Immediate versus Postponed Drainage for Infected Necrotizing Pancreatitis: a protocol for a systematic review and meta-analysis

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Research Article

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Abstract

BACKGROUND

Acute pancreatitis is the most common gastrointestinal disease worldwide for hospital admission, and infected pancreatic and peripancreatic necrosis is a potentially lethal complication, which is the most dreadful one associated with a poor prognosis: mortality is approximately 15% and up to 30–39%. Depending on the very high mortality and morbidity, infected necrotizing pancreatitis always requires intervention at the early stage. The current standard approach for infected necrotizing pancreatitis is a minimally invasive step-up approach with catheter drainage as the first step. International guidelines advise delay in catheter drainage and antibiotics treatment until the infected collection has become a “wall-off”, which takes 4 weeks to develop. However, no clear evidence from clinical studies was seen to suggest superiority for the postponed catheter drainage. We will perform the first systematic review and meta-analysis to explore whether immediate catheter drainage improves the survival rate of patients with infected necrotizing pancreatitis compare with postponed catheter drainage.

Methods

We will search the randomized controlled trial (RCT) literature involving and nonrandomized clinical cohort studies of immediate catheter drainage in patients with infected necrotizing pancreatitis in 5 electric databases, including PubMed, Web of Science, the Cochrane Library, Chinese National Knowledge Infrastructure (CNKI) and Chinese Biomedical Literature Database (CBM). Studies including patients under 18 years of age or pregnant women will be excluded. We will define the overall mortality of patients with infected necrotizing pancreatitis as the primary outcome. Besides, the incidences of bleeding resulting in intervention, perforation of a visceral organ leading to intervention, enterocutaneous fistula, pancreatic cutaneous fistula, incisional hernia and wound infection, the total length of stay, endocrine and exocrine pancreatic insufficiency, and severe complications will be regarded as the secondary outcomes. Quality assessment of the included studies will be independently performed according to the Version 2 of the Cochrane tool for assessing the risk of bias in a randomized trial (RoB2) for RCTs and the Non-Randomized Studies-of Interventions (ROBINS-I) Tool for Observational Studies. Meanwhile, the level of evidence for results will be assessed by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method. All analyses will be conducted by using the RevMan (Version 5.4; Cochrane, Oxford, UK).

Results

From our study, we will ascertain whether immediate catheter drainage improves the survival rate of patients with infected necrotizing pancreatitis compare with postponed catheter drainage.
Trial registration:

PROSPERO registration number CRD42021291734.

Background

Acute pancreatitis is the most common gastrointestinal disease worldwide for hospital admission, and infected pancreatic and peripancreatic necrosis is a potentially lethal complication. Necrotizing pancreatitis (NP) develops in approximately 30% of patients with acute pancreatitis. Infected pancreatic and peripancreatic necrosis nearly always need invasive intervention. The current standard approach for infected necrotizing pancreatitis is a minimally invasive step-up approach with catheter drainage as the first step. International guidelines advise delay in catheter drainage and antibiotics treatment until the infected collection has become “wall-off”; such “walled-off” necrosis usually takes 4 weeks to develop. Recently, the American Gastroenterological Association advised that catheter drainage should be strongly considered when there is a concern of infection, even in the early stage of the disease. However, whether earlier catheter drainage could improve patient outcomes is not known.

Description of the intervention

Patients will receive immediate catheter drainage within 24h when diagnosed with infected necrotizing pancreatitis. Immediate intervention contains catheter drainage and treatment with antibiotics. Additional drainage will be performed in the case of no improvement within 72h. Catheter drainage was managed with a “step-up approach” based on endoscopic and/or percutaneous catheter drainage, with subsequent video-assisted retroperitoneal debridement (VARD) and with endoscopic necrosectomy or open surgery as required. Endoscopic transluminal drainage (ETD) was the first-line treatment for the management of necrotic collections adjacent to the stomach and duodenum. Percutaneous drainage was the preferred initial approach for collections not in contact with the stomach or duodenum wall. Endoscopic debridement via sinus tract endoscopy (STE) was performed in the entirely retroperitoneal approach. Transperitoneal drain placement is required for collections not suited for a retroperitoneal approach.

