Management of Diabetes and Long-Term Outcome of Chronic Pancreatitis

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Chronic Pancreatitis: Long-Term Outcome After Medical and Surgical Treatment

Volker Aßfalg, Norbert Hüser, and Helmut Friess

Technical University of Munich, School of Medicine, Klinikum rechts der Isar, Department of Surgery, Munich, Germany

Introduction

Both interventional and surgical approaches can be used to treat outflow disorders of the pancreatic duct or the common bile duct and pseudocysts due to chronic pancreatitis. The best procedure for symptom-oriented therapy has to be decided on according to the clinical appearance of the patient and the varying disease patterns on the one hand and the long-term outcome on the other hand. A primary aim is the provision of adequate pain therapy. Whereas Chapters 55–60 focus on interventional and surgical procedures for pseudocysts, pain due to chronic pancreatitis, and biliary and pancreatic duct obstructions, this chapter reports on long-term results and discusses the significance within the context of complex treatment of chronic pancreatitis.

Outcomes of Interventional and Surgical Therapy for Pancreatic Pseudocysts

Results of Interventional Therapy for Pseudocysts

The etiology of pseudocysts has to be considered during therapy planning. Internal drainage techniques have increasingly replaced percutaneous methods. Today, computed tomography (CT)- or ultrasound-guided percutaneous puncture and drainage is almost always restricted to emergency relief of infected or necrotic cysts. The reason for this development is the observation of recurrence in as many as 70% of patients and cutaneous fistulas in up to 20% of patients. An analysis in terms of the effectiveness of percutanously drained pseudocysts remains difficult because of inconsistencies in the nomenclature of pseudocysts in different studies. Moreover, there are no data on long-term surveillance.

Pancreatic pseudocysts can be drained safely by transgastric, transduodenal, or transpapillary routes using an endoscopic approach with placement of stents in the cyst cavity. However, there are no prospective data concerning the best time point for changing the stents and the duration of stent therapy. In the case of a transmural drainage of cysts the distance between cyst cavity and the wall of the hollow organ should be as small as possible to reduce the risk of stent dislocation. Endoscopic ultrasound (EUS)-guided puncture and drainage of a cyst is technically superior to the non-ultrasound-guided transmural drainage (success rate 94% vs. 72%), whereas no differences exist with regard to complication rate and short-term treatment outcome [1]. The long-term results from endoscopically inserted stent therapy are difficult to determine because of an inconsistent nomenclature and consideration of the etiology (acute vs. chronic) of the pseudocysts. Recent studies report symptom resolution, and therefore therapeutic effectiveness, of up to 91% and mortality of less than 1%, on the one hand, and a maximum recurrence rate of 18% in long-term follow-up (median 6–43 months), on the other hand [2–4].

Results of Surgical Therapy for Pseudocysts

The aim of surgery is the eradication of the cyst. However, surgical therapy increasingly comes up against the complex pseudocysts frequently associated with chronic pancreatitis. These include huge pseudocysts, multiple pseudocysts, or those with simultaneous stone- or stricture-associated changes and truncation of the pancreatic duct [5]. The so-called internal and external drainage procedures can be expanded by a partial resection of the pancreas.

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External drainage surgery has no noteworthy status in the therapy of chronic pancreatitis. The long-term prospect of success is too low and these procedures are therefore at most performed to relieve infected pseudocysts in acute pancreatitis. There are no data on the long-term outcome of these procedures in chronic pancreatitis.

Internal drainage procedures include pseudocyst gastrostomy, pseudocyst duodenostomy, and pseudocyst jejunostomy. If possible, the anastomosis should be placed at the lowest part of the cysts to guarantee longstanding complete emptying. Depending on the localization of the pseudocysts and the underlying disease the technical feasibility ranges between 90% and 100%, with an average rate of recurrence of 12% in long-term follow-up. The procedure-associated mortality is 2.5% and the morbidity is approximately 16% [5]. Although there are no randomized trials, a center-specific overview suggests that pseudocyst jejunostomy is the preferred surgical procedure compared to pseudocyst gastrostomy.

