Review Article

Pain and its Management in Severe Acute Pancreatitis

Long, Yi; Jiang, Zhengying; Wu, Guixin

Author Information

Department of Critical Care Medicine, Chongqing University Cancer Hospital, Chongqing, China

Address for correspondence: Dr. Zhengying Jiang, Department of Critical Care Medicine, Chongqing University Cancer Hospital, Chongqing 400030, China. E-mail: zhengyingjiang@cqu.edu.cn

Received November 07, 2021; revision received February 27, 2022; Accepted March 30, 2022; previously published online April 22, 2022

Journal of Translational Critical Care Medicine 4(1):p 9, December 2022. | DOI: 10.4103/JTCCM-D-21-00026

Abstract

Pain is common in severe acute pancreatitis (SAP) and is associated with the disease severity and outcomes. The management of pain in SAP may not only relieve pain but also improve outcomes. However, pancreatic pain in SAP involves several complicated mechanisms. Poor understanding about the pain mechanism in SAP and lack of enough high-quality data on pharmacological and nonpharmacological intervention lead to a limited analgesia strategy in patients with SAP mainly managed using nonsteroidal anti-inflammatory drugs and opioids. This makes pain management in SAP challenging and may cause potential harm. This article reviewed the current management of pain in SAP by combining pain mechanisms with animal or clinical studies and proposed an analgesic ladder based on available evidence to improve pain management in patients with SAP.

Introduction

Acute pancreatitis (AP) is a disease of variable severity caused by the premature activation of pancreatic enzymes.[1] The global incidence of AP in 2019 is about 34.8/100,000, decreased by 8.4% compared with that in 1990, yet it is still high and continues to increase in some countries.[2] Severe AP (SAP) accounts for about 25% of the AP cases, and the mortality is still as high as 15%-30% despite the advancement of the management.[34] Pain is the most common clinical manifestation in AP and plays an important role in diagnosis and prognosis. Patients with SAP experience more severe pain than those with mild and moderate AP. Nowadays, pain management has drawn increasing concern as a part of comprehensive treatment measures in both AP and SAP.[567] However, the reality is that we

have a poor understanding of the pain mechanism, and pain in SAP is mainly managed by nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids. This study reviewed the knowledge about pain and its management in AP and SAP intending to improve pain management in SAP. Two points are important here. First, pain in patients with SAP may be caused by a variety of factors, such as inflammatory damage to the pancreas, surgical procedures, and mechanical ventilation. This review only focused on abdominal pain caused by SAP itself. Second, the studies on pain in SAP are limited. Given the high similarity in the etiology and pathogenesis of AP and SAP, it seems acceptable to use some studies on AP to illustrate the pain and its management in SAP.

Role Of Pain In Severe Acute Pancreatitis

Abdominal pain is the earliest and most common symptom and is considered a hallmark of AP. The features of abdominal pain in AP have been well described in the literature.[58] According to the modified Atlanta consensus guidelines, the hallmark abdominal pain is one of the diagnostic criteria for AP.[9] Resent studies suggested that the severity of pain correlated with the severity of AP, and the interval between onset of pain and hospitalization was also a prognostic factor for estimating the severity of AP.[1011] Patients with SAP experienced more severe abdominal pain and required more opioids for pain relief.[8121314] The severity of pain may be impacted by the underlying causes, biliary AP may cause more severe pain compared with alcoholic AP and autoimmune pancreatitis.[15161718]

Pain may lead to adverse outcomes such as impaired tissue perfusion, catabolic hypermetabolism, and immunosuppression. It is associated with prolonged mechanical ventilation duration and increased morbidity and mortality in critically ill patients.[19202122] As mentioned earlier, more severe pain is associated with more severe disease severity and worse outcomes. However, it is difficult to assess the impact of pain itself on the disease severity and outcomes in SAP. Clinical practice and several animal experiments showed that analgesic treatment not only relieved pain but also reduced damage to the pancreas and extrapancreatic organs and alleviated inflammation (described below), suggesting that pain might exacerbate disease progression. Consequently, pain management, fluid resuscitation, nutritional support, and organ support are considered the mainstays of treatment in SAP.[6723]

Pancreatic Pain Mechanisms

Providing appropriate analgesic therapy for patients with SAP is challenging, partly due to a poor understanding of the mechanisms of pancreatic pain. Since AP and SAP may share the same pain mechanism, we used AP as an example to illustrate the pain mechanism of SAP. Pain is defined as an unpleasant sensation that has an organic and a psychogenic component. Based on the underlying mechanism, pain is classified into three types: nociceptive (mediated by the activation of normal pain pathways), neuropathic (abnormal response to pain stimuli), and psychogenic (psychological/mental-driven pain). All three are involved in pancreatic pain, but the first two are the main causes of pancreatic pain. In AP, nociceptive pain plays the most important role.[24] A better understanding about the mechanism of pancreatic pain may help improve pain management. The pain mechanisms and potential therapeutics in SAP are summarized in Table 1.

T1-9
Table 1:
Mechanisms of pancreatic pain and potential therapeutics in severe acute pancreatitis

Sensory Mechanism Of The Pancreas To Nociceptive Stimulation

The afferent nerve endings (receptive fields) are located in the pancreas with their cell bodies in the nodose ganglia and dorsal root ganglia (DRG) for the vagal and spinal afferent (splanchnic) nerves, respectively. Nonpainful stimuli are primarily conducted through the vagus nerve, while painful stimuli are conducted by the splanchnic nerves. The cell bodies of pancreatic afferent nerves in DRG of the rodents are located at T5-L2, mainly at T10-T11, and project to the spinal cord.[25] These afferent nerves are activated during the onset and progression of AP.[26] The nerve endings can be activated by mechanical stimuli (such as stretch of the pancreas capsule caused by pancreatic edema owing to AP or dilatation of the bile duct caused by bile duct obstruction owing to the gallstones) and some chemical stimuli (such as cholecystokinin, histamine, and bradykinin).

A variety of receptors and ion channels are involved in the activation of nerve endings and are described in detail in the literature.[27] Some afferent nerves may be silent under normal physiological conditions and become excited only after tissue injury or inflammation; the excitability of afferent nerves can be altered by numerous factors in the neuronal environment (such as inflammatory mediators).[28] The activation of nerve endings leads to the generation and propagation of afferent nerve action potentials. The sympathetic nerve is the main afferent nerve for nociceptive stimulation of the pancreas. Visceral pain and somatic pain are conducted through C fibers and Aδ fibers, respectively.[29] Once the pancreatic afferent neurons are activated, neurotransmitters such as calcitonin gene-related peptide and substance P (SP) were released to activate second-order neurons in the dorsal horn of the spinal cord.[30] The nociceptive stimuli are projected through the primary pancreatic afferent neurons in DRG and the dorsal horn of the spinal cord to the neurons in the prefrontal cortex, the dorsal motor nucleus of the vagus nerve, and the nucleus tractus solitarius to form pain sensation.[3132] The neurons that innervate the nociceptive stimulation to the pancreas may also innervate somatosensory, somatic, and visceral afferent nerves, which may integrate and interact in the spinal cord. One consequence is that visceral pain may cause pain in the somatic structure near or far from the origin of the visceral pain, also termed as referred pain. Meanwhile, simultaneous cutaneous and visceral stimuli evoke a larger response than the response evolved by either stimulus on its own.[3334] The sensory mechanism of the pancreas to nociceptive stimulation is shown in Figure 1.


