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Surgical and Endoscopic Treatment of Pain in Chronic Pancreatitis: A Multidisciplinary Update

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Abstract
Chronic pancreatitis is an inflammatory disease of the pancreas with abdominal pain as the most prominent symptom. Adequate treatment of patients with chronic pancreatitis remains a major challenge, mainly because of the lack of evidence-based treatment protocols. The primary goal of treatment is to achieve long-term pain relief, control of the complications associated with the disease, and to restore the quality of life. Currently, a conservative step-up approach is often used for the treatment of pain; progression to severe and intractable pain is considered necessary before invasive treatment is considered. Recent studies, however, suggest that surgical intervention should not be considered only as last-resort treatment, since it can mitigate disease progression, achieve excellent pain control, and preserve pancreatic function. In this review, we present a state-of-the art overview of endoscopic and surgical treatment options for patients with painful chronic pancreatitis, and elaborate on the timing of surgery.

Introduction

Chronic pancreatitis (CP) is an inflammatory disease of the pancreas. The most prominent symptom is abdominal pain, which often leads to recurrent hospitalizations, absence from work, multiple interventions, and opioid addiction. The pain in CP is intense, recurrent, and long lasting, with a major impact on the quality of life and social functioning of patients [1, 2]. Ten years after onset of the disease, more than half of the patients are still suffering from pain [3]. The ongoing inflammation often leads to fibrosis and pancreatic function loss. Within 5 years, 50% of the patients become endocrine insufficient and 80% exocrine insufficient [4, 5]. CP patients have a 3.6-fold increased mortality rate compared with the general population [6].

The most frequent cause of CP is alcohol toxicity. In addition, a genetic predisposition, use of certain types of medication, anatomic abnormalities, and autoimmunity can play a role [7]. The pathogenesis of pain in CP is incompletely understood and is likely multifactorial. In patients with an outflow obstruction of the pancreatic duct (PD) due to strictures, calculi or both, it is hypothesized that pain arises from increased ductal and parenchymal pressure [8–11]. The observation that endoscopic or sur-

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gical treatment of the PD obstruction relieves pain supports this hypothesis [12, 13]. In addition, several other causes of pain have been suggested, such as ongoing inflammation, local complications (e.g. bile duct and duodenal stenosis), and alterations in pancreatic nerves, including an increase in nerve fibers and neurogenic inflammation [14–16].

Adequate treatment of pain in CP remains a major challenge because evidence-based treatment protocols are lacking. Treatment of pain in CP consists of medical, endoscopic, and surgical therapy. While some patients can be managed conservatively, endoscopic and surgical procedures are inevitable in cases with intractable pain and specific morphological abnormalities. To select the optimal treatment for the individual CP patient, one should consider the presence of ductal dilatation, the localization of the disease (i.e. head or tail), the presence of an enlarged pancreatic head, and other local complications (e.g. common bile duct stenosis, splenic vein thrombosis, portal hypertension, duodenal stenosis, and pseudocysts).

At present, conservative management is always the first step, even in patients with clear morphological changes. Longitudinal studies show that of all CP patients, 40–75% will require surgery in the course of the disease [1, 4, 17]. Progression to severe and intractable pain is considered necessary before invasive treatment is considered [18]. This approach can be questioned because evidence suggests that early intervention can mitigate the disease progression, achieve pain control, and preserve pancreatic function. The timing of surgery remains an important dilemma, as conclusive evidence is lacking [19–21]. In this review, we will discuss the endoscopic and surgical treatment options for patients with painful CP, in particular drainage of the PD (ductal decompression) and the timing of surgery.

Endoscopic Therapy

The aim of endoscopic therapy in patients with CP is to provide adequate drainage of the PD by decompression of the duct and restoring outflow of pancreatic juice. This may lower intraductal pressure and thereby reduce pain. This can be achieved by means of extracorporeal shock wave lithotripsy (ESWL) or endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and stone extraction and/or dilatation of PD strictures and temporarily stent insertion. Studies suggest that endoscopic therapy for PD pathology in patients with symptomatic CP is effective, technically feasible, and has an acceptable complication rate [22]. However, data on endoscopic treatment of CP are often difficult to interpret because of heterogeneous study populations, with different morphological problems (e.g. stones, strictures, and pseudocysts) and treatment combinations (e.g. ESWL, stone extraction, stricture dilation, sphincterotomy, and stent insertion).

PD Stones

Intraductal stones are found in 32–90% of patients presenting with CP irrespective of the underlying etiology and cause outflow obstruction and dilation of the PD [23–25]. It is thought that because the pancreatic parenchyma is non-compliant, the obstruction will lead to a rise in the intraductal pressure, which in turn can induce tissue hypertension and ischemia, and may be a major factor causing pain in patients with CP [26].

Extracorporeal Shock Wave Lithotripsy

Successful removal of PD stones depends on the density, number, and location of the stones, as well as on the presence of associated ductal strictures or pseudocysts. Endoscopic removal of pancreatic stones can be difficult, mainly because pancreatic stones tend to be multiple and hard, and because they are usually stuck or impacted behind strictures [24]. Since 1976, extraction of PD stones is attempted through endoscopic pancreatic sphincterotomy and transpapillary stone extraction. But this is usually limited to small intraductal stones (<10 mm), ≤3 stones, confined to the head and/or body of the pancreas, and without an upstream stricture or impacted stones [27]. Endoscopic attempts at PD stone extraction without prior stone fragmentation have yielded unsatisfactory results [22]. For larger stones (>5–7 mm), some form of lithotripsy is therefore mandatory [24].

