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Which pharmacological interventions are most effective for pain control in acute and chronic pancreatitis?

Anisah Hussain [1]*, Hannan Razvi [1], Bhavesh Raithatha [2], Neil Bhardwaj [2]

[1] University of Leicester Medical School, Leicester, UK
[2] University Hospitals of Leicester NHS Trust, Leicester, UK
***Corresponding Author:** ah693@student.le.ac.uk

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ABSTRACT

Acute pancreatitis is an inflammatory condition of the pancreas, most commonly caused by gallstone obstruction of the pancreatic duct or excessive alcohol consumption. It typically presents severe epigastric pain radiating to the back and can result in significant complications, including ascites, pleural effusions and renal failure. Prolonged or recurrent pancreatic inflammation may lead to irreversible structural changes, including fibrosis, ductal strictures, and cyst formation. Chronic pancreatitis is associated with persistent pain, impaired pancreatic function, and an increased risk of pancreatic cancer. The management is primarily supportive and includes aggressive fluid resuscitation, early enteral nutrition, adequate analgesia, and treatment of complications. Pain control remains a cornerstone of management in both acute and chronic pancreatitis. Analgesia is typically guided by the World Health Organization pain ladder, with non-opioid agents used initially; however, due to the severity of pain in acute pancreatitis, opioids are frequently required as first-line therapy. Despite the central role of analgesia in management, evidence comparing the efficacy and safety of different analgesics in pancreatitis remains limited. As a result, clinical practice varies and is often guided by clinician preference, perceived risk of complications, and individual patient factors.

Keywords: acute, chronic, pancreatitis, pain, analgesia, opioids

INTRODUCTION

Acute pancreatitis is a sudden inflammation of the pancreas, which is a gland located behind the stomach responsible for secreting pancreatic juices and enzymes to aid digestion as well as regulating blood glucose levels [1]. It usually presents sudden onset abdominal pain, often severe and debilitating, caused by premature activation of these enzymes before they leave the pancreas. This leads to autodigestion of the pancreas, causing irritation, swelling and damage to the tissues [1]. It is a common gastrointestinal emergency which is most commonly caused by gallstones and alcohol use. A gallstone in the distal end of the common bile duct can occlude the outflow of zymogens through the pancreatic duct [1]. This results in the premature activation of pancreatic enzymes, such as amylase and lipase leading to autodigestion, inflammation, and in severe cases, pancreatic necrosis and sepsis [1]. Alcohol can increase the viscosity of pancreatic juices which can lead to the accumulation of protein plugs in the small pancreatic ducts, ultimately leading to calculi formation [1]. This induces a progressive inflammatory process which can cause damage to the acinar and ductal cells as well as the islets of langerhans. Other causes of pancreatitis can be high blood triglyceride levels, infections or trauma to the abdomen [1]. The condition can range from mild to severe and, in some cases, can lead to life-threatening complications [2]. The severity of acute pancreatitis can be measured using the revised Atlanta classification which considers clinical course, complications and the presence of organ failure [2]. The severity of acute pancreatitis and the perceived amount of pain mentioned by the patient is important as it can impact the choice of analgesia used, in terms of potency [2]. Effective pain management is a crucial component of acute pancreatitis treatment, as uncontrolled pain can exacerbate stress responses, hinder patient recovery, and prolonged hospitalization [1].

Chronic pancreatitis occurs when long-term persistent inflammation of the pancreas leads to damage of both the endocrine and exocrine glands, leading to fibrotic tissue replacing normal healthy pancreatic tissue, which is often irreversible [1]. The condition often results in digestive problems as well as defective glucose regulation as a result of damage to the pancreatic glands [1]. The most predominant symptom of chronic pancreatitis is a dull, gnawing epigastric pain that radiates to the back. Similarly to acute pancreatic pain, it is often worse after meals, when lying down and is often relieved by leaning forward [1]. As seen in acute pancreatitis, autodigestion results in an inflammatory cause of pain, but in chronic pancreatitis, there are additional mechanisms which are neurogenic in nature [3]. Patients with pancreatitis, especially the chronic form, are at risk of hyperalgesia, which refers to having an increased sensitivity to pain and experiencing it more intensely than would be expected under

normal circumstances [3]. This is caused by sensitization of the peripheral and central nervous system due to the damaged pancreas. The pancreas can release inflammatory mediators that sensitize the peripheral nerves near the pancreas and can also lead to neuroplastic changes in the brain and spinal cord [3]. This results in the central nervous system interpreting the signals as more intense and hence causing an exaggerated pain response [3]. Other than managing other complications such as malabsorption, diabetes and obstruction of the pancreatic duct, biliary tree or duodenum, pain management is a vital part of managing pancreatic insufficiency. Pain management may be complex when dealing with chronic pancreatic pain due to potential social problems such as alcohol and opioid dependency [1]. The neurogenic changes that occur in chronic pain can also make the traditional pain management of non-steroidal anti-inflammatory drugs (NSAIDs) or opioids less effective due to the altered pain pathways [3].

Objective

The primary objective of this narrative review is to provide a comprehensive up to date overview of the different analgesic strategies employed in the management of acute and chronic pancreatitis. The review aims to evaluate the efficacy, safety, and clinical outcomes of various analgesics to guide clinicians in optimizing pain management for patients with this condition. This review also contains a critical analysis of the validity of the evidence used in various studies.

