

Review Article

Chronic Pancreatitis with Stones: What is the Best Way to Treat?

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Abstract

Pancreatic duct stones (PDS) are a common complication of chronic pancreatitis (CP). PDS can lead to duct obstruction and cause chronic abdominal pain. Ductal stone clearance, as well as short and long-term pain relief, is the cornerstone of endoscopic or surgical treatment. A step-up approach seems reasonable in pancreatic duct stone clearance. Extracorporeal shock wave lithotripsy (ESWL) combined with standard endoscopic retrograde cholangiopancreatography (ERCP) is as effective as a surgical approach for treating painful CP with less morbidity and medical costs. Therefore, endotherapy is considered a first-line therapy in selected patients. In case of insufficient pancreatic ductal clearance or strictures, advanced endoscopic techniques, per-oral pancreatoscopy (POP) with intraductal lithotripsy and/or endoscopic ultrasound-guided ductal drainage (EUS-PDD), will expand the role of the endoscopic approach. Because these new techniques are challenging, technically complex, and with high adverse events (AEs), they should be reserved for advanced tertiary care centers. Although there is increasing data that early surgical intervention may lead to better pain control and pancreatic duct stone clearance, surgery is reserved for patients failing endotherapy or patients with suspected malignancy.

Introduction

Chronic pancreatitis (CP) is defined as a progressive inflammatory disease of the pancreas. CP undergoes fibrotic remodeling of the pancreatic tissue, which affects endocrine and exocrine functions. CP is increasing globally with an incidence of 1.6 to 23 per 100000 people [1]. During the natural course of CP, pancreatic duct stones (PDS) are observed in 50% of patients. In 32% of cases, calculi are combined with pancreatic duct stricture, and in 18% of cases are alone [2,3]. The dominant symptom of CP is pain. Its pathophysiology is multifactorial. PD obstruction by stones and/or stricture. High intraductal pressure and ischemia from increased parenchymal pressure are the main pathophysiology mechanisms of pancreatic pain. Restoring pancreatic duct flow with complete pancreatic duct stone clearance and remodeling pancreatic duct stricture are the main objectives of the treatment of painful chronic pancreatitis. The aim of the present article is to review the appropriate current management of painful CP and to discuss the place of new techniques.

Diagnosis

To plan an appropriate treatment strategy for CP pain,

it is crucial to document the number of PD stones (single, multiple), location (head, body, or tail), distribution (parenchymal or intraductal, main pancreatic duct or branches), and the nature (radiopaque or radiolucent). At the same time, we must evaluate any dominant PD structure to determine its length and location and to exclude malignancy [4-9]. Abdominal plain films and ultrasound are not sufficiently accurate to identify and locate PD stones. The best pre-interventional diagnostic tests should be CT, MRCP, and EUS [10-12]. These tests can better detect pancreatic calcifications (size, position, and nature) and visualize the pancreatic duct morphology (size, cartography, and dilation) and any anomalies (stricture and pancreas divisum).

Pancreatic duct stones

PD stones are generally composed of an inner nidus of small quantities of trace elements such as sulfur, nickel, chromium, iron, and chlorine. Successive outer shell layers of calcium carbonate and calcite are deposited and form the typical pancreatic stone. It is suggested that the reduction of pancreatic stone protein (PSP) results in calcium precipitation in the pancreatic juice and deposition in layers over the inner nidus [13,14]. This pathway of pancreatic lithiasis is like all etiologies of chronic pancreatitis, but very large intraductal pancreatic calculi characterize tropical pancreatitis.

More Information

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In a recent study [15], 79.2% of calculi were radiopaque, 16% were radiolucent, and the rest were of the mixed type. Two-thirds of pancreatic calculi are single and found in the head and body, and in contrast, 15% of cases may be extensive and located in multiple areas.

Systems and techniques

Currently, endotherapy and surgery are the two available approaches to treat PDS and stricture in patients with painful CP. Non-steroidal anti-inflammatory drugs (NSAIDs) and opiates are the cornerstone of medication therapy following the WHO analgesic ladder. Other medications are considered to be beneficial for pain relief, like antioxidants, pregabalin, and S-ketamine. But their effects are still unclear, and larger-scale RCTs are still needed.

