stricture resolution. Thereby, treatment duration may be shortened when stenting is terminated as soon as the stricture has resolved, but this protocol has not been proven to be as effective as a fixed one-year stenting protocol. Criteria used during ERCP for stent removal are adequate outflow of contrast medium one to two minutes after ductal filling upstream from stricture, and easy passage of a 6-Fr catheter [6].

In our practice, we favor exchanging stents on a regular basis (i.e. every three months), and insert an increasing number of stents with each consecutive procedure to further dilate the stricture, analogous to the treatment of benign biliary strictures.

Effectiveness and Safety

Long-term clinical results after insertion of a single PD stent have been reported by several retrospective studies. Pain improvement was reportedly achieved in 52–94% of the patients after a mean follow-up ranging from 12 to 60 months [47–52]. One study observed excellent outcomes of multiple plastic stent insertion, with persistent pain relief in 84% after a mean follow-up of 38 months and only approximately 10% stricture recurrence [53]. After placement of a FC-SEMS, the clinical success rate, defined as more than 50% pain resolution, was reported to be 83%. Stricture resolution rates ranged between 83 and 93%, a median of seven months after stent removal [54,55]. Unfortunately, longer-term follow-up data are not available.

Complications associated with PD stenting include stent occlusion and migration, postprocedural abdominal pain, acute pancreatitis, and cholangitis [48,55].

EUS-guided Pancreaticogastrostomy

Technical Aspects

In cases where the PD is inaccessible through the major or minor papilla due to obstruction or rupture of the PD or surgically altered anatomy, access can be obtained by puncturing the PD under EUS guidance. First, the optimal access site is selected, with the smallest distance between the stomach and the PD, and without interposed vessels, taking into account the direction of the PD and fluoroscopic view. A fine-needle aspiration (FNA) needle is then used to access the PD, through which a guidewire is advanced (Figure 37.3). Fluoroscopic imaging is used to ensure maintenance of access and an adequate scope position. Subsequently, two drainage techniques are available. First, the rendezvous (retrograde) technique, in which the PD is punctured using a curvilinear array echoendoscope and a guidewire is maneuvered past the stricture and/or stone deep into the duodenum. The echoendoscope is changed for a duodenoscope whilst leaving the guidewire in place. Using the duodenoscope, the wire in the duodenum can be retrieved for a rendezvous procedure and a plastic stent is placed into the PD, in retrograde, via the papilla. With the antegrade technique (direct drainage), scopes are not exchanged and the echoendoscope is used to place a plastic stent in the PD through the gastrointestinal tract wall, either across the obstruction or not (Figure 37.4). For this technique it is obligatory to dilate the tract in order to pass the stent [56].

Figure 37.3 EUS-guided pancreaticogastrostomy: FNA needle puncturing the dilated PD. *Source:* courtesy of P.M.C. Stassen, P.J.F. de Jonge, J.W. Poley, D.L. Cahen, and M.J. Bruno.

Effectiveness and Safety

A recent meta-analysis reported a technical success rate of 77% among 222 reported patients [57]. In the largest retrospective series to date, clinical success was achieved in 23 of 32 patients (72%) in whom a stent was successfully placed, 16 complete and seven partial [58]. A similar clinical success rate was found in an earlier retrospective study, where 13 of 18 patients in whom successful PD drainage was achieved had long-term symptom relief after a median follow-up of 37 months [59]. It is important to note that most studies were not confined to CP patients, but also included patients with anastomotic strictures, malignant strictures, or a disconnected PD for example. However, some studies did report an improved pain score specific for CP patients [60,61].

Figure 37.4 Antegrade technique: plastic stent placement in the PD through the gastrointestinal tract wall. *Source:* courtesy of P.M.C. Stassen, P.J.F. de Jonge, J.W. Poley, D.L. Cahen, and M.J. Bruno.

Complications associated with this technique occurred in 19% of the patients according to the same meta-analysis and included abdominal pain, pancreatitis, bleeding, perforation, and peripancreatic abscess [57].

Celiac Plexus Block

EUS-guided celiac plexus block (CPB) should be saved for patients who do not respond to other forms of treatment for CP-related pain. It is aimed at inhibition of the afferent neurotransmission of pancreatic pain signals.

Technical Aspects

Using EUS, the celiac plexus can be easily identified and accessed. Local anesthetics (bupivacaine) are injected into the celiac plexus, together with a corticosteroid (triamcinolone). In contrast, celiac plexus neurolysis for pain resolution in pancreatic cancer involves injection of ethanol, and should not be used for benign pancreatic disease since neurolysis can cause adhesions and thereby make surgery difficult or even impossible. Direct injection of bupivacaine and triamcinolone results in enlargement of the ganglia and is typically associated with an immediate (but short-lived) onset of pain, which can manifest itself as an abrupt increase in patient movement, attempted verbalization, or an altered pulse and/or respiration rate, even in patients under general anesthesia, which resolves within seconds.

Effectiveness and Safety

Clinical success of CPB is less than for other types of pain treatment in CP. A meta-analysis found a pooled success rate of pain relief in 60% of the patients, with a median follow-up ranging from seven days to 15 weeks [62]. Unfortunately, pain relief and decreased use of opioids are short-lived. Santosh et al. [63] reported that only 10% of patients had pain relief for more than 24 weeks. Adverse events related to CPB are transient worsening of abdominal pain, diarrhea, and hypotension. This is mainly due to parasympathetic activation and occurs in approximately 40% of the patients [64].

Summary

Endoscopic treatment of pain in patients with CP is aimed at either decompression of the PD, by means of stone removal or stricture dilation, or at blocking the afferent pancreatic pain signals by EUS-guided CPB. First-line treatment for obstructing PD stones of more than 5 mm is ESWL. More recently, POP with EHL or LL has been introduced as an alternative endoscopic technique to fragment PD stones. For PD strictures, insertion of a single plastic stent is recommended. The optimal duration of stent therapy is unclear and should be based on clinical effect and the occurrence of complications. Alternatives for placement of a single plastic stent, in an attempt to improve stricture dilation, is employment of a progressive plastic stenting protocol or placement of a temporary FC-SEMS. EUS-guided pancreaticogastrostomy or rendezvous techniques provide an alternative technique for obtaining access to the PD in case of inaccessibility via ERCP. However, these are challenging procedures but with reasonably good clinical success rates when technically successful. Finally, EUS-guided CPB is a last resort option, but its effects are short-lived. The decision for and timing of ET in relation to surgical treatment options is challenging and should be reached by multidisciplinary team discussion.

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