Methods

To aid the writing of this narrative review on the analgesic strategies on acute and chronic pancreatitis, research of the literature provided on PubMed, Cochrane, Medline and the current NICE Guidelines, was conducted using the key terms acute pancreatitis, chronic pancreatitis, analgesia, and pain. All articles used were based on studies, conducted using randomized control trials and meta-analysis which assessed pain severity using the visual analogue scale (VAS) or the numerical rating scale (NRS) and compared the different types of analgesics used in acute and chronic pancreatitis. Other articles used in this review describe the mechanism at which these analgesics work and how it affects smooth muscle in the pancreatic-biliary and gastrointestinal system. The neuro-modulatory mechanisms of the drugs used for analgesic purposes are also described throughout the review.

How Is Pain Severity Assessed?

Pain can be measured in many different modalities but the gold-standard is the subjective self-report from a patient [4]. The most commonly assessed type of pain is the sensory intensity and this can be calculated using; categorical scales, NRS, VAS, and well-validated descriptor scales (descriptor differential scale). Pain quality and temporal characteristics can also be used, especially in chronic pain, as knowing the duration and pattern of pain onset can help guide when to take analgesia [4]. Pain is most frequently assessed using pain intensity and affect, and this is a beneficial way of gaining an understanding of the patient's current circumstance, especially in acute pain. However, multidimensional pain assessment tools such as the McGill pain questionnaire (MPQ) can help provide additional information about the sensory and affective qualities of pain [4]. The MPQ allows patients to pick from 20 groups of words to help describe their pain which helps clinicians distinguish between different types of pain [4]. It's also important to take into consideration the impact of a person's quality of life, especially with chronic pain, as this can lead to difficulties in activities of daily living, employment and increases the risk of mental health problems such as depression [4].

Step-Wise Escalation of Pain Management Strategies

Traditional pain management in acute pancreatitis has been decided by following the World Health Organization (WHO) pain ladder [1]. In recent years however, there has been a shift towards multimodal analgesic strategies to provide pain relief while minimising adverse effects [1]. This approach utilizes various classes of analgesics, including non-opioid medications like NSAIDs and paracetamol, as well as opioids such as morphine and tramadol [1]. These strategies aim to provide pain management tailored to the individual patient's needs and underlying health. Despite advancements, there remains no consensus on the optimal analgesic regimen for acute pancreatitis, requiring ongoing research and evaluation of current practices [1]. Similarly, the pain management of chronic pancreatitis follows a stepwise escalation using the WHO analgesic ladder [1]. Paracetamol can be given first-line with or without adjuvant medications such as antidepressants. This can then be escalated to tramadol and classical opioids such as morphine [1]. Other strategies such as pancreatic enzyme therapy can also be tried in order to achieve pain relief. More invasive techniques such as thoracic epidurals can help relieve pain in severe acute pancreatitis, although this is a rare analgesic used compared to more traditional paracetamol, NSAIDs and opioids [1]. When managing chronic pain, adverse side effects and the long-term complications of taking certain analgesics need to be taken into consideration to ensure the risks don't outweigh the benefits [1]. It is also important to consider the psychological implications for a patient experiencing chronic pain [5]. Chronic pain, whether it be pancreatitis or originating elsewhere, is a risk factor for depression and social isolation due to withdrawing from activities that make the pain worse [5]. Interventions such cognitive behavioral therapy used in conjunction with SSRIs or Tricyclic antidepressants can help patients cope with their pain as well as aid in reducing it [5].

PARACETAMOL

Paracetamol works as an analgesic by inhibiting cyclooxygenase (COX) enzymes, which results in reduction in the synthesis of prostaglandins that mediate pain and fever [6]. Paracetamol is used as grade I pain management as it has a favorable safety profile and minimal side effects when used appropriately [6]. However, most patients presenting with either acute or chronic pancreatitis often have severe pain, and paracetamol may not provide them with the analgesic effect they need. In cases such as this, clinical judgement may guide the use of opioids as a first-line treatment [1].

The limitations of using paracetamol as analgesia in acute pancreatitis have not been studied in great depth which poses an issue as paracetamol has been found to be a cause of acute pancreatitis in very rare cases [7]. A literature review on acetaminophen induced pancreatitis demonstrated how there are 11 confirmed case reports of paracetamol leading to acute pancreatitis [7]. The review highlights that there does not appear to be a dose dependent relationship between the severity of pancreatitis and quantity of paracetamol ingested

[7]. Although rare, clinicians should have awareness of this risk, especially in more vulnerable groups such as children, women and the elderly, so that prompt and suitable treatment can be provided [7]. It should be emphasized that this literature review relies on evidence from case reports which makes it challenging to establish causality, as there are no control groups for comparison. Thus, it is important that future studies are conducted to investigate the relationship between paracetamol and acute pancreatitis in greater depth [7]. Paracetamol is accepted as a first-line treatment for pain in pancreatitis and so it is important to emphasize that it is an extremely rare occurrence for paracetamol to be a cause of acute pancreatitis [7].

Paracetamol Versus Non-Steroidal Anti-Inflammatory Drugs

NSAIDs, such as ibuprofen and naproxen, also function by inhibiting COX enzymes, which play a vital role in the formation of prostaglandins and are especially useful in pain caused by inflammatory processes [8]. They are a widely used drug in acute pancreatitis due to their potent analgesic and anti-inflammatory properties [8]. Unlike NSAIDs, paracetamol has minimal anti-inflammatory action and does not significantly inhibit COX enzymes in peripheral tissues, making it a safer option for patients with gastrointestinal or renal issues [8]. In comparison to NSAIDs there is a reduced risk of gastric bleeding and peptic ulcer disease, in which chronic pancreatitis already disposes of you to, and so paracetamol is favored over NSAIDs for long-term pain control [8].