Surgical procedures for drainage of pseudocysts have slightly higher success rates but also have a higher morbidity compared to endoscopic pseudocyst drainage into the duodenum or the stomach. Surgical resection procedures are mainly performed in cases of obstruction of the pancreatic duct or of the bile duct in the course of chronic pancreatitis.

Unfortunately, there are currently no randomized trials comparing surgical and endoscopic and interventional drainage procedures for pseudocysts. Comparison and evaluation of operative, interventional, and endoscopic drainage procedures is difficult because of the different accompanying morbidities in what is a very heterogeneous patient group.

Laparoscopic surgery has been established for pseudocyst jejunostomy, a combined laparo-endoscopic intragastric pancreatic pseudocyst gastrostomy, and pseudocyst gastrostomy via an anterior approach. Hitherto, the significance of the different procedures has not been finally classified because there are no prospective randomized trails. The perioperative complication rate is less than 10% and the long-term follow-up of some studies is longer than 6 years [6]. Thanks to a recurrence rate between 0% and 13% [7], the effectiveness and safety of the laparoscopic procedures can be compared with open surgery. Both the comorbidities of the patients and the nature and localization of the pseudocysts are very heterogeneous. All these aspects impact on the short-term course, but also have a particular effect on the long-term outcome of interventional, endoscopic, and surgical treatments of pseudocysts. Needless to say, the experience and expertise of the treating endoscopist, interventional radiologist, or surgeon play important roles. To achieve reliable statements in terms of therapeutic procedures and follow-up there is a need for clear definitions of pseudocysts and comprehensive consideration of the etiology of pancreatitis [8].

Outcome of Pain Management in Chronic Pancreatitis

The morphologic correlates of recurrent pain in chronic pancreatitis are inflammatory cellular infiltration of the parenchyma and nerve sheaths, often associated with inflammatory pancreatic head enlargement or obliterating stones in the main pancreatic duct. The primary therapeutic step is the avoidance of triggering factors—most frequently a complete abstinence from alcohol and smoking—and adequate analgesia. In the case of persistent pain despite medical treatment, multidisciplinary therapy needs to be escalated by interventional or surgical methods [9]. This section focuses on the outcome of the therapeutic procedures presented in Chapters 51–54.

Results of Medical Treatment for Chronic Pain

According to the World Health Organization (WHO) scheme for pain therapy and as explained in Chapters 41 and 51, peripherally acting analgesics are combined with tricyclic antidepressants, anticonvulsive agents, or opioids to achieve a positive effect in the therapy of chronic pain due to chronic pancreatitis [10]. In the next step, more potent opioids can be applied with close attention to both the patient's pain symptoms and the efficacy profile of the drug.

There are no reliable long-term results from well-designed randomized controlled trials that identify any opioid as being better than others with regard to both pain relief and side-effects [11]. With regard to the genesis of neuropathic pain in chronic pancreatitis, pregabalin has been tested for its potency in pain relief and was found to be significantly suited [10], although long-term results on both persistent pain relief and late drug-related side-effects in chronic pancreatitis are still not available.

Results of Interventional Treatment Options for Chronic Pain

The so-called celiac plexus blockade can be performed endoscopically or under CT guidance. The aim is to interrupt pain sensations in sensory nerval fibers of the celiac ganglion region by either a mix of steroids and anesthetics (nerve block) or concentrated alcohol (50–90%) or phenol (neurolysis). In the short term, a

significant improvement should be found in the overall pain score. EUS-guided techniques seem to be safer, more effective, and more enduring compared to fluoroscopy-guided or CT-guided techniques [12–14]. The success rate of EUS-guided plexus blockade in terms of sufficient pain reduction was reported to be between 50% and 60% in two meta-analyses [12,13]. However, long-term data are rather sparse and the effect is only transient in most cases, as only 10% of the patients treated still enjoy persistent pain relief after 24 weeks [15].

