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Advances in the Management of Pain in Chronic Pancreatitis

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Abstract

Purpose of Review The data on recent advances in managing chronic pancreatitis (CP) pain is limited. This review highlights the role of endotherapy and the advances in the overall management of pain in CP.

Recent Findings Of late, pancreatic biodegradable stents have been used in endotherapy with appreciable success. These include slow, medium, and fast degrading stents, which optimize the overall management of CP and could prevent the need for multiple procedures. Endoscopic ultrasound-guided celiac plexus block is reserved in selected patients to treat debilitating pain. Total pancreatectomy with islet autotransplantation in small duct disease has shown promising results. The indications for treating pain in CP with endoscopy and surgery need to be better defined.

Summary The complexity of pain control due to the incomplete understanding of pathomorphology makes the management of CP challenging. The current treatment methods are still evolving. Therapy aims to reduce pain, optimize recovery, maintain quality of life, and meet postoperative needs. Initial management includes lifestyle modification, nutrition optimization, risk factor reduction with abstinence from alcohol, cessation of tobacco and smoking. Supportive medical management involves the judicial use of analgesics, neuromodulators, antioxidants, pancreatic enzyme replacement for insufficiency, and diabetes management. Patients with intractable pain are ideal for therapeutic intervention. Being less invasive with an acceptable complication rate makes endotherapy the preferred first-line treatment. If found to be cost-effective, biodegradable stents can reduce the overall cost. Unfortunately, if patients remain symptomatic, surgery is preferred in case of failure or recurrence. For optimal results, appropriate patient selection is vital to maximizing outcomes.

Keyword Chronic pancreatitis · Endotherapy · Pain management · Surgery

Introduction

Chronic pancreatitis (CP) is an inflammation of the pancreas that leads to extensive fibrotic tissue replacement, resulting in repetitive pain episodes, exocrine and endocrine pancreatic insufficiency, thereby severely impacting the quality of life [1–3]. The multifactorial etiology, changing incidence, and diverse morphological characteristics make its management challenging. The etiology, incidence, pathomorphology of CP are too variable. Pancreatitis can be tropical, idiopathic, or alcoholic [4]. Tropical pancreatitis is common in Africa and Asia, including India, while alcoholic pancreatitis is more common in western countries. Alcohol is the most common etiology of CP in the western world [5], while nonalcoholic CP is more prevalent in India [6]. The typical clinical manifestations in these patients include abdominal pain, weight loss, diabetes mellitus, and steatorrhea [7]. The indications and modalities of treating CP keep evolving. Endoscopically treatable morphology includes pancreatic stones, pancreatic ductal strictures, stones and strictures, pseudocysts, and biliary strictures [8, 9]. The established indication for endotherapy and surgery is pain relief. Other indications requiring treatment are increased intraductal/parenchymal pressure, neural remodeling / neuropathy, pancreatic ischemia, and acute inflammation [8]. The other possible indication is the improvement of

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endocrine / exocrine function, delaying disease progression. The European Society of Gastrointestinal Endoscopy recommends endotherapy as the first-line treatment for painful uncomplicated CP [10•]. The clinical response has to be evaluated at 6–8 weeks; if it appears unsatisfactory, the patient's pancreatic problems should be discussed in a multidisciplinary team with endoscopists, surgeons, and radiologists. Subsequently, surgical options are to be considered, particularly for patients with poor outcomes [10•]. This brief review focuses on the management of CP and its recent advances.

Pain in CP

Pain in CP is associated with a complex interplay of multiple mechanisms [11]. Peripheral pain perception and central pain processing of nociceptive signals are altered in CP. The hallmark of neuropathic pain syndrome is neuro-inflammation. Numerous molecular and morphological changes at intrapancreatic (peripheral) and extrapancreatic sites contribute to pain in CP. Neurological pain has three aspects: pancreatic neuropathy, central sensitization mechanism, and peripheral nociception [12]. Pancreatic quantitative sensory testing (P-QST) was developed as a pain assessment tool for CP [13]. It utilizes a nomogram that identifies patients with higher pain intensity scores and a higher prevalence of constant pain by sensory testing using standardized stimuli. Independent of psychiatric comorbidities, P-QST differentiates CP patients into specific pain phenotypes [14]. The initial results appear good but need validation of their findings.