A meta-analysis of 9 randomized control trials, with a total of 2719 patients, studied the use of rectal NSAIDs in the prevention of post-ERCP pancreatitis (PEP), a common complication that can occur following this procedure [9]. The inclusion criteria for this meta-analysis were; randomized control trials examining incidence of PEP after administering either rectal indomethacin or diclofenac and the effects of these drugs on pain relief. Non-human studies, studies only investigating high-risk patients, and insufficient data on PEP were excluded from the criteria [9]. The patients were given the NSAIDs prophylactically 30 minutes prior to their procedure. The results showed a significant benefit in preventing moderate to severe pancreatitis post-ERCP [9]. No difference was identified in regards to the efficacy of indomethacin and diclofenac in preventing PEP. Administration of either NSAID was beneficial if it was given before the procedure, regardless of whether it was given within 30 minutes [9]. This highlights how rectal NSAIDs are effective in prevention of PEP. This shows their utility not just in pain management but also in reducing complications associated with acute pancreatitis [9]. This meta-analysis utilizes a comprehensive search strategy across multiple databases and employs rigorous methodological assessment using Cochrane risk of bias tool, while presenting consistent findings through appropriate statistical analyses [9]. But lack of explicit strategy to address publication bias raises concerns, as studies with positive results are more likely to be published, potentially leading to an overestimation of the true benefit of NSAIDs for PEP [9].

Although these studies suggest its usefulness, there are some factors which raise concerns for the use of NSAIDs. Firstly, there is a lack of extensive research on the use of NSAIDs in the management of pain in acute pancreatitis [10]. This gap in research means that the actual benefit of NSAIDs in this context remains unclear [10]. Although very rare, there are case reports which have shown a link between NSAID use and acute pancreatitis [10]. In light of these reports, it has been suggested that serum amylase should be measured in patients who develop abdominal pain following NSAID use [10]. Whilst we should take note of this possibility, it is important to emphasize that these case reports do not provide sufficient evidence to establish a link between NSAIDs and acute pancreatitis [10]. This is due to the fact that a lack of a control group for comparison means there is no way of knowing whether acute pancreatitis was caused by NSAIDs or would have occurred anyway. Subsequent research should further explore this relationship in further depth to provide a more solid basis to change clinical practice and guidelines [10].

OPIOIDS

Opioids can be classified as their mechanism of action. They can either be agonists (morphine, fentanyl, and hydromorphone), partial agonists (buprenorphine), agonist-antagonists (pentazocine) and antagonists (naloxone) with classic pure opioid agonists being the most potent [11]. ‘Classic opioids’ are those in which agonize the Mu opioid receptor and are the gold standard for severe pancreatic pain. These receptors are abundantly found in both the central and peripheral nervous system and opioids act here to inhibit neurotransmitter release in the presynaptic and postsynaptic neurons which ultimately disrupts the transmission of pain signals [11].

There are numerous studies highlighting the efficacy of opioids in acute pancreatitis. A review evaluating a combination of 5 randomized control trials, involving 227 participants, aged between 23 and 76 years with 65% of participants being male, focused on the need for supplementary analgesia when taking opioids, the number of complications and adverse drug effects [11]. 5 different opioids, intravenous and intramuscular buprenorphine, intramuscular pethidine, intravenous pentazocine, transdermal fentanyl and subcutaneous morphine, were tried amongst the groups and pain intensity was measured using the VAS [11]. The control group included those taking any other type of analgesia, including other opioids at different doses, formulations and routes of administration [11]. The combined analysis showed that opioids showed a statistically significant difference in pain reduction compared to non-opioid analgesics [11]. Compared with other analgesic options, it demonstrated how opioids may decrease the need for supplementary analgesia. Additionally, it suggests that there is currently no difference in the risk of pancreatitis complications or clinically serious adverse events between opioids and other analgesia options [11]. Whilst giving valuable insight, this review has some limitations that should be addressed. The study highlights a lack of sufficient information to fully assess the risk of bias in the included trials. This lack of transparency can undermine the reliability of the results, as biases related to randomization, blinding, and selective reporting may not have been adequately reported, leading to inaccurate results [11]. Along with this, the inclusion of only five randomized controlled trials (RCTs) with a total of 227 participants is a notable limitation. Small sample sizes reduce the statistical power of the study, making it difficult to detect significant differences between treatment groups. Following studies should address these limitations to give a more comprehensive picture of the efficacy of opioids in acute pancreatitis [11].

Similar studies have been conducted to study the use of opioids in chronic pancreatitis. In contrast to managing acute pain, caution must be taken when administered long-term due to adverse effects such as dependence, fatigue and constipation [12]. Long-term administration of opioids, especially in higher doses also increases the risk of opioid induced hyperalgesia, addiction and hormonal abnormalities such as hypogonadism, reduced cortisol, growth hormone and insulin resistance which can increase the risk of metabolic syndrome [12]. Morphine is the most commonly used opioid, but Methadone may also be used as it additionally exhibits antagonistic activity to some N-methyl-D-aspartate (NMDA) receptors and is long-lasting. The NMDA receptor is known to be an important factor in central sensitization and so blocking this receptor can provide an analgesic effect [13]. Transdermal fentanyl has been studied as an alternative opioid due to having a higher analgesic potency than morphine, fewer side effects such as constipation and also has a better uptake into the brain [13]. The transdermal patch only needs to be changed every 3 days and keeps the plasma concentration of fentanyl stable to 12 hours after the first application [13]. A cross-over trial comparing transdermal fentanyl and standard release morphine tablets showed that the use of rescue medication was higher in transdermal fentanyl and there was no difference in patient preference and analgesic efficacy between the 2 methods of analgesic administration [13]. The overall results showed that slow-release morphine or methadone was superior but transdermal fentanyl may be used second-line depending on patient preference [13]. This study, although beneficial to our understanding, is limited by its small sample size of 18 participants. This restricts our capacity to generalize the findings to a larger population or to draw definitive conclusions with confidence [13]. Furthermore, the study only monitored patients for a duration of 4 weeks, preventing us from determining potential long-term differences in treatment outcomes between the two groups. This consideration is critical for clinical decision-making regarding treatment approaches [13].

