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Mechanisms and Unconventional Ways to Manage Abdominal Pain in Chronic Pancreatitis

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ABSTRACT

Abdominal pain is a common but challenging problem of chronic pancreatitis (CP). Major mechanisms of pain in CP are the pancreatic inflammation, ductal-parenchymal hypertension, pancreatic neuropathy and central nervous system sensitization. There are some unconventional or underused treatment options of CP pain. They are valuable when dealing with difficult-to-treat patients such as antioxidants, pregabalin, ketamine, cognitive-behavioral therapy, extracorporeal shock wave lithotripsy, early surgery and pancreatic radiation. All are summarized in this review.

Key words : probiotic, minimal hepatic encephalopathy

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Introduction

Chronic pancreatitis (CP) is a chronic persistent inflammatory of the pancreas. Almost all patients with CP experience abdominal pain during the course of the disease (except 50% of idiopathic CP patients, who can be painless)[1]. Abdominal pain in CP can be very easy to treat by simple analgesics and abstinence or can be very difficult and desperate to both patients and physicians. Constant severe pain is the strongest predictor of poor quality of life and disability in CP[2]. This is because the exact mechanisms of pain in CP are complex and mostly still unknown. There are also too many treatment options, which further confuse the physicians and results of most treatments, are far from satisfaction.

The commonly-used or conventional treatments of pain in CP in Thailand involve alcohol abstinence, smoking cessation, analgesics, pancreatic enzyme and endoscopic therapy. When they all fail, unconventional or uncommonly-used treatment options of pain in CP will become important.

This review will concisely summarize the novel understanding of the mechanisms of pain in CP and provide some underused options of treatment that might help dealing with difficult-to-treat patients.-

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NOVEL UNDERSTNDING IN THE MECHANISMS OF PAIN IN CP

Current understanding of the pain mechanisms in CP is that there are 3 pathogenic areas in the pancreatic pain pathway (Figure 1), which are the pancreas, the peripheral nervous system (PNS) and the central nervous system (CNS)[3-7].There are also non-pancreatic causes of pain that might confound and mimic the pancreatic pain.

The pancreas

The diseased pancreas is logically the primary origin of nociceptive stimuli of pain pathway. However, there are 3 possible mechanisms; the inflammation ("flaming"), the ductal-parenchymal hypertension ("plumbing") and the neuropathy ("wiring").

Inflammation

Exacerbation of acute pancreatitis, which commonly occurs during the early course of CP can cause abdominal pain directly by the intense inflammation, which is a noxious stimulation to the pancreatic sensory nerve.

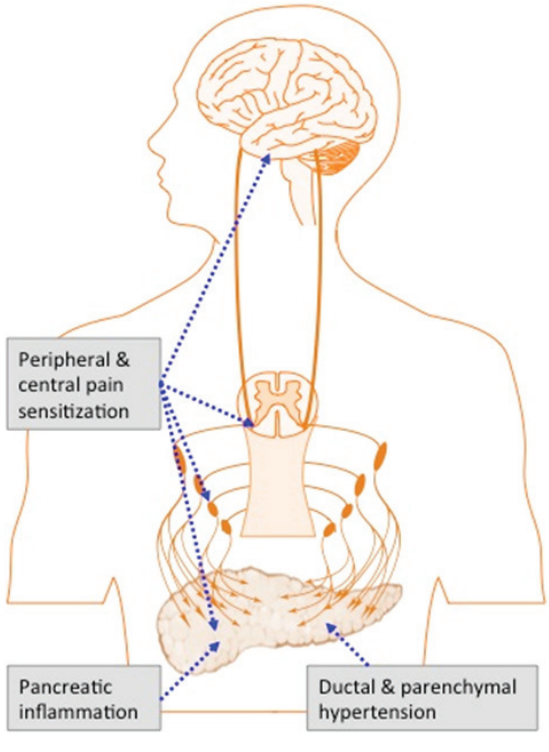

Figure 1. Common mechanisms of abdominal pain in chronic pancreatitis (courtesy of Amporn Atsawarungruangkit).

The patients who are likely to have this mechanism of pain are those who have elevated serum amylase/ lipase or pancreatic swelling or fat stranding by the imaging studies.

The treatments targeted at this mechanism are mainly alcohol abstinence, supportive treatment using potent analgesics. There is no much concern on the use of opioids by this pain mechanism because the pain usually subsides shortly, unless the attacks are frequent. Another option of treatment is anti-oxidants.