ESWL was first reported in 1987 to facilitate endoscopic extraction of PD stones in 8 patients [28]. In ESWL, several hundred to several thousand focused shock waves result in the gradual disintegration of the stones. ESWL is contraindicated in patients with coagulation disorders, pacemakers or defibrillators, in pregnant women, and when calcified aneurysms, lung tissue, or bone structures are in the shock wave path [29]. Complications are rare and the reported morbidity varies between 5 and 10% (most frequently acute pancreatitis). Other possible complications are hematuria, subcapsular hematoma of the liver, and lower back pain [30, 31]. Mortality rates are ex-

Table 1. Results of endoscopy and ESWL for pancreatic stones in series of >20 patients

First author	Year	Patients n	Mean follow-up months	Complete or partial pain relief %	Overall morbidity %	Late mortality %	Need for surgery %	Exocrine/endocrine function improved %	ESWL %	Fragmentation %	Complete clearance %
Delhaye [35]	1992	123	14	85	23	1.7	8	55/10	99	99	59
Sauerbruch [43]	1992	24	24	83	NR	NR	8	NR	100	87.5	42
Schneider [44]	1994	50	20	62	14	4	12	NR	100	86	60
Johanns [40]	1996	35	23	83	23	NR	14	NR	100	100	46
Ohara [42]	1996	32	44	86	25	NR	3	61/17	100	100	75
Dumonceau [46]	1996	70	24	50	13	NR	6	0/0	59	100	50
Costamagna [39]	1997	35	27	72	23	3	3	NR	100	100	74
Adamek [37]	1999	80	40	76	17.5	6	10	47/0	54	54	NR
Brand [32]	2000	48	7	82	10.5	0	4	77/15	100	60	44
Kozarek [41]	2002	40	29	80	20	10	20	NR	100	100	NR
Farnbacher [30]	2002	114	29	48	NR	7.8	13	NR	82	82	39
Rosch [25]	2002	1,018	59	69	13	12.2	24	51/8	26	NR	NR
Inui [31]	2005	555	44	91	6.3	3.2	4	38/24	92	92	73
Tadenuma [38]	2005	117	77	70	8.5	11.5	1.4	NR	100	97	56
Ong [149]	2006	250	NR	NR	6.8	NR	NR	NR	66	NR	60
Tandan [34]	2010	1,006	6	84	15	NR	3.8	NR	100	93	76
Seven [45]	2012	120	52	85	NR	17.6	16	NR	100	NR	NR

NR = Not reported.

tremely low; only two studies have reported mortality thus far. One case of fatal cholangitis was reported in a large retrospective Japanese multicenter survey of 555 patients who underwent ESWL [31]. Furthermore, in a prospective randomized controlled trial comparing endoscopic and surgical drainage, one death was reported that may have been related to ESWL, because the patient died of a perforated duodenal ulcer 4 days after ESWL [12].

Technical Results

Table 1 lists the outcomes of all reported series of >20 patients. Successful stone fragmentation following ESWL has been defined as stones broken into fragments ≤2 or 3 mm [32–34], or by the demonstration of a decreased stone density at X-ray, an increased stone surface, and a heterogeneity of the stone which may fill the main PD and adjacent side branches [22, 35]. Stone fragmentation is achieved in about 90% of cases. In a recent systematic review of a total of 1,149 patients in 11 studies, the success of stone fragmentation by ESWL was 89% [36]. Moreover, recently, a large prospective study reported a stone fragmentation rate of 93% [34], but in this study patients with isolated pancreatic tail calculi, extensive calculi in the head, body and tail, and multiple PD strictures were excluded. Lower fragmentation (54–60%) rates are also reported [32, 37]. Brand et al. [32] report a fragmentation rate of 60% and accomplished a complete stone clearance of 44% by as many as a median of 13 (range 2–74) ESWL sessions. Others have reported a mean of 5 sessions to achieve complete fragmentation [31]. A possible explanation of the lower success rates in some studies could be that more patients had multiple and/or large stones, a PD with multiple strictures, and that a lower setting of the shock wave level was used. Notably, ESWL of pancreatic stones requires considerable experience and specialized equipment. In the larger studies (>100 patients), the fragmentation rate is near 90% [31, 34, 35, 38].

Complete stone clearance rates vary between 39 and 76%, but complete stone clearance is probably not always required for symptom relief [25, 30–32, 35, 37–45]. Dumonceau et al. [46] reported a significant association between immediate disappearance of pain and complete or partial PD clearance. The independent predictors of long-term pain relapse in this study were a high frequency of pain attacks before treatment, a long duration of disease before treatment, and the presence of a non-papillary stenosis of the main PD [46].

Clinical Results

A meta-analysis including a total of 588 patients from 17 studies concluded that ESWL effectively relieves main PD obstruction and alleviates pain in chronic calcifying

pancreatitis, most often in combination with endoscopic therapy. The mean effect size (weighted correlation coefficient) was 0.62 for pain and 0.74 for duct clearance [47]. A complete or partial pain relief of 48–91% has been found in patients who underwent ESWL and endoscopy during a follow-up ranging from 6 to 77 months [30–32, 34, 35, 37–46]. Usually, an immediate relief of pain is associated with successful decompression of the main PD (as suggested by decrease in its diameter or stone clearance) [32, 35, 43, 46]. Whether ESWL should be preceded or followed by endoscopic therapy is debatable. Successful spontaneous passage rates between 56 and 75% of the residual fragmented stones have been reported [31, 38, 42]. Some institutes prefer to perform sphincterotomy prior to ESWL to facilitate stone passage [29].