The use of opioids is not without concerns. A multi-center cohort study including 1768 patients across 118 centers across 27 different countries investigated the association between opioid administration and the severity and mortality in patients with acute pancreatitis [14]. 59% of patients received an opioid on admission and 9% received it after [14]. The results showed that administering opioids the day after admission doubled the risk of developing more of a moderately severe or severe pancreatic disease. It also showed that administering opioids for 6 days or more was an independent risk factor for increasing the severity of pancreatitis [14]. The analysis of the results concluded that long-term opioid administration increased the severity but also an increase in mortality [14]. The study is robust due to its large sample size across many countries, which is advantageous for capturing diverse clinical scenarios. However, its observational nature inherently limits the ability to establish causation between opioid use and acute pancreatitis severity or mortality [14]. Confounding variables and biases could have influenced the reported associations. For example, patients with more severe disease tend to require more opioids, hence there may be an association with use of opioids and disease severity [14]. Future RCTs should be performed to further investigate the safety and efficacy of opioids in acute pancreatitis. RCTs would provide stronger evidence by controlling for confounders and establishing clearer causal relationships [14].

A systematic review was conducted to study the use of opioids in comparison to other analgesics when managing acute pancreatitis in an emergency setting, in which emphasis on emergency setting was used in the inclusion criteria [15]. There was no exclusion on age, gender, or demographic. The primary outcome was to assess the need for rescue analgesia as well as efficacy which was judged using the VAS [15]. Adverse events, duration of hospital stay and mortality were assessed as secondary outcomes. This meta-analysis containing 15 studies suggested that opioids do not provide significant superiority over other medications and should be avoided due to their addictive nature [15]. NSAIDs, metamizole, and local anesthetics were used as comparative analgesics however there was no significance when comparing the adverse effects, reduction in pain severity, supplemental analgesic and hospital stay duration [15]. The common side effects noted with opioid use was nausea, vomiting, and constipation, which may further impact patient recovery [15]. This review is beneficial to our understanding of how opioids compare to other analgesics in the emergency setting, although it lacks sufficient quantitative data on outcomes such as time to pain relief, length of stay and mortality [15]. Therefore, for these variables, narrative analysis was conducted which was inconclusive. These variables are fundamental to clinical decision making as they have a profound effect on pressure felt by healthcare institutions [15]. It is vital that further investigations reassess these variables so that a more holistic understanding of opioids in acute pancreatitis can be obtained [15].

A longitudinal retrospective cohort study including 22,385 patients analyzed the association between the duration of opioid use and the mortality after being admitted to intensive care unit (ICU) due to acute pancreatitis [16]. The suggested theory was that chronic opioid dependence leads to higher mortality while being in hospital, increased risk of readmission and worse outcomes in trauma cases [16]. The primary outcome of the study was to establish whether there's an association between chronic opioid dependence and mortality after an ICU admission [16]. Patients aged 18 years and above were included in the criteria. Those excluded from the criteria were patients presenting with an overdose, cancer, anoxic brain injury, and non-prescription opioid use [16]. The results concluded that there was a statistically significant increase in hospital and ICU stay, increased mortality at 30 days and 1-year post-admission [16]. However, there are some limitations to this study as the impact of opioid tolerance, dose difference and chronic use of other neuroleptics that could have been acting as confounding factors were not taken into consideration [16].

NSAIDs Versus Opioids

A study of 12 randomized control trials analyzed different analgesic modalities in those with acute pancreatic pain, 2 being opioids and NSAIDs [17]. VAS scores were obtained at the patients baseline and then reassessed at 24 hours. There was no statistically significant difference in analgesic effect between the 2 drugs but patients taking opioids had a larger incidence of nausea and vomiting [17]. NSAIDs may be preferred over opioids due to the sphincter of Oddi being more sensitive to opioids, causing an increased sphincter pressure with higher doses of morphine. The evidence is still limited in how this increase in pressure can worsen acute pancreatitis [17].

Both NSAIDs and opioids can affect the gastrointestinal tract, especially with prolonged use. Animal studies have recently been conducted to research the effect of morphine on the gut bacteria [17]. Opioids slow down small intestinal peristalsis which can promote bacterial overgrowth. The study has also shown that morphine can worsen the small intestinal barrier permeability and can delay the regeneration of pancreatic epithelial cells in response to inflammation [17]. However, studies in humans haven't been conducted and the evidence is limited as to how opioids can affect the regeneration and healing of the pancreas [17].

NSAIDs are effective in achieving an analgesic and anti-inflammatory effect by reducing pro-inflammatory cytokines and oxidative damage [17]. Two randomized control trials have studied the efficacy of diclofenac and dexketoprofen in comparison to opioids in which they had similar pain relief and no significant difference in side effects [17]. These studies focused on the first 24 hours and so data is limited to beyond this time frame therefore, more trials are needed to evaluate efficacy, complications and quality of life beyond this time [17]. It is important to clarify that these studies have substantial heterogeneity, which is to say that the differences in study results are more than what would be expected by chance alone [17]. This indicates that the studies may not be sufficiently comparable, and the results of the study should be interpreted with caution. In addition to this, these studies focused on pain relief only in the first 24 hours, and so data is limited beyond this time frame. Therefore, more trials are needed to evaluate efficacy, complications and quality of life beyond this time [17].