Figure 1::
Sensory mechanism of the pancreas to nociceptive stimulation. The nociceptive stimuli to the pancreas activate the nerve endings of the primary afferent nerve to generate electrical and chemical signals, which are transmitted through dorsal root ganglia and spinal dorsal horn to the brain to form pain sensations

Neuropathic Pain In Severe Acute Pancreatitis

Neuropathic pain is important pathogenesis in chronic pancreatitis.[2427] Despite lacking direct evidence, neuropathic pain may be associated with the development of pain in AP. Neuropathic pain is defined as the pain after a lesion or disease of the peripheral or central nervous system.[35] The damage to the endings of peripheral nerves can generate neuropathic pain states.[36] Thus, it is reasonable to hypothesize that the damage to the pancreatic afferent nerve endings and the sensitization of pancreatic afferent nerves by inflammation in SAP may cause neuropathic pain.[37] The stimulus-evoked pain types are classified as dysesthetic, hyperalgesic, or allodynic according to the

dynamic or static characteristic of the stimulus.[38] The mechanism of neuropathic pain involves peripheral and central sensitization, which are discussed in the following text

The molecular and cellular changes at the level of the uninjured primary afferent nociceptor after a nerve lesion may lead to sensitization and ectopic spontaneous activity of primary afferent nociceptors. The changes in the expression of voltage-gated sodium channels, transmembrane proteins such as vanilloid receptors and temperature-sensitive excitatory ion channels, and adrenoreceptors on the uninjured primary afferent nerves (DRG) may be involved in peripheral sensitization.[39,40,41,42] Nerve growth factors (NGF) released by the injured nerves may be associated with the aforementioned changes in the uninjured nerve receptors. It has been suggested that NGF not only plays an important role in the onset and progression of AP but also leads to sensitization in the afferent neurons.[43,44,45] Pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukin 6 (IL-6) released after nerve lesions may induce ectopic activity in both injured and adjacent uninjured primary afferent nociceptors at the lesion site also involved in the peripheral sensitization.[46] Furthermore, oral small-molecule IL-6 receptor inhibitor may reduce abdominal hyperalgesia during AP.[47]

The central sensitization in neuropathic pain includes sensitization in the spinal cord and brain. The current research mainly focuses on sensitization in the spinal cord. The first mechanism of sensitization in the spinal cord is the increased excitability of the multi-receptive spinal cord neurons (wide-dynamic-range neurons with multiple synaptic inputs from the nociceptive and non-nociceptive system multisensory neurons) in the dorsal horn. Research shows that glutamate and neuropeptide SP are released by C fibers, and the expression of sodium channels (Nav1.3) in second-order dorsal horn neurons is changed after peripheral nerve injury. Those changes increase the excitability of the multi-receptive spinal cord neurons. The consequence is increased neuronal activity in response to noxious stimuli, expansion of neuronal receptive fields, and spread hyperexcitability of the spinal cord to other segments.[48] Another mechanism of spinal cord sensitization is disinhibition. In rodents, peripheral nerve injury promotes selective apoptosis of inhibitory interneurons that release γ-aminobutyric acid in the superficial dorsal horn of the spinal cord, which may weaken the inhibition of spinal dorsal horn neurons.[49] The dorsal horn neurons of the spinal cord receive descending modulating control from supraspinal brainstem centers; the loss of function in descending inhibitory serotonergic and noradrenergic pathways may be involved in the central sensitization.[50] Finally, nonneural glial cells are also involved in the sensitization of the spinal cord. Excitatory neurotransmitters such as pro-inflammatory cytokines and glutamate released by nonneural glial cells, which are activated by injury to the peripheral nerves, may lead to spinal sensitization.[51] Animal studies and brain function studies have shown that the brain is also involved in central sensitization.[52,53]

Analgesics For Severe Acute Pancreatitis

Since pain in SAP involves multiple mechanisms, various analgesics may be available for its management. However, due to limited evidence, it is not possible for guidelines to make specific recommendations for analgesics. Analgesics used in SAP are listed in Table 2 and described in the following text.


Table 2:
Analgesics used in severe acute pancreatitis

Opioids

Opioids are one of the commonly used analgesics for patients with SAP that work through binding to opioid receptors. Opioid receptors are of three types: μ, δ, and κ receptors, with a total of seven subtypes (μ1 and μ2; δ1 and δ2; κ1, κ2, and κ3). These receptors are mainly located in the central nervous system, whereas the μ receptors are also located in the gastrointestinal tract. The pharmacological effects of opioids vary according to the activated opioid receptors, the ability to bind to different opioid receptors, and the pharmacokinetics of opioids; therefore, the time of onset, effect, duration, and side effects of opioids may vary among individuals.[6970] Many kinds of opioids used for the analgesia in AP include pethidine, morphine, buprenorphine, fentanyl, remifentanil, and pentazocine.[54557172] A few randomized controlled studies and systematic reviews compared the effects and safety of opioids for analgesia in AP. The aforementioned researches confirmed the analgesia effect of opioids in AP; buprenorphine and pentazocine seem to be more favorite options due to their better effects and safety. However, another meta-analysis showed no difference in adverse reactions and mortality between different opioids for pain management in AP.[56] Due to the limited number of studies and heterogeneity of study quality and methodology, we may not conclude the optimal opioid for analgesia in SAP.[555673] Opioids also showed other effects besides analgesia in AP. Rat AP animal model experiments showed that sufentanil combined with midazolam might reduce inflammation and pancreatic damage.[74] Fentanyl reduced myocardial injury in SAP in a rat model by regulating the NF-κB signaling pathway.[75]

However, opioids may cause potential harm. They may lead to the contraction of the Oddi sphincter and increased pressure of the bile duct, which may induce or exacerbate AP, especially when several case reports of opioid-induced AP exist; this effect of opioids may be related to the effect of μ-receptors.[7677787980] Morphine has the strongest effect on the Oddi sphincter, whereas low-dose fentanyl results in a lower incidence of the spasm of the Oddi sphincter.[8182] In the AP animal model induced by caerulein, L-arginine, and ethanol-palmitoleic acid, the administration of morphine increased neutrophil infiltration and necrosis of pancreatic tissue, leading to the exacerbation of pancreatitis. The pathways activated during pancreatic regeneration, such as sonic hedgehog, and activation of embryonic transcription factors, including pdx-1 and ptf-1, are downregulated after the administration of morphine, indicating that the recovery of pancreatitis is inhibited. Gut permeabilization and bacteremia caused by AP were exacerbated by morphine, and these effects seemed to be mediated by μ-receptors.[57] A recent retrospective nested case-control study of a commercial claims database for patients who underwent cholecystectomy showed that codeine increased the incidence of AP in patients after cholecystectomy.[83] The multiple logistic regression analysis of 93 patients with AP showed that opioid analgesic treatment in AP was associated with severity, complications, and mortality.[84] Besides potential damage to the pancreas, opioids might cause side effects such as ileus and immunosuppression, exacerbating the preexisting multiple-organ dysfunction syndrome in patients with SAP.[8586] A prospective cohort study in the surgical intensive care unit (ICU) demonstrated that adverse drug reactions were mainly caused by opioids, each adverse drug reaction was associated with an increase in ICU length of stay by 3.39 days, and the length of ICU stay increased by 2.31 days (increased by 53.2%) even when confounding variables were eliminated.[87] Therefore, opioids are a double-edged sword in AP and should be individualized according to the patient's condition and the pharmacokinetics/pharmacodynamics of the drugs.[70] Despite the lack of data from patients with SAP, data from ICU patients suggested the adjuvant use of non-opioids to minimize opioid-related adverse effects.[86]

Nonopioids

Nonsteroidal anti-inflammatory drugs

NSAIDs are commonly used anti-inflammatory and analgesic drugs. Since AP involves inflammation and pain, theoretically, it is a suitable option. Indeed, the analgesic effect of NSAIDs in AP has been confirmed. Besides analgesia, patients with SAP may receive other benefits from NASAID treatment. A retrospective study including 324 patients with AP in 2 large teaching hospitals in the UK showed that compared with patients who did not receive NSAIDs, patients who received NSAIDs for other complications had a lower rate of pancreatic necrosis and pseudocysts and a lower level of CRP ≥ 150 mg/L on the 2nd day, but no difference in the length of hospital stay, need for ICU admission, and mortality.[88] Some animal experiments also suggested that some NSAIDs might play a role in preventing or treating AP, although some research results are still controversial. However, current studies mainly focus on AP rather than on SAP. The most often used NSAIDs in AP are indomethacin and diclofenac.

Indomethacin

Lankisch used indomethacin in an AP animal model in 1978. The results showed no difference in serum enzymology and pancreatic tissue damage, but the mortality rate in the indomethacin group decreased.[89] Another acute hemorrhage pancreatitis animal experiment showed that adding indomethacin to drinking water might improve pancreatic tissue damage. However, 10 and 20 mg/L indomethacin in drinking water might worsen liver tissue damage; the overall result was that the 5 mg/L group revealed the highest survival rate.[90] A SAP mouse model found that indomethacin might protect pancreatic acinar cells from damage by inhibiting the NLRP3 pathway and reducing the severity of SAP, which might be a potential pancreatic protective mechanism of indomethacin.[91] However, another mouse pancreatitis animal model experiment suggested that indomethacin worsened pancreatic damage and death, while the subcutaneous injection of prostaglandin showed a better outcome.[92] Animal experiments evaluating the effect of indomethacin on hemodynamics showed that indomethacin might increase blood pressure in an animal model of acute hemorrhagic pancreatitis; the effect on cardiac output is controversial, but indomethacin might reduce pancreatic blood flow.[9394] Different results of animal experiments might be related to the different methodologies of the animal experiment.