General Supportive Measures

Supportive measures include alcohol, smoking, and tobacco cessation [15]. Restricting very high-fiber diets and high-protein food fortification is recommended. These patients are often advised to consume smaller meals, have adequate hydration, and should counsel on eating a healthy balanced diet and having sufficient sunlight exposure [16]. Medium-Chain Triglycerides have been used to treat fat malabsorption and also serve as calories to improve nutritional status [17]. Vitamins should be supplemented when clinically indicated.

The pain symptoms must be related to CP and not an alternative etiology. The pain mechanisms are complex; hence strategies for pain management have limited efficacy. Nonsteroidal antiinflammatory drugs (NSAIDs) are used initially, followed by opioids (tramadol) for uncontrolled pain. Patients should be counseled that pain can only be controlled. Adjunctive agents include antispasmodics, tricyclic antidepressants (amitriptyline), serotonin reuptake inhibitors, combined serotonin and norepinephrine reuptake inhibitors (duloxetine) or gabapentinoids (pregabalin) [18].

Subsequently, antioxidant therapy with methionine, beta-carotene, selenium, vitamin E and C are useful in managing pain in CP [19]. Pancreatic enzyme supplementation (non-enteric coated enzymes) helps to treat exocrine pancreatic insufficiency [20]. Proton pump inhibitors are used to avoid acid denaturation of lipase. Pancreatic proteases (high doses), when delivered to the duodenum, reduce cholecystokinin levels, which in turn reduces the stimulation of the pancreas. Cognitive-behavioral therapy is efficacious for patients with psychological comorbidities to reduce CP pain and can be used as an adjunctive treatment [21]. Failure of these options is not unusual.

Pancreatic Endotherapy

Patient Selection

The ideal candidates are patients with nonalcoholic etiology. If patients are alcoholic, then they should have a non-complex pathomorphology. Pain episodes should be intermittent. The duration of symptoms should be less than 5 years. Patients should not have an opiate addiction and be compliant to the cessation of smoking / tobacco / alcohol, if any and willing for repeated procedures, including long-term followup. Pancreatic head / body diseases are the ideal candidates for this procedure. Simple pathomorphology includes stone predominant disease, single dominant stricture or dilated Pancreatic duct (PD). By appropriately adhering to some of these criteria, the patients would have better outcomes from endotherapy.

Pancreatic Stones

The majority of pancreatic stones are radio-opaque in about 90% of patients. These can be hard, spiculed, impacted, associated with strictures or complex pathology and sometimes inaccessible. Radiolucent or small radio-opaque stones account for up to 10%. The stone density in such cases needs to be studied on non-contrast computed tomographic scan as this will predict the outcome of Extracorporeal shock wave lithotripsy (ESWL) for stones that may be resistant to ESWL [22]. For radiopaque stones, ESWL should be performed [4] before as this is the cornerstone of therapy (Fig. 1). The use of third and fourth-generation shock wave lithotripters has resulted in achieving good accuracy and higher success rates with adequate safety. End point of ESWL is pulverization of stone (< 3 mm), loss of stone density, the spread should be along the duct with disappearance. With radiopaque stones, ESWL should be followed by Endoscopic retrograde cholangiopancreatography (ERCP) with wide sphincterotomy and then stone extraction with wire-guided basket / balloon. For radio-opaque stones of size < 5 mm in a dilated duct,