PARACETAMOL VERSUS TRAMADOL

Between August 2019 and January 2020, an open label randomized study including 80 patients with acute pancreatic pain was conducted in a tertiary hospital in Nepal [7]. The mean age of participants was 39.33 with the youngest patient being 18 years of age. 62 of these patients were male [7]. The severity of acute pancreatitis was not taken into consideration. The following patients were excluded from the study; those with severe hepatic impairment, severe renal impairment with a creatinine clearance of under 30ml/min, ongoing treatment with NSAIDs, and a history of allergy to paracetamol and/or tramadol [7]. The primary objective of the study was to compare the efficacy of paracetamol and tramadol, especially as a rescue analgesic, and the secondary objective was to measure the side effects and duration of hospital stay [7]. Tramadol has a dual effect of being an opioid receptor antagonist and being monoaminergic (serotonergic & noradrenergic) which gives it an advantage of providing adequate pain relief [7]. All patients in the trial received the standard medical intervention of intravenous fluid resuscitation and nutritional support but instead one group was given 1000mg paracetamol and the other was given 50 mg tramadol [7]. A rescue dose of 25mg pethidine was given to both groups if needed. Their pain was then measured at baseline and 24 hours later using the VAS [7]. The results showed there was no significant difference between the two groups in regards to pain improvement. When evaluating the secondary objective, hospital stay was shorter in those who were administered paracetamol, but this was not statistically significant [7]. The side effect profile of paracetamol use showed to be less severe than tramadol as tramadol increased the reports of vomiting, constipation and headaches [7]. Considering there was no significant difference between analgesic efficacy, the side effect profile of paracetamol may result in less side effects and reduced hospital stay [7]. Although this study is useful, it has some limitations which should be taken into account. Firstly, a sample size of 80 patients limits the generalizability of these findings to the wider population, as a smaller sample size increases the likelihood of selection bias [7]. This means that the sample may not accurately represent the diversity of the broader population, leading to skewed results. Secondly, the fact that this study is carried out in a single hospital in Nepal raises further concerns about its generalizability [7]. This is because findings from a single institution may not be applicable to other settings with different patient demographics and healthcare practices [7]. It's also important to consider that the severity of pancreatitis was not factored into the study, which is important as more severe forms of the condition may require stronger analgesia and a longer hospital stay. Finally, the follow up period in these patients is short, and may not capture long term differences in outcomes between groups of patients [7].

Tramadol Versus Morphine

If grade I analgesia such as paracetamol and NSAIDs have not suppressed the patient's pain, tramadol is often used as a grade II analgesia [18]. A two-arm, parallel, double-blinded and randomized trial took a sample of 30 patients with chronic calcific pancreatitis, confirmed by ERCP, who has already had a 2-week treatment with NSAIDs and weak opioids but yet no effective pain relief [18]. The patients were recruited from gastrointestinal clinics in Cape Town and were admitted to the Groote Schuur Hospital for 5 days if they felt they had inadequate pain relief from NSAIDs which was defined as 'moderate' on a verbal rating scale which ranged from no or mild pain to severe or unbearable pain [18]. The patients were randomly selected to either receive tramadol or morphine and the aim was to assess the efficacy and toxicity of both analgesics, gastrointestinal motility and smooth muscle tone prior to and 5 days after the initial dose of analgesia [18]. This was assessed by recording pain severity on the VASand conducting bowel function questionnaires every evening. Patients with pancreatic duct dilations, hyperparathyroidism, previous surgery with bowel resections, severe renal or hepatic failure, pulmonary compromise, chronic constipation or antibiotic use in that last three weeks were excluded from the study [18]. The results of the trial showed pain intensity scores to decrease and pain relief scores to increase with no significant difference between the two comparative groups. The data also showed that morphine affected the transit time more than tramadol. There was no interference with upper gastrointestinal transit with tramadol and there was also less low gastrointestinal function hindrance than with morphine [18].

Opioids can affect the biliary system by increasing smooth muscle tone which can cause an increase in ductal pressure, leading to an exacerbation of symptoms [18]. Morphine can increase the pressure and contraction of the sphincter of Oddi, however tramadol does not increase the smooth muscle tone and so may be better for those patients with pancreatic pain [18]. This study provides valuable insight into the effects of tramadol and morphine, although there are some limitations which should be noted. The small sample size of 30 participants limits the generalizability and statistical power of the findings [18]. Alongside this, the study did not assess long-

term impact on pain management, bowel function, and overall quality of life, which are critical for chronic conditions such as chronic pancreatitis. The treatment and observation period was only five days, which may not capture long term impacts and side effects of medications [18].