1. Endotherapy

In most cases, pancreatic stones are spiculated with high density and rigidity, making endoscopic treatment of pancreatic stones challenging. Two main procedures, ERCP and lithotripsy, can be used for stone removal and remodeling of pancreatic stricture.

a. Standard ERCP techniques: Inui reported the first pancreatic stone extraction by ERCP in 1983 [16], and by Cremer earlier. In 1985, Fuji and colleagues reported the first pancreatic stent placement [17].

i. Stone retrieval: Balloons, baskets, or rat tooth forceps are used for stone retrieval from PD through the duodenum. Using balloons for PDS removal is safer than other systems and is recommended in clinical practice.

ii. Pancreatic stricture: A dominant PD stricture is defined as a significant narrowing of the main pancreatic duct with upstream dilation (> 6 mm) that prevents the flow of contrast [18]. Most PD strictures from chronic pancreatitis are fibrotic and refractory to balloon dilation alone. We recommend a combination of balloon dilation and a single plastic stent for the stricture for one year [19]. Stricture is classified as refractory if the dominant stricture persists or relapses after one year of using a single plastic stent. In this case, endoscopic options include multiple plastic stents side by side [20,21] or fully covered self-expandable metal stents (FCSEMS) [22].

b. Lithotripsy

I. Extracorporeal Shock Wave Lithotripsy (ESWL): Sauerbruch and colleagues first introduced ESWL in 1988 for the fragmentation of stones in CP [23]. ESWL shock waves generate compressive stress on the outer surface of PDS. There are three sources

for generating shock waves. Electrohydraulic was used first, where the electric spark gap is located at the base water-filled container [24,25]. The second one is piezoelectric shock waves, which create ultrasonic vibrations resulting in a shock wave to the focal point [24,25]. An electromagnetic device is the third source, which induces high-frequency vibration in an adjacent metallic membrane [24,25]. The 2 last two sources used a water cushion to create air-free contact with the patient's skin. 2 imaging systems are used to localize pancreatic duct stones as well to track the progress of fragmentation and consist of either fluoroscopy or ultrasonography. Piezoelectric or electromagnetic systems cause less tissue damage and less pain because they generate a smaller high-intensity focal zone. 90 shock waves per minute is the optimal frequency of shock waves to administer during ESWL [26]. Studies showed a range from 1 to 12 of the total number of ESWL sessions per patient to allow adequate fragmentation of PDS [27,31]. The mean number of sessions varied around 2 to 3 [27-33]. But in 50% - 60% of cases, one ESWL procedure is enabled to fragment the adequate PDS. ESWL requires anesthesia to provide better patient tolerance and reduce patient movements. The goal of ESWL is to fragment PDS to less than 3 mm in size or to decrease in density of the stone mass. It is admitted that pancreatic ductal clearance is complete if stone clearance is more than 90%, partial if it is between 50 and 90%, and unsuccessful if it is inferior than 50%. The most common complications of ESWL are pancreatitis, hematuria, infection, skin erythema, bleeding, and perforation.

II. Mechanical lithotripsy: After adequate trapping of the pancreatic stone by a basket, mechanical lithotripsy can fragment the stone to allow stone extraction. This procedure is difficult to maneuver, especially in smaller ducts, which can cause duct injuries [34].

III. Lithotripsy under direct visualization: per-oral pancreatography (POP) was introduced into clinical practice in 1976 [35]. However, the single-operator digital video cholangiopancreatography system (DSOP) (Spy Glass DVS, Boston Scientific, Natick, Massachusetts, US) was introduced in 2015. It's characterized by a larger working channel (1.3 mm), high-resolution imaging, and a specialized irrigation channel. This technology is used as a third option for the treatment of complicated pancreatic stones after ERCP and lithotripsy failure. After fragmentation, ERCP is required for

stone extraction. 2 techniques, electrohydraulic lithotripsy (EHL) and laser lithotripsy (LL), are available to achieve intraductal lithotripsy. EHL technique comprises a charge generator and a bipolar probe that produces sparks at its tip in an aqueous solution [36]. In 1999, Howell and colleagues used a baby scope through a therapeutic duodenoscope into PD to perform EHL on pancreatic stones under direct visualization [37]. For LL, there are 2 main fragmentation techniques: Neodymium: yttrium-aluminum-garnet (Nd: YAG) and Holmium: YAG. In Nd: YAG, the frequency is composed of 532nm green light (20%) and 1064 nm infrared light (80%). It breaks stones by producing plasma on the surface stone and then absorbs the infrared light energy, powerfully generating a strong shock wave [38]. In contrast, Holmium: YAG lithotripsy fragments stones via a photothermal mechanism transmitted directly to the stone and depends on laser energy absorption of the light with a large wavelength of around 2100 nm [39]. However, the laser technique is FDA-approved for PDS lithotripsy. Still, no prospective study compares the efficacy and safety of these 2 distinct lithotripsy techniques for pancreatic stone fragmentation. During lithotripsy, the patient should receive non-steroidal anti-inflammatory drugs, and it's recommended to place a large plastic stent (8 - 10F), especially in case of stricture.