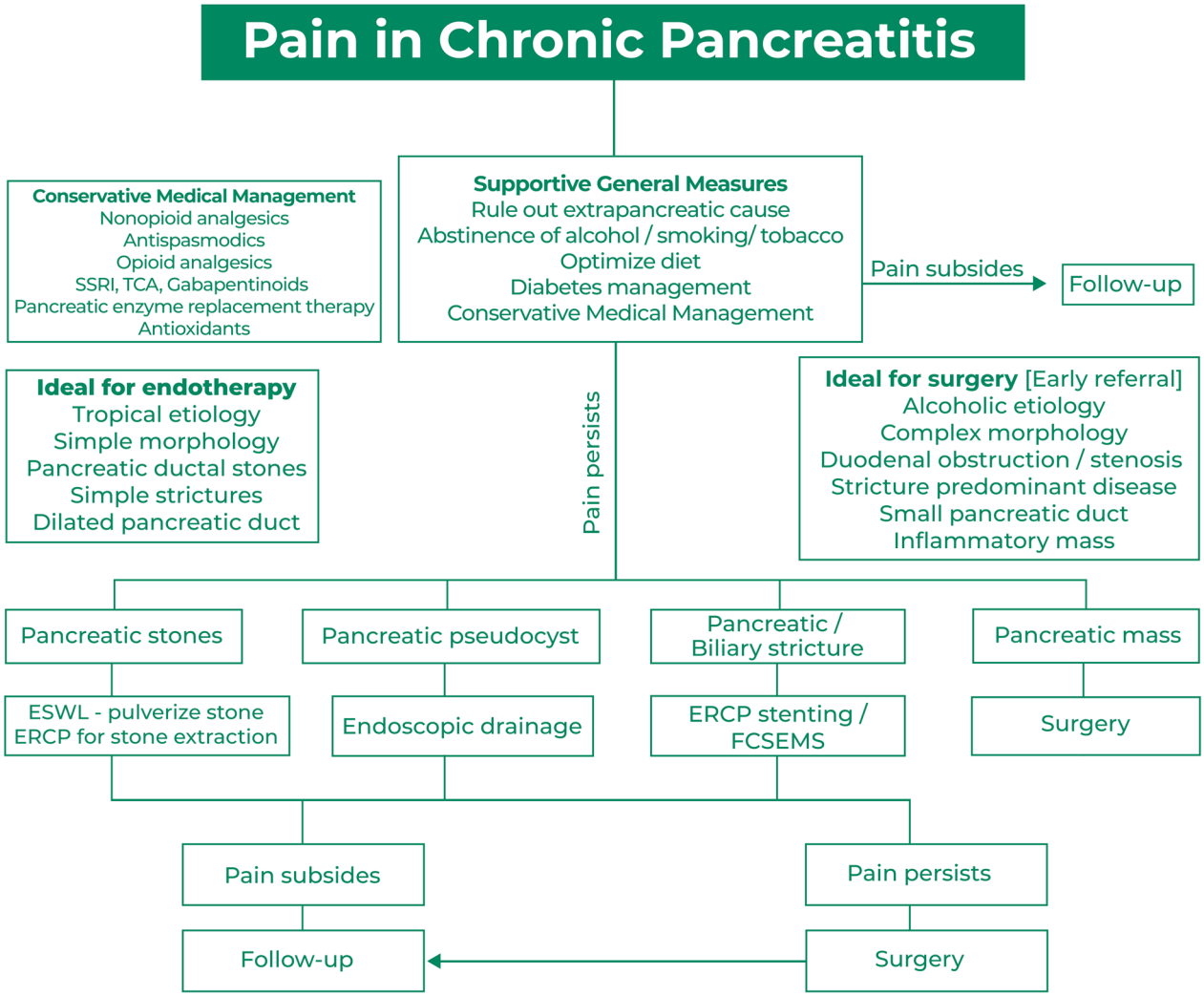

Fig. 1 Algorithm for management of pain in chronic pancreatitis

these patients should undergo a direct ERCP. All radiolucent stones should also undergo direct ERCP; wide sphincterotomy should be performed, with/without balloon sphincteroplasty and balloon sweeping. All patients should have a regular follow-up every 3 months. Patients may require repeat ESWL / ERCP until the end point is achieved. A temporary 5 / 7Fr stent can be used between sessions to allow the spontaneous passage of fragmented stones. The end point of therapy remains complete clearance of the PD [10•].