In 2007, Dumonceau et al. [33] performed a randomized trial comparing ESWL monotherapy (n = 26) with ESWL and endoscopic drainage (n = 29) in patients with uncomplicated painful CP and calcifications obstructing the main PD. These patients had at least one calcification of ≥4 mm in the pancreatic head or body with upstream dilation of the main PD and no previous intervention on the pancreas. After 2 years, 38% of the ESWL-only and 45% of the ESWL-plus-endoscopy group had experienced pain relapse (OR 0.77; 95% CI 0.23–2.57). Also, PD diameter and number of pain episodes/year are reduced with ESWL only compared with ESWL plus endoscopy. In addition, costs were 3 times higher using ESWL plus endoscopy, as compared to ESWL alone. Therefore, the authors conclude that systematically combining ESWL with endoscopy adds to the cost of patient care without improving pain outcome. However, it is important to note that only 42% in the ESWL-only group and 69% in the ESWL-plus-endoscopy group had pain at the time of inclusion. Moreover, 73 and 83% of the obstructive calcifications were in the pancreatic head and these results are therefore only applicable to a subgroup of patients with CP.

It has been suggested that early ductal decompression of the main PD may help prevent further fibrosis, and thereby prevent pancreatic insufficiency. Moreover, it may improve or mitigate pancreatic function in patients who have already developed pancreatic insufficiency [29]. Several studies have shown that pancreatic exocrine function improved after endoscopic treatment, while endocrine function remained largely unaffected [31, 32, 35, 42]. On the contrary, Maartense et al. [48] showed that surgery for CP did not influence the exocrine pancreatic function after either drainage or resection procedure. Clinical endocrine function was not affected after resection procedure but improved after drainage procedure [48].

The clinical guideline of the European Society of Gastrointestinal Endoscopy (ESGE) recommends ESWL as a first step, immediately followed by endoscopic extraction of stone fragments, as a treatment for patients with uncomplicated painful CP and stones ≥5 mm obstructing the PD [22].

PD Strictures

Benign strictures of the main PD are generally due to inflammation or fibrosis and may contribute to pain, bouts of acute pancreatitis, and exocrine insufficiency. About one third of the strictures appear in combination with calcifications. In a large retrospective multicenter cohort study of >1,000 patients treated endoscopically for CP strictures and stones in the pancreatic head and body, 47% of the patients were identified with strictures, 18% with stones, and 32% with stones and strictures [25].

PD strictures can be single or multiple and are classified as dominant or non-dominant. Dominant strictures are strictures with an upstream PD dilatation ≥6 mm or strictures that prevent the outflow of contrast medium. Treatment of a dominant stricture is technically successful if at least one stent is inserted across the stricture; dilatation alone is not sufficient [22]. The goal of pancreatic stenting is to adequately dilate the stricture for good drainage and flow from the PD after the stent is removed. Because of the lack of comparative prospective studies, evidence-based guidelines for the treatment of main PD strictures do not exist regarding sphincterotomy, dilatation, stenting, or the duration of treatment. Despite this lack of evidence, pancreatic sphincterotomy is usually performed to facilitate endoscopic therapy of the PD, with a reported serious complication rate of 4% (e.g. bleeding, pancreatitis, and retroduodenal perforation) [49]. Biliary sphincterotomy to avoid possible cholestasis and infection due to edema after pancreatic sphincterotomy should not be performed routinely. Only in selected cases (i.e. cholangitis, jaundice, a dilated common bile duct with elevated alkaline phosphatases, or in a difficult access to the PD) biliary sphincterotomy is advised, based on the results of a randomized controlled trial by Kim et al. [50].

PD Stenting

After PD cannulation, a guidewire is maneuvered across the stricture. The ESGE recommends inserting a

single (10-Fr) plastic stent, with stent exchange planned within 12 months. Only when stricture persists after 12 months of single plastic stenting, multiple stenting or surgery are suggested as treatment options by the ESGE [22], but firm evidence for the recommended sequence and timeframe is lacking. Stenting for a short period (6 months) has shown poor results, despite repeated balloon dilatation of the stricture [51]; therefore, stenting is performed for longer periods. The choice of stent is influenced by the stricture severity, its location, and the size of the PD. Pancreatic stenting is technically successful in 85–98%, has a short-term pain relief of 65–95% and a long-term pain relief of 52–90% during a follow-up of 14–69 months [12, 51–59]. The timing of pancreatic stent exchange is variable in practice: routine exchange every 6–12 weeks prior to stent occlusion versus on-demand exchange based on recurrence of symptoms. Criteria used during ERCP for terminating PD stenting are adequate outflow of contrast medium 1–2 min after ductal filling upstream from the stricture location after stent removal, and easy passage of a 6-Fr catheter through the stricture location [52, 54, 57]. Costamagna et al. [60] investigated multiple pancreatic stenting for PD strictures. In this prospective study, 19 patients with a dominant refractory PD stricture in the pancreatic head, an upstream PD dilatation, and previous single stent treatment of the PD for symptomatic CP for at least 3 months participated. A median of 3 simultaneous stents had been inserted (8.5–11.5 Fr) for a mean period of 7 (range 5–11) months per stent. After a mean follow-up of 38 months after stent removal 84% of the patients were asymptomatic, with 10.5% stricture recurrence and 5.5% persistent stricture. No major complications were reported [60]. An advantage of multiple stents is the more rigorous dilatation of the PD stricture with the prospect of a more durable result after stent removal. However, these promising results should be confirmed by larger, preferably randomized controlled studies.

In this setting, self-expendable metal stents have also been tested for the treatment of PD strictures, but because of the frequent stent dysfunction due to tissue in-growth, especially in uncovered stents, the results were unsatisfactory. Temporarily, placement of fully covered stents seems to be safe and relieve the pain symptoms, but these data are from preliminary studies with short-term follow-up [61, 62].