A controlled double-blind trial conducted in 1985 evaluated indomethacin treatment in AP. The indomethacin group had a shorter time of pain and a lower opioid consumption, but no differences were found in serum amylase level, blood calcium level, and gastrointestinal bleeding.[95] Five clinical studies evaluated the use of indomethacin in preventing or treating AP after endoscopic retrograde cholangiopancreatography (ERCP); of these, two were randomized controlled trials (RCTs) and three were cohort studies (two of which were retrospective studies and one was prospective study). Among these, one RCT and two cohort studies (one prospective and one retrospective) showed that indomethacin might reduce the incidence and severity of pancreatitis after ERCP (PEP).[585960] However, one RCT and one retrospective cohort study showed that indomethacin might not reduce the incidence of PEP.[9697]

Diclofenac

Diclofenac is another NSAID used for treating pain in AP. Two studies evaluated the analgesic effect of diclofenac in AP. The results showed that diclofenac 1 mg/kg two times per day had a similar analgesic effect as tramadol 1 mg/kg two times per day, while diclofenac 75 mg three times per day had a weaker analgesic effect than pentazocine 30 mg three times per day.[5598] Besides its analgesic effects, diclofenac may also prevent and treat AP and related complications. Two AP animal model studies

suggested that diclofenac might reduce pancreatic injury, pulmonary edema, and damage to tissues besides the pancreas when combined with other drugs.[99100101]

Two RCTs suggested that diclofenac reduced the incidence of PEP. The European Society of Gastrointestinal Endoscopy suggested rectal administration of diclofenac or indomethacin before ERCP to prevent PEP.[616263] However, a recently published RCT suggested that diclofenac might not lower the incidence and severity of PEP in patients with primary biliary cirrhosis. This might be related to the higher incidence of PEP associated with the special disease state in this patient group.[98]

Other nonsteroidal anti-inflammatory drugs

Two animal studies assessed the role of aspirin in preventing and treating AP. The results suggested that aspirin pretreatment might prevent and/or improve cerulein-induced AP, aspirin prevented the necrosis of the acinar cells of the mouse SAP model, and no gastrointestinal side effects were observed.[102103] However, no clinical studies evaluated the analgesic effect of aspirin in patients with AP, especially those with SAP.

Animal studies suggested that celecoxib might reduce the serum IL-6 levels and the injury to the pancreas, lung, and kidney of rats with acute necrotizing pancreatitis. However, case-control studies suggested that the use of celecoxib was associated with an increased risk of AP.[104105106] The use of parecoxib was also evaluated in treating AP. The results suggest that the early use of parecoxib might improve the incidence of complications of moderate AP. However, parecoxib did not relieve pain in patients with AP.[107]

Acetaminophen

Acetaminophen is a commonly used analgesic suggested as an adjuvant to opioids by the guidelines because research suggests that acetaminophen may reduce the consumption of opioids in patients after cardiac and abdominal surgery.[86108109] To date, no clinical research has evaluated the role of acetaminophen in SAP. However, the potential side effects such as hypotension caused by acetaminophen may worsen shock and MODS in patients with SAP.[85110] Moreover, acetaminophen may be associated with the onset of AP. Several case reports of acetaminophen-induced AP exist.[111] A population-based retrospective cohort study suggested that, compared with patients without acetaminophen poisoning, the risk of AP in patients with acetaminophen poisoning increased by 2.4 times.[64] Therefore, the efficacy and safety of acetaminophen for analgesia in patients with SAP require further research.

Ketamine

Ketamine is an N-methyl-D-aspartate (NMDA) receptor inhibitor, which contains two optical isomers (S-ketamine and R-ketamine), with anesthetic, analgesic, antidepressant, and anti-inflammatory activities. It has been used for general anesthesia, but its use has gradually decreased due to side effects such as dissociative anesthesia, hallucinations, and potential drug abuse. A much lower dose of ketamine may be sufficient for analgesia (plasma concentration: 70-160 ng/mL vs. 1200-2400 ng/mL).[112] The side effects of ketamine are usually dose-dependent and temporary; a low dose of ketamine has little impact on the incidence of psychotomimetic effects and cognitive impairment.[113114115] Several results suggested that low-dose ketamine, as an adjuvant to opioids, might reduce opioid consumption and improve outcomes.[115116] Nevertheless, a randomized, controlled, double-blind study, including 162 mechanically ventilated patients in the ICU, demonstrated that the adjuvant

low dose of ketamine to opioids did not reduce the consumption of opioids, but might lower the incidence of delirium.[117] A recent published systematic review and meta-analysis performed by Atm *et al*. included 3 RCTs and 12 observational studies involving 892 mechanically ventilated patients; it concluded that the adjuvant ketamine to opioids did not reduce the consumption of opioids. However, due to some limitations in terms of both quantity and methodological quality in the included studies, more high-quality studies are needed to verify the conclusion.[118] Based on the data from other critically ill populations and the animal experiment suggesting that NMDA receptors were associated with pancreatic pain, ketamine may serve as an appropriate option for analgesia in SAP. Future research should be conducted to evaluate the role of ketamine for analgesia in patients with SAP.

Other analgesics

Nefopam exerts analgesic effects by inhibiting the reuptake of dopamine, norepinephrine, and serotonin in the spine and supraspinal space but has no impact on hemodynamics, liver function, and gastrointestinal function. A clinical study evaluated the role of nefopam in patient-controlled analgesia in the ICU after cardiac surgery. The results suggested that nefopam might reduce opioid consumption and opioid-related adverse effects.[119] Although no clinical studies have evaluated the role of nefopam in pain management in SAP, it is considered a potential drug that can be used in this condition.

The PADIS guideline recommended that neuropathic pain medications (e.g., gabapentin, carbamazepine, and pregabalin) should be used as an adjunct to opioids for managing neuropathic pain in critically ill adults.[86] Neuropathic pain is involved in the onset of pain in SAP. An AP animal model experiment suggested that the intrathecal injection of gabapentin might enhance the analgesic effect of subtherapeutic doses of morphine.[120] However, to date, no clinical research has evaluated the role of neuropathic pain medication in SAP. Evidence to help speculate whether neuropathic pain medication can be used for pain management in SAP is insufficient.

Procaine intravenous infusion has been used to treat pain in AP. However, an RCT suggested that the intravenous infusion of procaine 2 g per day did not improve pain in AP compared with the intravenous infusion of placebo (normal saline).[65] In another RCT, patients with AP were divided into two groups; one group received a continuous intravenous infusion of procaine 2 g/day, while the other group received intravenous bolus of pentazocine 30 mg every 6. Pentazocine was used as a supplement when needed. Both the groups showed no difference in the consumption of pentazocine, while the procaine group had a higher pain score.[66] Although animal experiments suggested that the intra-arterial lidocaine infusion might reduce pancreatic damage in cerulein-induced AP, no clinical research evaluated the role of lidocaine in SAP.[67] A randomized, controlled, double-blind study in patients who needed to be admitted to the ICU after cardiac surgery showed that lidocaine had no impact on pain intensity, postoperative consumption of fentanyl and sedative, time to extubation, length of ICU stay, and hospital stay compared with placebo.[68] Considering the safety concerns of lidocaine intravenous infusion, the routine use of lidocaine as an adjuvant to opioids in ICU patients is not recommended. This general principle is also valid for patients with SAP. The aforementioned research results showed that the intravenous infusion of local anesthetics should not be used for the analgesic treatment of SAP.

Epidural Analgesia and Other Analgesia Measures

Although analgesics (especially opioids) are the mainstay for pain management in AP and SAP, direct interruption of afferent nociceptive visceral stimulation is thought to be a more effective approach. Clinically, epidural analgesia and celiac plexus block are currently available analgesia measures.