Pain therapy includes treatment for pancreatic duct strictures and impacted stones, so lithotripsy, sphincterotomy, dilatation, or stenting of the pancreatic duct may become necessary. Pancreatic duct drainage hypothetically initiates decompression of the duct and reduced pressure in the segments behind, which consecutively leads to pain reduction or even freedom from pain. Nevertheless, it remains difficult to evaluate the individual impact of the changes on the character of pain. The clinical guideline of the European Society of Gastrointestinal Endoscopy (ESGE) recommends extracorporeal shock wave lithotripsy (ESWL) for first-line therapy in uncomplicated, painful chronic pancreatitis and (head)stones larger than 5 mm which obstruct the main pancreatic duct, followed by endoscopic removal of the fragments [16]. During a follow-up period of up to 77 months after this procedure, complete freedom from pain and partial freedom from pain were reported in 48% and 91% of patients, respectively [17]. However, only one randomized controlled trial exists comparing ESWL versus ESWL plus endoscopy in patients with obstructive chronic pancreatitis. Interestingly, both intensity and number of pain relapses were similar during a 2-year follow-up [18].

Evidence-based recommendations for endoscopic therapy of pancreatic duct strictures are lacking. Overall, the long-term pain relief of different studies varies between 52% and 90% over 14–69 months [19]. Multiple stenting was found to be successful in terms of freedom of pain and symptoms in more than 80% of the patients treated in an interval of 38 months [20]. However, prospective studies are necessary to investigate this therapeutic approach because single versus multiple stenting have not been compared to date.

Results of Surgical Therapy for Chronic Pain

Direct comparison of surgical therapy (80% resections, 20% draining procedures) and endoscopic therapy with and without stenting revealed the superiority of the surgical approach for long-term pain and weight control in a prospective, controlled, randomized study. The results in terms of at least partial pain relief were still comparable (more than 90%) in both groups after 1 year. However, surgery aiming for freedom from pain turned out to be significantly advantageous in chronic obstructive pancreatitis after 3 and 5 years (surgery: 41% vs. endoscopic: 11% and surgery: 37% vs. endoscopic 14%, respectively) during further observation. In addition, the percentage of so-called "non-responders" (failure) was significantly higher in the interventionally treated group of patients. The monitoring of the course of the body weight of patients who received either surgery or intervention revealed similar results of superiority of the surgery group with an increase of body weight (surgery vs. endoscopy: 60% vs. 66% after 1 year but more than 50% and 27% after 5 years) [21].

Another prospective, randomized controlled study investigated approaches for refractory pain and compared endoscopical stenting and operative lateral pancreaticojejunostomy [22]. Patients from the surgical group reported partial or complete freedom of pain in 75% whereas only 32% of the patients of the interventionally treated group showed this improvement. The study had to be stopped prematurely because the advantage of the operative strategy was obvious and therefore continuing patient recruitment for study completion was ethically unacceptable. During the long-term follow-up of 79 months, another important finding was that patients who initially received surgical drainage reported markedly less pain and less frequently required additional therapy, either endoscopic or operative. However, surgical or interventional reintervention was required in almost 50% of the primarily endoscopically treated patients [23]. Moreover, physicians should bear in mind that early surgical therapy within the first 3 years after diagnosis apparently results in the best outcome in terms of pain reduction [24].

In a multicenter randomized trial initiated by the Dutch Pancreatitis Study Group the best time point for operative therapy after diagnosis is currently being investigated. The aim of this trial is to clarify whether early surgical intervention is better in terms of pain control and organ function compared to the step-up model of medical, endoscopic, and surgical treatment [25].

However, there are data indicating increased morbidity of salvage surgery after failed endoscopic treatment of pancreatic disease [26].

