Effectiveness of thoracic epidural anesthesia in reducing morbidity and mortality in adults with acute pancreatitis: a systematic review protocol and meta-analysis

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Abstract

Objective: The objective of this review is to evaluate the effectiveness of thoracic epidural in reducing morbidity and mortality in adults with acute pancreatitis.

Introduction: Acute pancreatitis is a common disease that often results in significant morbidity and mortality. Although the use of a thoracic epidural anesthesia in patients with acute pancreatitis provides effective analgesia, there appears to be additional non-analgesic benefits associated with thoracic epidural anesthesia.

Inclusion criteria: Randomized controlled trials will be sought for inclusion, but this review will also consider quasi-experimental studies, cohort studies, case-controlled studies, cross-sectional studies, and case-series studies. Studies will include patients 18 years of age and older with acute pancreatitis, with no exclusion to comorbidity. Studies published in a language other than English will be excluded unless a translated version is available.

Methods: The key databases to be searched include MEDLINE, CINAHL, OpenGrey, ClinicalTrials.gov, and Google Scholar. Studies will be assessed for inclusion by at least two independent reviewers. Included studies will be critically appraised by two independent reviewers using standardized critical appraisal instruments from JBI. Data will be extracted from studies included in the review using a standardized extraction tool. Studies will, where possible, be pooled in statistical meta-analysis using JBI SUMARI.

Systematic review registration number: The title of this protocol has been registered with the JBI Systematic Review Register. This manuscript has been registered with PROSPERO (CRD42020177756).

Keywords: analgesia; anesthesia; epidural; pancreatitis; thoracic


Introduction

In the United States, acute pancreatitis is the third-most-common gastrointestinal disease, and ranks as a top cause of death from gastrointestinal diseases. Worldwide, the incidence of acute pancreatitis is estimated to be up to 73.4 cases per 100,000 patients per year. In the United States alone, acute pancreatitis accounts for 275,000 hospital admissions per year, costing over $2.6 billion with primary causes being gallstones (40% to 70%) and alcohol abuse (25% to 30%). In addition to the tremendous financial burden, the excruciating pain and high mortality rate of acute pancreatitis exerts a substantial emotional and physical burden to those involved.

Through a variety of mechanisms and pathways, injury to the pancreas causes the release of numerous proinflammatory mediators that produce local and systemic inflammatory responses. Locally, the proinflammatory mediators increase pancreatic vascular permeability causing pancreatic hemorrhage, hypoperfusion, edema, ischemia, and necrosis. Sympathetic nervous system (SNS) activation causes arteriolar vasoconstriction exacerbating pancreatic hypoperfusion, often leading to pancreatic necrosis. When intrapancreatic inflammatory mediators and enzyme-rich pancreatic exudate spill to surrounding organs, systematic inflammatory response syndrome (SIRS) can result. Systemic inflammatory response syndrome often involves pancreatic necrosis, and extrapancreatic manifestations that include...
pulmonary insufficiency, acute respiratory distress, pleural effusion, gastrointestinal hemorrhage, renal failure, and hypovolemic shock.\textsuperscript{3}

The Atlanta classification of acute pancreatitis offers global consensus on the classification of acute pancreatitis.\textsuperscript{5} Classifications include mild, moderate, and severe forms.\textsuperscript{6} Severity is determined by organ failure of one or more systems: respiratory, cardiovascular, or renal.\textsuperscript{6} While 80\% of patients with acute pancreatitis present with the mild form, 20\% progress to the severe form.\textsuperscript{3} Severe acute pancreatitis is associated with mortality as high as 36\% to 50\%.\textsuperscript{2}

Treatment of acute pancreatitis involves aggressive pain control, supportive care, nutritional support, aggressive hydration, and antibiotics.\textsuperscript{2} Pancreatic pain is perceived when nociception is carried from afferent nerves to dorsal root ganglia (DRG) and dorsal roots into the spinal cord and then up spinothalamic tracts to the brain.\textsuperscript{7} More specifically, sensory innervation of the pancreas is carried primarily by spinal pathways that originate with a network of afferent fibers from pancreatic tissue joining at the celiac plexus and splanchnic nerves.\textsuperscript{7} This network of sensory afferent nerves continues from the celiac plexus and splanchnic nerves to the T6-L2 (DRG) where their cell bodies reside, and then into the spinal cord through dorsal roots.\textsuperscript{7} Sympathetic efferent innervation of the pancreas differs by exiting the spinal column via ventral roots that briefly run alongside afferent innervation in what is known as a spinal nerve, before exiting through thoracic and lumbar communicating rami supplying paravertebral ganglia of the sympathetic chain, splanchnic nerves, and the celiac plexus.\textsuperscript{7} Once these sympathetic fibers have crossed through the celiac plexus, they are able to provide innervation to pancreatic tissue, vessels, and ducts.\textsuperscript{7}

