91228_Auto_Edited.docx

WORD COUNT 2558
TIME SUBMITTED 20-MAR-2024 10:44AM
PAPER ID 107691240

Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 91228

Manuscript Type: EDITORIAL

Pain Management in Chronic Pancreatitis

Pain Management in Chronic Pancreatitis

Deb Sanjay Nag, Bhanu Pratap Swain, Rishi Anand, Tapas Kumar Barman, Vatsala .

Abstract

Pain in chronic pancreatitis (CP) is infamously difficult to manage. Many patients suffer this pain due to inadequate pain relief, completely incapacitating them in their daily activities. Historically, despite their well-known adverse effects, opioids have been the pillar of treatment regimens in painful CP. The management is now gradually evolving with a better understanding of the underlying pathophysiology of CP-related pain. Clinicians should follow a holistic approach to the management of CP-associated pain, which must involve lifestyle changes that are coupled with analgesic medications and other pain-relieving interventions. Furthermore, there is no easy cure for vanquishing CP-associated pain. Each patient must be evaluated on a case-by-case basis by a multidisciplinary team to decide which treatment option is best suited for that individual.

Key Words: Pancreatitis; Abdominal Pain; Palliative Care; Analgesics; Life Style; Psychology.

Nag DS, Swain BP, Anand R, Barman TK, . V. Pain Management in Chronic Pancreatitis. *World J Clin Cases* 2024; In press

Core Tip: Management of pain associated with chronic pancreatitis (CP) is difficult because of the intricate pathophysiology of this pain and the lack of universal guidelines. Recent evidence suggests an altered central response to the chronic inflammatory changes in the pancreas, which may rewrite the approach to control pain in CP. Currently, several treatment modalities are available to clinicians. However, optimal patient care must be taken into account comprehensively with inputs from multiple disciplines.

INTRODUCTION

Severe abdominal pain is the most debilitating symptom that is associated with chronic pancreatitis (CP) [1]. The patients typically describe a dull-aching pain around the

epigastrium, which frequently radiates to the back and flanks. As the disease progresses, the pain becomes severe and excruciating [2]. This intractable pain, if not managed adequately, may drastically reduce the quality of life of patients by interfering with their physical, psychological, and social domains. Since there is no definitive cure for CP, its pain management is primarily aimed at providing patients with symptomatic relief and palliative care. Hence, adequate pain relief is fundamental to the pain management of CP. Despite our improved knowledge of chronic pain management, clinicians still face challenges in treating painful CP because of the complex nature of the disease process and the paucity of universal treatment guidelines. In the current editorial, we have delved into the pathophysiology of CP-associated pain and reviewed the recommended treatment modalities.

Pathophysiology of pain

Pain in CP is multifactorial and poorly understood. The pathophysiology of pain was believed earlier to be primarily due to the nociceptive inputs that arise from the inflammatory changes in the pancreas. However, recent evidence suggests that the pain is more neuropathic [3,4]. In the background of continuous bombardment of nociceptive inputs from the inflamed pancreas, there is neural modulation or sensitization of the peripheral and central nervous system. Neural sensitization is clinically exhibited by hyperalgesia and allodynia observed commonly in CP [5,6]. Additionally, electroencephalographic and imaging studies have shown neural remodeling and functional changes in the central nervous system [7,8]. Histopathologically, it is exhibited by neural hypertrophy, edema, and increased density of intrapancreatic nerves. These changes result in the development of neuroplasticity and a maladaptive response to pain [9]. There are two distinct types of clinical manifestations of pain in CP. The "A-type pain" or intermittent pain is characterized by discrete episodes of pain with pain-free periods in between. The "B-type pain" is described as persistent background pain with episodes of acute exacerbation [10]. Studies have shown that the intermittent type of pain has a more predicted response to treatment than the latter one ("B-type pain") [11]. The mechanism of pain is summarized in Figure 1 (Mechanism of pain in Chronic Pancreatitis).

Pain management approaches in CP

Management of pain in CP requires a structured approach that focuses on the stage, type, and primary pathophysiology of the disease process. A consensus guideline has recently suggested a stepwise approach to managing pain in CP [12]. Even so, one approach may not fit all patients considering that every patient is different. Thus, an individualized treatment plan is the best means to provide optimum benefit to the patient.

Pain management in CP can be divided into the following sections: pain assessment, lifestyle modification, dietary changes, pharmacotherapy, interventional pain management, endoscopic treatment, and surgical interventions.

Pain assessment in CP

The first step of pain management is the accurate assessment of the severity of pain. Multiple pain assessment tools are available, but very few have been validated to be employed in the pain management of CP. Simple pain rating scales such as the numeric rating scale and visual analog scale only measure the intensity of pain and neglect other aspects of pain [13]. CP-associated pain is complex, with a significant psychosocial undertone; hence, it must be assessed through multidimensional pain scales. The Izbicki pain scale is specifically developed to address this aspect of pancreatic pain, but it is not appropriately validated to be applied in the pain management of CP [14].