Ductal and parenchymal hypertension

Early studies addressed this plumbing mechanisms by demonstrating ductal hypertension[8], parenchymal hypertension and possible compartment syndrome in CP patients with pain[9,10]. However, later studies failed to confirm the relationship between the ductal pressure[11], the parenchymal pressure[12] and the pain. Thus, this mechanism may hold true in only some patients.

Candidate patients with this mechanism are possibly those who have severe pain with marked dilatation of main pancreatic duct (PD), obstructing PD stone or stricture with upstream duct dilatation.

The treatment options for this mechanism are endoscopic therapy to clear PD stones or strictures and drainage surgeries including modified Peustow or Frey operations.

Neuropathy

The pathologic pancreatic nerve, along with the abnormalities of PNS and CNS (see below) have lately become an area of interest in the studies of pain in CP[3-7].This mechanism is explained together with the PNS below.

The peripheral nervous system

Data in the past demonstrated the pancreatic nerve hypertrophy, intra/perineural inflammation and correlation with the pain severity[13]. Recent data from both animals and humans showed an increased sensory nerve excitability, up-regulation of many neurotransmitters such as calcitonin gene-regulated peptide (CGRP), substance P and brain-derived neurotrophic factor (BDNF) and increases neuronal expression of genes that cause neuronal sensitization, which are TRPV1, TRPA1, TRPV4 and PAR2[3,5,7].

Patients who might have pain due to the neurogenic and PNS mechanisms are, in fact, every CP pa-

tient. It is the author's opinion that it is more likely in patients with "small duct" CP and those who complain predominantly neuropathic-type pain or back pain.

Treatments targeted at this mechanism are analgesics, opioids, denervation therapy (celiac plexus block and thoracic splanchnicectomy) and pancreatic head resection.

The central nervous system

Some CP patients have alterations in central pain processing of pain causing hyperalgesia (excessive pain response to stimuli), allodynia (spontaneous pain without real stimuli) and extensive referred pain[3-7]. Their brain MRI showed a reduction of cortical thickness and microstructure changes of cingulate gyri and prefrontal cortex[14,15]. These result in central pain sensitization and might explain the reason why some CP patients remain having pain despite epidural block, which blocks all sensory input to the spinal cord or persistent pain after total pancreatectomy.

Patients who likely have pain due to the CNS mechanisms are those who have long-lasting intractable chronic pain, receiving too much opioids, suspicious of chronic opioid addiction without any pain improvement.

Treatments targeted at this mechanism are mainly analgesics, neuropathic drugs (pregabalin), ketamine and cognitive and behavioral therapy.

Non-pancreatic causes of pain

CP patients may have pain due to other unexpected causes. Peptic ulcer is more common in CP patients[16], as well as gallstone is common in alcoholic patients. In the author's experience, left ureteric stone can sometimes mimic pancreatic pain in patients with initial painless idiopathic CP.

Maldigestion from pancreatic exocrine insufficiency can cause dyspepsia, which is sometimes so severe and mimics pancreatic pain. Effect of pancreatic enzyme treatment in reducing pain in CP in the past studies might partly due to the correction of maldigestion rather than the inhibition of pancreatic secretion[17]. This possibility is supported by recent study on the use of pancreatic enzyme therapy for exocrine insufficiency that unexpectedly showed an increase numbers of pain-free patients from 37% before to 66% after treatment[18].

Non-pancreatic causes of pain should be suspected in every CP patient with pain, particularly those who initially have painless late-onset idiopathic CP or already have "burnt-out" spontaneous pain relief for years before having unexplained pain recurrence. In these cases, thorough work-ups are required before accusing the pain from CP.

Unconventional Treatment Options for Pain in CP

There are some treatment options for abdominal pain in CP, which have been underused or even unrecognized (Table 1). All of them are valuable and probably helpful when facing intractable patients.

Table 1. Conventional and unconventional treatment options for pain in chronic pancreatitis according to the mechanisms of pain.

Targeted mechanisms	Treatment options	
	Conventional	Unconventional
Pancreatic inflammation	Alcohol abstinence	Antioxidants
	Smoking cessation	Single dose radiation
Ductal or parenchymal hypertension	Pancreatic enzyme	ESWL
	Endoscopic therapy	Pancreatic drainage surgery
Pancreatic neuropathy	Analgesics	Pancreatic head resection
	Celiac plexus block	
	Thoracic splanchnicectomy	
Central sensitization	Tricyclic antidepressants	Pregabalin
		Ketamine
		Cognitive & behavioral therapy

ESWL, extracorporeal shock wave lithotripsy

Reduction of inflammation

Antioxidant therapy

Antioxidant therapy targets at the reduction of pancreatic inflammation. Patients with CP often have depletion of antioxidants, increased reactive oxygen species, which might accelerate inflammation. Antioxidant cocktail composing of selenium, vitamin A, vitamin C, vitamin E and methionine has been studies in 2 randomized controlled trials (RCT). The first RCT from India included mainly idiopathic CP showed significant pain reduction by antioxidants over placebo[19]. Subgroup analysis of alcoholic CP patients showed no benefit. Second RCT from the United Kingdom involving mainly alcoholic CP confirmed that antioxidants had no benefit[20]. Meta-analysis concluded that antioxidants had benefits[21-23].