Epidural analgesia was reported as early as 1950 for pain relief in AP. SAP and AP animal model studies showed that thoracic epidural analgesia might increase the perfusion of viscera and pancreas, improve the microcirculation of the pancreas, alleviate liver damage, and significantly reduce mortality.[121] However, the clinical applications of epidural analgesia in AP or SAP are limited.[122] A multicenter retrospective cohort study included 1300 patients with AP in 17 ICUs in France and Belgium. The propensity score matching analysis found that the risk of all-cause 30-day mortality in patients with AP who received epidural analgesia was significantly lower than that in matched patients who did not receive epidural analgesia (2% vs. 17%; $P = 0.01$).[123] A multicenter randomized controlled study is underway to evaluate the role of epidural analgesia in SAP.[124] EA is an invasive treatment, the implementation of EA in patients with SAP has potential risks, and patient and intervention timing are important. EA may be undertaken in some experienced centers with special concern on the potential risks and side effects.[125] Although epidural analgesia has shown advantages in terms of both pain relief and clinical outcomes in AP, some patients may have a poor response to epidural analgesia. For such patients, intermittent or continuous celiac plexus block may offer an effective alternative treatment for pain in SAP.[126] However, celiac plexus block is more commonly used for analgesia in chronic pancreatitis and pancreatic cancer rather than in AP. Furthermore, case reports of using the radiofrequency ablation of the splanchnic nerve to manage pain in acute and chronic pancreatitis exist.[127128] These sporadic case reports or case sequences showed that the radiofrequency ablation of splanchnic nerves achieved a good response in pain management in AP. However, given the requirements for special equipment and technology and potential risks, some barriers are encountered in clinical use.

Management Of Pain In Severe Acute Pancreatitis

Pain management in SAP includes pharmaceutical interventions (such as NSAIDs, opioids, and other auxiliary analgesics) and nonpharmaceutical interventions (such as epidural analgesia). Clinically, pain is typically managed with NSAIDs and intravenous opioids. This may result from the poor understanding of the complex pain mechanism in AP and SAP and the lack of enough high-quality clinical research in this specific population.

The treatment of pain should be initiated and titrated based on accurate pain assessment to achieve a balance between the benefits and the potential adverse effects of analgesics. It is definite that 0-10 numeric rating scale should be adopted for critically ill patients who are able to self-report pain, and the behavioral pain scale and critical care pain observation tool should be adopted for critically ill patients who are unable to self-report pain.[86]

Despite the lack of recommended proposal in pharmaceutical pain management in SAP, some generally accepted principles are available for reference. The World Health Organization (WHO) developed a useful algorithm on pain management, suggesting that pain should be treated according to the degrees of severity, which is termed as “analgesic ladder.” Although it has only been validated in cancer pain, it has also been extended to managing noncancerous pain. Due to the extensive potential side effects of opioids, the adjuvant use of multiple drugs to opioids (i.e., multimodal analgesia) is recommended to lower the consumption of opioids.[86] Based on the WHO analgesic ladder and the aforementioned evidence, we provide a practical analgesic ladder for pain management in SAP [Figure 2].


Figure 2::
A practical analgesic ladder for pain management in severe acute pancreatitis

The responses to noxious stimuli, pain mechanisms, and pharmacokinetics and pharmacodynamics of analgesics vary among individuals, which may be related to the heritability of nociception and polymorphisms of the endogenous opioid system.[129130] Therefore, “one model fit all” may have potential drawbacks. However, it is difficult to formulate precise analgesic treatment measures for specific patients due to the huge individual differences and current knowledge gaps. Thankfully, interdisciplinary collaborations such as pain counseling may help improve pain management in SAP.[131] It has been supposed that a new strategy based on the analysis of different underlying pain mechanisms, rather than the traditional strategy based on lesion topography and underlying pathology, may achieve a better treatment outcome in neuropathic pain.[132133134] Mechanism-based therapy assumes that a specific symptom predicts a specific underlying mechanism, while clinical experimental studies indicate that a specific symptom may be generated by several entirely different underlying pathophysiological mechanisms. Therefore, a specific symptom profile rather than a single symptom may be required to predict the underlying mechanism. In 2002, Germany established the Neuropathic Pain Research Network; a standardized quantitative somatosensory phenotype protocol was introduced to establish a link between clinical manifestations and underlying mechanisms. An optimal comprehensive treatment and individual drug combination that target based on a specific mechanism may be formed using this information.[135] It is reasonable to hypothesize that this method may be used in pharmaceutical pain management in AP and SAP in the future.

Conclusion and Future Directions

Unlike other studies, this study reviewed the current pain management in SAP by combining the pain mechanisms with animal or clinical studies. We also proposed an analgesia ladder based on current evidence. Overall, although pain management is the mainstay of SAP treatment, our understanding of pancreatic pain in AP is limited and the research on pain management in patients with SAP is severely under-researched. Future research should focus on gaining insight into and differentiating the pain mechanisms in AP, besides developing new drugs targeting these mechanisms. Meanwhile, evaluating the impact of the currently available drugs and different management strategies of pain on the outcomes of patients with SAP may fill gaps in current knowledge and improve the outcomes of this specific population. This may lead to precise analgesia treatments and improved outcomes for patients with SAP in the future.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Bhatia M, Wong FL, Cao Y, Lau HY, Huang J, Puneet P, *et al*. Pathophysiology of acute pancreatitis. Pancreatology 2005;5:132-44.

- Cited Here |
- PubMed | CrossRef

2. Li CL, Jiang M, Pan CQ, Li J, Xu LG. The global, regional, and national burden of acute pancreatitis in 204 countries and territories, 1990-2019. BMC Gastroenterol 2021;21:332.

- Cited Here |
- PubMed

3. van Santvoort HC, Bakker OJ, Bollen TL, Besselink MG, Ahmed Ali U, Schrijver AM, *et al*. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology 2011;141:1254-63.

- Cited Here |
- PubMed | CrossRef

4. Párniczky A, Kui B, Szentesi A, Balázs A, Szűcs Á Mosztbacher D, *et al*. Prospective, multicentre, nationwide clinical data from 600 cases of acute pancreatitis. PLoS One 2016;11:e0165309.

- Cited Here |
- PubMed | CrossRef

5. Schorn S, Ceyhan GO, Tieftrunk E, Friess H, Demir IE. Pain Management in Acute Pancreatitis. Pancreapedia: Exocrine Pancreas Knowledge Base 2015. doi: 10.3998/panc.2015.15.

- Cited Here

6. Yokoe M, Takada T, Mayumi T, Yoshida M, Isaji S, Wada K, *et al*. Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. J Hepatobiliary Pancreat Sci 2015;22:405-32.

- Cited Here |
- View Full Text | PubMed | CrossRef

7. Leppäniemi A, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, Kirkpatrick AW, *et al*. 2019 WSES guidelines for the management of severe acute pancreatitis. World J Emerg Surg 2019;14:27.

- Cited Here

8. Frossard JL, Steer ML, Pastor CM. Acute pancreatitis. Lancet 2008;371:143-52.

- Cited Here |
- PubMed | CrossRef

9. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, *et al*. Classification of acute pancreatitis - 2012: Revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102-11.

- Cited Here |
- View Full Text | PubMed | CrossRef

10. Kapoor K, Repas K, Singh VK, Conwell DL, Mortele KJ, Wu BU, *et al*. Does the duration of abdominal pain prior to admission influence the severity of acute pancreatitis? JOP 2013;14:171-5.

- Cited Here |
- PubMed

11. Phillip V, Schuster T, Hagemes F, Lorenz S, Matheis U, Preinfalk S, *et al*. Time period from onset of pain to hospital admission and patients' awareness in acute pancreatitis. Pancreas 2013;42:647-54.

- Cited Here |

- View Full Text | PubMed | CrossRef

12. Mayerle J, Simon P, Lerch MM. Medical treatment of acute pancreatitis. Gastroenterol Clin North Am 2004;4:855-69 viii.

- Cited Here |
- PubMed | CrossRef

13. Parsa N, Faghih M, Garcia Gonzalez F, Moran RA, Kamal A, Jalaly NY, *et al*. Early hemoconcentration is associated with increased opioid use in hospitalized patients with acute pancreatitis. Pancreas 2019;48:193-8.

- Cited Here |
- View Full Text | PubMed | CrossRef

14. Ashok A, Faghih M, Azadi JR, Parsa N, Fan C, Bhullar F, *et al*. Morphologic severity of acute pancreatitis on imaging is independently associated with opioid dose requirements in hospitalized patients. Dig Dis Sci 2022;67:1362-1370.