ADJUVANT METHODS

If first-line analgesics are not enough to control a patient's pain, adjuvant analgesics such antidepressants (e.g., tricyclic antidepressants or SSRIs) and anticonvulsants (e.g., gabapentin or pregabalin), can be used in addition [3]. These adjuvants can help modulate central and peripheral nerve sensitivity, which plays a role in chronic pancreatitis [3]. Sensitization can complicate the management of chronic pancreatitis, by altering the way pain is processed in the body [3]. Pregabalin exerts an antiepileptic and analgesic effect and is used in numerous conditions. It antagonizes the alpha2-delta subunit of voltage-gated calcium channels which alters the transmission of excitatory neurons which will ultimately inhibit pain signals [19]. The exact etiology of pain in chronic pancreatitis currently remains ambiguous but some studies have shown that the pancreatic nerves have a larger diameter in chronic pancreatitis and the area that is usually innervated by one of these nerves is smaller [19]. The neurogenic production of pain is due to an alteration in neuropeptides such as SP and CGRP which has an increased transcription rate when the concentration of growth factor (NGF) and its receptor TrKA is increased in inflammatory areas [19]. Despite many adjuvant analgesics being used, only pregabalin has been investigated in patients with chronic pancreatitis and was found to induce moderate pain relief by reducing the release of SP [19]. Pregabalin has also shown to inhibit voltage-gated calcium channels which prevents calcium influx at the nerve terminal and therefore less excitatory neurons can be released, ultimately inhibiting pain signal transmission [19]. Despite pregabalin being effective in pain relief in acute pancreatitis, there are limited studies which show the benefits and risks of using it for chronic pancreatic pain. In chronic pancreatitis especially, there is malabsorption of fat and so these patients often suffer from diarrhea, This can cause changes in the mucosa in the small intestine, where pregabalin is absorbed and so can alter the drug absorption and linear kinetics of pregabalin [19].

A study including 64 participants with chronic pancreatic pain were assigned randomly to receive either pregabalin or a placebo for 3 weeks as an outpatient [20]. Patients with pancreatic cancer were excluded [20]. The aim was to assess the benefits and harms of taking pregabalin and the results concluded that there was a shorter-term use of opioids and a decrease in pain scores in those taking pregabalin compared to those on the placebo [20]. It was also concluded that those who took pregabalin experienced more adverse side effects compared to those on the placebo which can slow down the patient's recovery [20]. There is very limited evidence in its use, especially in long-term usage in regards to the number of hospital admissions and the socioeconomic impact on a patient's life and so the long term implications of use in chronic pancreatic pain is still unknown [20].

A double blind, placebo-controlled, parallel-group studied the use of increasing doses of pregabalin in those with chronic pancreatitis [21]. The focus was to assess the efficacy of pregabalin to combat hyperalgesia in those with chronic pancreatic pain. Hyperalgesia can occur in those receiving pain management in chronic pancreatitis [21]. This is due to changes in the nervous system which occur when the system is constantly in a high level of activity. This leads to a decreased sensitivity to the action potentials that are fired and so the processing of pain is altered and will contribute to chronic pain [21]. This results in central sensitization where the nervous system intensifies nerve signal transmission and so a patient will experience increased pain. Opioids are not an effective form of analgesia in this situation and may cause hyperalgesia itself [21]. In this study, quantitative sensory testing was used to measure the pain threshold to electrical and pressure stimulation in six body dermatomes after receiving either pregabalin or a placebo for 3 weeks [22]. The results showed that the pressure and electric pain thresholds in all the dermatomes collectively were similar in both groups. In contrast, when looking at individual dermatomes, both the electric and pressure pain thresholds were significantly higher with pregabalin administration than the placebo [22]. Overall, the study concluded that a 3 week treatment of pregabalin in those with chronic pancreatitis resulted in an anti hyper analgesic effect associated with a reduced central sensitization. However, the study didn't include long term outcomes and so complications and adverse reactions associated with pregabalin in chronic pancreatitis are still unknown [22].

Besides gabapentin, other adjuvant methods can be used to combat central sensitization in chronic pancreatitis [3]. Cognitive behavioral therapy can help manage the psychological aspects of chronic pain and help the patient to develop coping strategies as well as neuromodulation techniques such as transcutaneous electrical nerve stimulation or spinal cord stimulation which may help reduce pain signals sent to the brain [3].

REGIONAL ANESTHESIA (EPIDURAL)

Epidural anesthesia involves the injection of local anesthetics, often combined with opioids into the epidural space [23]. It works to relieve pain in 2 main ways: by blocking the transmission of pain signals from the pancreatic region to the central nervous system by inhibiting the sensory nerves emerging from spinal segments and by directly targeting the nerves responsible for transmitting pain from the inflamed pancreas [23]. Another keyway it works is by inducing a sympathetic blockade, which results in improved blood flow to the pancreas. This enhanced blood flow helps reduce ischemia and damage, which thereby alleviates pain by reducing systemic inflammation [23].

Several studies highlight its advantages in terms of pain relief and improved clinical outcomes. The secondary objective of a study involving 11 ICUs focused on patients admitted for acute pancreatitis [24]. The patients were split into an interventional group and a standard group, with the interventional group receiving a thoracic epidural anesthesia (TEA) between the 6^{th} and 9^{th} thoracic vertebrae through an epidural catheter [24]. TEA was found to provide effective pain relief in acute pancreatitis. By blocking pain stimuli and inducing sympathetic blockade; this not only alleviates pain but also improves organ perfusion and reduces complications, potentially decreasing the length of hospital stay and

improving survival [24]. This trial had strict exclusion criteria making sure the patients involved were of similar age, the number of admissions with acute pancreatitis and so there was a reduced risk of confounding [24]. The trial is also said to be the largest randomized control trial for those critically ill with acute pancreatitis making it less likely to have bias [24]. This study supports the benefits of using epidural anesthesia such as restoring pancreatic microcirculation, decreasing the severity of pancreatitis and improving survival [24].