Pancreatic Strictures Associated with CP

The most commonly accepted protocol is stenting for stricture-predominant disease with single, multiple, tight, soft, or complex strictures. It is advisable to place the largest possible stent in the first sitting (5, 7, 10 Fr) [10•] (Recommendation—Grade C). If 10 Fr is not feasible, one must repeat every 3 months until one or two 10 Fr stenting is done. The patient should be directly called after 1 year (contact patient every 3 months for follow-up history and imaging); intervene only if symptomatic. The stent should be removed after 1 year, and the stricture should be reassessed. If stricture persists, a multiple stent regime [23] is required, or the patient needs to undergo surgical drainage [10•]. Fully covered self-expandable metal stents (FCSEMS) are safe, and associated with good resolution of stricture and pain relief [24]. A concern with these stents is intra-ductal stricture or stent migration; hence these should be used only in the trial setting [25–27]. A surgical opinion must be taken if patients constantly return despite successful endotherapy.

Biliary Strictures and Pseudocysts Associated with CP

The same protocol for the PD stricture is followed for biliary strictures. FCSEMS should be used for benign biliary

strictures [28]. The FCSEMS should be removed after 7 months and reassessed [29, 30]. If stricture persists, such patients should be referred for surgery (Pancreatic head coring, Whipple's Procedure). With Pancreatic Pseudocysts, only about 9–10% resolves spontaneously. About 40- 60% have communication with main pancreatic duct. Transpapillary stenting (10Fr) (Recommendation Grade A) is the first line of treatment in these patients [30–33].

Biodegradable Stents

The biodegradable pancreatic stents (Archimedes, amg International GmbH, Germany) drain obstructed pancreatic duct with different degradation profiles ranging from 12 days to 11 weeks [34•, 35, 36]. The biodegradation profile was reliable with expected times in multiple indications [35]. Long-term data is currently lacking regarding their use.

EUS Celiac Plexus Block and Neurolysis

EUS-guided celiac plexus block involves injecting a local anesthetic together with a corticosteroid. Celiac plexus neurolysis involves injecting alcohol which has a more permanent effect [37]. But, due to the possibility of nerve injury from neurolytic agents, steroids are recommended. Puli SR et al. in a meta-analysis, reported a response rate of 59% in CP with 3 months of pain relief but did not interrupt analgesic medication [38]. EUS-guided celiac plexus block needs expertise and is principally used for pancreatic cancer pain.

Surgery

Surgery is indicated early in the disease (Fig. 1) or in those who failed maximal medical and endoscopic therapy. The surgical approach includes pancreatic duct drainage, partial pancreatic parenchymal resection or a combination of drainage-resection and is preferred in patients with inflammatory head mass or pancreatic duct dilation [39, 40•]. The common modalities include the following:

For Non-Dilated PD

Head-dominant—Classic Pancreaticoduodenectomy, pylorus-preserving total pancreatectomy or duodenal-preserving pancreatic head resection (DPPHR) (Berger procedure).

Diffuse parenchymal disease — Total pancreatectomy with islet autotransplantation.

Tail-dominant disease—Distal pancreatectomy [39, 40•]

Dilated PD

Lateral pancreaticojejunostomy (Puestow), longitudinal pancreaticojejunostomy (modified Puestow) [without inflammatory pancreatic head mass], Lateral Pancreaticojejunostomy with head resection (Frey).

Post-operative complications include exocrine pancreatic insufficiency, pancreatic fistula, pancreatogenic diabetes mellitus, and (EPI) which can lead to morbidity [40•].

Total pancreatectomy with islet autotransplantation is preferred in genetic predispositions, when drainage or partial resection is not feasible or when other conventional surgeries have failed [40•, 41]. Children with CP secondary to genetic/ hereditary causes are ideal candidates for this procedure. Improved pain relief has been noted with this procedure [42]. Since this surgery removes the endocrine tissue, more than 50% of the patients may not achieve insulin independence.