- Cited Here |
- PubMed | CrossRef

15. Cappell MS. Acute pancreatitis: Etiology, clinical presentation, diagnosis, and therapy. Med Clin North Am 2008;92:889-923 ix-x.

- Cited Here |
- PubMed | CrossRef

16. Whitcomb DC. Clinical practice. Acute pancreatitis. N Engl J Med 2006;354:2142-50.

- Cited Here |
- View Full Text | PubMed | CrossRef

17. Finkelberg DL, Sahani D, Deshpande V, Brugge WR. Autoimmune pancreatitis. N Engl J Med 2006;355:2670-6.

- Cited Here |
- View Full Text | PubMed | CrossRef

18. Klöppel G, Lüttges J, Löhr M, Zamboni G, Longnecker D. Autoimmune pancreatitis: Pathological, clinical, and immunological features. Pancreas 2003;27:14-9.

- Cited Here |
- View Full Text | PubMed | CrossRef

19. Hedderich R, Ness TJ. Analgesia for trauma and burns. Crit Care Clin 1999;15:167-84.

- Cited Here |
- PubMed | CrossRef

20. Akça O, Melischek M, Scheck T, Hellwagner K, Arkiliç CF, Kurz A, *et al*. Postoperative pain and subcutaneous oxygen tension. Lancet 1999;354:41-2.

- Cited Here |
- PubMed | CrossRef

21. Beilin B, Shavit Y, Hart J, Mordashov B, Cohn S, Notti I, *et al*. Effects of anesthesia based on large versus small doses of fentanyl on natural killer cell cytotoxicity in the perioperative period. Anesth Analg 1996;82:492-7.

- Cited Here |
- View Full Text | PubMed | CrossRef

22. Yamashita A, Yamasaki M, Matsuyama H, Amaya F. Risk factors and prognosis of pain events during mechanical ventilation: A retrospective study. J Intensive Care 2017;5:17.

- Cited Here |
- PubMed

23. Greenberg JA, Hsu J, Bawazeer M, Marshall J, Friedrich JO, Nathens A, *et al*. Clinical practice guideline: Management of acute pancreatitis. Can J Surg 2016;59:128-40.

- Cited Here |
- View Full Text | PubMed | CrossRef

24. Cruciani RA, Jain S. Pancreatic pain: A mini review. Pancreatology 2008;8:230-5.

- Cited Here |
- PubMed | CrossRef

25. Won MH, Park HS, Jeong YG, Park HJ. Afferent innervation of the rat pancreas: Retrograde tracing and immunohistochemistry in the dorsal root ganglia. Pancreas 1998;16:80-7.

- Cited Here |
- View Full Text | PubMed | CrossRef

26. Kim EH, Hoge SG, Lightner AM, Grady EF, Coelho AM, Kirkwood KS. Activation of nociceptive neurons in T9 and T10 in cerulein pancreatitis. J Surg Res 2004;117:195-201.

- Cited Here |
- PubMed | CrossRef

27. Barreto SG, Saccone GT. Pancreatic nociception - Revisiting the physiology and pathophysiology. Pancreatology 2012;12:104-12.

- Cited Here |
- PubMed | CrossRef

28. Blackshaw LA, Brookes SJ, Grundy D, Schemann M. Sensory transmission in the gastrointestinal tract. Neurogastroenterol Motil 2007;19:1-19.

- Cited Here |
- PubMed | CrossRef

29. Cervero F, Tattersall JE. Somatic and visceral sensory integration in the thoracic spinal cord. Prog Brain Res 1986;67:189-205.

- Cited Here |
- PubMed

30. Lindsay TH, Halvorson KG, Peters CM, Ghilardi JR, Kuskowski MA, Wong GY, *et al*. A quantitative analysis of the sensory and sympathetic innervation of the mouse pancreas. Neuroscience 2006;137:1417-26.

- Cited Here |
- PubMed | CrossRef

31. Chung EK, Zhang XJ, Xu HX, Sung JJ, Bian ZX. Visceral hyperalgesia induced by neonatal maternal separation is associated with nerve growth factor-mediated central neuronal plasticity in rat spinal cord. Neuroscience 2007;149:685-95.

- Cited Here |
- PubMed | CrossRef

32. Buijs RM, Chun SJ, Niijima A, Romijn HJ, Nagai K. Parasympathetic and sympathetic control of the pancreas: A role for the suprachiasmatic nucleus and other hypothalamic centers that are involved in the regulation of food intake. J Comp Neurol 2001;431:405-23.

- Cited Here |
- PubMed | CrossRef

33. Vera-Portocarrero LP, Lu Y, Westlund KN. Nociception in persistent pancreatitis in rats: Effects of morphine and neuropeptide alterations. Anesthesiology 2003;98:474-84.

- Cited Here |
- View Full Text | PubMed | CrossRef

34. Pomeranz B, Wall PD, Weber WV. Cord cells responding to fine myelinated afferents from viscera, muscle and skin. J Physiol 1968;199:511-32.

- Cited Here |
- PubMed | CrossRef

35. Baron R. Mechanisms of disease: Neuropathic pain - A clinical perspective. Nat Clin Pract Neurol 2006;2:95-106.

- Cited Here |
- View Full Text | PubMed | CrossRef

36. Scholz J, Woolf CJ. The neuropathic pain triad: Neurons, immune cells and glia. Nat Neurosci 2007;10:1361-8.

- Cited Here |
- PubMed | CrossRef

37. Lindsay TH, Jonas BM, Sevcik MA, Kubota K, Halvorson KG, Ghilardi JR, *et al*. Pancreatic cancer pain and its correlation with changes in tumor vasculature, macrophage infiltration, neuronal innervation, body weight and disease progression. Pain 2005;119:233-46.

- Cited Here |
- View Full Text | PubMed | CrossRef

38. Rasmussen PV, Sindrup SH, Jensen TS, Bach FW. Symptoms and signs in patients with suspected neuropathic pain. Pain 2004;110:461-9.

- Cited Here |
- View Full Text | PubMed | CrossRef

39. Lai J, Hunter JC, Porreca F. The role of voltage-gated sodium channels in neuropathic pain. Curr Opin Neurobiol 2003;13:291-7.

- Cited Here |
- PubMed | CrossRef

40. Davis JB, Gray J, Gunthorpe MJ, Hatcher JP, Davey PT, Overend P, *et al*. Vanilloid receptor-1 is essential for inflammatory thermal hyperalgesia. Nature 2000;405:183-7.

- Cited Here |
- View Full Text | PubMed | CrossRef

41. Alessandri-Haber N, Dina OA, Yeh JJ, Parada CA, Reichling DB, Levine JD. Transient receptor potential vanilloid 4 is essential in chemotherapy-induced neuropathic pain in the rat. J Neurosci 2004;24:4444-52.

- Cited Here |
- PubMed | CrossRef

42. Choi B, Rowbotham MC. Effect of adrenergic receptor activation on post-herpetic neuralgia pain and sensory disturbances. Pain 1997;69:55-63.

- Cited Here |
- View Full Text | PubMed | CrossRef

43. Winston J, Toma H, Shenoy M, Pasricha PJ. Nerve growth factor regulates VR-1 mRNA levels in cultures of adult dorsal root ganglion neurons. Pain 2001;89:181-6.

- Cited Here |
- View Full Text | PubMed | CrossRef

44. Winston JH, Toma H, Shenoy M, He ZJ, Zou L, Xiao SY, *et al*. Acute pancreatitis results in referred mechanical hypersensitivity and neuropeptide up-regulation that can be suppressed by the protein kinase inhibitor k252a. J Pain 2003;4:329-37.

- Cited Here |
- PubMed | CrossRef

45. Liu L, Shenoy M, Pasricha PJ. Substance P and calcitonin gene related peptide mediate pain in chronic pancreatitis and their expression is driven by nerve growth factor. JOP 2011;12:389-94.

- Cited Here |
- PubMed

46. Marchand F, Perretti M, McMahon SB. Role of the immune system in chronic pain. Nat Rev Neurosci 2005;6:521-32.

- Cited Here |
- PubMed | CrossRef

47. Vardanyan M, Melemedjian OK, Price TJ, Ossipov MH, Lai J, Roberts E, *et al*. Reversal of pancreatitis-induced pain by an orally available, small molecule interleukin-6 receptor antagonist.