Taken together, the results of two randomized controlled clinical trials reveal the superiority of surgery compared to interventional endoscopy in the treatment of chronic pancreatitis. In addition to local pancreatic surgery, the efficacy of bilateral thoracoscopic transection of the splanchnic nerves has been shown to have long-lasting or even permanent positive effects in terms of pain control and quality-of-life improvement in chronic pancreatitis [27–29].

Outcome of Therapeutic Options for Biliary and Pancreatic Ductal Stenoses

In association with inflammatory reactions and advancing glandular remodeling, stenoses of the pancreatic duct and the intrapancreatic biliary duct may develop. In addition to endoscopic methods, resective and operative drainage procedures must be evaluated. However, it should be remembered that the possibility of malignant lesions in the pancreatic tissue should be considered. After all, the cumulative risk for pancreatic cancer is considerably increased with an incidence of 4.6% after 5 years and 14% after 25 years in patients with chronic pancreatitis compared to disease-free controls [30].

Results of Endoscopic Therapy for Ductal Stenoses

Different factors have relevant impacts on the success of endoscopically treated pancreatic duct strictures and stenoses. These are, for example, the number of impacted stones and/or strictures, the length of the latter, and the dilatation of the distal duct segment. Endoscopic therapy has been shown to be particularly effective in treating dominant strictures and dilatation of the pancreatic duct. In an overview including approximately 1500 patients, pain relief was reported in 31–100% during an observation time of 8–72 months [31]. A multicenter study concentrated on the long-term course after decompression of the pancreatic duct including strictures, stones, and the combination of both in more than 1000 individuals. During the follow-up period of up to 12 years, pain reduction, independently from the localization of the stricture and stone impaction, was achieved in 86% and in 65% in an intention-to-treat analysis. Over the long term (2–12 years; mean 4.9 years), surgical intervention was inevitable in a quarter of the patients [32]. Previous stent application was not rated as an obstacle during the subsequent operation.

The incidence of bile duct strictures in the context of chronic pancreatitis ranges between <5% and approximately 50% [33]. Both plastic and metal stents can be placed endoscopically. During a follow-up of nearly 5 years the disappearance of strictures was reported in 10–38% only [34]. Multiple stenting over 4 years resulted in a long-term resolution rate of 44% [35]. These results appear rather unsatisfactory with regard to effective treatment of bile duct obstructions in patients with chronic pancreatitis. Therefore, surgical options should be taken into consideration whenever other chronic pancreatitis-related complications such as duodenal stenosis or pain exist.

Late Outcome of Resective Versus Draining Procedures

Operative strategies for chronic pancreatitis for both draining and resection should consider pathophysiology and the underlying morphologic changes. Details of the various surgical procedures mentioned in the next paragraph can be found in Chapters 56–60.

In brief, surgical drainage procedures are performed if the pancreatic head is not enlarged but the pancreatic duct shows congestion. The most common surgical technique is longitudinal pancreaticojejunostomy, according to Partington–Rochelle. In addition to a low morbidity of 21% and a mortality of less than 1%, sufficient and lasting pain-release has been reported in 80% for an observation period of 15–110 months [24,36].

The rationale behind a (limited) pancreatic head resection is the hypothesis that pain persists due to incomplete decompression of the duct in the pancreatic head by a drainage-only procedure. For long time classical pancreatoduodenectomy (Kausch–Whipple) was the first choice in surgical therapy of chronic pancreatitis with head-related complications. However, despite a low mortality (less than 5% in high-volume centers) more than half of the patients showed long-term gastrointestinal problems such as dumping, diarrhea, peptic ulcers, delayed gastric emptying, and diabetes. Alternatively, the pylorus-preserving modification according to Traverso was developed, but this modification was found to be no better than the classical Kausch–Whipple procedure with regard to morbidity, mortality, and adverse side-effects.