Therefore, antioxidant cocktail can be tried in patients with idiopathic CP, particularly those with recurrent attacks of pancreatitis or pain.

Radiation

Five small studies and 1 meta-analysis have shown that a single dose 8 Gy radiation to the pancreas could reduce abdominal pain of CP in >50% of patients[24]. However, RCT is lacking.

Therefore, single dose radiation can be tried as last resource in patients with severe pain despite surgery or denervation therapy.

Reduction of ductal and parenchyma hypertension

Extracorporeal shock wave lithotripsy (ESWL)

Although endoscopic therapy has an important role in the treatment of pain in CP and has been recommended by guideline[25], it needs expertise and carries unneglectable complications. The best candidates for endoscopic therapy are those with significant continuous pain with dominant stricture or PD stone in pancreatic head, pseudocyst or biliary stricture[3, 25].

ESWL is one of the underrated treatment for CP pain. Clearance of large PD stone is usually difficult with ERCP alone. However, ESWL can clear large PD stone (>5 mm) in >75% of the cases and associated with pain relief[26]. A large RCT comparing ESWL alone versus ESWL plus ERCP showed equal resultsbut ESWL alone was much less expensive[27].

For these reasons, ESWL should be used more often when facing large PD stones instead of trying to remove the stone desperately with ERCP alone.

Surgery

Inarguably, surgery is the treatment option for CP pain that has the most supporting evidences. When comparing to endoscopic therapy in RCTs[28-30], surgery was clearly shown to be more effective and more durable[28,29], including in the long-term[30] and was confirmed by a recent meta-analysis[31]. Despite its superiority, surgery is usually chosen and indicated only after failed medical and/or endoscopic therapy[3], probably due to the more invasive nature and morbidity of the procedure. Recently, a systematic review has shown that early surgery (<3 years) for CP was associated with more pain relief, re-interventions and better preservation of the exocrine function compared to late (>3 years) surgery[32].

Good candidates for early pancreatic surgery are patients with severe pain with 1) heavy stone burden at body/tail with PD dilatation and/or stricture (drainage surgery) or 2) inflammatory head mass, especially when worrying about cancer[3].

Thus, do not hesitate to proceed to surgery when facing difficult cases with severe pain that already fails medical and endoscopic treatments.

Reduction of central sensitization

Pregabalin

Pregabalin has an inhibitory effect on the central sensitization process and can reduce hyperalgesia in patients with CP[33,34]. An RCT of pregabalin (dose 150-600 mg/day) versus placebo for 3 weeks in 64 opioid-using CP patients showed that pregabalin reduced pain score and improved overall feeling compared to placebo[35]. However, medium- and long-term studies are lacking.

Thus, pregabalin is an interesting adjuvant therapy in CP, particularly those who are on opioid treatment[3,36].

Ketamine

Ketamine is an N-methyl-D-aspatate (NMDA) receptor antagonist. NMDA has an important role in the central sensitization process[37]. Thus, ketamine reduces central sensitization by anti-hyperalgesic effect as well as analgesic effect via opioid receptor activation. Ketamine has been used successfully in some non-cancer pain. A pilot study in CP showed that intravenous

ketamine could reduce hyperalgesia. An RCT of intravenous ketamine followed by oral ketamine for 1 month for CP pain (RESET trial) is now on the way[38].

Cognitive and behavioral therapy

Cognitive and behavioral therapy have an important role in the management of any chronic pain syndrome. Although there is no study on their effectiveness in the treatment of pain in CP, pain specialist and psychiatrist should be consulted when dealing with severe intractable patients.

Conclusion

The main mechanisms of pain in CP are the pancreatic inflammation, ductal-parenchymal hypertension, pancreatic neuropathy and CNS sensitization. Aside from conventional treatments, unconventional treatments of CP consist of antioxidants, pregabalin, ketamine, cognitive-behavioral therapy, ESWL, early surgery and pancreatic radiation.

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