Thoracic epidural anesthesia can provide effective pain relief in patients with acute pancreatitis because thoracic epidurals bilaterally disrupt the sensory and sympathetic signals at the spinal nerve.\textsuperscript{7} In obstetrics, sensory blockade using an epidural catheter to infuse local anesthetic and low-dose narcotic medication is a well-known and long-established treatment to provide patients with pain relief. The spinal level at which an epidural catheter is best placed is determined in part based on the spinal nerve roots involved in pain transmission. In obstetrics, an epidural catheter is generally placed in the lumbar spine region, while a patient with pancreatitis can benefit from an epidural catheter placed in the thoracic epidural space.

While the sensory blockade results in pain relief, the sympathetic blockade results in increased splanchnic circulation and decreased inflammation.\textsuperscript{5} The increased splanchnic circulation is thought to redistribute pancreatic blood flow to poorly perfused pancreatic tissues. As a result, pancreatic perfusion increases, attenuating pancreatic ischemia and necrosis.\textsuperscript{4} Meanwhile, the decreased inflammation is thought to improve the imbalance between anti-inflammatory and inflammatory factors.\textsuperscript{3,5,8} This improvement is important given the key role inflammatory imbalance is thought to have in the progression and severity of acute pancreatitis.\textsuperscript{3} The beneficial effects of thoracic epidural anesthesia on SNS modulation and inflammation reduction appears distinct from the expected analgesic effects.\textsuperscript{4} Furthermore, SNS modulation and inflammation reduction appears to attenuate progression and decrease the severity of the disease process.\textsuperscript{4}

The major risks associated with epidural anesthesia are bleeding, infection, hemodynamic decompensation, and nerve trauma.\textsuperscript{8,9} In light of these risks, several studies established a favorable safety profile for thoracic epidural anesthesia.\textsuperscript{8-10} The risks of epidural-related complications can depend on the patient profile, but even in patients with severe acute pancreatitis, a population at particularly high risk for sepsis, one study found no infections or hematoma associated with epidural catheter injection.\textsuperscript{8}

Current practice guidelines in treating severe pain associated with pancreatitis often involve high dose opioids.\textsuperscript{5} The respiratory depression accompanying high dose opioids can exacerbate the already compromised pulmonary function of patients with acute pancreatitis. Since epidurals have relatively little respiratory depressant effects compared to systemic opioids, analgesic treatment incorporating thoracic epidural anesthesia can provide effective analgesia, without deleterious respiratory effects.\textsuperscript{4,11}

While epidural anesthesia has been a mainstay in obstetrics, current practice guidelines for treating acute pancreatitis do not include the use of an epidural catheter for pain control.\textsuperscript{3,4} The absence of epidurals in current practice guidelines forgoes the compelling potential for decreased pain and suffering without the deleterious effects of opioids. Moreover, the SNS modulation and inflammatory reduction that thoracic
epidural anesthesia provides may prevent the progression of pancreatitis to its severe form.\textsuperscript{4,5,8} Numerous animal and human studies have been published demonstrating measurable intrinsic, non-analgesic benefits of treating acute pancreatitis with thoracic epidurals.\textsuperscript{4,5,8-10,12-18} The benefits measured in these studies include reduction in mortality rates, increased ventilator-free days in the intensive care unit, reduced end-organ complications or failure, shorter lengths of hospital stay, and improved pancreatic perfusion. The findings of this systematic review may better inform practice as to other potential benefits provided through the use of thoracic epidural anesthesia, beyond analgesia, for patients suffering from acute pancreatitis.

A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the JBI Database of Systematic Reviews and Implementation Reports was conducted and no current or in-progress systematic reviews on the topic were identified.

The objective of this review is to evaluate the effectiveness of thoracic epidural anesthesia in reducing morbidity and mortality in adults with acute pancreatitis.

**Review question**

What is the effect of thoracic epidural anesthesia on reducing morbidity and mortality in adults with acute pancreatitis?

**Inclusion criteria**

**Participants**

This review will consider studies that include patients of any gender, race, or ethnicity who are 18 years of age or older. Participants include patients with acute pancreatitis of any severity. Studies that include patients under age 18, and animal studies, will be excluded from this review.