How the intervention might work

Due to the presence of persistent organ failure, necrotizing pancreatitis is considered severe, with mortality exceeding 30% (Banks 2013; Johnson 2004). A meta-analysis showed that organ failure was associated with worse outcomes and mortality in one-third of NP patients (Petrov 2010). The immediate catheter drainage based step-up approach improves organ function which in turn improves the mortality by blunting the inflammatory response. The early drainage of infected necrotic collections and fluid could temporize sepsis and organ failure. The PENGUIN trial demonstrated that catheter drainage is associated with a reduction in the inflammatory response and new-onset organ failure (Bakker 2012; Kumar 2014). Percutaneous drainage could lower the risk of cavity rupture and consequent peritoneal contamination at the early stage of necrotizing pancreatitis. Utilizing immediate catheter drainage when feasible, organ function was substantially improved after early intervention.
The rationale of immediate catheter drainage is to drain infected fluid under pressure, which initially aims to control the source of infection without removal of the infected necrosis. During the early period of 3–4 weeks, patients with necrotizing pancreatitis are often admitted to the intensive care unit; however, catheter drainage would technically be feasible in most of these patients (van Baal 2011).

**Why it is important to do this systematic review and meta-analysis**

Depending on the very high mortality and morbidity, infected necrotizing pancreatitis always requires intervention at the early stage. The cornerstones of early treatment are catheter drainage, a step-up approach and antibiotics treatment (van Santvoort 2011). However, whether immediate catheter drainage (< 4 weeks) or postponed (≥ 4 weeks) is confusing. The timing of catheter drainage varied greatly between studies. In an international survey, 55% of expert pancreatologists used the postpone catheter drainage in infected necrotizing pancreatitis, whereas the other 45% drained immediately after diagnosing infected necrosis (van Grinsven 2015).

A rationale for postponing catheter drainage is for easier drainage once the stage of walled-off necrosis has been reached and a collection has become more liquefied. Moreover, some patients with infected necrotizing pancreatitis could recover using the antibiotic treatment in the first 4 weeks only. Endoscopic subsequent catheter drainage requires a walled-off collection, which could mitigate the risk of death and complications (van Grinsven 2016). However, this evidence is primarily based on studies involving surgical intervention. Whether catheter drainage needs to delay at least 4 weeks is a pertinent question, particularly as 1/3 of patients seem to recover after catheter drainage without the need to undergo necrosectomy (van Baal 2011). Moreover, this delay would slow down recovery.

However, no clear evidence from clinical studies was seen to suggest superiority for the postponed catheter drainage. Earlier catheter drainage of infected necrosis could have the potential to improve outcomes (van Grinsven 2016). Aims to control the source of infection without removal of the infected necrosis, catheter drainage of the infected fluid immediately could temporize sepsis and improve the clinical condition of patients. From a theoretical standpoint, it is not always mandatory to wait 4 weeks until the collection to become “walled-off” and catheter drainage can be performed safely in the first weeks after the onset of disease (Trikudanathan 2018; van Grinsven 2016). Immediate catheter drainage is technically feasible in > 95% of patients when diagnosed infected necrotizing pancreatitis, often via the preferred left-sided retroperitoneal route (Horvath 2001; van Santvoort 2010). Other studies show that patients with infected necrotizing pancreatitis could benefit from earlier catheter drainage by reducing complications and length of hospital stay (van Baal 2011).

Clinicians are puzzled by the conflicting nature of the evidence. A systematic review and meta-analysis to synthesize the current evidence is needed for practitioners faced with the decision of using immediate catheter drainage or postponed one. In this systematic review of RCTs, we evaluated the clinical outcomes of catheter drainage to infected necrotizing pancreatitis when initiated before versus after 4 weeks.
OBJECTIVES

We aim to establish whether immediate catheter drainage improves the survival rate of patients with infected necrotizing pancreatitis compared with postponed catheter drainage?

Methods

Criteria for considering studies for this review

Types of studies

Randomized controlled trials and nonrandomized clinical cohort studies of immediate catheter drainage in patients with infected necrotizing pancreatitis. Studies including patients under 18 years of age or pregnant women will be excluded.

Types of participants

Patients aged 18 years and above with infected necrotizing pancreatitis. Key exclusion criteria were symptoms of acute pancreatitis for more than 35 days and previous intervention for necrotizing pancreatitis.