Pain 2010;151:257-65.

- Cited Here |
- View Full Text | PubMed | CrossRef

48. Hains BC, Saab CY, Klein JP, Craner MJ, Waxman SG. Altered sodium channel expression in second-order spinal sensory neurons contributes to pain after peripheral nerve injury. J Neurosci 2004;24:4832-9.

- Cited Here |
- PubMed | CrossRef

49. Moore KA, Kohno T, Karchewski LA, Scholz J, Baba H, Woolf CJ. Partial peripheral nerve injury promotes a selective loss of GABAergic inhibition in the superficial dorsal horn of the spinal cord. J Neurosci 2002;22:6724-31.

- Cited Here |
- PubMed | CrossRef

50. Vanegas H, Schaible HG. Descending control of persistent pain: Inhibitory or facilitatory? Brain Res Brain Res Rev 2004;46:295-309.

- Cited Here |
- PubMed | CrossRef

51. Wieseler-Frank J, Maier SF, Watkins LR. Central proinflammatory cytokines and pain enhancement. Neurosignals 2005;14:166-74.

- Cited Here |
- PubMed | CrossRef

52. Maihöfner C, Forster C, Birklein F, Neundörfer B, Handwerker HO. Brain processing during mechanical hyperalgesia in complex regional pain syndrome: A functional MRI study. Pain 2005;114:93-103.

- Cited Here |
- View Full Text | PubMed | CrossRef

53. Willoch F, Schindler F, Wester HJ, Empl M, Straube A, Schwaiger M, *et al*. Central poststroke pain and reduced opioid receptor binding within pain processing circuitries: A [11 C] diprenorphine PET study. Pain 2004;108:213-20.

- Cited Here |
- View Full Text | PubMed | CrossRef

54. Jakobs R, Adamek MU, von Bubnoff AC, Riemann JF. Buprenorphine or procaine for pain relief in acute pancreatitis. A prospective randomized study. Scand J Gastroenterol 2000;35:1319-23.

- Cited Here |
- PubMed

55. Mahapatra SJ, Jain S, Bopanna S, Gupta S, Singh P, Trikha A, *et al*. Pentazocine, a kappa-opioid agonist, is better than diclofenac for analgesia in acute pancreatitis: A randomized controlled trial. Am J Gastroenterol 2019;114:813-21.

- Cited Here |
- View Full Text | PubMed | CrossRef

56. Meng W, Yuan J, Zhang C, Bai Z, Zhou W, Yan J, *et al*. Parenteral analgesics for pain relief in acute pancreatitis: A systematic review. Pancreatology 2013;13:201-6.

- Cited Here |
- PubMed | CrossRef

57. Barlass U, Dutta R, Cheema H, George J, Sareen A, Dixit A, *et al*. Morphine worsens the severity and prevents pancreatic regeneration in mouse models of acute pancreatitis. Gut 2018;67:600-2.

- Cited Here |
- View Full Text | PubMed

58. Sotoudehmanesh R, Khatibian M, Kolahdoozan S, Ainechi S, Malboosbaf R, Nouraie M. Indomethacin may reduce the incidence and severity of acute pancreatitis after ERCP. Am J Gastroenterol 2007;102:978-83.

- Cited Here |
- View Full Text | PubMed | CrossRef

59. Guglielmi V, Tutino M, Guerra V, Giorgio P. Rectal indomethacin or intravenous gabexate mesylate as prophylaxis for acute pancreatitis post-endoscopic retrograde cholangiopancreatography. Eur Rev Med Pharmacol Sci 2017;21:5268-74.

- Cited Here |
- PubMed

60. Icacan G, Onalan E, Yucesoy M. Comparison of stent and indomethacin suppository efficacy in the prevention of acute pancreatitis after ERCP. Acta Biomed 2021;92:e2021178.

- Cited Here |
- PubMed

61. Oiofinlade O. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. Gastroenterology 2004;126:632.

- Cited Here |
- PubMed | CrossRef

62. Geraci G, Palumbo VD, D'orazio B, Maffongelli A, Fazzotta S, Lo Monte AI. Rectal Diclofenac administration for prevention of post-Endoscopic Retrograde Cholangio-Pancreatography (ERCP) acute pancreatitis. Randomized prospective study. Clin Ter 2019;170:e332-6.

- Cited Here |
- PubMed

63. Dumonceau JM, Andriulli A, Elmunzer BJ, Mariani A, Meister T, Deviere J, *et al*. Prophylaxis of post-ERCP pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Updated June 2014. Endoscopy 2014;46:799-815.

- Cited Here |
- PubMed | CrossRef

64. Chen SJ, Lin CS, Hsu CW, Lin CL, Kao CH. Acetaminophen poisoning and risk of acute pancreatitis: A population-based cohort study. Medicine (Baltimore) 2015;94:e1195.

- Cited Here

65. Wilms B, Meffert KS, Schultes B. Procaine infusion for pain treatment of acute pancreatitis: A randomized, placebo-controlled double-blind trial. Dtsch Med Wochenschr 2010;135:2290-5.

- Cited Here |
- PubMed | CrossRef

66. Kahl S, Zimmermann S, Pross M, Schulz HU, Schmidt U, Malfertheiner P. Procaine hydrochloride fails to relieve pain in patients with acute pancreatitis. Digestion 2004;69:5-9.

- Cited Here |
- PubMed | CrossRef

67. Antkowiak R, Antkowiak Ł, Grzegorczyn S, Nalik-Iwaniak K, Kabała N, Arent Z, *et al*. Efficacy of intra-arterial lidocaine infusion in the treatment of cerulein-induced acute pancreatitis. Adv Clin Exp Med 2020;29:587-95.

- Cited Here |
- PubMed

68. Insler SR, O'Connor M, Samonte AF, Bazaral MG. Lidocaine and the inhibition of postoperative pain in coronary artery bypass patients. J Cardiothorac Vasc Anesth 1995;9:541-6.

- Cited Here |
- PubMed | CrossRef

69. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Physician 2008;11:S133-53.

- Cited Here |
- PubMed

70. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, *et al*. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263-306.

- Cited Here |
- View Full Text | PubMed | CrossRef

71. Stevens M, Esler R, Asher G. Transdermal fentanyl for the management of acute pancreatitis pain. Appl Nurs Res 2002;15:102-10.

- Cited Here |
- PubMed | CrossRef

72. Gopal ST, Lane MP, Park GR. Remifentanil for the pain of pancreatitis. Anaesthesia 2003;58:1137-8.

- Cited Here |
- View Full Text | PubMed | CrossRef

73. Basurto Ona X, Rigau Comas D, Urrútia G. Opioids for acute pancreatitis pain. Cochrane Database Syst Rev 2013;26:CD009179.

- Cited Here |
- PubMed

74. Zhou H, Zhu ZH, Liu Y, Liu YY. Effects of midazolam combined with sufentanil on injury and expression of HMGB1 and NF-κB in rats with pancreatitis. Eur Rev Med Pharmacol Sci 2020;24:2102-9.

- Cited Here |
- PubMed

75. Wang Y, Chen M. Fentanyl ameliorates severe acute pancreatitis-induced myocardial injury in rats by regulating NF-κB signaling pathway. Med Sci Monit 2017;23:3276-83.

- Cited Here |
- PubMed | CrossRef

76. Thompson DR. Narcotic analgesic effects on the sphincter of Oddi: A review of the data and therapeutic implications in treating pancreatitis. Am J Gastroenterol 2001;96:1266-72.

- Cited Here |
- View Full Text | PubMed | CrossRef

77. Fujita W, Gomes I, Dove LS, Prohaska D, McIntyre G, Devi LA. Molecular characterization of eluxadoline as a potential ligand targeting mu-delta opioid receptor heteromers. Biochem Pharmacol 2014;92:448-56.

- Cited Here |
- View Full Text | PubMed | CrossRef

78. Famularo G, Pozzessere C, Polchi S, De Simone C. Acute pancreatitis after morphine administration. Ital J Gastroenterol Hepatol 1999;31:522-3.

- Cited Here |
- PubMed

79. Sepulveda S, Dermine H, Mulot A, Villard M, Haberer JP. Acute pancreatitis after intravenous buprenorphine misuse in a heroin addict. Ann Fr Anesth Reanim 2004;23:658-9.