Complications of PD stenting include stent occlusion, pain, acute pancreatitis, bleeding, stent migration, duodenal erosions, ductal perforation, stone formation, ductal and parenchymal changes, bowel perforation, cholangitis, and guidewire fracture requiring surgical removal of the broken fragment. Fatalities from sepsis and pancreatitis have been reported [51, 53, 57, 63, 64]. Stent occlusion rates vary greatly, probably due to the caliber of stents used. In a study by Sauer et al. [65], patients with stents ≤8.5 Fr were 3 times more likely to be hospitalized for abdominal pain than those with 10-Fr stents. Protein adherence to the stent seems to play a central role in stent occlusion [66, 67]. Dilation and narrowing of the main PD and side branches are associated with use of pancreatic stents. These pathologic changes are observed in 18–80%, in which a proportion is reversible, in both animal models and humans studies [56, 67–70].

The ESGE recommends ESWL/ERCP as the first-line interventional option for patients with uncomplicated CP. They advise that after a period of 6–8 weeks of treatment, the clinical response should be evaluated and when unsatisfactory, surgical options should be considered [22]. For the treatment choice, the success rate should be weighed carefully against the number of procedures to accomplish and maintain this success rate and the risk of complications associated with these procedures.

Surgical Therapy

The most common indication for surgery for CP is intractable pain. Traditionally, a long period of medical pain management and multiple endoscopic interventions precede surgery. Recently, an expert center published their results of a large cohort of patients with CP who underwent surgery for CP. After a median period of 40 months (10–90th percentile; 12–132 months) after start of pain complaints and after a median of 2 (range 0–29) endoscopic procedures, patients were referred for surgery [21]. Other indications for surgery are a suspicion of neoplasm and local complications of adjacent organs, such as duodenal or common bile duct stenosis, pseudoaneurysm or erosion of the large vessels, large pancreatic pseudocysts, and internal pancreatic fistula.

The primary goal is long-term pain relief and control of the complications associated with CP. The optimal surgical procedure should manage the pain, preserve a maximum of endocrine and exocrine function still present, resolve complications of adjacent structures whenever possible (e.g. duodenal stenosis), reduce or free of opioid use, and restore quality of life. Several surgical strategies are available for the treatment of pain in CP and can be categorized into three major groups of procedures: drainage procedures, procedures combining drainage and re-

section, and resectional procedures. One of these strategies is chosen based on the presence of morphological features of the pancreas (e.g. inflammatory mass of head or tail, strictures/dilatation of the PD, and duct disruption) and involvement of adjacent structures (e.g. duodenal or common bile duct stenosis and portal hypertension with newly formed vascular collaterals).

Drainage Procedures

Lateral Pancreaticojejunostomy

The first drainage procedure was described in 1909 by Coffey [71] in an animal model using pancreaticoenterostomy. He was followed by Link [72] who described the first drainage operation for CP in humans in 1911, where he placed a catheter in the PD to drain the pancreatic juice through the skin, which provided pain relief and restored the patient's weight. Fifty years later, Du Val [73] performed a distal pancreatectomy, splenectomy, and pancreaticojejunostomy for ductal drainage procedures. Puestow and Gillesby [74] improved the procedure and described a distal pancreatectomy and a side-to-side pancreaticojejunostomy. And finally, in 1960, Partington and Rochelle [75] modified and optimized the procedure.

The longitudinal pancreaticojejunostomy according to Partington-Rochelle is the treatment of choice in patients with dilated PD (≥5 mm) without an inflammatory mass. In this procedure, the PD is opened along the anterior surface of the pancreas, from the tail on extending as far into the head as possible (to 1–2 cm from the duodenal inner curve). A Roux-en-Y jejunal limb is sutured side-to-side to the pancreas [75]. The procedure is associated with low morbidity and mortality rates (about 1%) [20, 21]. Immediate and lasting pain relief is reported in 80% (range 42–100%) of the patients with a follow-up of 62 (range 15–110) months [20]. It is a relatively simple, safe, and effective surgical treatment option in patients with dilated main PD including the advantage of no resection of pancreatic parenchyma. Some studies report a delay in the deterioration of pancreatic function in patients who were treated by pancreaticojejunostomy compared to patients who were treated conservatively [76, 77]. Patients with pain but non-dilated PDs are not considered candidates for drainage procedures by most pancreatic surgeons. Several studies have shown that ductal decompression in patients with non-dilated PD (<5 mm) is associated with inadequate relief of pain [78–80].

Combined Drainage and Resection

In patients with CP who present with an inflammatory mass in the pancreatic head and have dilation of the main PD and/or side branches in the head (and corpus/tail) region performing a combined drainage and resection, such as a Frey or a Beger procedure, may be the treatment of choice. Various methods have been proposed, i.e. the Beger, Frey, Berne, and V-shaped procedures [81–84]. The combined procedures are aimed at drainage of the PD and have the theoretical advantage of removal of the inflammatory mass in the pancreatic head and resolution of the biliary tract obstruction (by decompression or drainage) in a single operation [85].

Frey Procedure

This procedure was first described by Frey and Smith [82] in 1987. It consists of a pancreaticojejunostomy with coring out the pancreatic head, leaving a narrow rim of pancreatic capsule on the duodenum and the posterior part of the head and adjacent to the portal and mesenteric veins. No transection is necessary and reconstruction is done by one pancreatic anastomosis; thus, bleeding complications and anastomotic leakage are less likely to occur compared with the Beger procedure.

In 1994, Frey and Amikura [86] reported their results in 50 cases with a mean follow-up of 3.5 years. Three quarter of the patients demonstrated excellent pain relief, 13% had improved pain symptoms, and 13% showed no improvement. With regard to the pancreatic function, 11% had progression of their diabetes and none had worsened exocrine function. Negi et al. [87] presented similar results in terms of pain relief and pancreatic function in 60 patients. Pain relief was seen in 75% of patients; 7% developed diabetes mellitus de novo; none of the patients showed deterioration of pancreatic exocrine function or development of steatorrhea over a median follow-up of 6.4 years. Van der Gaag et al. [21], in their single-center retrospective cohort, reported that enzyme suppletion because of exocrine insufficiency increased modestly from 52% preoperatively to 59% after head resection (usually by Frey procedure). New-onset endocrine insufficiency was seen in 57% of patients after head resection versus 33% after pancreaticojejunostomy. This was also seen in a retrospective cohort study of 155 patients who underwent surgery for CP. A significantly higher proportion of patients developed new-onset endocrine insufficiency after resection [including duodenum-preserving pancreatic head resection (DPPHR)] than after a pancreaticojejunostomy (32 vs. 8%). No significant difference

was found in newly developed exocrine insufficiency [88].