Acute pancreatitis in pregnancy follows the same presentation and management and so pain relief is integral. A retrospective observational study of 6 years studied different analgesic methods [25]. The study included 12 pregnant patients, aged between 20 and 35 years, with acute pancreatitis who were admitted between January 2018 and December 2018. 75% of these patients were in the third trimester while the remainder were in their second trimester [25]. The aim was to investigate the efficacy of different analgesics and maternal-fetal outcomes with different techniques [25]. 7 out of the 12 patients were given IV fentanyl infusions at a rate of 1 mcg/kg/hour with tramadol given as an IV bolus at 8 hour intervals [25]. 5 patients were given an epidural with boluses of 10-15 ml of 0.15% ropivacaine at 2 or 3 hour intervals. This same dose is used via the same catheter for labor analgesia [25]. When epidural anesthesia was administered, the VAS scores decreased to 1-2 points from an original 8-9 points compared to patients receiving intravenous tramadol and fentanyl, in which the VAS score didn't descend below 3 points [25]. Conveniently, in these patients, analgesia for labor and anesthesia for caesarean section can be provided through the same catheter, presenting a potentially innovative approach for managing acute pancreatitis in pregnancy [25]. This study was conducted on a small scale and a larger sample size is needed to validate these results. The retrospective nature of this study means that it may be more prone to recall or misclassification bias as well as the control group being recruited not being representative of the population in question [25].

A systematic review and meta-analysis looking at the analgesic efficacy after 24 hours from a patient's baseline compared 7 trial drugs: NSAIDs, opioids, local anesthetics, epidural, paracetamol and metamizole and a placebo [17]. These drugs were used in 12 randomized control trials which included 542 patients [17]. The collective sum of VAS scores concluded that epidural analgesia provided the greatest improvement in analgesic effect. However, after 48 hours, opioids provided the same effect as an epidural and were less invasive for the patient and also easier to administer [17]. This study was attentive to the risk and so patient selection was analyzed before the trials commenced. However, there is only one trial which provides evidence of moderate efficacy of epidural anesthesia [17].

Despite the evidence supporting the use of epidural anesthesia, there are some limitations of this mode of analgesia that should be taken into consideration [23]. Epidural analgesia can lead to complications such as hypotension, infection, hematoma, and neurological damage [24]. The procedure requires careful monitoring and expertise, particularly in critically ill patients with hemodynamic instability [23]. Most knowledge of epidural analgesia in acute pancreatitis comes from experimental studies and animal studies and so the evidence is limited. Although clinicians should be cautious of these side effects, hypotension should not be seen as a contraindication for epidural anesthesia, as it can be managed by fluid resuscitation or pharmacological interventions [23].

CONCLUSIONS

Alongside fluid resuscitation and nutritional support, pain management is a vital aspect of managing both acute and chronic pancreatitis. Pancreatic pain, classically described as severe epigastric pain radiating to the back, can be debilitating to the patient and significantly reduce quality of life. Grade I analgesia is often paracetamol due to its safety and very few side effects. Studies have shown that paracetamol can reduce hospital stay and adverse effects in comparison to opioids. However, the severity of pancreatic pain is often vast, and paracetamol may not adequately provide an analgesic effect. NSAIDs can also be used as first-line but are contraindicated in those with cardiac and renal failure as well as those prone to gastrointestinal bleeding and ulcers. NSAIDs are particularly useful in reducing the risk of PEP and so may be given prophylactically. When compared with opioids, they provided the same pain relief, especially in the first 24 hours. However, opioids may increase the Sphincter of Oddi tone which can increase pain and worsen prognosis, but the evidence is limited. Opioid use was shown to reduce the need for supplementary analgesia in comparison to non-opioids but side effects such as nausea, constipation and fatigue were reported in multiple studies.

Adjuvant analgesia such as pregabalin may be effective in managing chronic pancreatic pain and studies showed that it could reduce the time period of opioid use. The evidence for pregabalin use is limited and longer studies need to be conducted to evaluate the complications of long-term use. Epidural anesthesia provides highly effective pain relief in the first 24 hours; however, this is more invasive and requires more technical skill to administer. Overall, there is no evidence or studies to state which mode of analgesia is most effective in either acute and chronic pancreatitis and so administration is often based on factors such a stepwise escalation of analgesic strategies, patient preference, and the risks and contraindications.