Endotherapy vs Surgery

The high-quality research publications are sparse for pancreatic endotherapy. The technique still needs to be standardized, is difficult to perform and labor intensive. The case volumes are only limited to few selected centers across the world. The concepts of patient selection and the end point of therapy have remained unclear. The first randomized study by Dite et al. in 2003 [43] compared endotherapy with surgery. Of 140 eligible patients, only 72 agreed to be randomized. The authors concluded that in patients with painful obstructive CP, surgery showed better long-term pain reduction than endotherapy. Cahen et al. [44] in 2007 and followed up in 2011 with a long-term study [45]. The first concluded that in patients with PD obstruction, surgical drainage fared better than endotherapy [44]. In the subsequent study, symptomatic patients with advanced CP who had initial surgery for PD obstruction had better pain relief, with fewer procedures, than patients treated endoscopically [45]. Notably, almost half of the patients treated with endoscopy eventually underwent surgery. In the ESCAPE trial, early surgery resulted in lower pain scores than endoscopy when followed for 18 months [46]. In the post hoc analysis, the endoscopic subgroup with complete ductal clearance had a significant improvement in pain score (comparable to the surgical group) than the endoscopic subgroup with incomplete ductal clearance [46]. Most were done with small sample size and in an era when endotherapy was not adequately explored or utilities and accessories for endotherapy were not as advanced as available in 2023. Therefore, future studies must consider these outcomes by including a largely homogenous population with ideal candidates for endotherapy and surgery.

When to Stop Endotherapy?

Endotherapy could be stopped only after the endpoint is achieved, i.e. complete stone clearance and patient stent / pain-free for more than 6 months. In case of stricturing disease, complete stricture resolution and no stricture recurrence / pain after 6 months. For patients who are intermittently symptomatic during endotherapy with repeated visits may need to be investigated for complex pathology including malignancy. There is no clear end point in sight in spite of endotherapy for 3 years. One may decide to stop if the patient is non-compliant with continued alcohol consumption, smoking and irregular visits, despite adequate counselling.

Future Research and Recommendations

Can there be a consensus for endotherapy in CP? The selection criteria remain unclear. The availability and experience with ESWL remain unknown. The stenting regime is arbitrary. The endpoints of therapy are undefined. Therefore, a randomized controlled study is necessary to compare the outcomes of the initial ESWL strategy, multistep-intervention strategy, and surgery in patients with coexisting CP. Although there is no limitation in the size and number of pancreatic stones for ESWL treatment, very large and multiple stones will require repeated ESWL sessions which may not be cost-effective. Hence, a cost-effectiveness analysis with surgical modalities would be useful. The recurrence of calculi following ESWL has been well documented. There is a need to identify pharmacological agents which can prevent this reformation and would be very beneficial in preventing stone recurrence and reducing the need for repeat interventions. Emerging therapies include vagal nerve stimulation to treat abdominal pain [47].

Conclusions

The incidence of CP is increasing, and there is no definite therapy. Pain in CP should be initially managed by supportive general measures, including diet modification and nutrition optimization followed by appropriate medical therapy. Pancreatic ductal hypertension is a major contributory factor to pain which is relieved by decompression at ERCP. Surgery in CP is performed based on the ductal anatomy and gland morphology. Patients with non-dilated duct should undergo one of the resection procedures. Total pancreatectomy with islet autotransplantation has shown good outcomes for pain relief in children. Patients with alcoholic etiology, complex morphology, small duct disease and stricture predominant disease are ideal candidates for surgery. In contrast, tropical etiology, simple morphology, pancreatic ductal stones, simple strictures and dilated ducts are ideal candidates for endotherapy. Pancreatic biodegradable stents might offer benefit in stricturing CP. EUS-guided celiac plexus block is useful in pancreatic cancer pain. Endotherapy of CP is progressing rapidly, but we need to define which patients will benefit from endotherapy and surgery and not withhold one over the other. The need of the hour is to have appropriate radiological investigations before subjecting patients to a definitive therapy and then treat these patients based on pathomorphology.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international / national / institutional guidelines).

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