In a recently published retrospective analysis of 73 patients undergoing a Frey procedure, a high rate of complete pain relief of 91.4% after a median postoperative follow-up period of 77 (range 12–204) months was reported [89]. In this study, 36.7% of the patients developed new-onset diabetes during a median follow-up time of 59.7 (range 3–180) months after surgery and 49% of patients developed new-onset exocrine insufficiency, which is higher than reported in other studies. The median weight gain of the operated patients was 9.4 (range 1.2–22) kg. Late biliary complications occurred in 8.2% of the patients [89]. For the Frey procedure, morbidity between 7.5 and 39% and mortality between 0 and 2.4% are reported [90–95].

Beger Procedure

In 1980, Beger first described the DPPHR which consists of a subtotal resection of the pancreatic head with conservation of the duodenum by a rim of pancreatic parenchyma at the inner duodenal wall containing the duodenal arterial blood supply. This is followed by an end-to-end or end-to-side pancreaticojejunostomy using a Roux-en-Y loop [96–98]. The goal of this technique is to decompress the PD and treat the enlarged pancreatic head. Beger et al. [99] reported their 26-year (1972–1998) experience of this procedure in 504 patients with CP, with a hospital mortality of 0.8%. They reinvestigated 388 of the 504 patients treated between 1982 and 1996 to evaluate the late outcome. They reported a pain-free rate of 91.7% after a median follow-up of 5.7 years in 303 patients with a late death rate of 12.6% [99].

Comparison of Frey and Beger Procedures

Both procedures are directed primarily at the pancreatic head inflammation and drainage of the PD. The results of both operations in terms of pain relief and quality of life seem to be comparable. But there are also differences. In the Frey procedure, the posterior part of the pancreatic head is preserved, which allows the remnant head and the PD in corpus and tail to be drained into a single anastomosis and without dividing the neck of the pancreas overlaying the superior mesenteric and portal veins [100].

Izbicki and Bloechle [101] allocated 42 patients with CP with an inflammatory mass in the head of the pancreas (>3.5 cm) and severe recurrent pain attacks (≥1 per month requiring opiates) randomly to either a Beger (n = 20) or a Frey procedure (n = 22). Patients with pseudocysts without duct pathology, portal vein thrombosis, or a malignant pancreatic tumor and co-existing malignancy of other organs were excluded. No patients died in this study. The Beger procedure was accompanied by 20% morbidity, while a significantly lower morbidity rate (9%, e.g. anastomotic leakage was less frequent) was found for the Frey procedure after a mean follow-up of 1.5 years (range 6–24 months). A decrease of 95 and 94% in pain scores, respectively, was found with an overall increase of 67% in quality of life in both groups. Endocrine and exocrine insufficiency was comparable among groups. This same study continued to recruit patients until 74 patients were included [102]. In 2005, the long-term results of these 74 patients with a median follow-up of 104 months were reported [95]. No significant differences between the groups with regard to pain scores, global quality of life, late mortality, and pancreatic exocrine and endocrine insufficiency were found. Given the lower morbidity rate with a comparable effect on pain control and quality of life, a Frey procedure is preferred over a Beger procedure. Randomized controlled trials evaluating various surgical procedures in CP are listed in table 2.

Resectional Procedures

Pure resection procedures for the treatment of CP comprise (pylorus-preserving) pancreaticoduodenectomy, distal pancreatectomy, and total pancreatectomy. Usually, resection is considered in patients who are no candidates for a drainage procedure, who have an inflammatory mass primarily in the head or tail, or in whom other forms of therapy have failed (e.g. endoscopic, surgical).

Pancreaticoduodenectomy

Pancreaticoduodenectomy (introduced by Whipple-Kausch) and pylorus-preserving pancreaticoduodenectomy (Longmire/Traverso) have served for many years as the primary surgical resectional procedures in patients with CP who present with an inflammatory mass in the pancreatic head with or without dilated PD [103, 104]. They are basically oncological procedures initially introduced as a treatment option for suspicion of periampullary carcinoma, but are also used in the treatment of benign conditions such as CP. These procedures provide long-term pain relief in 75–95% of the patients [86, 101, 105]. Pancreaticoduodenectomy is a relatively safe procedure with a hospital mortality rate <1% (range 0–5%) when performed in high-volume centers, with a compli-

Table 2. Summary of randomized controlled trials evaluating interventions in patients with CP