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REFERENCES

1. Drewes AM, Bouwense SAW, Campbell CM, et al. Guidelines for the understanding and management of pain in chronic pancreatitis. Pancreatology. 2017;17(4):564-75. https://doi.org/10.1016/j.pan.2017.07.006 PMid:28734722
2. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: Revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102-11. https://doi.org/10.1136/gutjnl-2012-302779 PMid:23100216
3. Olesen SS, Krauss T, Demir IE, et al. Towards a neurobiological understanding of pain in chronic pancreatitis: Mechanisms and implications for treatment. Pain Rep. 2017;2(6):e625. https://doi.org/10.1097/PR9.0000000000000625 PMid:29392239 PMCid:PMC5741325
4. Fillingim RB, Loeser JD, Baron R, Edwards RR. Assessment of chronic pain: Domains, methods, and mechanisms. J Pain. 2016;17(9):T10-20. https://doi.org/10.1016/j.jpain.2015.08.010 PMid:27586827 PMCid:PMC5010652
5. Robinson SM, Rasch S, Beer S, et al. Systemic inflammation contributes to impairment of quality of life in chronic pancreatitis. Sci Rep. 2019;9:7318. https://doi.org/10.1038/s41598-019-43846-8 PMid:31086257 PMCid:PMC6513859
6. Graham GG, Scott KF. Mechanism of action of paracetamol. Am J Ther. 2005;12(1):46-55. https://doi.org/10.1097/00045391-200501000-00008 PMid:15662292
7. Shrestha R, Khanal A, Paudel N, Karki S, Sah M. Intravenous paracetamol vs tramadol for pain management in patients with acute pancreatitis. J Patan Acad Health Sci. 2020;7(2):64-9. https://doi.org/10.3126/jpahs.v7i2.31116
8. Vargas A, Dutta P, Hawa F, et al. Effect of selective COX-2 inhibitors and non-selective non-steroidal anti-inflammatory drugs on severity of acute pancreatitis: A systematic review and meta-analysis. Pancreatology. 2025;25(4):499-507. https://doi.org/10.1016/j.pan.2025.03.008 PMid:40155261
9. Shen C, Shi Y, Liang T, Su P. Rectal NSAIDs in the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis in unselected patients: Systematic review and meta-analysis. Dig Endosc. 2017;29(3):281-90. https://doi.org/10.1111/den.12816 PMid:28112441
10. Reyes JV, Patel BM, Malik F, Gonzalez MO. Non-steroidal anti-inflammatory drug-induced acute pancreatitis: A case report. Cureus. 2019;11(10):e5926. https://doi.org/10.7759/cureus.5926
11. Ona XB, Comas DR, Urrútia G. Opioids for acute pancreatitis pain. Cochrane Database SYST Rev. 2013;2013(7):CD009179. https://doi.org/10.1002/14651858.CD009179.pub2
12. Fountas A, Van Uum S, Karavitaki N. Opioid-induced endocrinopathies. Lancet Diabetes Endocrinol. 2020;8(1):68-80. https://doi.org/10.1016/S2213-8587(19)30254-2 PMid:31624023
13. van Esch AAJ, Wilder-Smith OHG, Jansen LBMJ, van Goor H, Drenth JPH. Pharmacological management of pain in chronic pancreatitis. Dig Liver Dis. 2006;38(7):518-26. https://doi.org/10.1016/j.dld.2006.02.002 PMid:16627019
14. Pandanaboyana S, Knoph C, Olesen SS, et al. Opioid analgesia and severity of acute pancreatitis: An international multicentre cohort study on pain management in acute pancreatitis. United European Gastroenterol J. 2024;12(3):326-38. https://doi.org/10.1002/ueg2.12542 PMid:38439202 PMCid:PMC11017759
15. Almulhim M, Almulihi S, Almumtin HS, Alghanim MH, AlAbdulbaqi D, Almulihi FAA. The efficacy and safety of using opioids in acute pancreatitis: An update on systematic review and meta-analysis. Med Arch. 2023;77(4):281-7. https://doi.org/10.5455/medarh.2023.77.281-287 PMid:37876565 PMCid:PMC10591254
16. Hardy N, Zeba S, Ovalle A, et al. Association of prescription opioid use on mortality and hospital length of stay in the intensive care unit. PLoS One. 2021;16(8):e0250320. https://doi.org/10.1371/journal.pone.0250320 PMid:33886667 PMCid:PMC8061930
17. Thavanesan N, White K, Sharp L, et al. The association between opioid use and the development of chronic pancreatitis: A systematic review. J Gastrointest Surg. 2022;26(5):1193-203.
18. Wilder-Smith CH. Effect of tramadol and morphine on pain and gastrointestinal motor function in patients with chronic pancreatitis. Dig Dis Sci. 1999;44(6):1107-16. https://doi.org/10.1023/A:1026607703352 PMid:10389680
19. Verma V, Singh N, Jaggi A. Pregabalin in neuropathic pain: Evidence and possible mechanisms. Curr Neuropharmacol. 2014;12(1):44-56. https://doi.org/10.2174/1570159X1201140117162802 PMid:24533015 PMCid:PMC3915349
20. Gurusamy KS, Lusuku C, Davidson BR. Pregabalin for decreasing pancreatic pain in chronic pancreatitis. Cochrane Database Syst Rev. 2016;2016(3):CD011671. https://doi.org/10.1002/14651858.CD011521.pub2 PMid:26837472 PMCid:PMC8278566
21. Dydyk AM, Chiebuka E, Stretanski MF, Givler A. Central pain syndrome. Treasure Island (FL): StatPearls Publishing; 2025.
22. Bouwense SAW, Olesen S, Drewes AM, Poley J-W, van Goor H, Wilder-Smith OHG. Effects of pregabalin on central sensitization in patients with chronic pancreatitis in a randomized, controlled trial. PLoS One. 2012;7(8):e43000. https://doi.org/10.1371/journal.pone.0042096 PMid:22879908 PMCid:PMC3412837
23. Windisch O, Heidegger CP, Giraud R, Morel P, Bühler L. Thoracic epidural analgesia: A new approach for the treatment of acute pancreatitis? Crit Care. 2016;20(1):116. https://doi.org/10.1186/s13054-016-1292-7 PMid:27141977 PMCid:PMC4855315
24. Bulyez S, Pereira B, Caumon E, et al. Epidural analgesia in critically ill patients with acute pancreatitis: the multicentre randomised controlled EPIPAN study protocol. BMJ Open. 2017;7(9):e015280. https://doi.org/10.1136/bmjopen-2016-015280 PMid:28554928 PMCid:PMC5730003
25. Dogra S, Sharma S, Pandya S, et al. Epidural analgesia for pain management in acute pancreatitis during pregnancy and its effect on maternal and fetal outcome. Obstet Gynecol. 2022;139(5):847-54. https://doi.org/10.1155/2022/3238613 PMid:36157323 PMCid:PMC9492404