c. Endoscopic ultrasound-guided pancreatic duct drainage (EUS-PDD)

ERCP fails in 3% - 10% of the cases with native anatomy. Many reasons make pancreatic duct access difficult or not feasible, like tight strictures or stones, anatomic duct variants that prevent deep cannulation, surgically altered foregut anatomy, luminal obstruction preventing access to the papilla, and a disconnected pancreatic duct. Currently, EUS has become a new frontier for accessing pancreatic ducts when ERCP fails, and it can offer an alternative to surgery. EUS-PDD can be performed in 2 ways: EUS-assisted pancreatic rendezvous (EUS-PRV) and EUS-guided pancreatico-gastrostomy (EUS-PG) [40].

I. EUS-PRV: Bataille and colleagues reported it for the first time [41]. This approach is performed by puncturing the PD typically with a 19-gauge needle, which allows the passage of the guide-wire into the MPD. Guide-wire is advanced toward the papilla or surgical anastomosis across the papilla to the duodenum. Then the echoendoscope is exchanged for a duodenoscope, colonoscope, or enteroscope, which allows endoscopists to perform retrograde interventions: cannulation of PD, dilation of a stricture, extraction of stones, or placement of stents [41-44].

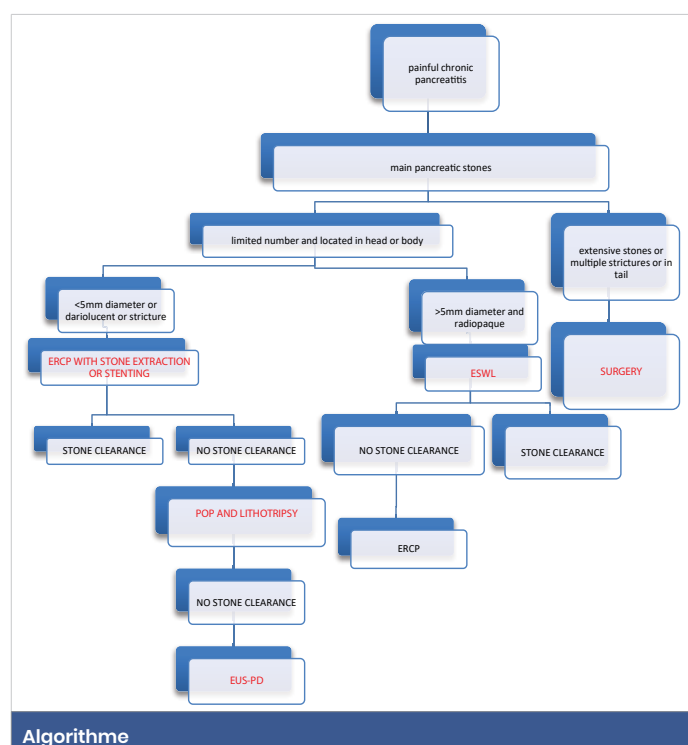
II. EUS-PG: Francis and colleagues reported it for the first time in 2002 [45]. Generally, the procedure is achieved through the stomach. When the guidewire is placed into MPD as described above. Mechanical or cautery devices create a fistulous tract between the stomach and PD over the guidewire. Then, a plastic stent of 5F or 7F is placed transmurally and positioned toward the head of the pancreas. After 1 month, the tract becomes mature for further interventions: balloon dilation, stent replacement, or direct pancreatoscopy with direct visualization lithotripsy [46-48].

2. Surgery

Pearce reported the first surgical stone removal in 1891 [49]. Surgery adopts one of three different approaches: resection of diseased tissue, ductal drainage, or a combination of the latter techniques. The nature of surgery depends on disease distribution and the size and morphology of the MPD [50]. Many surgical procedures were described. It includes the Whipple procedure, Puestow procedure, Frey procedure, total pancreatectomy, islet auto-transplantation, etc. The most commonly used surgical procedures are focused on duodenum-preserving resection of the head of the pancreas. In RCT, duodenum-preserving procedures have reduced in-hospital complications and better improvement of quality of life compared to duodenum-resecting procedures [51].