First author	Year	Interventions	Patients n	Mean follow-up months	Results	Risk of bias
Surgery						
Klempa [115]	1995	Beger vs. PD	43	36–66	Beger: less pain (100 vs. 70%), shorter hospital stay, better pancreatic function, equal mortality and morbidity	No allocation concealment, not powered, and no ITT analysis
Büchler [113]	1995	Beger vs. PPPD	40	6	Beger: more pain relief (75 vs. 40%) and better pancreatic function; comparable hospital mortality, overall morbidity, mean hospitalization time, and hospital readmission	No allocation concealment, not powered, and no ITT analysis
Izbicki [105]	1995	Frey vs. Beger	42	18*	Frey: less morbidity (9 vs. 20%); comparable pain relief (94 and 95%), increase in quality of life and pancreatic function	No ITT analysis
Izbicki [151]**	1997	Frey vs. Beger	74	30*	Frey: less morbidity (22 vs. 32%); comparable pain relief (93 vs. 95%), increase in quality of life and pancreatic function	No allocation concealment, not powered, and no ITT analysis
Müller [152]	1997	Beger vs. PPPD	20	26*	Beger: less frequent delayed gastric empting; comparable rates of pain relief, hospital readmission, and weight gain	No allocation concealment, not powered, and no ITT analysis
Izbicki [84]	1998	Frey vs. PPPD	61	24*	Frey: lower morbidity (19 vs. 53%), quality of life improvement (71 vs. 43%); equal pain relief (94 vs. 95%)	No ITT analysis
Farkas [114]	2006	Beger vs. OPPHR	40	12*	OPPHR: shorter operation time, less morbidity (0 vs. 40%), shorter hospital stay, and more increase in body weight; comparable hospital mortality, total relief of the symptoms (85 vs. 90%), pancreatic function, and hospital readmission	No allocation concealment, not powered, and no ITT analysis
Köninger [153]	2008	Beger vs. Bern	65	24	Berne: shorter operative time (46 min) and shorter hospital stay (11 vs. 15); equal quality of life; 3 patients in the Berne group were re-operated on during the follow-up period due to ongoing pancreatitis and bile duct obstruction	Low risk of bias
Long-term follow-up						
Strate [95]	2005	Frey vs. Beger	74	104*	Comparable pain relief, morbidity, mortality, quality of life, and pancreatic function	Long-term follow-up [151]
Strate [150]	2008	Frey vs. PPPD	46	84*	Comparable pain relief, quality of life, and pancreatic function	Long-term follow-up [84]
Müller [148]	2008	Beger vs. PPPD	40	168	No difference on the long term in terms of pain relief, quality of life, and pancreatic function	Long-term follow-up [113]
Endoscopy versus surgery						
Dite [13]	2003	Endoscopy vs. surgery	72	60	Surgery: higher complete or partial pain relief (86 vs. 61%), more increase in weight (47 vs. 29%) Surgery: 20% drainage vs. 80% resectional procedures Endoscopic therapy: without ESWL	Pseudo-randomization, no allocation concealment, not powered, lack of baseline characteristics, and no ITT analysis
Cahen [12]	2007	Endoscopy vs. surgery	39	24	Surgery: higher complete or partial pain relief (75 vs. 32%), better physical quality of life; comparable morbidity Surgery: pancreaticojejunostomy Endoscopic therapy: with ESWL	Low risk of bias
ESWL versus ESWL + endoscopy						
Dumonceau [33]	2007	ESWL vs. ESWL + endoscopy	55	24	Comparable results in terms of pain relapse and morbidity; treatment costs per patient were 3 times higher in the ESWL + endoscopy group	Low risk of bias

* Median. ** Part of the patients same as [105]

PD = Pancreaticoduodenectomy; PPPD = pylorus-preserving pancreaticoduodenectomy; OPPHR = organ-preserving pancreatic head resection; ITT = intention to treat.

cation rate of 20–40% [106–111]. The major disadvantage of a PD for CP is the removal of the surrounding non-diseased organs, such as the duodenum and the entire pancreatic head, leading to significantly reduced pancreatic exocrine and endocrine functions [112].

Comparison of DPPHR and Pancreaticoduodenectomy

Several randomized controlled trials have been performed comparing DPPHR with pancreaticoduodenectomy [84, 113–115]. A systematic review and meta-analysis of 4 randomized controlled trials comparing DPPHR (Beger and Frey procedures and modifications) with pancreaticoduodenectomy [116] showed no significant differences in terms of postoperative pain relief, overall morbidity, postoperative pancreatic fistula development, or operating time. Only for the Frey procedure a significant reduction of operating time, delayed gastric emptying, duration of hospital stay, and need for perioperative blood transfusion was seen compared to pylorus-preserving pancreaticoduodenectomy. Furthermore, the DPPHR group had a higher quality of life, postoperative weight gain, and more exocrine function impairment compared with the pancreaticoduodenectomy group [116]. A cautious interpretation is warranted, because there is a fair amount of heterogeneity of the included studies.

Several alternatives to the Beger procedure, such as the Frey procedure and the Berne modification, have been developed to prevent dissection of the pancreas above the portal and superior mesenteric veins, which is a potential source of hemorrhage, in particular in the case of portal hypertension and removal of the dorsal pancreatic capsule [117].

Both Beger and Frey procedures compare favorably with the (pylorus-preserving) pancreaticoduodenectomy in terms of morbidity and mortality, length of hospital stay, weight gain, nutrition, and quality of life. Pylorus-preserving pancreaticoduodenectomy should be reserved for patients suspected of carcinoma [100].

Distal Pancreatectomy

Distal pancreatectomy or left-sided pancreas resection is the resection of pancreatic tissue to the left of the superior mesenteric artery and vein. Distal pancreatectomy has been performed in the past as a part of the various pancreaticojejunostomy procedures used for drainage of the pancreatic PD [73, 74, 118]. In 1948, Eliason and Welty [119] described distal pancreatectomy as a resection procedure rather than a drainage procedure in 3 patients with painful CP. During the 1960s and 1970s, distal pancreatectomy became the most commonly performed operation for pain relief in CP [120]. In the 1980s, it fell in disfavor because of the high incidence of endocrine and exocrine insufficiencies after 80–95% pancreatectomy and the development of other less aggressive surgical procedures for the treatment of CP.