- Cited Here |
- PubMed

80. Ciobanu C, Jadav RS, Colon Ramos A, Sequeira Gross HG, Brazzarola C. Heroin-induced acute pancreatitis. Cureus 2021;13:e15470.

- Cited Here

81. Helm JF, Venu RP, Geenen JE, Hogan WJ, Dodds WJ, Toouli J, *et al*. Effects of morphine on the human sphincter of Oddi. Gut 1988;29:1402-7.

- Cited Here |
- PubMed | CrossRef

82. Chai X, Gao Y, Chai Z. Study of fentanyl/pethidine induced spasm of the sphincter of oddi. J Hepatobiliary Surg 1997;04:239-40.

- Cited Here

83. Kim J, Tabner AJ, Johnson GD, Brumback BA, Hartzema A. Increased risk of acute pancreatitis with codeine use in patients with a history of cholecystectomy. Dig Dis Sci 2020;65:292-300.

- Cited Here |
- PubMed | CrossRef

84. Matic S, Radosavljevic I, Jankovic S, Natasa D. IL-10-1082G>A polymorphism, use of opioids and age affect the course of acute pancreatitis. Eur J Gastroenterol Hepatol 2021;32:178-85.

- Cited Here |
- View Full Text | PubMed | CrossRef

85. Halonen KI, Pettilä V, Leppäniemi AK, Kemppainen EA, Puolakkainen PA, Haapiainen RK. Multiple organ dysfunction associated with severe acute pancreatitis. Crit Care Med 2002;30:1274-9.

- Cited Here |
- View Full Text | PubMed | CrossRef

86. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJ, Pandharipande PP, *et al*. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med 2018;46:e825-73.

- Cited Here |
- View Full Text | PubMed | CrossRef

87. Vargas E, Terleira A, Hernando F, Perez E, Cordón C, Moreno A, *et al*. Effect of adverse drug reactions on length of stay in surgical intensive care units. Crit Care Med 2003;31:694-8.

- Cited Here |
- View Full Text | PubMed | CrossRef

88. Baxter KA, Pucher PH, Berry DP, Elberm H, Abu-Hilal M, Marangoni G, *et al*. The effect of non-steroidal anti-inflammatory drugs on severity of acute pancreatitis and pancreatic necrosis. Ann R Coll Surg Engl 2018;100:199-202.

- Cited Here |
- View Full Text | PubMed | CrossRef

89. Lankisch PG, Koop H, Winckler K, Kunze H, Vogt W. Indomethacin treatment of acute experimental pancreatitis in the rat. Scand J Gastroenterol 1978;13:629-33.

- Cited Here |
- PubMed

90. Wildenhain PM, Melhem MF, Birsic WI, Sell HW, Rao KN. Acute hemorrhagic pancreatitis in mice: Improved survival after indomethacin administration. Digestion 1989;44:41-51.

- Cited Here |
- PubMed | CrossRef

91. Lu G, Pan Y, Kayoumu A, Zhang L, Yin T, Tong Z, *et al*. Indomethacin inhabits the NLRP3 inflammasome pathway and protects severe acute pancreatitis in mice. Biochem Biophys Res Commun 2017;493:827-32.

- Cited Here |
- PubMed | CrossRef

92. Coelle EF, Adham N, Elashoff J, Lewin K, Taylor IL. Effects of prostaglandin and indomethacin on diet-induced acute pancreatitis in mice. Gastroenterology 1983;85:1307-12.

- Cited Here |
- PubMed | CrossRef

93. Kiviniemi H, Rämö OJ, Ståhlberg M, Kairaluoma MI. Indomethacin in canine acute hemorrhagic pancreatitis. Res Exp Med (Berl) 1988;188:35-40.

- Cited Here

94. Studley JG, Lee JB, Schenk WG Jr, Pathophysiology of acute pancreatitis: Evaluation of the effects and mode of action of indomethacin in experimental pancreatitis in dogs. J Surg Res 1982;32:563-8.

- Cited Here |
- PubMed | CrossRef

95. Ebbehøj N, Friis J, Svendsen LB, Bülow S, Madsen P. Indomethacin treatment of acute pancreatitis. A controlled double-blind trial. Scand J Gastroenterol 1985;20:798-800.

- Cited Here |
- PubMed | CrossRef

96. Döbrönte Z, Toldy E, Márk L, Sarang K, Lakner L. Effects of rectal indomethacin in the prevention of post-ERCP acute pancreatitis. Orv Hetil 2012;153:990-6.

- Cited Here |
- PubMed | CrossRef

97. Lindo Ricce M, Rodríguez López-Salazar T, Mendoza Jiménez-Ridruejo J, Moreno Monteagudo JA, Santander Vaquero C. Effectiveness of rectal indomethacin in the prevention of acute pancreatitis after endoscopic retrograde cholangiopancreatography in unselected patients. Rev Esp Enferm Dig 2020;112:183-8.

- Cited Here |
- PubMed

98. Kumar NS, Muktesh G, Samra T, Sarma P, Samanta J, Sinha SK, *et al*. Comparison of efficacy of diclofenac and tramadol in relieving pain in patients of acute pancreatitis: A randomized parallel group double blind active controlled pilot study. Eur J Pain 2020;24:639-48.

- Cited Here |
- View Full Text | PubMed

99. Ozer Cakir O, Esen H, Toker A, Ataseven H, Demir A, Polat H. Effects of diclofenac sodium and octreotide on treatment of caerulein-induced acute pancreatitis in mice. Int J Clin Exp Med 2015;8:17551-64.

- Cited Here

100. Bhatia M, Sidhapuriwala JN, Sparatore A, Moore PK. Treatment with H2S-releasing diclofenac protects mice against acute pancreatitis-associated lung injury. Shock 2008;29:84-8.

- Cited Here |
- View Full Text | PubMed

101. Ozer Cakir O, Findik S. Diclofenac sodium treatment ameliorates extrapancreatic organ injuries in a murine model of acute pancreatitis induced by caerulein. Gastroenterol Res Pract 2018;2018:9829208.

- Cited Here

102. Akyazi I, Eraslan E, Gülçubuk A, Ekiz EE, Cırakli ZL, Haktanir D, *et al*. Long-term aspirin pretreatment in the prevention of cerulein-induced acute pancreatitis in rats. World J Gastroenterol 2013;19:2894-903.

- Cited Here |
- PubMed | CrossRef

103. Lu G, Tong Z, Ding Y, Liu J, Pan Y, Gao L, *et al*. Aspirin protects against acinar cells necrosis in severe acute pancreatitis in mice. Biomed Res Int 2016;2016:6089430.

- Cited Here

104. Alhan E, Kalyoncu NI, Ercin C, Kural BV. Effects of the celecoxib on the acute necrotizing pancreatitis in rats. Inflammation 2004;28:303-9.

- Cited Here |
- View Full Text | PubMed | CrossRef

105. Hung SC, Hung SR, Lin CL, Lai SW, Hung HC. Use of celecoxib correlates with increased relative risk of acute pancreatitis: A case-control study in Taiwan. Am J Gastroenterol 2015;110:1490-6.

- Cited Here |
- View Full Text | PubMed | CrossRef

106. Yeomans ND, Graham DY, Wang Q, Wolski K, Borer J, Husni EM, *et al*. Acute pancreatitis with long-term celecoxib vs. ibuprofen or naproxen: Data from the PRECISION trial. Am J Gastroenterol 2018;113:1053-4.

- Cited Here |
- View Full Text | PubMed | CrossRef

107. Tan JH, Zhou L, Kan HP, Zhang GW. Parecoxib improves the outcomes of acute mild and moderate pancreatitis: A 3-year matched cohort study based on a prospective database. Pancreas 2019;48:1148-54.

- Cited Here |
- View Full Text | PubMed | CrossRef

108. Cattabriga I, Pacini D, Lamazza G, Talarico F, Di Bartolomeo R, Grillone G, *et al*. Intravenous paracetamol as adjunctive treatment for postoperative pain after cardiac surgery: A double blind randomized controlled trial. Eur J Cardiothorac Surg 2007;32:527-31.

- Cited Here |
- View Full Text | PubMed | CrossRef

109. Memis D, Inal MT, Kavalci G, Sezer A, Sut N. Intravenous paracetamol reduced the use of opioids, extubation time, and opioid-related adverse effects after major surgery in intensive care unit. J Crit Care 2010;25:458-62.

