Conservative Treatment of Chronic Pancreatitis

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Pain Management in Chronic Pancreatitis

Kai Bachmann, Stephanie Plagemann, Yogesh Kumar Vashist, and Jakob R. Izbicki

Department of General, Visceral and Thoracic Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Introduction

Pain is the leading symptom in patients with chronic pancreatitis. The aim of treatment is symptom control, improvement in quality of life, and prevention of ongoing damage to the gland. Chronic pancreatitis cannot be cured.

The main reason for hospitalization in patients with chronic pancreatitis is a constant severe and dull pain located in the mid-epigastrium, which radiates to the back and worsens after fatty meals. Because the pain has a multifactorial etiology, treatment needs to be variable. There are various theories as to the origin of the pain but, to date, its development is not fully understood and various different theories exist. More detailed information is presented in Chapter 41.

Neuropathologic Theory

The pancreas is highly innervated through the vagal and splanchnic nerves. Unlike other visceral organs, it has primary afferent nociceptors that only respond to pain stimuli. These fibers have a subgroup called "silent nociceptors," which are only active during inflammation. Pancreatic nociceptors are activated by a variety of noxious stimuli. Those located on the supplying blood vessels are activated mechanically through stretching, ischemia, and necrosis. Others are affected chemically by inflammatory mediators [1].

The inflammation is mostly caused by noxious stimuli (the most common being alcohol and nicotine). These damage the parenchyma and the damaged tissue supports the inflammation by releasing proinflammatory mediators. The nerve endings then become sensitized to further stimulation. The silent nociceptors can be activated by peripheral inflammation, which increases the afferent activity in the spinal cord. The stimulation is transferred to the central nervous system and by repeated stimulation a peripheral sensitization develops. Released neurotransmitters are also transported to nerve endings located on the pancreas where they act as proinflammatory transmitters, resulting in neurogenic inflammation which causes edema and the infiltration of inflammatory mediators.

In summary, three factors lead to neurogenic pain: chronic stimulation through nociceptive pathways, peripheral sensitization due to inflammatory processes in the pancreas itself, and neural damage [2]. Currently these neurophysiologic aspects are the main focus of studies on pain in patients with chronic pancreatitis.

The Plumbing Theory

According to the "plumbing theory," pain in patients with chronic pancreatitis originates in the plumbing of the pancreatic duct and is caused by intraductal calculi or duct strictures, leading to increased pressure in the gland. This is the theory on which interventional therapy is based. Compared to recently discovered neuropathologic factors, the theory that pancreatic duct hypertension causes pain is rather old. It was first described in the 1970s and interventions to drain the pancreatic duct based upon it became an option for treating pain.

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Presently, few studies exist on the measurement of intraductal and intraparenchymal pressure. In addition, there is no evidence for the impact of developing chronic pancreatitis and evolving chronic pain in existing studies.

According to the plumbing theory, intrapancreatic pressure is described as a "compartment-like-syndrome," with chronic inflammation leading to fibrosis of the parenchyma and capsule, resulting in tension [3]. Different studies, however, have failed to substantiate these theories. The neurophysiologic theory seems to be closest to reality.

If pain in chronic pancreatitis develops due to a combination of the neuropathic pathway and the plumbing theory, it explains why treatments aiming at the nociceptive pain, such as opioid analgesia, and endoscopic or surgical interventions sometimes fail to ease the pain. To visualize possible central sensitization, electroencephalography and (functional) magnetic resonance imaging have been used [4].

Pain Measurement

When evaluating therapy for a patient with chronic pancreatitis, objective parameters are needed to find out how much the patient is limited in his or her daily life by the symptoms of chronic pancreatitis. To measure quality of life, the European Organisation for Research and Treatment of Cancer (EORTC) questionnaire is a reliable base. The Izbicki pain score questionnaire correspondingly measures pain that lowers the quality of life with regard to pain frequency, its intensity (using a visual analog scale), the effectiveness of analgesia, and disease-related inability to work or take part in social activities [5] (Table 51.1). It is designed specifically for patients with chronic pancreatitis and is a reliable and comparable instrument, which focuses on the particular burdens of these patients. The score ranges from 0 to 100 in total [5]. A pain score of ≥50 is considered to be strong pain.

Examples of analgesic medication are given in Table 51.2.

Table 51.1 Izbicki pain score.

											Points
Frequency of pain attacks											
Daily											100
Several times a week											75
Several times a week											50
Several times a week											25
None											0
Visual analog scale (VAS)											
0	1	2	3	4	5	6	7	8	9	10	
No pain		mild		moderate		severe		very severe		worst imaginable pain	
0 points										100 points	
Analgesic medication											
Morphine											100
Buprenorphine											80
Pethidine											20
Tramadol (μ-agonist, max. 600 mg/day)											15
Metamizole											3
Acetylic acid											1
Duration of inability to work due to disease											
Permanent											100
1 year											75
1 month											50
1 week											25
No inability to work during the last year											0

Table 51.2 Examples of analgesic medication for chronic pancreatitis.