Types of interventions

The immediate intervention included treatment with antibiotics and catheter drainage within 24 hours once infected necrosis was diagnosed.

Types of comparators

Postponed catheter drainage included treatment with antibiotics and supportive treatment aimed at postponing the drainage procedure until the stage of walled-off necrosis when necrotic collections were largely or fully encapsulated.

Types of outcome measures

Mortality and comprehensive complication will be defined and measured by the study trialists.

Primary outcomes

The overall mortality of patients with infected necrotizing pancreatitis

Secondary outcomes

Incidence of bleeding resulting in intervention

Incidence of perforation of a visceral organ leading to intervention

Incidence of enterocutaneous fistula
Incidence of pancreatic cutaneous fistula

Incidence of incisional hernia

Incidence of wound infection

The total length of stay

Endocrine and exocrine pancreatic insufficiency

Severe complications

**Search methods for identification of studies**

Standard search terms will be used to identify relevant studies for each database. Any potential articles will be identified using the “related article” function. Relevant publications in all languages will be included in the search.

**Electronic searches**

A comprehensive search of the PubMed, Web of Science, the Cochrane Library, Chinese National Knowledge Infrastructure (CNKI) and Chinese Biomedical Literature Database (CBM) will be performed to identify studies that evaluate immediate catheter drainage in patients with infected necrotizing pancreatitis. Relevant studies will be identified using the search strategy in all languages. Potential non-English language studies will be assessed using the translate function. Standard search terms will be connected by Boolean operators AND/OR. Population: Adults patients. Intervention: Immediate Catheter Drainage. Disease: Infected Necrotizing Pancreatitis. The complete strategy is listed in Supplementary 1.

**Searching other resources**

The references of relevant studies, systematic reviews and meta-analyses will be hand-searched for potential articles that were missed by the electronic search. Conference abstracts and pre-printed articles will be identified by the search strategy. Clinical trial registers will be checked to identify ongoing or unpublished RCTs. Registrants will be consulted to make sure that no unpublished article has been missed. Any ongoing studies will be identified from following sources: clinical trials registry(http://clinicaltrials.gov/), Chinese Clinical Trial Registry (http://www.chictr.org.cn/index.aspx), International Clinical Trials Registry Platform (ICTRP) (https://trialsearch.who.int/), UK National Research Register(http://www.update-software.com/national/default.htm) and ISRCTN Registry(https://www.isrctn.com). Conference abstracts from APA (American Pancreatic Association), CSGE (Chinese Society of Gastroenterology), AGA (American Gastroenterological Association), ASGE (American Society for Gastrointestinal Endoscopy), and SSAT (Society Surgery of Alimentary) will be reviewed from the past 5 years.

**Selection of studies**
The quality assessment of the included trials was performed by the two reviewers independently using the modified Jadad’s score scale (Jadad 1996). The following questions will be asked (yes, no or no described):

- Was the study described as randomized?
- Was the method of randomization appropriate?
- Did the patients undergo immediate catheter drainage?
- Was the study described as blinded (double-blind or single-blind)?
- Was the method of blinding appropriate?
- Was there concealment of allocation of treatment?
- Was there a description of withdrawals and dropouts?
- Was there a description of the inclusion/exclusion criteria?

**Data extraction**

Two investigators (WK, HYW) independently will extract relevant information from the included study and compile them into a shared sheet. Any disagreements will be resolved by a third reviewer (ZQ) through consensus. We will collect the following information from included studies: study identifier (first author and year of publication); duration of observation; country of a study conducted; study design; inclusion and exclusion criteria; intervention, number of subjects, as well as primary and secondary outcomes. In addition, we will collect information about potential sources of significant clinical heterogeneity, such as body mass index.

**Risk of bias assessment**

Two investigators (WK, HYW) independently assessed the risk of bias in the included studies. The quality of studies was evaluated by the Version 2 of the Cochrane tool for assessing the risk of bias in a randomized trial (RoB2) for RCTs and the Non-Randomized Studies-of Interventions (ROBINS-I) Tool for Observational Studies. The domains of the risk of bias for RCT assessed by RoB2 include five dimensions (randomization, deviation, missing data, outcome measurement, and outcome reporting); the domains of ROBINS-I tool to evaluate the risk of bias for observational studies involving confounding adjustment, selection, classification of intervention, deviation, missing data, outcome measurement, and outcome reporting. Any disagreement is determined by the third investigator (ZJ).

**Strategy for data synthesis and measures of treatment effect**
We used the software RevMan (Version 5.4; Cochrane, Oxford, UK) for meta-analysis. To avoid data entry errors, forest plots were performed double-checked by the 2 reviewers (WK, LKX). RCTs and observational studies were separately pooled for methodological heterogeneity. The risk ratio (RR) for RCTs and Odds ratio (OR) for observational studies along with a 95% confidence interval (95% CI) were calculated for dichotomous variables and the mean difference (MD) with 95% CI for continuous variables. The standardized mean difference will be used to calculate different scales outcomes.

**Dealing with missing data**

Missing data will be obtained by contacting the trial authors as appropriate.

**Assessment of heterogeneity**

Statistical heterogeneity was assessed by the I² (I²) index. If I² 25%, the pooled outcomes were low statistical heterogeneity and if I² 75% to deem as high statistical heterogeneity. Where heterogeneity remained, a random-effects model was applied, and then the source of the heterogeneity would be analyzed. Otherwise, the fixed-effects model was used. P values statistical significance was set at p < 0.05.

**Assessment of publication biases**

Publication bias will be explored by a funnel plot when no less than 10 trials were included in the meta-analysis.

**Subgroup analysis and investigation of heterogeneity**

Subgroup analyses were planned to allow for different types of studies (RCTs VS. no-RCTs).

**Sensitivity analysis**

We will perform a sensitivity analysis by the sequential removal of trials for each outcome.

**Abbreviations**

- APCHE scores: Acute Physiology and Chronic Health Evaluation scores; PubMed: US National Library of Medicine;
- CBM: Chinese Biomedicine Database;
- CENTRAL: The Cochrane Library 2021, Issue 11;
- ISI: Web of Science: Science Citation Index Expanded;
- CNKI: China Knowledge Resource Integrated Database.

**Declarations**
ETHICS APPROVAL AND CONSENT TO PARTICIPATE

No human subject participants will be involved. On completion of the analysis, we will prepare a manuscript for publication in a peer-reviewed journal.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

This protocol also has been registered on the International Prospective Register of Systematic Reviews, and the trial registration number is CRD42021291734 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=291734).

COMPETING INTERESTS

The authors report no conflicts of interest in this work.

TRIALS STATUS

Not yet started, the first systematic search is scheduled to 20 July.

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AUTHORS’ CONTRIBUTIONS

Yu-wei Hu: conduction of the study, selection of the trial protocols, drafting the manuscript, data extraction from trial protocols.

Qin Zeng: writing the statistical analysis plan, drafting the manuscript, resolving disagreements through consensus.

Guang-yu Yang: conduction of the study, drafting the manuscript.

Wang Yu: conduction of the study, selection of the trial protocols, drafting the manuscript.

Lu Wang: conduction of the study, selection of the trial protocols, drafting the manuscript.
Ming-we Sun: providing methodological supervision, critical revision of the manuscript.

Zeng Jun: provided methodological supervision, critical revision of the manuscript, resolving disagreements through consensus.

Kai Wang: an expert in the field of Emergency medicine and critical care, who supervised the conduction of the study, providing key knowledge and critical revision, data extraction from trial protocols.

Hua Jiang: an expert in the field of Emergency medicine and critical care, Gastroenterology and hepatology, and Surgery, who supervised the conduction of the study, provided key knowledge and critical revision.

The authors read and approved the final manuscript.

Supplementary information

Supplementary information accompanies this paper at https://xxxxxx

Additional file 1: Supplementary Table 1: Search Terms and Complete Strategy.

Additional file 2: Inclusion and exclusion criterion for considering studies for this review.

References

Bakker 2012


Banks 2013


Horvath 2001


Jadad 1996

Johnson 2004


Kumar 2014


Petrov 2010


Trikudanathan 2018


van Baal 2011


van Grinsven 2015


van Grinsven 2016

van Santvoort 2011


van Santvoort 2010


Additional File 2

Additional file 2 is not available with this version.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementary.docx
- SPIRITChecklistforTrials.docx