The brief pain inventory pain assessment scale is a self-administered questionnaire-based tool validated to be used in CP-related pain management [15]. It quantifies the severity of pain and its impact on daily function including general activity, mood, behavior, and sleep [16]. The McGill Pain Questionnaire is another self-reporting measure of pain that can be useful in the pain management of CP. It provides a holistic view of pain severity by measuring the sensory, cognitive, and emotional aspects of pain [17]. Quantitative sensory testing helps assess and characterize pain mechanisms in patients with CP [18]. It can be employed in treatment-resistant cases of CP to assess pain sensitivity and to check the response of medications to pain [19].

Lifestyle modification and dietary changes

Patients with CP are strongly advised to abstain from alcohol and smoking. Studies have demonstrated that refraining from alcohol intake significantly reduces the frequency of recurrences in pancreatitis and painful episodes [20]. Smoking is frequently associated with alcoholism, and it can be an independent risk factor for pain exacerbation in CP [21]. A low-fat elemental diet has been extensively studied in CP for pain control, considering that it reduces pancreatic secretion and reduces pain by decreasing ductal pressure [22,23]. It is suggested to be more effective in the early stage of the disease when the exocrine function of the pancreas is preserved [23]. The early institution of the nasojejunal tube is also recommended. Besides improving the nutritional status of the patient, nasojejunal feeding also reduces pain [24]. The benefit is achieved probably by a reduction in pancreatic secretion or may be due to bypassing of the stomach. The latter explanation is more plausible since delayed gastric emptying is common in CP cases [25].

Pancreatic enzymes have been shown to ameliorate pain in CP by negative feedback inhibition of pancreatic secretion [26]. It works by degrading the cholecystokinin-releasing factor that releases cholecystokinin responsible for the stimulation of pancreatic secretion [27]. The preparation of pancreatic enzyme must be in the uncoated form (nonacid protected form) to be effective, since the acid resistance form (coated form) may not get released in the duodenum. Nevertheless, a systemic review and meta-analysis was not able to come up with significant evidence of pain relief in CP by using pancreatic enzymes [28].

Antioxidants are advocated with the rationale that there is micronutrient deficiency in CP that results in oxidative stress and free radical injury [29]. A combination of antioxidants (β-carotene, vitamin C, vitamin E, selenium, and methionine) with other pain-relieving medication (Pregabalin) has been shown to avert painful episodes and recurrences [30,31].

Analgesic medication

The World Health Organization (WHO) analgesic ladder has been an enduring guide for the management of cancer pain for more than two decades, and it is still applicable in planning treatment for pain in CP [32]. The WHO ladder recommends stepwise escalation

of analgesics with increasing potency until pain relief is achieved. Paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs)[Editor1] are the first line of analgesics advocated for mild to moderate pain. Although paracetamol is safe in CP, it cannot be a standalone medication to provide satisfactory pain relief [26]. It is usually effective when combined with other medications. NSAIDs are better avoided, considering that patients suffering from CP are prone to develop duodenal and gastric ulcers [33,34].

Opioids are invariably added to the pain management regimen as pain severity increases in CP. Despite this, opioids are the most prescribed medications to manage pain, and their role is controversial in nonmalignant chronic pain scenarios such as those of CP-related pain [35]. The controversy is further aggravated by the widespread prevalence of opioid abuse. The recommendation is that opioids should never be the first-line therapy [36]. Before initiating opioid therapy, clinicians must be aware of the long-term side effects including misuse, addiction, opioid-induced hyperalgesia, and bowel dysfunction [37]. The patient who is on opioid therapy, especially strong opioids such as morphine, must be monitored closely to look for the development of such adverse effects. Tramadol, a weak opioid, is suggested to be more effective than morphine in controlling pain in CP with an equianalgesic dose [38]. It does not have any serious adverse effects or dependency potential in therapeutic doses, unlike strong opioids. Tramadol has weak activity on the μ-opioid receptor with an additional inhibitory effect on noradrenaline and serotonin reuptake [39]. It modulates the descending inhibitory pain pathway and can play a significant role in managing central sensitization associated with CP [40]. A maximum adult dose of 400 mg/day can be advocated safely in patients with CP. Transdermal preparation of opioids is also used, but it is usually reserved for patients who cannot tolerate oral preparations [41].

Considering that the neural mechanism of pain in CP is now well established, the drugs interfering with neural transmission are expected to be efficacious. Anticonvulsants (pregabalin and gabapentin), tricyclic antidepressants (amitriptyline), and selective noradrenaline reuptake inhibitors or SNRI (duloxetine) are the centrally acting drugs commonly used to treat neuropathic pain and can be beneficial in CP [42]. Pregabalin has

been extensively researched in patients with CP. It reduces synaptic release of neurotransmitters (glutamate, noradrenaline, and substance-P) by binding to alpha2-delta subunits of voltage-gated Ca2+ channel and thereby reducing neuronal excitability. Pregabalin must be started at a low dose to prevent its neurological adverse effects and slowly escalate until clinical benefit is appreciated[Editor2] [43]. The maximum recommended dose of pregabalin is 600 mg. Likewise, gabapentin, amitriptyline, and duloxetine can be tried as monotherapy or preferably in combination with other analgesics.