Indications

The current American Society for Gastrointestinal Endoscopy (ASGE) and European Society of Gastrointestinal





Endoscopy (ESGE) guidelines for treatment of PDS in CP are most often applied by endoscopist teams [52,53]. There is no indication of treatment in case of asymptomatic and uncomplicated CP.

Interventional therapy is indicated for patients with refractory pain after lifestyle modifications and pharmacotherapy. Endoscopic therapy and/or ESWL are now the first-line therapy for painful, uncomplicated CP with an obstructed MPD in the head and/or body of the pancreas. The selection of patients with the absence of MPD stricture, a short disease duration, absence of cigarette and alcohol intake, and complete removal of obstructive PDS had the best long-term outcome.

Guidelines recommend ERCP for MPD radiopaque stones smaller than 5mm and radiolucent stones located in the head and/or body of the pancreas. ESWL is recommended for the fragmentation of radiopaque obstructive MPD stones larger than 5mm, and in case of failure ERCP procedure. Isolated tail stones are not treated by ESWL because of the risk of spleen damage. ESWL is limited in its ability to address radiolucent stones, multiple strictures, and multiple stones in cases of ascites or coexistent pseudocyst. Coagulopathy must be corrected before ESWL. Guidelines suggest restricting the use of ERCP after ESWL in case of no spontaneous clearance of adequately fragmented pancreatic stones by ESWL. In ESWL, solitary stones, stones in the main pancreatic duct of the head, stones with a density on CT scans of < 820Hu, secretin or stenting before ESWL or ERCP delayed by 2 days are related to better outcome.

POP-guided intraductal lithotripsy (PGL) is an efficient alternative endotherapy for obstructing PDS. POP is especially indicated in the case of refractory and stent-dependent strictures with obstructing PDS, rendering the standard ERCP approach limited and inefficient. POP-PGL could directly visualize strictures for laser stricturoplasty and target calculi within the same session. So, it is suggested as third-line therapy when ERCP and ESWL fail to clear the MPD from stones, especially in the presence of pancreatic duct stricture.

Currently, EUS-PDD is an emerging technique. It is considered a salvage procedure after the technical failure of ERCP. EUS-RDV is selected if the papilla or anastomosis is easily accessible. EUS-PG is considered for patients with altered anatomy or in cases of guidewire failure to pass an obstruction during EUS-PRV. This technique is a challenging procedure with high rates of adverse events, and it is not widely adopted.

We know to date that surgery is widely accepted as the more effective treatment for painful CP. But endotherapy is considered the first-line treatment because it is a minimally invasive procedure.

Results

All scientific societies favor ERCP and/or ESWL as a first-line approach to pancreatic duct drainage, given endoscopic advancements, minimal invasiveness, and low adverse events compared to surgery.

2 early monocentric open-label randomized clinical trials (RCTs) suggest that surgery was superior to endoscopy to relieve pain in patients with obstructive CP [54,55]. These 2 trials suffer from several limitations. In the trial of Dite, et al. the results of the endoscopy and the surgery were not satisfactory (15% in endoscopy and 34% in surgery), and neither ESWL nor cumulative stenting was used. In the Cahen, et al. study, the number of patients included was very low (only 39 patients), so the results cannot be extrapolated to all painful obstructive CP patients. Also, data from the ESCAPE trial, a recent multicenter RCT, favor surgical intervention at an earlier stage to alleviate disease progression, leading to improved pain management [56]. But, this trial had two limitations, including the subjectivity of the pain score and the absence of sham-control. In a recent systematic review and meta-analysis, no difference between surgery and endotherapy was found in the short term. However, surgery was more efficient in pain relief than endoscopy in the long term [57].

Recent studies showed better clinical success with long-term results of ESWL combined with ERCP. The reason is due to better selection of patients for endotherapy and technical advancements. In fact, concerning clinical success, in a large prospective single-center series (1006 patients), ESWL achieved fragmentation of large PDS in 90% with less than 3 sessions, leading to pain relief in 84% of cases [58]. Likewise, in the most recent meta-analysis of 3668 patients, 86.3% of cases achieve complete fragmentation, leading to ductal clearance in 69.9% of cases and resulting in the absence of pain in over 50% [59]. Concerning long-term results, a recent systematic review showed that patients who remained asymptomatic at 2 years follow-up after complete pancreatic ductal clearance rarely experienced pain relapse thereafter [59]. Delhaye M, et al. followed for 14 years patients with painful CP treated by endotherapy. In their study, he reported long-term benefits for about two-thirds of these patients with a decrease in hospitalization rate and delayed impairment in exocrine pancreatic function [60]. Most of these patients were young, and maybe early intervention after the course of the disease. A Japanese RCT explored the efficacy of early endotherapy in 20 patients with mild painful CP in comparison with a wait-and-see policy. Preliminary results showed a benefit in terms of reducing the frequency of acute attacks and preventing gland atrophy [61].

One matter of debate is the benefit of the combination of ESWL and ERCP compared to ESWL alone. Only two studies, one randomized controlled trial and one retrospective clinical

study, compared head-to-head ESWL alone to a combination with ERCP. No additional benefit in pain control was found in the systematic combination of the two procedures [62,63].

With the advancement of endoscopic techniques, new procedures have become an alternative to conventional ERCP and ESWL. When first introduced, several retrospective studies of POP-PGL showed high rates of stone clearance between 80% and 90% [64,65]. Likewise, two meta-analyses evaluated the performance of POP-PGL with either LL or EHL techniques. The first one includes 16 studies with a technical and clinical success rate of 76% and of 77% respectively [66]. The second one includes ten studies with large stones, with a mean size of 10.6mm, and found a technical success of 91% without a significant difference between EHL and LL [67]. Recently, a prospective multicenter RCT was published from Germany evaluating the efficacy of POP-PGL in painful CP. They selected patients with three or more stones, > 5 mm in diameter, and located in the pancreatic head or body. Complete stone clearance was achieved in 90% of cases [68]. The most recent systematic review and meta-analysis evaluating the safety and efficacy of POP-PGL treatment for symptomatic pancreatic duct stones included 17 studies, 5 prospective and 12 retrospective, with 441 patients [69]. The pooled complete stone clearance rate, clinical success rate, and adverse event rate were 81%, 90%, and 12%, respectively. POP-PGL can be considered a second-line endoscopic treatment for CP, evidenced by a high rate of safety and efficacy.

Finally, we review recent literature focused on EUS-PDD, encompassing clinical and technical success as well as complication rate. The overview showed a technical success rate ranging from 25 to 92%, long-term success within a range of 65%-85%, and a complication rate spanning from 14 to 40% [70]. In 2018, EUS-PG, followed by antegrade pancreatoscopy via PG and intraductal lithotripsy, was described for the first time [71]. A recent systematic review compared head-to-head ERCP-guided to EUS-guided pancreatic access in altered anatomy. EUS-PD had the higher technical success rate. The success rates concerning pancreatic duct cannulation were 86% vs. 20%, pancreatography was 86% vs. 25%, and stent placement was 73% vs. 20% [72]. In one center, EUS-PD was also compared to enteroscopy-assisted ERCP on pancreatic duct access in altered anatomy. The technical success rates were 100% vs. 70, 7%, with a high rate of complications in the EUS approach. The overall clinical success rate, when the two approaches were combined, reached 85% [73].

Conclusion

In painful CP, pancreatic duct clearance is the mainstay of our treatment after medication treatment failure. Guidelines recommend a step-up approach. In selected cases, conventional ERCP and/or ESWL are offered as a first-line therapy. When endotherapy fails to sufficiently clear the pancreatic duct from stones or in altered anatomy, new

endoscopic techniques may be offered as an alternative approach. POP is considered a second-line therapy. It can directly visualize the stones and the strictures and allow intraductal lithotripsy in the same session. EUS-PD is reserved for cases of ERCP technical failure or in patients with an inaccessible papilla. EUS-PD is a challenging and complex technique. It will be regarded as an alternative endoscopic approach in challenging and complex cases. Finally, surgery will be reserved for patients failing endotherapy or in cases with suspected malignancy. Despite all the technical and endoscopic advances, the management of painful chronic pancreatitis and pancreatic lithiasis remains insufficient and complex, with a high rate of complications. We need new devices that make direct access to the main pancreatic duct easier and powerful techniques capable of fragmenting calculi completely and quickly. As the pathophysiology of CP is multifactorial, new medications are needed as complementary treatment to endotherapy. What role does artificial intelligence play in the future?

Author contributions

Abboud B designed the research; Boujaoude J and Al Bacha R performed the research; Boujaoude J, Al Bacha R, and Abboud B analysed the data; Boujaoude J, Al Bacha R, and Abboud B wrote the paper.

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