In patients with inflammatory enlargement of the pancreatic head and pancreatic duct dilatation a combination of both resection and drainage has been suggested. Several techniques have been developed, including the duodenum-preserving pancreatic head resection pioneered by Hans Beger from the early 1970s. The encouraging long-term outcome of this technique performed in 504 patients revealed 91% freedom from pain, 69% professional rehabilitation, and 72% of the patients had a Karnofsky index of 90–100% whereas only 9% had a recurrence of pancreatitis during up to 14-year follow-up [37].

Beger's original idea of performing organ-preserving surgery for chronic pancreatitis-related complications was subsequently modified by Frey, Büchler/Bern, and Farkas in the following years. Recently, the results from a randomized controlled trial comparing the Beger procedure and the Bern modification showed no difference in patient-relevant long-term outcome during a median 129 months follow-up [38].

In a first randomized trial investigating both short- and long-term outcomes, the superiority of duodenum-preserving pancreatic head resection compared to the classical Kausch–Whipple procedure was demonstrated

with regard to pain relief, gain of body weight, and time of hospital stay [39]. In addition to comparable results concerning morbidity, course of pain intensity, and endocrine function, a meta-analysis showed advantages of the duodenum-preserving procedures (Beger, Frey, Büchler/Bern procedures) concerning hospital stay, exocrine function, and quality of life [40]. However, especially with regard to effective long-term absence of pain and quality of life these results have to be treated with caution because a meta-analysis could not find a significant superiority [41]. In 2008 the long-term results (14-year follow-up) from a randomized clinical trial comparing pylorus-preserving resection and Beger procedure demonstrated no presence of the early advantages of the latter [42]. The results from the ongoing randomized multicenter study (ChroPac) comparing duodenum-preserving pancreatic head resection and classical pylorus-preserving duodenopancreatectomy with regard to the primary end-point "quality of life" 2 years after surgery will be available within the next few years. In 2013, the 15-year follow-up data from a randomized controlled trial on pylorus-preserving pancreatoduodenectomy versus Frey procedure in chronic pancreatitis was published [43]. Whereas pain control was comparable between both groups in the long-term follow-up, the authors reported better quality of life after Frey procedure and an increased long-term mortality after pylorus-preserving duodenopancreatectomy [43]. Furthermore, no correlation between endocrine and exocrine pancreatic function and pain could be identified. Taken together, this study clearly recommends duodenum-preserving pancreatic head resection in chronic pancreatitis whenever possible.

Another study investigated the differences between the Beger procedure and the Frey procedure but could not identify any superiority with regard to morbidity, quality of life, pain relief, and endocrine or exocrine function [44]. Recently, the data from a 16-year follow-up analysis after Beger and Frey procedure agreed with these findings [45]. Comparison of the two duodenum-preserving resections—"Beger procedure" and "Büchler/Bern procedure"—revealed a shorter operation time and a shorter hospital stay for the latter [38,46] but no differences with regard to quality of life, pain control, occupational disability, exocrine and endocrine pancreatic function, endoscopic interventions, and reoperations during the 10-year follow-up [38]. Finally, there are no published studies in the literature comparing the "Büchler/Bern procedure" and the "Frey procedure."

Conclusion

Currently, surgeons and gastroenterologist do not always agree in terms of the right time point and indications for interventional or surgical therapy in patients with obstructive chronic pancreatitis. Even among surgeons there are different opinions concerning the respective operative procedures. Both individual experience and local or interdisciplinary expertise have crucial impacts on decision making. This inhomogeneity is caused by the weak evidence of existing analyses, which are small and underpowered in most cases. New comprehensive, randomized controlled trials should clearly be initiated to support or refute these data. Complex cases have to be discussed and planned in an interdisciplinary approach. Nevertheless, in the light of the currently existing data there should be some change in decision making in favor of earlier initiation of a surgical approach, because studies report better and more long-lasting pain control and maximum possible preservation of function after organ-sparing operations. Early surgery can also prevent damage to the parenchyma which leads to better postoperative function of the remaining pancreatic tissue and reduces the risk of malignant transformation.

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