**Intervention**

This review will consider studies that evaluate acute pancreatitis treatment involving the use of a thoracic epidural catheter for the delivery of local anesthetics and other analgesics.

**Comparator**

This review will consider studies that compare the intervention to patients with acute pancreatitis who did not receive treatment with a thoracic epidural catheter.

**Outcomes**

This review will consider studies that include the following primary outcomes: mortality and morbidity. Mortality will be defined as death as a result of acute pancreatitis or complications secondary to the disease. Mortality will be measured by mortality rate. Morbidity will be defined as the ongoing presence of acute pancreatitis or secondary disease processes resulting from the deranged pancreatic function, whether acute or chronic. Morbidity will be measured by days of hospital stay, percent needing ICU stay, length of ICU stay, percent needing mechanical ventilation, percent needing surgical intervention, pain, and C-reactive protein level. Secondary outcomes that will be reported include blood stream infection, use of and duration of antimicrobials, ileus, enteral tolerance, hematoma, and abscess formation. All secondary outcomes will be included in the reporting of key characteristics of included studies; however, only outcomes found in two or more studies will be included in a meta-analysis.

**Types of studies**

Randomized controlled trials will be sought for inclusion, but this review will also consider quasi-experimental studies, cohort studies, case-controlled studies, cross-sectional studies, and case-series studies. Studies will include patients 18 years of age and older with acute pancreatitis, with no exclusion to comorbidity. Studies published in a language other than English will be excluded unless a translated version is available.

**Methods**

The proposed systematic review will be conducted in accordance with JBI methodology for systematic reviews of effectiveness.\textsuperscript{19}
be adapted for each included information source. The reference list of all studies selected for critical appraisal will be screened for additional studies.

The databases to be searched include MEDLINE, CINAHL, and Google Scholar. Both the Ovid and PubMed interfaces will be used to search the MEDLINE database, since algorithmic differences between these two interfaces often yield different search results. CINAHL Complete will be used as the interface to search the CINAHL database. Sources of unpublished studies and gray literature searched include reports, conference proceedings, doctoral theses/dissertations, and trial registers. The databases to be searched for gray literature are Open Grey and ClinicalTrials.gov.

Study selection
Following the search, all identified citations will be collated and uploaded to EndNote v.X9 (Clarivate Analytics, PA, USA) and duplicates removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant studies will be retrieved in full and their citation details imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia). The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved through discussion or with a third reviewer. The results of the search will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Assessment of methodological quality
Eligible studies will be critically appraised by two independent reviewers at the study level for methodological quality in the review using standardized critical appraisal instruments from JBI. Authors of papers will be contacted to request missing or additional data for clarification, where required. Any disagreements that arise will be resolved through discussion or with a third reviewer. The results of critical appraisal will be reported in narrative form and in a table.

All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possible).

Data extraction
Data will be extracted from studies included in the review by two independent reviewers using the standardized JBI data extraction tool within JBI SUMARI. The data extracted will include specific details about the populations, study methods, interventions, and outcomes of significance to the review objective. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Authors of papers will be contacted to request missing or additional data, where required.

Data synthesis
Studies will, where possible, be pooled with statistical meta-analysis using JBI SUMARI. Effect sizes will be expressed as either odds ratios (for dichotomous data) or weighted (or standardized) final post-intervention mean differences (for continuous data), and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard $\chi^2$ and $I^2$ tests. Statistical analyses will be performed via the fixed effect model. Sensitivity analyses will be conducted to test decisions made regarding the inclusion or exclusion of studies during the review process. Where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures to aid in data presentation, where appropriate.

A funnel plot will be generated using janovi 1.1.9 (The janovi project, Sydney, Australia) to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test) will be performed where appropriate.

Assessing certainty in the findings
The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed and a Summary of Findings (SoF) will be created using GRADEpro GDT Free 2019 (McMaster
University, ON, Canada). The SoF will present the following information where appropriate: absolute risks for the treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision and risk of publication bias of the review results. The outcomes reported in the SoF will be: mortality, days of hospital stay, percent needing mechanical ventilation, percent needing ICU stay, length of stay in ICU, percent needing surgical intervention (cholecystectomy or necrosectomy), and pain.

Acknowledgments
This systematic review acts as partial contribution towards a Doctor of Nursing Practice (DNP) degree for authors CE and RO.

References
Appendix I: Search strategy

**MEDLINE (PubMed)**

Search conducted on February 2020

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