Distal pancreatectomy is a safe procedure, with a reported hospital mortality of 0–3.8% and a morbidity of 15–31% [121–124]. Recently, the results of the DISPACT trial (stapler vs. hand-sewn closure of the pancreas after distal pancreatectomy; a randomized controlled trial) showed no difference in the pancreatic fistula rate (32 vs. 28%) or mortality rate (0 vs. 1 patient died) between the stapler and hand-sewn closure technique, respectively [125]. The results for pain relief after distal pancreatectomy differ in the literature. Sawyer and Frey [126] reported a pain relief of 90% after distal pancreatectomy in patients with distal CP (body and/or tail, without PD dilatation) at a mean follow-up of 4 years. This is in the range of other publications which report a pain relief of 77–88% [127–129]. Hutchins et al. [130] published a series of 84 patients who had undergone distal pancreatectomy for CP with a mean postoperative follow-up of 34 (range 1–247) months in which 48 patients (57%) had no or minimal intermitted abdominal pain. There was 1 perioperative death, and complications occurred in 29 patients (34%), of which 6 needed early re-exploration. The late mortality rate over the follow-up period was 10%. Almost half of the patients became diabetic at a median follow-up of 27 months, related to the percentage of parenchymal resection [128–130]. Van der Gaag et al. [21] recently reported the results of a cross-sectional cohort of 223 consecutive patients who underwent surgical drainage, head resection, or left-sided pancreas resection for the treatment of CP with a median follow-up of 60 (IQR 29–104) months. Of the 223 patients, 37 (17%) underwent a left-sided resection of the pancreas. The risk of developing endocrine and exocrine insufficiency after surgery was higher after drainage or head resection than after a left-sided resection [21].

Total Pancreatectomy

Total pancreatectomy is a radical procedure that aims to completely remove the diseased pancreas and is rarely used for the treatment of pain in patients with CP. The indication might be failure of previous surgical interventions (e.g. resection) or severely disabling pain with complete endocrine and exocrine pancreatic failure, and it can be used as a prophylactic procedure for pancreatic cancer

with hereditary pancreatitis or familial pancreatic cancer [131–134]. Historically, aversion for total pancreatectomy arose from the end result of the procedure, with a significant postoperative morbidity and brittle diabetes, and significant malabsorption due to exocrine insufficiency. Introduction of islet autotransplantation [135] led to renewed interest in the treatment of pain in CP as a treatment modality for end-stage CP. In a large single-center cohort, 409 patients (53 children) with CP underwent a total pancreatectomy with intraportal islet autotransplantation [136]. After 24 months of follow-up, 40% of patients were still using narcotics 2 years after total pancreatectomy and 23% of the patients reported a similar pain score as before total pancreatectomy. Hospital mortality was 1.2%, but 53 of 409 (13%) patients died after discharge. Five-year survival was 89% in adults and 98% in children. Complications requiring relaparotomy occurred in 15.9% with bleeding (9.5%) as the most frequent complication. At 3-year follow-up, 30% were insulin independent (25% adults, 55% children) and 33% had partial endocrine function [136].

The results of 33 patients with CP undergoing extensive pancreatectomy with islet autotransplantation were recently reported. A decrease in mean pain score was seen, from 7 (range 2–10) points prior to total pancreatectomy to 4 (range 0–7) points after a mean follow-up of 9 months (6–12) [137]. Alexakis et al. [131] performed a duodenum- and spleen-preserving total pancreatectomy in 19 patients with CP and reported that, after a median follow-up of 8.5 months, 81% experienced complete pain relief. Perhaps in a selected category of patients with CP, total pancreatectomy with islet autotransplantation can be effective. Further studies on this topic are needed.

Head-to-Head Comparison of Endoscopic and Surgical Treatment

The results of randomized controlled trials comparing endoscopic treatment with surgical treatment in CP are summarized in table 2. Thus far, two randomized trials have compared endoscopy with surgery in patients with CP [12, 13]. Dite et al. [13] included 140 patients with advanced CP (patients had CP for >5 years and were medically treated for their symptoms for at least 3 years) with PD obstruction and pain. Only 72 patients were randomized between endoscopic (without ESWL) and surgical treatment, and 68 patients refused due to a preference for one of the treatment arms. Some outcomes were reported separately for the randomized group, while others (e.g. baseline characteristics or complications) were only reported for the complete cohort. In the randomized patients, complete pain relief was more frequently seen after surgery (34 vs. 15%) compared to the endoscopic treatment after 5 years of follow-up. The results were similar for the entire cohort at the 5-year follow-up (37 vs. 14%). There was no difference in new-onset diabetes in both groups (34 vs. 43 %). Exocrine pancreatic function was not measured, but the study reported a higher proportion of patients with an increase in body weight in the surgical group compared to the endoscopic group (47 vs. 28%) [13].

Cahen et al. [12] randomized 39 patients with advanced CP and a distal obstruction of the PD without pancreatic head enlargement to multimodal endoscopic therapy (including ESWL) or operative pancreaticojejunostomy. The primary end point was the average Izbicki pain score during a median of 24 (range 6–24) months of follow-up. The study was prematurely terminated by the safety committee based on a significant difference in the primary outcome [12]. Patients undergoing surgery had significantly lower Izbicki pain scores (25 vs. 51), more complete or partial pain relief (75 vs. 32%), required less procedures (median 3 vs. 8), and had better physical health summary scores compared to patients with endoscopic treatment. Overall complications, length of hospital stay, and changes in pancreatic function were similar in both groups. In a recent publication, the long-term results of this trial confirmed that initial surgical drainage of the PD is superior to endoscopic treatment in patients with symptomatic advanced CP [138]. During the 79-month follow-up period, 1 patient was lost to follow-up and 7 died from unrelated causes, leaving 31 patients for long-term evaluation. The mean difference in Izbicki pain scores was no longer significant, but in terms of pain relief, surgery was still superior. Patients treated in the endoscopic group required significantly more additional drainage (68 vs. 5%) and underwent more procedures (median 12 vs. 4) compared with the surgery group. Almost half (n = 9; 47%) of the patients in the endoscopic group received surgery eventually, but only 2 of these patients had complete pain relief after surgery. None of the patients in the surgical group developed a recurrent PD obstruction. This suggests that postponing surgery probably has a negative influence on treatment outcome. No difference was found in quality of life, pancreatic function, hospital stay, and costs between the groups [138].