- Cited Here |
- View Full Text | PubMed | CrossRef

110. Cantais A, Schnell D, Vincent F, Hammouda Z, Perinel S, Balichard S, *et al*. Acetaminophen-induced changes in systemic blood pressure in critically ill patients: Results of a multicenter cohort study. Crit Care Med 2016;44:2192-8.

- Cited Here |
- View Full Text | PubMed | CrossRef

111. He YH, Lu L, Wang YF, Huang JS, Zhu WQ, Guo Y, *et al*. Acetaminophen-induced acute pancreatitis: A case report and literature review. World J Clin Cases 2018;6:291-5.

- Cited Here

112. Zanos P, Moaddel R, Morris PJ, Riggs LM, Highland JN, Georgiou P, *et al*. Ketamine and ketamine metabolite pharmacology: Insights into therapeutic mechanisms. Pharmacol Rev 2018;70:621-60.

- Cited Here |
- PubMed | CrossRef

113. Wan LB, Levitch CF, Perez AM, Brallier JW, Iosifescu DV, Chang LC, *et al*. Ketamine safety and tolerability in clinical trials for treatment-resistant depression. J Clin Psychiatry 2015;76:247-52.

- Cited Here |
- PubMed | CrossRef

114. Manasco AT, Stephens RJ, Yaeger LH, Roberts BW, Fuller BM. Ketamine sedation in mechanically ventilated patients: A systematic review and meta-analysis. J Crit Care 2020;56:80-88.

- Cited Here |
- View Full Text | PubMed | CrossRef

115. Guillou N, Tanguy M, Seguin P, Branger B, Campion JP, Mallédant Y. The effects of small-dose ketamine on morphine consumption in surgical intensive care unit patients after major abdominal surgery. Anesth Analg 2003;97:843-7.

- Cited Here |
- View Full Text | PubMed | CrossRef

116. Mogahd MM, Mahran MS, Elbaradi GF. Safety and efficacy of ketamine-dexmedetomidine versus ketamine-propofol combinations for sedation in patients after coronary artery bypass graft surgery. Ann Card Anaesth 2017;20:182-7.

- Cited Here |
- View Full Text | CrossRef

117. Perbet S, Verdonk F, Godet T, Jabaudon M, Chartier C, Cayot S, *et al*. Low doses of ketamine reduce delirium but not opiate consumption in mechanically ventilated and sedated ICU patients: A randomised double-blind control trial. Anaesth Crit Care Pain Med 2018;37:589-95.

- Cited Here |
- PubMed

118. Manasco AT, Stephens RJ, Yaeger LH, Roberts BW, Fuller BM. Ketamine sedation in mechanically ventilated patients: A systematic review and meta-analysis. J Crit Care 2020;56:80-8.

- Cited Here |
- View Full Text | PubMed | CrossRef

119. Kim K, Kim WJ, Choi DK, Lee YK, Choi IC, Sim JY. The analgesic efficacy and safety of nefopam in patient-controlled analgesia after cardiac surgery: A randomized, double-blind, prospective study. J Int Med Res 2014;42:684-92.

- Cited Here |
- PubMed | CrossRef

120. Smiley MM, Lu Y, Vera-Portocarrero LP, Zidan A, Westlund KN. Intrathecal gabapentin enhances the analgesic effects of subtherapeutic dose morphine in a rat experimental pancreatitis model. Anesthesiology 2004;101:759-65.

- Cited Here |
- View Full Text | PubMed | CrossRef

121. Orr RB, Warren KW. Continuous epidural analgesia in acute pancreatitis. Lahey Clin Bull 1950;6:204-10.

- Cited Here |
- PubMed

122. Sasabuchi Y, Yasunaga H, Matsui H, Lefor AK, Fushimi K, Sanui M. Epidural analgesia is infrequently used in patients with acute pancreatitis: A retrospective cohort study. Acta Gastroenterol Belg 2017;80:381-4.

- Cited Here |
- PubMed

123. Jabaudon M, Belhadj-Tahar N, Rimmelé T, Joannes-Boyau O, Bulyez S, Lefrant JY, *et al*. Thoracic epidural analgesia and mortality in acute pancreatitis: A multicenter propensity analysis. Crit Care Med 2018;46:e198-205.

- Cited Here |
- View Full Text | PubMed | CrossRef

124. Bulyez S, Pereira B, Caumon E, Imhoff E, Roszyk L, Bernard L, *et al*. Epidural analgesia in critically ill patients with acute pancreatitis: The multicentre randomised controlled EPIPAN study protocol. BMJ Open 2017;7:e015280.

- Cited Here

125. Bos EM, Hollmann MW, Lirk P. Safety and efficacy of epidural analgesia. Curr Opin Anaesthesiol 2017;30:736-42.

- Cited Here |
- View Full Text | PubMed | CrossRef

126. Rykowski JJ, Hilgier M. Continuous celiac plexus block in acute pancreatitis. Reg Anesth 1995;20:528-32.

- Cited Here

127. Verhaegh BP, van Kleef M, Geurts JW, Puylaert M, van Zundert J, Kessels AG, *et al*. Percutaneous radiofrequency ablation of the splanchnic nerves in patients with chronic pancreatitis: Results of single and repeated procedures in 11 patients. Pain Pract 2013;13:621-6.

- Cited Here |
- View Full Text | PubMed | CrossRef

128. Thapa D, Ahuja V, Gombar S, Ramakumar N, Dass C. Radiofrequency ablation of bilateral splanchnic nerve in acute pancreatitis pain: Interventional approach. J Anaesthesiol Clin Pharmacol 2017;33:278-9.

- Cited Here |
- View Full Text | PubMed | CrossRef

129. Mogil JS, Wilson SG, Bon K, Lee SE, Chung K, Raber P, *et al*. Heritability of nociception I: Responses of 11 inbred mouse strains on 12 measures of nociception. Pain 1999;80:67-82.

- Cited Here |
- View Full Text | PubMed | CrossRef

130. Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, *et al*. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. Science 2003;299:1240-3.

- Cited Here |
- View Full Text | PubMed | CrossRef

131. Ushe T, Lakhan SE, Locklear T, Muthukattil R, Whitehead P, Benson A, *et al*. Pain management consultation for acute pancreatitis: Impact on length of stay and opioid utilization. Pain Manag 2022;12:159-66.

- Cited Here |
- PubMed

132. Jensen TS, Baron R. Translation of symptoms and signs into mechanisms in neuropathic pain. Pain 2003;102:1-8.

- Cited Here |
- View Full Text | PubMed | CrossRef

133. Woolf CJ, Bennett GJ, Doherty M, Dubner R, Kidd B, Koltzenburg M, *et al*. Towards a mechanism-based classification of pain? Pain 1998;77:227-9.

- Cited Here |

- View Full Text | PubMed | CrossRef

134. Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, *et al*. Advances in neuropathic pain: Diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003;60:1524-34.

- Cited Here |
- View Full Text | PubMed | CrossRef

135. Rolke R, Baron R, Maier C, Tölle TR, Treede -DR, Beyer A, *et al*. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. Pain 2006;123:231-43.

- Cited Here |
- View Full Text | PubMed | CrossRef

View full references list

Keywords:

Management; mechanism; pain; severe acute pancreatitis

View full article text

Related Articles

- **Timing and Route of Nutritional Therapy for Severe Acute Pancreatitis: From Bench to Bedside**
- **Update of Thoracic Epidural Analgesia Used in Acute Pancreatitis**
- **A Step-up Approach for the Management of Infected Pancreatic Necrosis**
- **Acute cerebral edema reduction due to dexamethasone in a patient with acute respiratory distress syndrome due to severe acute respiratory syndrome coronavirus 2**
- **Severe Burns Complicated by Acute Kidney Injury: Some Nuances Regarding Risk Factors and Mortality Rate**
- **Optimizing healthcare professional performance in COVID-19 airway management: The role of interprofessional simulation training**

Most Popular

Service is not available please try again later.

^Back to Top

Never Miss an Issue

Get new journal Tables of Contents sent right to your email inbox Type your email
Get New Issue Alerts

Browse Journal Content

- Register on the website
- Get eTOC Alerts

Customer Service

- Contact us at:
  - Support:
    Submit a Service Request
- Manage Cookie Preferences
- Privacy Policy
- Legal Disclaimer
- Terms of Use
- Open Access Policy
- Your California Privacy Choices
-