Medication	Dose
Morphine	
Buprenorphine	Partial opioid agonist with full effect at the μ-receptor
	Not first choice for acute pain
	Daily dose depends on chosen application form
Pethidine	Opioid agonist with high affinity to the μ-receptor
	max. 500 mg/day
	Metabolism through the liver with active metabolite norpethidine and elimination through the kidneys
	May induce a serotonin syndrome
Tramadol	Serotonin and noradrenaline reuptake inhibitor and μ-agonist (strong relation to nausea and vomitus, may induce a serotonin syndrome)
	Max. 400 mg/day
	Metabolism through the liver
Metamizole	As prodrug activation through hydrolysis, bioavailability is a bit higher when taken orally rather than parenterally
	Unselective COX inhibitor
	Analgesic, antipyretic, and spasmolytic
	Max. 4 g/day
	Elimination mostly through the kidneys
Acetylic acid (as representative for NSAID)	Unselective and irreversable COX inhibitor, analgesic, antipyretic, and anti-inflammatory, high first-pass effect
	Max. 3 g/day
	Inactivation through the liver and elimination through the kidneys

This is not a complete list. Prior to any medical treatment the daily medication, individual risk factors, and side-effects should be evaluated.

Treatment Options for Patients with Chronic Pancreatitis

As the cause of pain in chronic pancreatitis is not completely clear, the most useful hypothesis for optimal therapy might be a multifactorial understanding of the development of pain.

Change of lifestyle, diet, and medical treatment form the basis of initial treatment and in a small number of patients symptoms will be treated satisfactorily. In most cases, however, nutritional and medical treatments are the first step in the management of chronic pancreatitis before considering endoscopic or surgical approaches.

Even when patients remain abstinent from alcohol and nicotine, pain often persists. Abstinence is recommended to reduce the noxious stimuli to decelerate the progression of the chronic inflammation. Pain relief is attempted by analgesia, beginning with nonsteroidal anti-inflammatory drugs and ending with a combination of strong opioids (as recommended by the World Health Organization). Opioids may have substantial adverse gastrointestinal effects, including constipation, reflux, nausea, and abdominal pain—a phenomenon known as opioid-induced bowel dysfunction.

Recent studies have shown a positive effect of pregabalin in pain management, including in patients with persistent pain after surgery. The side-effects of pregabalin were only moderate. Patients complained of a slightly drunk feeling, which is negligible compared to strong opioids and their gastrointestinal side-effects [6,7].

Because of the pain, patients often abuse analgesics. Medical and dietary therapy can ameliorate the symptoms for a small number of patients. Nonetheless, alcohol abstinence does not disrupt the destructive progress nor alleviate the pain [8,9]. In patients where conservative treatment fails to provide improvement, interventional procedures are indicated.

The major challenge in managing chronic pancreatitis seems to be the evaluation of the optimal interventional treatment for each patient individually. Not only is it a question of what kind of therapy the patient will profit from, but also a question of finding the right time when each therapy is best.

The vast majority of patients present with dilatation of the duct or enlarged pancreatic head. Therefore, endoscopic procedures such as extracorporeal shock wave lithotripsy (ESWL) or stenting and surgical drainage or resection procedures are offered. Thoracoscopic splanchniectomy is also described as an alternative treatment with adequate pain relief [10].

Various interventional treatment options are available to restore pancreatic drainage. Endoscopic drainage of the pancreatic duct is an alternative to surgical intervention [11]. Another alternative is ESWL combined with endoscopic clearance [12,13]. Endoscopic interventions must often be repeated and are seen as more symptom control than definite therapy. Stents must be removed and replaced after a short period of time and are still accompanied by complications which may be severe.

Current studies have shown that a surgical approach is superior to endoscopic therapy with regard to pain reduction and drainage [14,15]. Studies also show that patients who undergo surgical treatment as initial therapy have fewer consecutive interventions, shorter hospital stay, and a better quality of life [16]. Nevertheless,

the surgical approach must be evaluated carefully with regard to personal risk of mortality and morbidity. There are different approaches depending on a patient's leading symptoms/complications. Therapeutic options are either drainage of a pancreatic or intestinal stricture, resection of the inflammatory center, or denervation of the supplying nerves [17].

In addition to the Whipple procedure, duodenum-preserving pancreatic head resection (DPPHR) has become the standard operation procedure for treatment of chronic pancreatitis [18]. Overall it can be concluded that because of the significantly better short-term outcome results and reproducible long-term results the DPPHR is the favorable surgical procedure.

Timing

The greatest challenge seems to lie in evaluating the right time and the right treatment for each patient individually. Traditionally, surgery was evaluated as adequate treatment at an advanced stage of the disease because of its higher morbidity and mortality compared to conservative treatments.

Current studies have shown that an early surgical approach may be beneficial for pain relief and should be performed before the gland is irreversible damaged in its functional and morphology [19,20]. Patients who underwent surgical treatment earlier than 3 years after symptom onset had a higher chance of pain relief and lower odds of developing endocrine insufficiency, regardless of the surgical technique [21]. Therefore surgical treatment should be evaluated 1–3 years after onset of the disease.

Conclusions

Pain treatment in patients with chronic pancreatitis is interdisciplinary. The baseline therapy for patients dealing with chronic pancreatitis lies in the reduction of noxious stimuli supporting the chronic inflammation and in the medical pain treatment. Endoscopic treatment is beneficial at the beginning of the disease, while dealing with complications, and prior to surgery to reduce the individual surgical risk. Considering the individual's reduction in quality of life and personal morbidity, surgical intervention should be evaluated at an early stage of the disease.

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