A Cochrane review of endoscopic or surgical intervention for painful CP pooled the data of both randomized trials (111 patients) [12, 13, 139]. The pooled data showed

that there was a higher proportion of patients with pain relief in the surgical group compared to the endoscopic group (partial or complete pain relief: RR 1.62, CI 1.11–2.37; complete pain relief: RR 2.45, CI 1.18–5.09) [139]. The authors also describe the risk of bias in these randomized controlled trials. They conclude that the study of Cahen et al. [12] has a low risk of bias. There are some methodological shortcomings in the study of Dite et al. [13] concerning the randomization, concealment of allocation, lack of baseline characteristics, and absence of intention-to-treat analysis. Finally, it is important to note that both trials include patients with severe late-stage CP, and these results can only be extrapolated to patients in the late stage of the disease.

Endoscopic drainage seems inferior to surgery in symptomatic patients with advanced CP. The question is if this is also true for patients in an early phase of the disease. There is some evidence (i.e. from retrospective case series and experimental animal studies) that the course of the disease is favorably altered by an early intervention.

Future Challenges: Timing of Surgery

Despite currently available medical, endoscopic, and surgical therapies, the treatment of pain in CP remains a great challenge to physicians, mainly because of the lack of evidence-based treatment protocols. Currently, a conservative step-up approach is used for the treatment of pain in which patients are treated with opioid analgesics, with patients only referred for endoscopic therapy when pain symptoms persist. Eventually, in a late stage of the disease, patients may be referred for a surgical intervention if pain still persists despite prolonged opioid use and multiple endoscopic interventions. This step-up approach is used even with the knowledge that longitudinal studies show that, of all CP patients, 40–75% will still require surgery for pain in the course of the disease [1, 4, 17] and even though it has been demonstrated in a head-to-head comparison study in advanced CP patients with severe pain that surgery is more effective than endoscopic treatment [12].

Although opioid treatment may suppress the symptoms in some patients, it does little to influence the progression of disease and symptoms on the long run. Furthermore, tolerance, dependency, and adverse events are frequently reported drawbacks of opioid use and have a large impact on the quality of life and social functioning [140]. Likewise, several recent studies have shown that preoperative opioid use predisposes to failure of achieving complete long-term relief of pain after endoscopic and surgical intervention [21, 46, 87, 141–143]. Negi et al. [87] conclude that patients should be referred for surgery before opiates are needed to relieve pain. These results are confirmed by Ahmed Ali et al. [141], who found that duration of pain (>3 year), the number of endoscopic interventions (>5), and preoperative daily opioid use are independently associated with persistent severe pain after pancreatic surgery. Interestingly, this also applies for endoscopic treatment. Clarke et al. [143] have shown that patients who respond to endoscopic therapy among others have a shorter period of time between diagnosis of CP and start of endoscopic therapy. A plausible explanation could be peripheral and central sensitization, i.e. opioid-induced hyperalgesia. It is thought to result from neuroplastic changes in the peripheral and central nervous system (CNS) that lead to sensitization of the sensory pathways [144]. There is also increasing evidence suggesting that the strategy of early surgical intervention, compared to the current step-up approach, may be better in terms of pain control and pancreatic function. Different experimental studies in animal models and clinical cohort studies suggest that surgical intervention early in the course of the disease may slow disease progression. Piglets undergoing PD ligation and subsequent longitudinal pancreaticojejunostomy show improved histology and pancreatic exocrine function when early surgical drainage is performed versus late drainage [145]. Clinical studies reported stabilization and postponement of both endocrine and exocrine insufficiency after surgical drainage procedures [48, 76, 146].

Retrospective studies comparing endoscopic drainage and surgical drainage of the PD in CP also suggest that surgery should be considered early for the treatment of CP. Rutter et al. [19] analyzed a total of 292 patients with initial endoscopic, surgical, or conservative medical treatment and found that patients undergoing surgery spent a significantly shorter time in the hospital, had fewer subsequent interventions and a longer relapse-free interval compared with endoscopically treated patients. The complication rate was 32%, both after surgery and endoscopy. In a small retrospective study of 68 CP patients, those with endoscopic treatment for >1 year demonstrated significantly longer hospital stays, more frequent hospitalizations, and higher medical expenses than a short-period endoscopic treatment group as well as a surgery group. However, hospital stays, number of admissions, and medical expenses were comparable between the short-period endoscopic treatment group and the surgery group [147].

The timing of surgery has also been studied in a small randomized trial, in which 17 patients with CP and dilated PD and pain were randomized to early surgical drainage (pancreaticojejunostomy) or a conservative 'non-operative' approach [77]. The early surgery group had significantly better pain relief as well as endocrine and exocrine pancreatic function compared to the conservative group. Shortcomings of this study include a small sample size and a not well-defined 'non-surgical' group [77].

The optimal timing of surgery remains an important clinical management dilemma and it is pivotal that more scientific data are acquired in order to develop evidence-based guidelines. Currently, an open-label randomized controlled multicenter superiority trial by the Dutch Pancreatitis Study Group is recruiting patients: the ESCAPE trial (Early Surgery versus Optimal Current Step-Up Practice for Chronic Pancreatitis trial; ISRCTN45877994). The ESCAPE trial compares two treatment strategies in CP patients with a dilated PD and pain, who develop the need for opioid analgesics, by randomizing them between early surgery and the current step-up treatment strategy. The ESCAPE trial will answer the question of whether early surgical intervention for CP will lead to better pain control and pancreatic function compared to the current step-up practice in patients with CP.

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