Other novel medications such as ketamine, an N-methyl-D-aspartate antagonist, can be effective by enhancing of descending inhibition of pain in CP [43]. The S-enantiomer of ketamine is particularly more effective with fewer psychosomatic side effects and is currently being used in an ongoing trial that involves CP patients [44]. Somatostatin-analog inhibits pancreatic secretions and can lessen pain by reducing ductal pressure. However, current data are limited to suggest its use. Certain experimental drugs such as clonidine and benzodiazepines may be tried in the patient's refractory to conventional medications [12].

Interventional pain management approaches

Recent evidence suggested that patients of CP may benefit from sympathetic blocks such as celiac plexus and splanchnic nerve blocks [45,46]. These minimally invasive interventions can reduce analgesic requirements and may be considered as parts of a multimodal analgesic strategy. In one study, pulsed radiofrequency ablation of celiac plexus provided excellent pain relief in two cases of CP [47]. Spinal cord stimulation has shown significant pain relief in multiple studies [48,49]. It may be used in cases of CP refractory to analgesic medications.

Psychological intervention and standardized nursing interventions

The emotional and psychological impact of pain in CP is often a neglected aspect. Recent data support the use of behavioral interventions as part of a multidisciplinary approach in the management of pain in CP. Cognitive–behavioral therapy is one such intervention that has proved to be useful in reducing pain intensity and enhancing quality of life by

helping patients cope with pain better [50]. Protocolized nursing interventions with focused stress reduction can effectively mitigate pain, anxiety, and depression in pancreatitis [51].

Endoscopic therapy and surgical management

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the most common modalities utilized in the treatment of painful CP. Endoscopic therapy is particularly useful in patients with obstructive pathology in the main pancreatic duct. The rationale behind it is that it releases the outflow obstruction and decompresses the pancreas, thereby reducing the pain [52]. Often extracorporeal shockwave lithotripsy is carried out to reduce pain in CP, especially in cases of large pancreatic stones localized in the head of the pancreas [53].

Surgical management was once the last resort employed when all other modalities failed to provide pain relief in CP. Nevertheless, evidence for the benefits of early surgical interventions is now emerging [54,55]. The surgical approach for pain management in CP depends on the morphological changes in the pancreas, duration of the disease, and response to other treatment modalities. Three modalities of surgery are commonly employed: decompression surgery, resection, and a combined procedure depending on the pathology in the pancreas. The optimal timing of surgery is controversial. However, surgery should not be delayed beyond 2–3 years of onset of CP and should be done before the patient develops central sensitization [56].

CONCLUSION

The current evidence suggests that CP-associated pain is less of a nociceptive and more of a neuropathic type with significant psychosocial connotation. Neural sensitization along with neuroplastic changes in the nervous system causes the pain refractory to conventional treatment. Therefore, treatment modality should be aimed at preventing the development of neural sensitization by judicious use of medications and other interventional modalities. Pain assessment in CP should be conducted by using validated multidimensional pain scales to have a better understanding of the pain and its impact

on daily living. To minimize painful episodes, lifestyle modification by complete abstinence from alcohol and smoking is strongly recommended. A low-fat elemental diet and nutritional delivery by nasojejunal tube may have an impact on pain recurrence by reducing pancreatic secretion. Pancreatic enzymes and antioxidants in combination with other medications are useful pain-relieving measures, although evidence regarding their effectiveness is equivocal. The WHO pain ladder should be employed as a guide for the timing and escalation of analgesics. NSAIDs should be avoided, and paracetamol should be used in combination with other drugs. Tramadol has proven beneficial in painful CP with a good safety profile. Stronger opioids like morphine must be used cautiously because of their serious long-term impact on pain pathophysiology. Central medications like pregabalin appear to be the mainstay of treatment as monotherapy or in combination with other modalities. Endoscopic treatment (ERCP) should be the first line of management in cases of ductal obstruction due to stricture or stone. Surgery can be a game changer in pain management selected cases, but the optimal timing of surgery is crucial for its success. The various intervention methods in CP is summarized in Figure 2 (Intervention methods in Chronic Pancreatitis).

In conclusion, our current understanding of the etiopathogenesis of pain in CP opens multiple pain-relieving options for clinicians. However, to provide the best possible treatment modalities for the successful management of pain in chronic pancreatitis, a multidisciplinary approach that involves gastroenterologists, surgeons, and pain physicians must be developed.

91228_Auto_Edited.docx

ORIGINALITY REPORT

1%
SIMILARITY INDEX

PRIMARY SOURCES

1	repository.ubn.ru.nl Internet	14 words — 1%
2	www.ama-cmeonline.com Internet	12 words — < 1%
3	www.ncbi.nlm.nih.gov Internet	12 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS