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Opioids for acute pancreatitis pain (Review)

Basurto Ona X, Rigau Comas D, Urrútia G

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[Intervention Review]

Opioids for acute pancreatitis pain

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ABSTRACT

Background

Acute pancreatitis is an acute inflammatory process of the pancreas that may also involve adjacent tissues and/or remote organ systems. Abdominal pain is the main symptom and is usually accompanied by nausea, vomiting and fever. Opoids are commonly used to manage pain in acute pancreatitis but there are still some uncertainties about their clinical effectiveness and safety.

Objectives

To assess the effectiveness and safety of opioids for treating acute pancreatitis pain.

Search methods

The search strategy included the Cochrane Upper Gastrointestinal and Pancreatic Diseases Review Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (2013, Issue 6), MEDLINE (from 1950 to June 2013) and EMBASE (from 1980 to June 2013). There were no restrictions by language or publication status.

Selection criteria

We considered randomised clinical trials (RCTs) assessing the effectiveness of any opioid drug used for treating acute pancreatitis pain.

Data collection and analysis

Two review authors independently selected studies, assessed risks of bias and extracted data. We estimated risk ratios (RRs) for dichotomous data and calculated a 95% confidence interval (CI) for each RR. We performed an intention-to-treat (ITT) analysis. We undertook meta-analysis for some outcomes.

Main results

We included five RCTs with a total of 227 participants (age range 23 to 76 years; 65% men) with acute pancreatitis pain. The opioids assessed were intravenous and intramuscular buprenorphine, intramuscular pethidine, intravenous pentazocine, transdermal fentanyl and subcutaneous morphine.

One RCT, comparing subcutaneous morphine with intravenous metamizole reported non-significant reduction in the number of participants with improvements in pain intensity (primary outcome) (RR 0.50, 95% CI 0.19 to 1.33). Three studies compared analgesia using opioids with non-opioid treatments. After excluding one study that used opioids through continuous intravenous infusion, there was a decrease in the number of patients requiring supplementary analgesia (RR 0.53, 95% CI 0.30 to 0.93). In a single study, there were no differences in the number of patients requiring supplementary analgesia between buprenorphine and pethidine (RR 0.82, 95% CI 0.61 to 1.10).

Pancreatitis complications were not associated with a significant difference between the drugs tested. No clinically serious or life-threatening adverse events occurred related to treatment. No differences for this outcome were found between opioid and non-opioid treatments, or for type of adverse event (nausea-vomiting and somnolence-sedation). One death in the procaine group was reported across all the trials.

One RCT comparing pethidine with intramuscular buprenorphine reported non-significant differences of supplementary analgesic, adverse events or deaths. One RCT comparing fentanyl with placebo found no difference in adverse events.

The findings of this review are limited by the lack of information to allow full appraisal of the risk of bias, the measurement of relevant outcomes and the small numbers of participants and events covered by the trials.

Authors' conclusions

Opioids may be an appropriate choice in the treatment of acute pancreatitis pain. Compared with other analgesic options, opioids may decrease the need for supplementary analgesia. There is currently no difference in the risk of pancreatitis complications or clinically serious adverse events between opioids and other analgesia options.

Future research should focus on the design of trials with larger samples and the measurement of relevant outcomes for decision-making, such as the number of participants showing reductions in pain intensity. The reporting of these RCTs should also be improved to allow users of the medical literature to appraise their results accurately. Large longitudinal studies are also needed to establish the risk of pancreatitis complications and adverse events related to drugs.

PLAIN LANGUAGE SUMMARY

Opioids for abdominal pain in acute pancreatitis

The pancreas is a gland behind the stomach and close to the first part of the small intestine. It produces digestive juices, amylase, secreted into the small intestine and releases hormones, insulin and glucagon, into the bloodstream. Acute pancreatitis refers to a sudden inflammation of the pancreas. It happens when digestive juices become active inside the pancreas, causing swelling, bleeding and damage to the pancreas and its blood vessels. It is a serious condition and can lead to further problems. Common symptoms are severe pain in the upper abdomen, nausea, and vomiting. Treatment is usually a few days in hospital for fluids, antibiotics, and medicines to relieve pain, delivered by drip.

If there is severe pain, at least one type of pain relief (e.g. paracetamol, non-steroidal anti-inflammatory drugs, opioids) is generally used. Opioids, such as morphine and its derivatives, are commonly used, but without firm evidence for their effectiveness and safety. It is possible that they may hide the resolution of the disease, and may increase pain by causing spasms. The aim of this review is to clarify the appropriate use of opioids for abdominal pain in acute pancreatitis.

We searched a number of electronic databases up to June 2013. We include five randomised clinical trials (RCTs), with a total of 227 participants in this review. The opioids evaluated were buprenorphine, pethidine, pentazocine, fentanyl and morphine.

For participants needing additional pain relief, combined analysis of opioids (pentazocine and morphine) showed a significant benefit when compared with non-opioid treatments. Two trials showed that buprenorphine and pentazocine were each more effective than procaine. Our confidence in the stability of these effects is low, however, due to limitations in the number of studies and participants, and the low quality of the way the trials were run and reported. No serious or life-threatening adverse events were linked to the drugs being studied. One death was reported, in a procaine group, across all the included trials.

On the evidence so far, opioids may be an appropriate treatment option and might have the advantage of decreasing the need for additional pain relief. We found no clear difference in the risk of pancreatitis complications or serious adverse event between opioids and other pain relief treatments. However, the findings of this review are limited by the lack of information to allow full appraisal of the risk of bias, the measurement of relevant outcomes and the small numbers of participants covered by the trials.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Morphine compared to metamizole for acute pancreatitis pain

Morphine compared to metamizole for acute pancreatitis pain

Patient or population: participants with acute pancreatitis pain
Settings:
Intervention: Morphine
Comparison: Metamizole

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Metamizole	Morphine				
Improvements in pain intensity as defined by the trialist (primary outcome) Follow-up: 2 days	**38 per 100**	**19 per 100** (7 to 50)	**RR 0.50** (0.19 to 1.33)	16 (1 study)	⊕⊕⊖⊖ Low[1]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Few participants included, few events reported and methodological limitations.

Summary of findings 2. Opioids versus no opioids for acute pancreatitis pain

Opioids versus no opioids for acute pancreatitis pain

Patient or population: participants with acute pancreatitis pain
Settings:
Intervention: Opioids versus no opioids

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Opioids versus no opioids				
Supplementary analgesic option offered (primary outcome 2) Follow-up: 2 to 4 days	**73 per 100**	**30 per 100** (21 to 42)	**RR 0.41** (0.29 to 0.57)	162 (3 studies)	⊕⊕⊝⊝ **Low**[1,2]	
Pancreatitis complications (secondary outcome 1) Follow-up: 2 to 4 days	**49 per 100**	**52 per 100** (41 to 66)	**RR 1.05** (0.82 to 1.34)	162 (3 studies)	⊕⊕⊝⊝ **Low**[1,2]	
Any drug-related adverse event (secondary outcome 2) Follow-up: 2 to 3 days	**11 per 100**	**21 per 100** (10 to 48)	**RR 2** (0.9 to 4.46)	110 (2 studies)	⊕⊕⊝⊝ **low**[1,2]	
Nausea and vomiting (secondary outcome 2) Follow-up: 2 to 3 days	**21 per 100**	**36 per 100** (15 to 86)	**RR 1.68** (0.7 to 4)	55 (2 studies)	⊕⊕⊝⊝ **low**[1,2]	
Sedation and somnolence (secondary outcome 2) Follow-up: 2 to 3 days	**0 per 1000**	**0 per 1000** (0 to 0)	**RR 5.54** (0.69 to 44.79)	55 (2 studies)	⊕⊕⊝⊝ **low**[1,2]	
Death from any cause (secondary outcome 3) Follow-up: 1 to 4 days	**10 per 1000**	**4 per 1000** (0 to 83)	**RR 0.35** (0.02 to 8.1)	194 (4 studies)	⊕⊝⊝⊝ **very low**[1,3]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High risk of performance and detection bias
[2] Low frequency of events
[3] Very low frequency of events

BACKGROUND

Description of the condition

Acute pancreatitis was defined in 1992 at the Atlanta Symposium (Bradley 1993) as an acute inflammatory process of the pancreas that may also involve adjacent tissues and/or remote organ systems. Mild acute pancreatitis was defined as that associated with minimal organ dysfunction, whereas severe acute pancreatitis was defined as that associated with organ failure and/or local complications (necrosis, abscess, or pseudocyst) accompanied by adverse prognostic scores (Banks 2006).

The incidence rate of acute pancreatitis ranges between 5 and 80 per 100,000 people per year, with the highest incidence recorded in the United States and Finland (Banks 2002).

In 75% to 80% of sufferers, the aetiology of acute pancreatitis is identified. In developed countries, the most frequent causes are bile duct obstruction (38%) and alcohol abuse (36% to 44%).

The mechanisms by which bile duct obstruction or alcohol consumption initiate acute pancreatitis are not completely known. It seems, however, that a common pathogenic pathway might be related to inappropriate activation of trypsinogen to trypsin and to a lack of prompt elimination of active trypsin inside the pancreas (Wang 2009; Whitcomb 2006; Whitcomb 2008).

Other less common causes of pancreatitis are elevated triglyceride levels, cancer, viral and bacterial infections, surgery, peptic ulcers, pancreas divisum, medications and other genetic, metabolic and autoimmune causes.

Abdominal pain is the most common symptom of acute pancreatitis and is usually accompanied by nausea, vomiting and fever. Acute, constant and intense abdominal pain might last for several days, is mostly experienced in the epigastric region or the right upper quadrant and may radiate to the back. Physical examination often reveals severe upper abdominal tenderness at times associated with guarding (Carroll 2007; Frossard 2008).

It is generally accepted that a diagnosis of acute pancreatitis requires at least two of the following three features: 1) abdominal pain characteristic of acute pancreatitis; 2) serum amylase and/or lipase greater than three times the upper limit of normal; and 3) characteristic findings of acute pancreatitis on abdominal scan (Banks 2006). Contrast-enhanced computerised tomography (CECT) can be done after admission to confirm diagnosis of disease (87% to 90% sensitivity and 90% to 92% specificity), or after four days, to assess local complications and to score the disease.

Most cases of acute pancreatitis are mild and self-limiting, but 20% of cases develop severe disease with local complications, such as necrosis, pseudocyst or abscess of the gland, and/or extrapancreatic complications (Bradley 1993). Several risk scales, general or specific, are used to classify disease severity and survival, including Computed Tomography Severity Index (CTSI), Ranson's criteria, Imrie scoring system, Acute Physiology And Chronic Health Evaluation (APACHE II), and the Sequential Organ Failure Assessment (SOFA) (Carroll 2007; Frossard 2008). General mortality is estimated to be around 2% to 3%, but can reach 80% (Johnson 2005). While mortality in sterile pancreatic necrosis is 10%, infected necrosis generates a mortality of 25%. Nearly half of deaths occur during the first one to two weeks after admission because of multiple organ failure from systemic inflammatory response. Deaths beyond this time are also due to multiple organ failure, but are secondary to infected pancreatic necrosis.

Description of the intervention

Treatment of acute pancreatitis depends mainly on the severity of the progression but almost all cases will need supportive treatment, such as analgesics.

Several types of opioids exist under the N02A Anatomical Therapeutic Chemical ATC code (ATC Classification). This group comprises strong analgesics of the opiate type and analgesics with similar structure or action. Opioids can be classified by their actions: agonist (e.g. morphine, hydromorphone, fentanyl), partial agonist (e.g. buprenorphine), agonist-antagonist (e.g. pentazocine), and antagonist opioids (e.g. naloxone). Pure opioid agonists are the most potent analgesics (Trescot 2008). These drugs are stronger pain relievers than non-opioids; oral 650 mg paracetamol or aspirin is oral dose equianalgesic to 30 mg codeine, 50 mg meperidine or 5 mg morphine. Apart from pain relief, opioid uses include treatment of opioid dependence, cough suppressants, epidural analgesia or as an antispasmodic.

Opioids are commonly used to manage pain in acute pancreatitis. However, it has been suggested that, apart from meperidine, opioids may mask the resolution of the disease and increase pain due to their spasmogenic effect, which in turn increases intraluminal pressure in the sphincter of Oddi (Isenhower 1998). This increased bile pressure appears to be related to the dose and plasma concentration of the opioid, and is apparently mediated by the Mu (μ) receptor. However, the clinical significance of this increased pressure is uncertain, because many studies are anecdotal observations, with small numbers of participants without known pancreatic disease, and there is no clear evidence from controlled clinical trials that would support this theory (Cebrián 2003).

How the intervention might work

Treatment with analgesics for abdominal pain in acute pancreatitis probably does not modify the course of disease or mortality. However, the treatment of pain as a symptom improves comfort and patient-reported outcomes.

An opioid is a psychoactive chemical that works by binding to opioid receptors; Mu (μ) with Mu1 and Mu2 subtypes receptors stimulated by pure opioid agonists, Kappa (κ) and Delta (δ). These receptors are found principally in the central and peripheral nervous system and the gastrointestinal tract. The opioid drugs produce analgesia by actions at several levels of the nervous system, in particular, inhibition of neurotransmitter release on presynaptic neuronal terminals in the spinal cord, considered to be the major mechanism of action responsible for the clinical effects of opioids, and inhibition of postsynaptic neurons, preventing the ascending transmission of the pain signal.

Why it is important to do this review

All people suffering from pain with acute pancreatitis would be considered for at least one type of analgesic (e.g. paracetamol, non-steroidal anti-inflammatory drugs, opioids). No clear advantage for any particular type of analgesia has been demonstrated in the treatment of abdominal pain in people with acute pancreatitis

(Banks 2006). We have been unable to identify any meta-analysis or systematic reviews comparing opioids versus other drugs for this condition.

The aim of this review is to clarify the appropriate use of opioids for abdominal pain management in acute pancreatitis.

OBJECTIVES

To assess the efficacy and safety of opioids for abdominal pain in acute pancreatitis, compared with other analgesics or different opioids.

METHODS

Criteria for considering studies for this review

Types of studies

We include randomised clinical trials (RCTs) with a parallel design, developed in any setting. We excluded quasi-randomised clinical trials.

Since abdominal pain in acute pancreatitis is not a stable and chronic condition, we excluded cross-over design trials.

Types of participants

We include studies with men or women, of any age, with abdominal pain due to acute pancreatitis. We have not used an explicit definition of acute pancreatitis, but have accepted the definition used by study authors.

Types of interventions

We considered treatment with opioids, i.e. those classified under the N02A Anatomical Therapeutic Chemical ATC code (e.g. morphine, hydromorphone, oxycodone, dihydrocodeine, diamorphine, codeine, pethidine, fentanyl, dextropropoxyphene, methadone, pentazocine, buprenorphine, tramadol, nicomorphine, meperidine, among others), used as an analgesic drug at any dose, drug-release formulation or route of administration.

Control groups included any other type of analgesic drug treatment, including other opioids, at any dose, drug-release formulation or route of administration.

Types of outcome measures

Primary outcomes

1. Number of participants showing improvements in pain intensity as defined by the trialist.
2. Number of participants requiring supplementary analgesia (offered when trial drug intervention fails to relieve pain and following trial protocol).

Secondary outcomes

1. Number of participants with pancreatitis complications.
2. Number of participants with drug-related adverse events.
3. Number of deaths from any cause.

For the first primary outcome 'Number of participants showing improvements in pain intensity' we accepted any degree of improvement reported by the authors. In the case of multiple degrees described by a trial, we took all of them into account. For meta-analysis, we combined only comparable degrees of improvement.

Search methods for identification of studies

Electronic searches

We attempted to identify all relevant trials regardless of language in the following databases:

- Cochrane Upper Gastrointestinal and Pancreatic Diseases Review Group Specialised Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*; 2013, Issue 6), Appendix 1;
- MEDLINE (via PubMed): from 1950 to June 2013, Appendix 2;
- EMBASE (via OVID): from 1980 to June 2013, Appendix 3.

We designed a search strategy through a combination of thesaurus-based terms and a broad list of free-text terms covering both the intervention and the problem of interest. The most recent search was in June 2013.

We combined our strategies with validated filters to retrieve trials (Cochrane Handbook).

Searching other resources

We checked the reference lists of all included studies in order to identify any potentially relevant RCT not found through electronic searches.
We also contacted study authors where necessary, to obtain additional information.

Data collection and analysis

Selection of studies

Two authors (XBO and GU) independently screened titles and abstracts of all references identified by the literature search for eligibility.

We obtained the full text of all potentially eligible studies and independently evaluated the for inclusion in the review. We excluded any studies that did not provide results for adults and children separately (as a subgroup analysis), or if this information could not be obtained after contacting the authors. We resolved disagreements by consensus or by contacting the authors for clarification. We document reasons for excluding studies (see Characteristics of excluded studies table).

Data extraction and management

Two authors (XBO and GU) independently extracted data using a standardised data extraction sheet. For all included studies we extracted information on the number of participants randomised and number for which outcome(s) were measured. We extracted the number of events and the number of participants in each treatment arm for dichotomous outcomes.

We resolved any inadequacies or discrepancies between the extracted data by discussion and if necessary by contacting the study authors for further details.

Assessment of risk of bias in included studies

Two authors (XBO and GU) independently assessed the risk of bias for each included trial using an assessment form outlined in Chapter 8 of the Cochrane Handbook. We resolved any disagreements by discussion or by involving a third assessor.

We assessed the following five components for each of the trials: sequence generation (selection bias), allocation concealment (selection bias), blinding (performance and detection biases), incomplete outcome data (attrition bias through withdrawals, drop-outs, protocol deviations) and selective reporting bias.

For each of these components, we assigned a judgement of low, high or unclear risk of bias (Cochrane Handbook). We recorded the results in a standard table in Review Manager 5 (RevMan), and summarised the findings in a 'Risk of bias' table and figures.

Measures of treatment effect

We measured the effect of treatment as a dichotomous outcome using the risk ratio (RR) with a 95% confidence interval (CI).

Dealing with missing data

Due to the acute condition being assessed in this review, we did not expect a significant drop-out rate in the studies included in the review. As shown below, missing data were generally not a problem for the included trials.

Assessment of heterogeneity

We pooled data only for clinically homogeneous studies based on comparability of interventions and outcome measures. We assessed statistical heterogeneity using the I^2 statistic (Higgins 2003). I^2 values above 75% indicate substantial heterogeneity between studies.

Assessment of reporting biases

There were insufficient studies included in the review to support the use of a funnel plots or other methods to test for publication bias.

Data synthesis

Where pooling of data was possible (i.e. the trials assessed a common comparison providing adequate data for a specific outcome), we carried out a meta-analysis using the Mantel-Haenszel random-effects model.

When pooling was not possible, we provide a qualitative description of the results. All statistical analyses were performed using Cochrane Review Manager 5 (RevMan) statistical package, following the recommendations of the Cochrane Handbook.

Subgroup analysis and investigation of heterogeneity

In future updates of this review, provided that sufficient data are available, we plan to carry out the following subgroup analyses to examine the effect of opioids on specific group of participants:

- Disease severity (severe versus less severe). Severe acute pancreatitis is defined as having any of the following criteria: organ failure, local complications, Ranson's criteria > 3 or APACHE-II score ≥ 8;
- Disease aetiology (alcohol versus other causes);
- Opioid class (pure agonists, partial agonist, agonist-antagonists, antagonists);
- Opioid administration route (oral versus parenteral).

Sensitivity analysis

In future updates of this review, we will conduct sensitivity analyses formulated a priori to investigate the robustness of the results modified by various components of the risk of bias assessments. We will examine the effect on the primary outcome of excluding any RCT judged to be at a high risk of bias by three of the domains, i.e. sequence generation, allocation concealment and blinding.

We will also carry out sensitivity analysis to compare the random-effects model with a fixed-effect model.

RESULTS

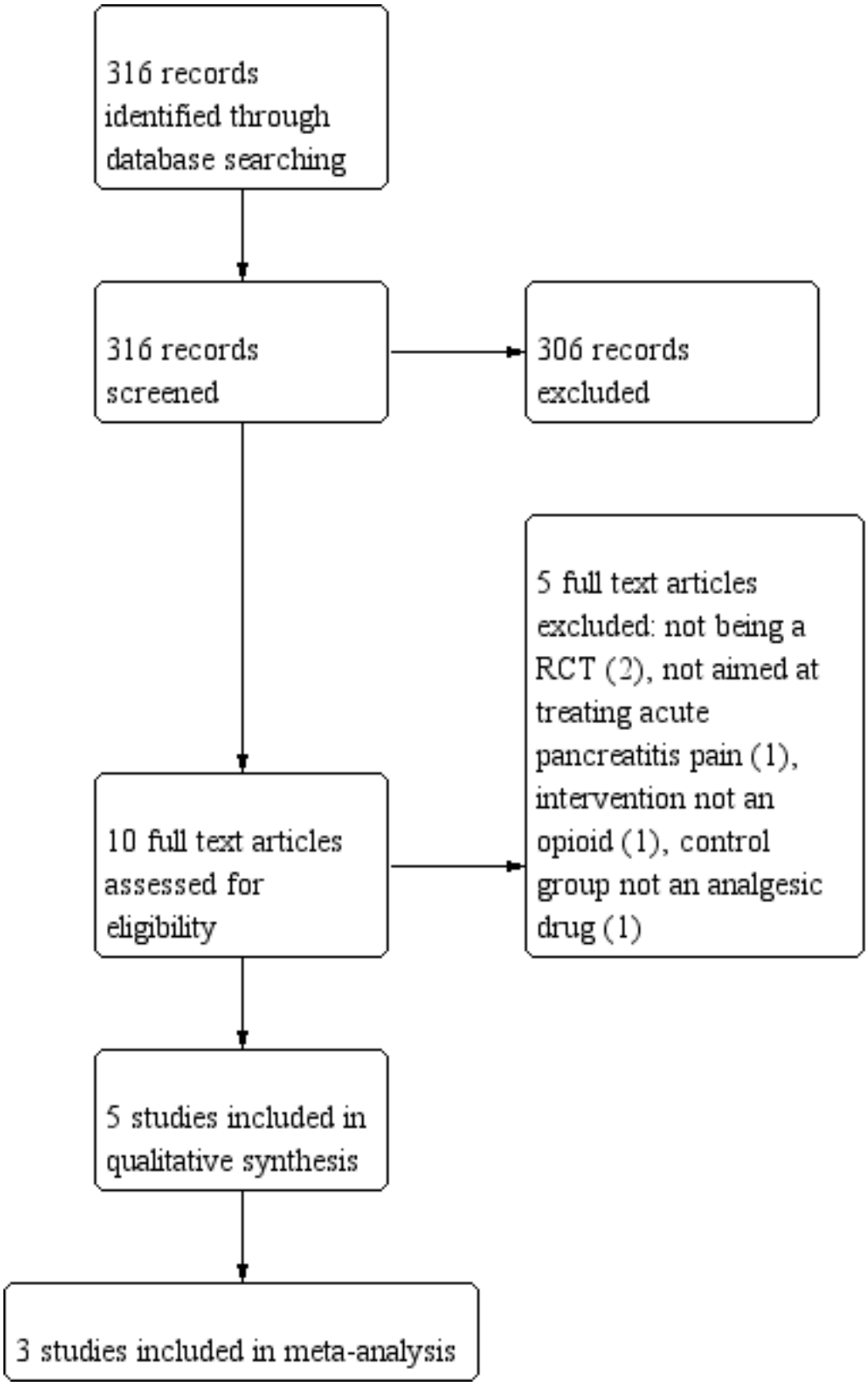
Description of studies

Results of the search

The search identified 316 references in our primary electronic databases. We excluded 302 references on the basis of title and abstract alone. We then obtained the full-text report for the remaining 14 references to check whether they met all the inclusion criteria. We finally excluded nine of these studies after a complete full-text review, and after we had contacted the study authors for more information to decide eligibility. Five studies met the inclusion criteria for this review (Blamey 1984; Jakobs 2000; Kahl 2004; Peiro 2008; Stevens 2002).

The study flow is shown in Figure 1.

Figure 1. Study flow diagram.



Included studies

A detailed description of included studies is provided in the Characteristics of included studies table.

Study design

All five studies, involving a total of 227 participants, were randomised clinical trials (RCTs) with a parallel design. All were active-control trials except Stevens 2002, which used a placebo-controlled group.

Setting

All the RCTs were single-centre trials conducted in Germany (Jakobs 2000; Kahl 2004), the UK (Blamey 1984), the USA (Stevens 2002), and Spain (Peiro 2008).

All the RCTs recruited their participants from hospital settings, with the intervention conducted while they were in acute care units.

Sample size

The smallest trial had 16 participants (Peiro 2008) and the largest 107 (Kahl 2004). Peiro 2008 was the only trial that described how the sample size was calculated.

Participants

The majority of participants were men (at least 127/195; 65%) with an age range between 23 and 76 years. Blamey 1984, with 32 participants, did not report details of gender or age of their participants.

Intervention

Five different opioids were used in the five RCTs included in this review. Two trials assessed buprenorphine, comparing it with another opioid (pethidine; Blamey 1984) and with procaine, a local anaesthetic (Jakobs 2000). Pentazocine was compared with procaine in Kahl 2004, morphine was compared with metamizole (Peiro 2008) and fentanyl with placebo (Stevens 2002).

All intervention and control groups used a parenteral route of administration. Two trials used the intravenous route (Jakobs 2000; Kahl 2004), the intramuscular route was used in Blamey 1984, the transdermal route in Stevens 2002 and subcutaneous route in Peiro 2008.

Opioids were the supplementary analgesic drugs (rescue treatment) most used when the intervention drug failed to resolve the acute abdominal pain. Four RCTs used pethidine (Blamey 1984; Jakobs 2000; Peiro 2008; Stevens 2002) and Kahl 2004 used pentazocine. A pyrazolone derivate was also used in Jakobs 2000.

Outcomes of interest

Peiro 2008 was the only trial reporting data on our first primary outcome, i.e. the number of participants showing improvements in pain intensity, assessed after 24 hours of starting treatment. Using a 100 mm Visual Analogue Scale (VAS), the treatment was considered effective when the VAS score was less than 15 mm in two consecutive VAS evaluations.

All RCTs except Stevens 2002 reported data on our second primary outcome, i.e. the number of participants with a supplementary analgesic option.

The number of participants with drug-related adverse events was reported by all the RCTs. The number of deaths from any cause was reported by all the RCTs except for Stevens 2002, and the least-reported secondary outcome was the number of participants with pancreatitis complications, reported by three trials (Jakobs 2000; Kahl 2004; Peiro 2008).

Most of the RCTs reported the results at the end of the trial. Blamey 1984 and Peiro 2008 at 24 hours, Kahl 2004 at four days, Jakobs 2000 at 72 hours and Stevens 2002 at three days after discharge. Peiro 2008 also reported results at 48 hours for pain assessment and at six months for adverse events.

Excluded studies

Five trials did not fulfil the inclusion criteria and were excluded. (Hopton 1971; Salazar 1987; Salim 1991; Santosh 2010; Spiegel 2001).

For a summary of the reasons for exclusion please see the Characteristics of excluded studies table.

Risk of bias in included studies

Our assessment of the risk of bias in the included studies is summarised in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

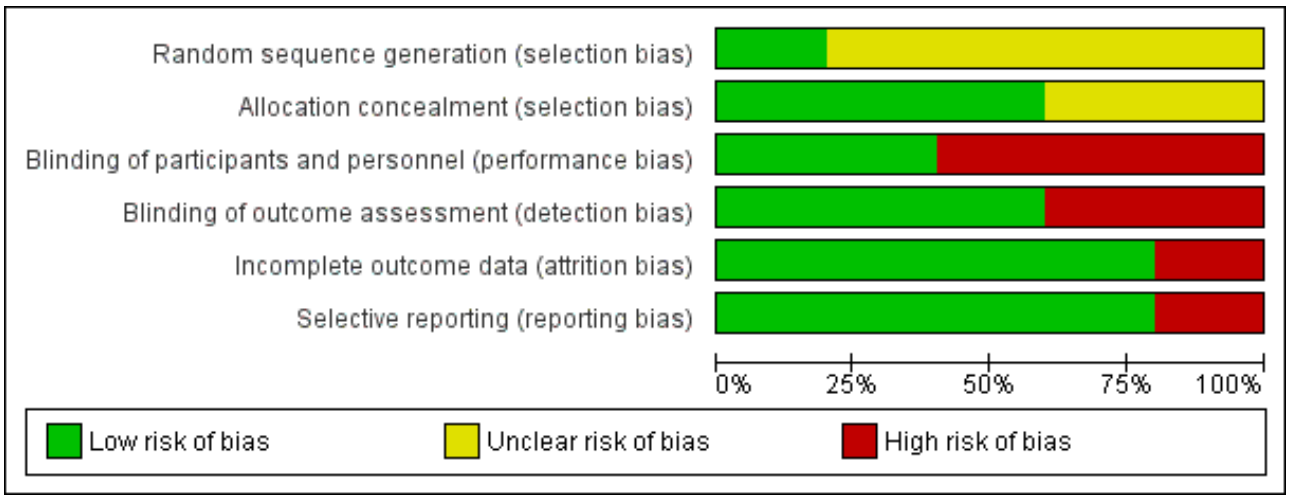
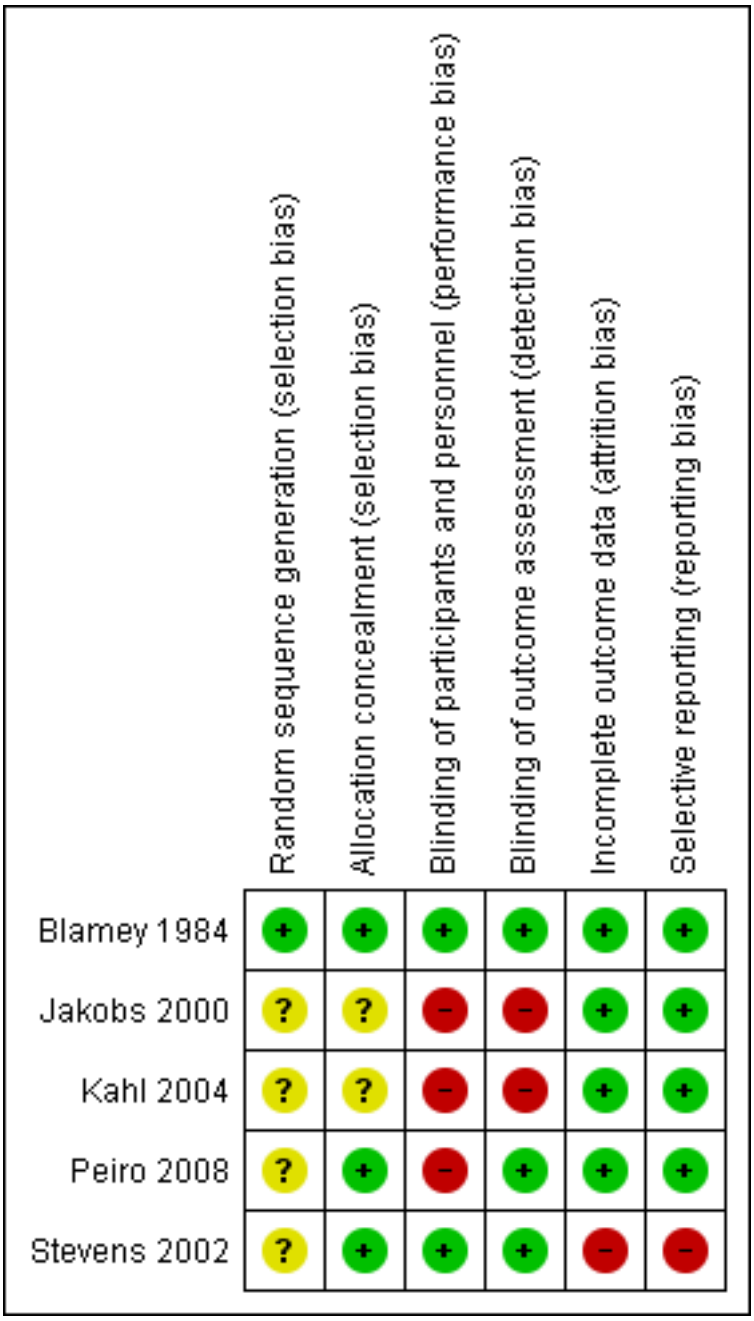


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation

Allocation sequence was adequately generated in one RCT (Blamey 1984) using a computerised random numbers series. The other four RCTs did not report the method used for sequence generation (Jakobs 2000; Kahl 2004; Peiro 2008: Stevens 2002).

Allocation concealment

Three RCTs had adequately concealed randomisation sequences: Blamey 1984 and Peiro 2008 by central randomisation and Stevens 2002 by sealed envelopes. The other two included RCTs did not provide information regarding allocation concealment (Jakobs 2000; Kahl 2004).

Blinding

Blinding of participants and personnel (performance bias):

The blinding method was judged as adequate in two RCTs (Blamey 1984; Stevens 2002). The rest of the trials reported no blinding of participants or study personnel.

Blinding of outcome assessment (detection bias):

Three trials used a blinded method to assess outcomes (Blamey 1984; Peiro 2008: Stevens 2002). Outcome assessment in Jakobs 2000 and Kahl 2004 was reported as not blinded.

Incomplete outcome data

All RCTs included in this review except Stevens 2002 had a low risk of attrition bias, because of the low rate of withdrawals: 6/107 participants in Kahl 2004, 1/40 in Jakobs 2000 and none in Blamey 1984 and Peiro 2008. The principal author of one study (Stevens 2002) indicated that 38.5% of participants had withdrawn and could not report how those patients were distributed. The study was therefore judged to be at high risk of attrition bias.

Selective reporting

All RCTs included in this review except Stevens 2002 reported results for all the key outcomes that would be expected to have been reported for such a trial and were therefore judged to be at low risk of reporting bias.

Effects of interventions

See: **Summary of findings for the main comparison** Morphine compared to metamizole for acute pancreatitis pain; **Summary of findings 2** Opioids versus no opioids for acute pancreatitis pain

We present in this section a narrative synthesis of the results for the different outcomes of interest, with illustrative forest plots (not pooled, apart from Analysis 4).

Number of participants showing improvements in pain intensity as defined by the trialist

Only one RCT reported data for this primary outcome (Peiro 2008), showing non-significant differences in the number of participants with subcutaneous morphine compared with intravenously metamizole (RR 0.50, 95% CI 0.19 to 1.33; Analysis 2.1).

Number of participants with a supplementary analgesic option offered when trial drug intervention fails to relieve pain

All the RCTs reported data for this primary outcome except Stevens 2002.

Results of RCTs comparing opioids versus non-opioids (Jakobs 2000; Kahl 2004; Peiro 2008) have been combined, showing no difference in the number of participants demanding supplementary analgesia (RR 0.41, 95% CI 0.14 to 1.19; Analysis 4.1).

After excluding Jakobs 2000 in a sensitivity analysis, the combined analysis of Kahl 2004 and Peiro 2008 showed low heterogeneity (I^2 = 25%) with a statistically significant reduction in the number of participants demanding supplementary analgesia favouring opioids compared to non-opioids (RR 0.53, 95% CI 0.30 to 0.93). The heterogeneity contributed by Jakobs 2000 may be attributable to its continuous intravenously infusion of opioids, compared to Kahl 2004 and Peiro 2008, in which opioids were administered every six and four hours respectively.

Jakobs 2000 and Kahl 2004 both showed a statistically significant reduction in the number of participants demanding supplementary analgesia, favouring buprenorphine (RR 0.08, 95% CI 0.01 to 0.52; Analysis 4.1) and pentazocine (RR 0.47, 95% CI 0.34 to 0.65; Analysis 4.1) respectively, compared to procaine. Peiro 2008 showed no difference between groups (RR 1.00, 95% CI 0.28 to 3.54; Analysis 4.1).

The only study comparing an opioid (intramuscular buprenorphine) versus another opioid (intramuscular pethidine) (Blamey 1984) showed no difference between groups (RR 0.82, 95% CI 0.61 to 1.10; Analysis 1.1).

Number of participants with pancreatitis complications

Three RCTs reported data for this outcome (Jakobs 2000; Kahl 2004; Peiro 2008); results of all three RCTs have been combined showing no difference in the number of participants with pancreatitis complications in comparison to non-opioid treatment (RR 1.05, 95% CI 0.82 to 1.34; Analysis 4.2) without heterogeneity (I^2 = 0%).

None of these trials individually showed a statistical significant difference between groups.

Number of participants with drug-related adverse events

All the RCTs included reported data for this outcome, with a total of 22 events reported.

Stevens 2002, comparing an opioid (fentanyl) versus placebo, reported that none of the participants suffered a serious adverse event related to the interventions.

Results of RCTs comparing opioids versus non-opioids with at least one event (Jakobs 2000; Peiro 2008) have been combined showing a statistically non-significant increase associated with opioids (RR 2.00, 95% CI 0.90 to 4.46; Analysis 4.3) without heterogeneity (I^2 = 0%).

When combining results by type of adverse events, nauseas-vomiting and somnolence-sedation, neither showed a statistical significant increase associated with opioids. Nausea or vomiting in two RCTs (RR 1.68, 95% CI 0.70 to 4.00) without heterogeneity (I^2 = 0%) and somnolence or sedation in two RCTs (RR 5.54, 95% CI 0.69 to 44.79) also without heterogeneity (I^2 = 0%).

Kahl 2004 reported that none of the participants suffered an adverse event related to the intervention.

The only study comparing an opioid (intramuscular buprenorphine) versus another opioid (intramuscular pethidine) (Blamey 1984) showed no difference between groups (RR 2.67, 95% CI 0.12 to 60.93; Analysis 1.1)

Number of deaths from any cause

All the included RCTs except Stevens 2002 reported data for this outcome. Blamey 1984, Kahl 2004 and Peiro 2008 reported that none of the participants died and Jakobs 2000 reported one death from acute pancreatitis, in the procaine group.

DISCUSSION

Summary of main results

This systematic review identified two RCTs assessing buprenorphine for treating acute pancreatitis pain; Blamey 1984 using intramuscular buprenorphine compared to the opioid pethidine, and Jakobs 2000 comparing intravenous buprenorphine

compared to procaine. Three other RCTs were included assessing other opioid drugs for treating acute pancreatitis pain: pentazocine versus procaine (Kahl 2004), morphine versus metamizole (Peiro 2008), and fentanyl versus placebo (Stevens 2002).

For the number of participants showing improvements in pain intensity (primary outcome), subcutaneous morphine did not show a significant reduction in the likelihood of a reduction in pain intensity compared with metamizole (Peiro 2008).

For the number of participants requiring a supplementary analgesic option (primary outcome), the combined analysis of three RCTs (Jakobs 2000; Kahl 2004; Peiro 2008) comparing opioids versus non-opioids found no difference between groups. After excluding Jakobs 2000 in a sensitivity analysis, the combined analysis of Kahl 2004 and Peiro 2008 showed low heterogeneity (I^2 = 25%) with a statistically significant reduction in the number of participants demanding supplementary analgesia favouring opioids compared to non-opioids (RR 0.53, 95% CI 0.30 to 0.93). The results of the sensitivity analysis should be interpreted with caution. The confidence in this effect estimate, however, is low due to methodological limitations and the variability of results among individual studies. The large heterogeneity detected in the analysis and a so different effect size in Jakobs 2000 could be explained because this study offered continuous intravenous opioid infusion to participants, whereas in Kahl 2004 and Peiro 2008 opioids were administered every four to six hours respectively. We do not know this beneficial effect responds only to the manner of administering analgesia, continuous or intermittent, the type of opioid used or other circumstances, but it is a fact that we state and could be considered in future trials.

Blamey 1984 comparing an opioid, buprenorphine, versus another opioid, pethidine, and found no difference between groups.

Pancreatitis complications were assessed with three different opioids, buprenorphine (Jakobs 2000), pentazocine (Kahl 2004) and morphine (Peiro 2008); the combined analysis of these three RCTs did not show a significant difference.

The included RCTs did not report any clinically serious or life-threatening adverse events for opioids compared with the control drugs.

Only one death was reported, in a procaine group, across all the included trials. None of the included trials reported opioid-induced sphincter of Oddi spasm or increased bile pressure related to opioids.

The results for pancreatitis complications and adverse effects should be interpreted with caution, because clinical trials are not the best source for establishing the risk of low-frequency events related to drug treatments.

Overall completeness and applicability of evidence

Although we cannot differentiate the severity of acute pancreatitis experienced in these trials, all participants were admitted to acute care hospitals, and none to intensive care or outpatient departments. This is the setting in which the majority of people with acute pancreatitis are managed nowadays. We noted no anomalies in gender and age reported in these trials, and would take them to be a typical patient population.

All the opioids tested in the included RCTs are widely available and frequently used, so the findings are readily generalisable.

All the RCTs included in this review included one or more outcomes relevant to patients. Only one RCT reported data on the first primary outcome: number of participants showing improvements in pain intensity, defined as a 15 mm reduction in a 100 mm VAS scale over two consecutive evaluations. Even though the outcome is of relevance for patients, 15 mm reduction in a 100 mm VAS scale might be considered as not being clinically meaningful.

The number of participants requesting supplementary analgesic options can be considered as a surrogate measure of pain relief. This was also included as a primary outcome, since it is frequently reported in studies on pain management.

Although most of the included RCTs reported data on the second primary outcome (number of participants with a supplementary analgesic option), an overall lack of information limits the possibility of evaluating accurately and comprehensively the effects of opioids for acute pancreatitis pain.

Quality of the evidence

The results should be interpreted with caution, due to the limited number of trials identified, the diversity of drugs assessed and outcomes measured, the small sample sizes, and the levels of bias in the conduct and reporting of the trials.

Potential biases in the review process

The review was conducted in accordance with a previously published protocol. We believe the search strategy used here ensures an unbiased study selection, but we did not locate any trials other than English language reports, nor any unpublished trials, and it is possible that we might have missed such studies. The selection, data collection and analyses were all performed by more than one person to minimise bias. We also contacted study authors for clarification on study data.

None of the authors of this report has been involved in any of the included trials and none has any commercial or other conflict of interest.

Agreements and disagreements with other studies or reviews

We have found no other systematic review specifically investigating the efficacy of opioids for treating acute pancreatitis pain and its possible adverse events. Despite earlier investigation and clinical recommendations advising against the use of opioids, especially meperidine (Munoz 2000), recent studies (Thompson 2001) have failed to establish an association between opioids and clinically significant adverse events related to opioid-induced sphincter of Oddi spasm and basal pressure. These studies are compatible with our conclusions that neither deaths nor serious or life-threatening adverse events have been shown to be associated with opioid treatment.

AUTHORS' CONCLUSIONS

Implications for practice

Opioids may be an appropriate choice for the treatment of acute pancreatitis pain. Compared with other analgesic options, opioids

might decrease the need for supplementary analgesia. There is no difference in the risk of pancreatitis complications or clinically serious adverse events between opioids and other analgesic options.

Implications for research

Future research in this field should focus on the design of trials with larger samples (reporting how sample size was determined), the measurement of relevant outcomes for decision-making, such as the number of participants showing a certain level of improvement in pain intensity, different opioids or routes of delivery, and opioids versus other techniques. Effectiveness of continuous analgesic infusion in acute pancreatitis could be tested in future RCTs. The reporting of these trials should also be improved (i.e. using the CONSORT statement (Schulz 2010)) to allow users of the medical literature to accurately appraise the results of these RCTs. Large longitudinal studies are also needed to establish the risk of less frequent pancreatitis complications and adverse events related to drug treatments.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Blamey 1984

Methods	**Study type**: Double-blind, randomised trial, controlled with active treatment, parallel design. Single centre. Country and setting: UK and acute care hospital
Participants	**Randomised**: 32 (17 buprenorphine; 15 pethidine) **Excluded:** None **Gender:** Not specified **Age:** Not specified **Inclusion criteria:** Consecutive participants with acute pancreatitis **Exclusion criteria**: Not specified
Interventions	Intramuscular buprenorphine (0.3 mg) versus intramuscular pethidine (100 mg) **Co-interventions**: Routine supportive treatment was used. Subsequent analgesia (pethidine 100 mg) was provided on demand
Outcomes	1. Number of participants demanding further analgesia 2. Adverse events 3. Death Follow-up was 24 hours after administration of treatment
Notes	**Acute pancreatitis defined as:** Quote: "(serum amylase activity > 1200 IU/l or urinary amylase activity >3000 IU/1) ". (Page 1494) **Sample size calculation**: Not specified

Blamey 1984 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Quote: "randomly number coded by a computer in the hospital pharmacy". (Page 1494)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical ampoules. Quote: "identical ampoules that had been randomly number coded". (Page 1494)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Identical ampoules
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or incomplete outcome reporting
Selective reporting (reporting bias)	Low risk	

Jakobs 2000

Methods	**Study type**: Open, randomised trial, controlled with active treatment, parallel design. Single centre. Country and setting: Germany and acute care hospital
Participants	**Randomised**: 40 (20 buprenorphine; 20 procaine) **Excluded:** one participant in buprenorphine group lost to follow-up (2.5%) **Gender:** Men: women. buprenorphine 12:8; procaine 11:9 **Age:** Buprenorphine: mean 51.5 (range 26 - 76); procaine: mean 47.5 (range 23 - 72) **Inclusion criteria:** acute abdominal pain consistent with the clinical diagnosis of acute pancreatitis (pain localised in the epigastrium or the upper abdomen; in some cases radiating to the back), elevated levels of serum amylase or serum lipase (minimum two-fold of normal) at any time of treatment and signs of acute pancreatitis on abdominal ultrasound or contrast-enhanced computed tomography. **Exclusion criteria**: < 18 or > 75 years old, pregnancy, cardiac arrhythmias on initial electrocardiogram, known severe arrhythmias in the past, allergies to any of the study medications or individual follow-up < 24 hours
Interventions	Buprenorphine initial bolus of 0.3 mg and then 2.4 mg/day as a constant i.v. infusion, versus procaine 2 g/day intravenously as a constant infusion **Co-interventions**: Besides study medication, all the participants were treated with the standard therapeutic regimen including i.v. fluids and parenteral feeding via a central venous catheter, and prophylactic antibiotics in case of necrotising pancreatitis. Participants in the procaine group who were not satisfied with the analgesic effect received pethidine (50 mg bolus i.v.), while those in the buprenorphine group received a pyrazolone derivate or pethidine if necessary
Outcomes	1. Number of participants demanding further analgesia

Jakobs 2000 *(Continued)*

	2. Number of participants with pancreatitis complications 3. Adverse events 4. Deaths Follow-up was 72 hours after drug administration
Notes	**Acute pancreatitis defined as:** Quote: "pain localized in the epigastrium or the upper abdomen; in some cases radiating to the back, elevated levels of serum amylase or serum lipase (minimum two-fold of normal) at any time of treatment and signs of acute pancreatitis on abdominal ultrasound or contrast-enhanced computed tomography". (Page 1319) Acute pancreatitis / acute bout of a chronic pancreatitis: 14/20 (70%) in the buprenorphine group and 13/20 (65%) in the procaine group At least one participant was 76 years old, despite the exclusion criteria **Sample size calculation**: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods of list generation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study. Quote: "The study design was open (not blind)". (Page 1320)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study. Quote: "The study design was open (not blind)". (Page 1320)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low number of participants withdrawn from the analysis
Selective reporting (reporting bias)	Low risk	

Kahl 2004

Methods	**Study type**: Open, randomised trial, controlled with active treatment, parallel design. Single centre. Country and setting: Germany and acute care hospital
Participants	**Randomised**: 107 (55 procaine; 52 pentazocine) **Excluded:** 6 (5 procaine, 1 pentazocine) **Gender:** Men: women. pentazocine 38:12; procaine 34:17 **Age: p**entazocine: mean 43 (SD 11); procaine: mean 47 (SD 14)

Kahl 2004 *(Continued)*

	Inclusion criteria: Acute pancreatitis, onset of abdominal pain < 72 hours prior to hospitalisation, without analgesic treatment, written informed consent and age > 18 years **Exclusion criteria**: onset of abdominal pain > 72 hours prior to hospitalisation, any analgesic treatment, age < 18 years, pregnancy, no written informed consent
Interventions	Pentazocine 30 mg / 6 hour intravenously or Procaine 2 g/24 hours continuous intravenous infusion **Co-interventions**: Besides pain treatment, participants were under standard therapeutic regimen including intravenous fluids, enteral or parenteral nutrition and antibiotics if necessary
Outcomes	1. Number of participants demanding further analgesia 2. Number of participants with pancreatitis complications 3. Adverse events 4. Deaths Follow-up was four days (for analysis purposes)
Notes	**Acute pancreatitis defined as:** Quote: "Acute abdominal pain of sudden onset and threefold elevation of serum pancreatic enzymes". (Page 6) **Sample size calculation**: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low number of participants withdrawn from the analysis
Selective reporting (reporting bias)	Low risk	

Peiro 2008

Methods	**Study type**: Open, randomised trial, controlled with active treatment, parallel design. Single centre. Country and setting: Spain and acute care hospital
Participants	**Randomised**: 16 (8 metamizole; 8 morphine)

Peiro 2008 *(Continued)*

	Excluded: At 24 hours only 4 /16 participants were assessed for pain. It is not clear if for safety analysis all the participants were included **Gender:** Men: women. metamizole 3:5 ; morphine 5:3 **Age:** Metamizole: mean 54.4 (SD 13.5); Morphine: mean 55.1 (SD 18.8) **Inclusion criteria:** Acute pancreatitis with admission within 12 hours of onset of symptoms **Exclusion criteria**: significant chronic renal or hepatic insufficiency, anaemia, agranulocytosis, any contraindication for receiving morphine, metamizole, pethidine, anyone considered unable to complete the study
Interventions	Morphine 1% 10 mg/4 hours s.c or metamizole 2 g/8 hours i.v. in a slow perfusion for 3 minutes **Co-interventions**: Besides pain treatment, participants received the standard care for acute pancreatitis, including intravenous fluids, artificial nutrition or antibiotics if necessary. Pethidine was additionally administered on demand as a rescue treatment whenever required to participants of both groups
Outcomes	1. Number of participants showing improvements 2. Number of participants demanding further analgesia 3. Number of participants with pancreatitis complications 4. Adverse events 5. Deaths Follow-up was 48 hours after admission for pain assessment, and six months for adverse events
Notes	**Acute pancreatitis defined as:** Quote: “upper abdominal pain plus hyperamylasemia or hyperlipasemia three fold the normal upper limit”. (Page 26) **Sample size calculation**: Quote: “16 patients were necessary to provide 80% statistical power (at a type I error rate of 0.05) to detect relevant differences of 30% on VAS between both groups”. (Page 26) Email contact with Dr Juan Martínez in September 2011 for clarification about randomisation method used, follow-up period, duration of intervention and dose of supplementary pethidine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods of list generation not stated
Allocation concealment (selection bias)	Low risk	Quote: “Assignments of patients were made according to a randomization list held by the Clinical Pharmacology Unit”. (Page 26)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Pain score was recorded every 4 h by a blinded researcher”. (Page 26)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low number of participants withdrawn from the analysis

Peiro 2008 *(Continued)*

Selective reporting (reporting bias)	Low risk

Stevens 2002

Methods	**Study type**: Double-blind, randomised trial, controlled with placebo, parallel design. Single centre. Country and setting: USA and acute care hospital
Participants	**Randomised**: 32 (15 fentanyl, 17 placebo) **Excluded:** at least 9 people at some point of the trial **Gender:** 18 men; 14 women **Age:** Range: 26 - 47 years **Inclusion criteria:** participants admitted to hospital and: 1) primary diagnosis of acute pancreatitis confirmed by a gastrointestinal specialist; 2) pain as a chief complaint; 3) pain on admission measuring ≥2 on a verbal self-reported scale of 0 to 5; 4) English-speaking; 5) alert and oriented at admission; 6) ≥ 18 years old **Exclusion criteria**: acute or chronic respiratory diseases, known sensitivity to the investigational medication
Interventions	Transdermal fentanyl (Transdermal Therapeutic System, TTS) 50 mcg/hour versus transdermal placebo (TTS)) **Co-interventions**: All patients received Demerol (Meperidine) Intramuscular 50-100 mg/every 3 hours (increase dosage at rate of 25 mg every 3 hours until patient reports pain intensity is 2 or less on a 0-5 scale); antiemetics; oral acetaminophen up to 1.300 mg/d Titration algorithm to determine adjustment of TTS fentanyl (or placebo) system*: Total doses used past 24 hours: 0 - 100 mg, decrease 25 mcg; 101 - 175 mg, continue present dose; 176 - 350 mg, increase 25 mcg; 351 - 575 mg, increase 50 mcg; 576 - 800 mg, increase 75 mcg; 801 - 1025 mg, increase 100 mcg
Outcomes	1. Self-reported pain intensity 2. Satisfaction with pain management 3. Adverse events Follow-up was from 3 to 72 hours after hospital admission (for analysis purposes)
Notes	**Acute pancreatitis defined as:** Quote: “acute pancreatitis confirmed by a gastrointestinal specialist”. (Page 103) **Sample size calculation**: not described **Email contact** with Gregg W. Asher, Ph.D on October 2011 for clarification about randomisation method used, allocation concealment, exclusions and outcome data not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided. Reported as randomised
Allocation concealment (selection bias)	Low risk	Quote: “subjects were randomly assigned by the sealed-envelope technique”. (Page 104)

Stevens 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "For staff to remain blind to the patients' true experimental condition, the inducting research assistant placed the placebo system or active TTS fentanyl system on the back of the upper torso and covered it with waterproof foam adhesive tape". (Page 104)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "To maintain the integrity of the study, the assistants did not participate in collecting self-reported pain intensity or satisfaction data and they did not provide direct nursing care to the subject during the course of his or her hospitalisation". (Page 104)
Incomplete outcome data (attrition bias) All outcomes	High risk	Email contact revealed 38.5% withdraw after randomization
Selective reporting (reporting bias)	High risk	Gave results for outcomes not specified in the methods section

i.v: intravenous; s.c.: sub-cutaneous

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Hopton 1971	Intervention was not aimed at treating acute pancreatitis pain
Salazar 1987	Not RCT (case series)
Salim 1991	Intervention was not an opioid
Santosh 2010	Control group was not a drug but a technique
Spiegel 2001	Not RCT (letter)

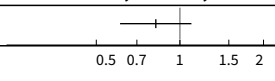
DATA AND ANALYSES

Comparison 1. Buprenorphine versus pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with a supplementary analgesic option offered (primary outcome 2)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Number of participants with drug-related adverse events (secondary outcome 2)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Number of deaths from any cause (secondary outcome 3)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

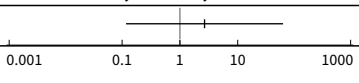
Analysis 1.1. Comparison 1 Buprenorphine versus pethidine, Outcome 1 Number of participants with a supplementary analgesic option offered (primary outcome 2).

Study or subgroup	Buprenorphine n/N	Pethidine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Blamey 1984	13/17	14/15		0%	0.82[0.61,1.1]



Analysis 1.2. Comparison 1 Buprenorphine versus pethidine, Outcome 2 Number of participants with drug-related adverse events (secondary outcome 2).

Study or subgroup	Buprenorphine n/N	Pethidine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Blamey 1984	1/17	0/15		0%	2.67[0.12,60.93]



Analysis 1.3. Comparison 1 Buprenorphine versus pethidine, Outcome 3 Number of deaths from any cause (secondary outcome 3).

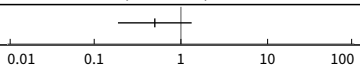
Study or subgroup	Buprenorphine n/N	Pethidine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Blamey 1984	0/17	0/15			Not estimable

Comparison 2. Morphine versus metamizole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants showing improvements in pain intensity (primary outcome 1)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Number of participants with a supplementary analgesic option offered (primary outcome 2)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Number of participants with pancreatitis complications (secondary outcome 1)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4 Number of participants with drug-related adverse events (secondary outcome 2)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5 Number of deaths from any cause (secondary outcome 3)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

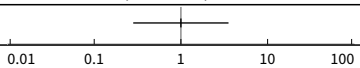
Analysis 2.1. Comparison 2 Morphine versus metamizole, Outcome 1 Number of participants showing improvements in pain intensity (primary outcome 1).

Study or subgroup	Morphine n/N	Metamizole n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Peiro 2008	3/8	6/8		0%	0.5[0.19,1.33]



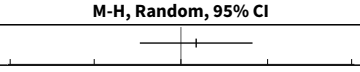
Analysis 2.2. Comparison 2 Morphine versus metamizole, Outcome 2 Number of participants with a supplementary analgesic option offered (primary outcome 2).

Study or subgroup	Morphine n/N	Metamizole n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Peiro 2008	3/8	3/8		0%	1[0.28,3.54]



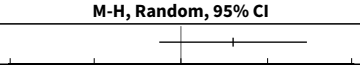
Analysis 2.3. Comparison 2 Morphine versus metamizole, Outcome 3 Number of participants with pancreatitis complications (secondary outcome 1).

Study or subgroup	Morphine n/N	Metamizole n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Peiro 2008	3/8	2/8		0%	1.5[0.34,6.7]



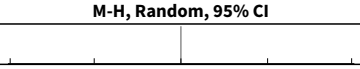
Analysis 2.4. Comparison 2 Morphine versus metamizole, Outcome 4 Number of participants with drug-related adverse events (secondary outcome 2).

Study or subgroup	Morphine n/N	Metamizole n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Peiro 2008	4/8	1/8		0%	4[0.56,28.4]



Analysis 2.5. Comparison 2 Morphine versus metamizole, Outcome 5 Number of deaths from any cause (secondary outcome 3).

Study or subgroup	Morphine n/N	Metamizole n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Peiro 2008	0/8	0/8			Not estimable



Comparison 3. Pentazocine versus procaine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with a supplementary analgesic option offered (primary outcome 2)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Number of participants with pancreatitis complications (secondary outcome 1)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Number of participants with drug-related adverse events (secondary outcome 2)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4 Number of deaths from any cause (secondary outcome 3)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 3.1. Comparison 3 Pentazocine versus procaine, Outcome 1 Number of participants with a supplementary analgesic option offered (primary outcome 2).

Study or subgroup	Pentazocine n/N	Procaine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Kahl 2004	22/52	50/55		0%	0.47[0.34,0.65]

Favours pentazocine 0.01 0.1 1 10 100 Favours procaine

Analysis 3.2. Comparison 3 Pentazocine versus procaine, Outcome 2 Number of participants with pancreatitis complications (secondary outcome 1).

Study or subgroup	Pentazocine n/N	Procaine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Kahl 2004	37/52	38/55		0%	1.03[0.8,1.32]

Favours pentazocine 0.01 0.1 1 10 100 Favours procaine

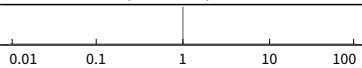
Analysis 3.3. Comparison 3 Pentazocine versus procaine, Outcome 3 Number of participants with drug-related adverse events (secondary outcome 2).

Study or subgroup	Pentazocine n/N	Procaine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Kahl 2004	0/52	0/55			Not estimable

Favours pentazocine 0.01 0.1 1 10 100 Favours procaine

Analysis 3.4. Comparison 3 Pentazocine versus procaine, Outcome 4 Number of deaths from any cause (secondary outcome 3).

Study or subgroup	Pentazocine n/N	Procaine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Kahl 2004	0/52	0/55			Not estimable



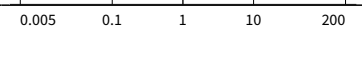
Favours pentazocine — Favours procaine

Comparison 4. Opioids versus no opioids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with a supplementary analgesic option offered (primary outcome 2)	3	162	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.14, 1.19]
2 Number of participants with pancreatitis complications (secondary outcome 1)	3	162	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.82, 1.34]
3 Number of participants with drug-related adverse events (secondary outcome 2)	2	110	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.90, 4.46]
3.1 Nausea and vomiting	2	55	Risk Ratio (M-H, Random, 95% CI)	1.68 [0.70, 4.00]
3.2 Sedation and somnolence	2	55	Risk Ratio (M-H, Random, 95% CI)	5.54 [0.69, 44.79]
4 Number of deaths from any cause (secondary outcome 3)	4	194	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.02, 8.10]

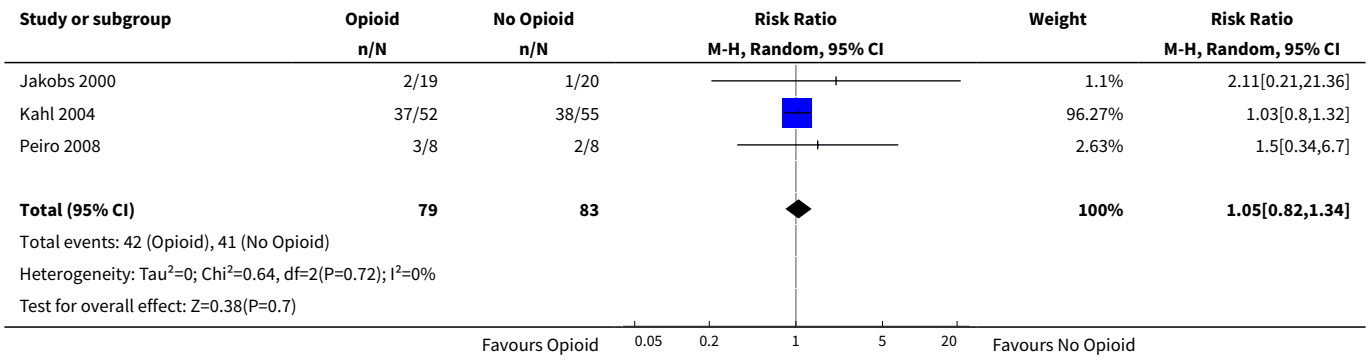
Analysis 4.1. Comparison 4 Opioids versus no opioids, Outcome 1 Number of participants with a supplementary analgesic option offered (primary outcome 2).

Study or subgroup	Opioid n/N	No Opioid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Jakobs 2000	1/19	14/20		19.19%	0.08[0.01,0.52]
Kahl 2004	22/52	50/55		50.62%	0.47[0.34,0.65]
Peiro 2008	3/8	3/8		30.19%	1[0.28,3.54]
Total (95% CI)	**79**	**83**		**100%**	**0.41[0.14,1.19]**
Total events: 26 (Opioid), 67 (No Opioid)					
Heterogeneity: Tau^2=0.55; Chi^2=5.49, df=2(P=0.06); I^2=63.57%					
Test for overall effect: Z=1.64(P=0.1)					

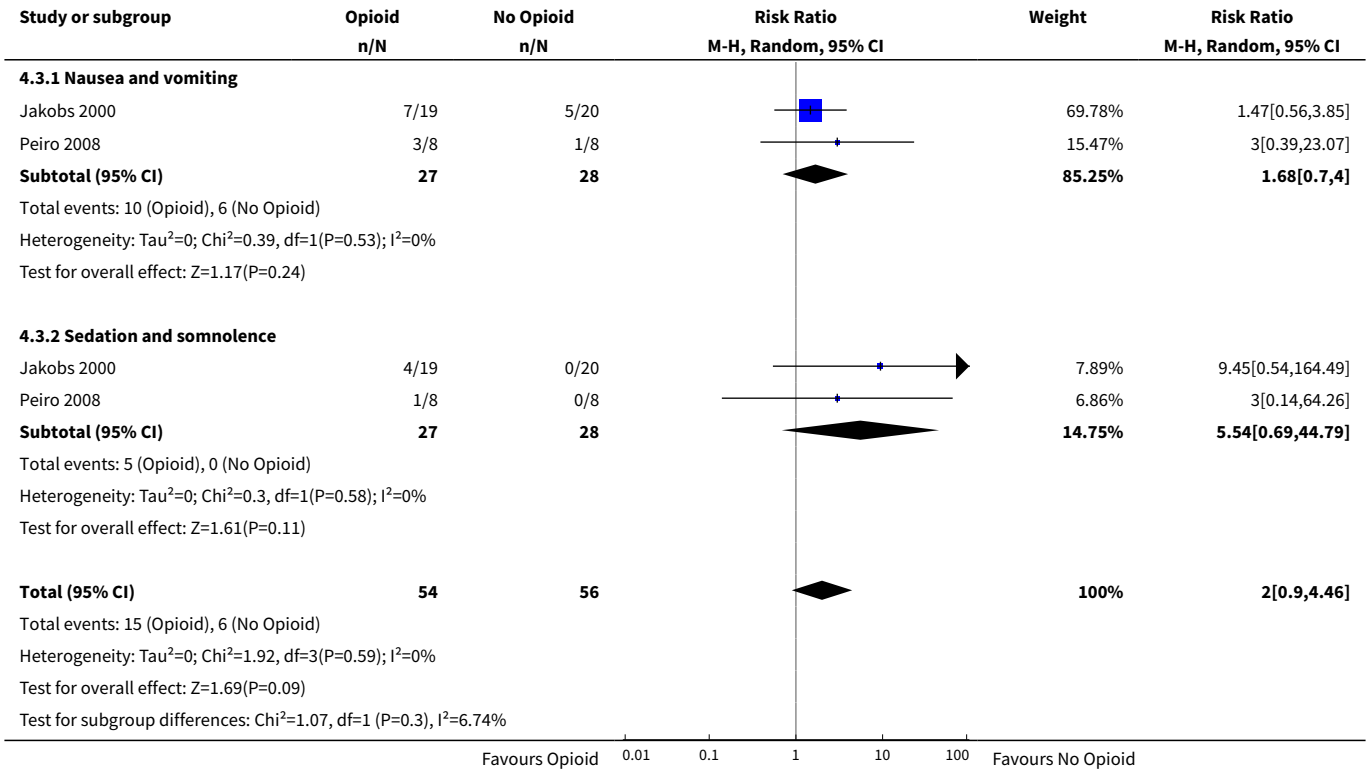


Favours Opioids — Favours No Opioids

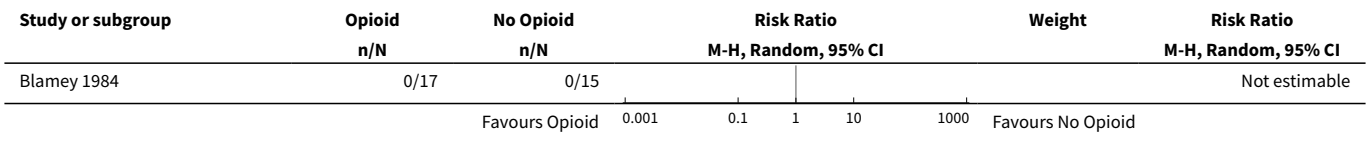
Analysis 4.2. Comparison 4 Opioids versus no opioids, Outcome 2 Number of participants with pancreatitis complications (secondary outcome 1).

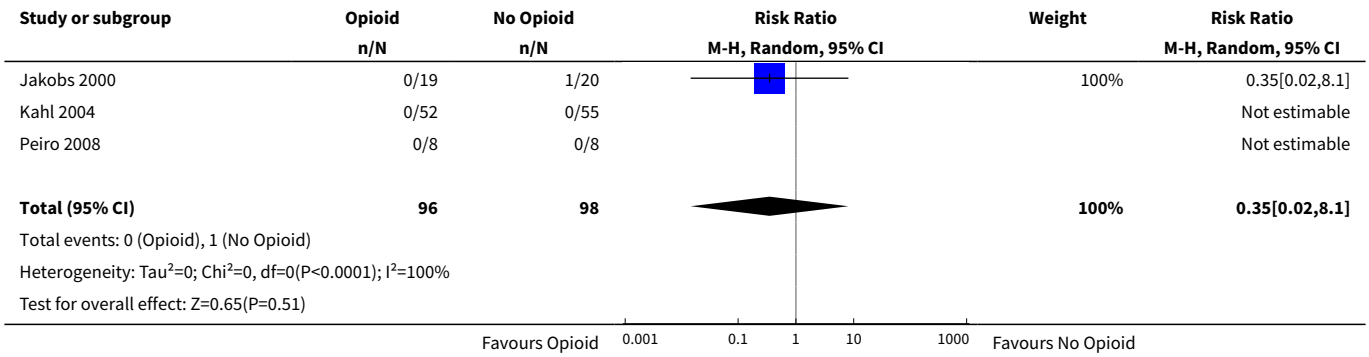


Analysis 4.3. Comparison 4 Opioids versus no opioids, Outcome 3 Number of participants with drug-related adverse events (secondary outcome 2).



Analysis 4.4. Comparison 4 Opioids versus no opioids, Outcome 4 Number of deaths from any cause (secondary outcome 3).





APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials

1. exp Pancreatitis, Acute Necrotizing/
2. exp Pancreatitis, Alcoholic/
3. Pancreatitis/et [Etiology]
4. exp Pancreas/ab, de, pa [Abnormalities, Drug Effects, Pathology]
5. (acute adj3 pancrea*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6. (necro* adj3 pancrea*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7. (Alcohol* adj3 pancrea*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8. (Gallstone* adj3 pancrea*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
9. or/1-8
10. exp Analgesics, Opioid/
11. exp Narcotics/
12. (Opioid$ or Opiate$ or Narcotic$).mp.
13. exp Morphine/
14. (morphine or Astramorph or avinza or depodur or duramorph or embeda or infumorph or kadian or m-eslon or morcap or morphia or ms contin or msir or mst or nepenthe or oramorph or rescudose or rms or roxanol or sevredol or statex or zomorph).mp.
15. exp Opium/
16. (opium or omnopon or pantopon or papaveretum).mp.
17. exp Hydromorphone/
18. (Hydromorphone or dihydromorphinone or dilaudid or dimorphone or exalgo or hydmrphn or hydromorph$ or hydrostat or hymorphan or laudicon or novolauden or palladone).mp.
19. Nicomorphine.mp.
20. exp Oxycodone/
21. (oxycodone or Dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon or endocodone or eth-oxydose or eucodal or hydroxycodeinon or m-oxy or oxiconum or oxycdn or oxycone or oxycontin or oxyfast or oxyir or pancodine or percocet or percolone or remoxy or roxicodone or theocodin).mp.
22. (Dihydrocodeine or contugesic or dhc mundipharma or dicodin or dihydcdn or paracodin or paramol or parzone or rikodeine or tiamon or tosidrin or tuscodin).mp.
23. (Diamorphine or acetomorphine or diacetylmorphine or diagesil or diamorf or heroin or min-i-jet morphine sulfate or skag).mp.
24. exp Codeine/
25. (Codeine or ardinex or galcodine or isocodeine or methyl morphine or rx 336m or stanley-linctus or stanley-syrup).mp.
26. Ketobemidone.mp.
27. exp Meperidine/
28. (Pethidine or demerol or dolantin or dolargan or dolcontral or dolosal or dolsin or isonipecain or isonipecaine hydrochloride or lydol or meperidine or operidine epj or pethilorfan).mp.
29. exp Fentanyl/

30. (Fentanyl or abstral or actiq or duragesic or fentanest or fentora or fentyl or ionsys or matrifen or nasalfent or onsolis or oralet or phentanyl or sublimaze).mp.
31. exp Dextromoramide/
32. Dextromoramide.mp.
33. (Piritramide or Dipidolor or dipydolor or Piridolan or Pirium).mp.
34. exp Dextropropoxyphene/
35. (Dextropropoxyphene or darvon or dolene or doloxene or levopropoxyphene or pp-cap or propoxyphene or proxyphen).mp.
36. (Bezitramide or Burgodin).mp.
37. exp Methadone/
38. (methadone or adanon or althose or amidines or amidone or biodone or diskets or dolophine or Heptadon or metadol or metasedin or methaddict or metharose or Methadose or methdn or methex or phy or phymet or physeptone or pinadone or symoron).mp.
39. exp Benzomorphans/
40. exp Pentazocine/
41. (Pentazocine or Fortral or Fortwin or lexir or Talacen or talwin).mp.
42. exp Phenazocine/
43. (Phenazocine or Prinadol or Narphen).mp.
44. Oripavine.mp.
45. exp Buprenorphine/
46. (Buprenorphine or '6029-m' or buprenex or buprex or prefin or Suboxone or subutex or temgesic).mp.
47. exp Etorphine/
48. (Etorphine or Immobilon or M99).mp.
49. exp Morphinans/
50. exp Butorphanol/
51. (Butorphanol or 'bc2627' or beforal or dolorex or moradol or stadol or torbugesic).mp.
52. exp Tilidine/
53. (Tilidine or tilidate or Valoron or Valtran or Tilidin).mp.
54. exp Tramadol/
55. (Tramadol or 'k-315' or ralivia or ryzolt or tramahexal or tramake insts or tramal$ or tramedo or ultram or zamadol or zydol).mp.
56. (Dezocine or Dalgan or 'WY-16225').mp.
57. exp Meptazinol/
58. (Meptazinol or Meptid).mp.
59. (Tapentadol or cg5503 or nucynta).mp.
60. (Remifentanil or 'gi 87084b' or remifentanyl or ultiva).mp.
61. exp Procaine/
62. (Procaine or allocaine or anuject or gerokit or mericaine or novocaine or procaina serra).mp.
63. or/10-62
64. 9 and 63

Appendix 2. MEDLINE search strategy

1. exp Pancreatitis, Acute Necrotizing/
2. exp Pancreatitis, Alcoholic/
3. Pancreatitis/et [Etiology]
4. exp Pancreas/ab, de, pa [Abnormalities, Drug Effects, Pathology]
5. (acute adj3 pancrea*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6. (necro* adj3 pancrea*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7. (Alcohol* adj3 pancrea*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8. (Gallstone* adj3 pancrea*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
9. or/1-8
10. exp Analgesics, Opioid/
11. exp Narcotics/
12. (Opioid$ or Opiate$ or Narcotic$).mp.
13. exp Morphine/

14. (morphine or Astramorph or avinza or depodur or duramorph or embeda or infumorph or kadian or m-eslon or morcap or morphia or ms contin or msir or mst or nepenthe or oramorph or rescudose or rms or roxanol or sevredol or statex or zomorph).mp.
15. exp Opium/
16. (opium or omnopon or pantopon or papaveretum).mp.
17. exp Hydromorphone/
18. (Hydromorphone or dihydromorphinone or dilaudid or dimorphone or exalgo or hydmrphn or hydromorph$ or hydrostat or hymorphan or laudicon or novolauden or palladone).mp.
19. Nicomorphine.mp.
20. exp Oxycodone/
21. (oxycodone or Dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon or endocodone or eth-oxydose or eucodal or hydroxycodeinon or m-oxy or oxiconum or oxycdn or oxycone or oxycontin or oxyfast or oxyir or pancodine or percocet or percolone or remoxy or roxicodone or theocodin).mp.
22. (Dihydrocodeine or contugesic or dhc mundipharma or dicodin or dihydcdn or paracodin or paramol or parzone or rikodeine or tiamon or tosidrin or tuscodin).mp.
23. (Diamorphine or acetomorphine or diacetylmorphine or diagesil or diamorf or heroin or min-i-jet morphine sulfate or skag).mp.
24. exp Codeine/
25. (Codeine or ardinex or galcodine or isocodeine or methyl morphine or rx 336m or stanley-linctus or stanley-syrup).mp.
26. Ketobemidone.mp.
27. exp Meperidine/
28. (Pethidine or demerol or dolantin or dolargan or dolcontral or dolosal or dolsin or isonipecain or isonipecaine hydrochloride or lydol or meperidine or operidine epj or pethilorfan).mp.
29. exp Fentanyl/
30. (Fentanyl or abstral or actiq or duragesic or fentanest or fentora or fentyl or ionsys or matrifen or nasalfent or onsolis or oralet or phentanyl or sublimaze).mp.
31. exp Dextromoramide/
32. Dextromoramide.mp.
33. (Piritramide or Dipidolor or dipydolor or Piridolan or Pirium).mp.
34. exp Dextropropoxyphene/
35. (Dextropropoxyphene or darvon or dolene or doloxene or levopropoxyphene or pp-cap or propoxyphene or proxyphen).mp.
36. (Bezitramide or Burgodin).mp.
37. exp Methadone/
38. (methadone or adanon or althose or amidines or amidone or biodone or diskets or dolophine or Heptadon or metadol or metasedin or methaddict or metharose or Methadose or methdn or methex or phy or phymet or physeptone or pinadone or symoron).mp.
39. exp Benzomorphans/
40. exp Pentazocine/
41. (Pentazocine or Fortral or Fortwin or lexir or Talacen or talwin).mp.
42. exp Phenazocine/
43. (Phenazocine or Prinadol or Narphen).mp.
44. Oripavine.mp.
45. exp Buprenorphine/
46. (Buprenorphine or '6029-m' or buprenex or buprex or prefin or Suboxone or subutex or temgesic).mp.
47. exp Etorphine/
48. (Etorphine or Immobilon or M99).mp.
49. exp Morphinans/
50. exp Butorphanol/
51. (Butorphanol or 'bc2627' or beforal or dolorex or moradol or stadol or torbugesic).mp.
52. exp Tilidine/
53. (Tilidine or tilidate or Valoron or Valtran or Tilidin).mp.
54. exp Tramadol/
55. (Tramadol or 'k-315' or ralivia or ryzolt or tramahexal or tramake insts or tramal$ or tramedo or ultram or zamadol or zydol).mp.
56. (Dezocine or Dalgan or 'WY-16225').mp.
57. exp Meptazinol/
58. (Meptazinol or Meptid).mp.

59.(Tapentadol or cg5503 or nucynta).mp.
60.(Remifentanil or 'gi 87084b' or remifentanyl or ultiva).mp.
61.exp Procaine/
62.(Procaine or allocaine or anuject or gerokit or mericaine or novocaine or procaina serra).mp.
63.or/10-62
64.randomised controlled trial.pt.
65.controlled clinical trial.pt.
66.randomized.ab.
67.placebo.ab.
68.drug therapy.fs.
69.randomly.ab.
70.trial.ab.
71.groups.ab.
72.or/64-71
73.exp animals/ not humans.sh.
74.72 not 73
75.9 and 63 and 74

Appendix 3. EMBASE search strategy

1. exp Pancreatitis, Acute Necrotizing/
2. exp Pancreatitis, Alcoholic/
3. Pancreatitis/et [Etiology]
4. (acute adj3 pancrea$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
5. (necro$ adj3 pancrea$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6. (Alcohol$ adj3 pancrea$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7. (Gallstone$ adj3 pancrea$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8. or/1-7
9. exp narcotic analgesic agent/
10.exp Analgesics, Opioid/
11.exp Narcotics/
12.(Opioid$ or Opiate$ or Narcotic$).mp.
13.exp Morphine/
14.(morphine or Astramorph or avinza or depodur or duramorph or embeda or infumorph or kadian or m-eslon or morcap or morphia or ms contin or msir or mst or nepenthe or oramorph or rescudose or rms or roxanol or sevredol or statex or zomorph).mp.
15.exp Opium/
16.(opium or omnopon or pantopon or papaveretum).mp.
17.exp Hydromorphone/
18.(Hydromorphone or dihydromorphinone or dilaudid or dimorphone or exalgo or hydmrphn or hydromorph$ or hydrostat or hymorphan or laudicon or novolauden or palladone).mp.
19.Nicomorphine.mp.
20.exp Oxycodone/
21.(oxycodone or Dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon or endocodone or eth-oxydose or eucodal or hydroxycodeinon or m-oxy or oxiconum or oxycdn or oxycone or oxycontin or oxyfast or oxyir or pancodine or percocet or percolone or remoxy or roxicodone or theocodin).mp.
22.(Dihydrocodeine or contugesic or dhc mundipharma or dicodin or dihydcdn or paracodin or paramol or parzone or rikodeine or tiamon or tosidrin or tuscodin).mp.
23.(Diamorphine or acetomorphine or diacetylmorphine or diagesil or diamorf or heroin or min-i-jet morphine sulfate or skag).mp.
24.exp Codeine/
25.(Codeine or ardinex or galcodine or isocodeine or methyl morphine or rx 336m or stanley-linctus or stanley-syrup).mp.
26.Ketobemidone.mp.
27.exp Meperidine/
28.(Pethidine or demerol or dolantin or dolargan or dolcontral or dolosal or dolsin or isonipecain or isonipecaine hydrochloride or lydol or meperidine or operidine epj or pethilorfan).mp.

29. exp Fentanyl/
30. (Fentanyl or abstral or actiq or duragesic or fentanest or fentora or fentyl or ionsys or matrifen or nasalfent or onsolis or oralet or phentanyl or sublimaze).mp.
31. exp Dextromoramide/
32. Dextromoramide.mp.
33. (Piritramide or Dipidolor or dipydolor or Piridolan or Pirium).mp.
34. exp Dextropropoxyphene/
35. (Dextropropoxyphene or darvon or dolene or doloxene or levopropoxyphene or pp-cap or propoxyphene or proxyphen).mp.
36. (Bezitramide or Burgodin).mp.
37. exp Methadone/
38. (methadone or adanon or althose or amidines or amidone or biodone or diskets or dolophine or Heptadon or metadol or metasedin or methaddict or metharose or Methadose or methdn or methex or phy or phymet or physeptone or pinadone or symoron).mp.
39. exp Benzomorphans/
40. exp Pentazocine/
41. (Pentazocine or Fortral or Fortwin or lexir or Talacen or talwin).mp.
42. exp Phenazocine/
43. (Phenazocine or Prinadol or Narphen).mp.
44. Oripavine.mp.
45. exp Buprenorphine/
46. (Buprenorphine or '6029-m' or buprenex or buprex or prefin or Suboxone or subutex or temgesic).mp.
47. exp Etorphine/
48. (Etorphine or Immobilon or M99).mp.
49. exp Morphinans/
50. exp Butorphanol/
51. (Butorphanol or 'bc2627' or beforal or dolorex or moradol or stadol or torbugesic).mp.
52. exp Tilidine/
53. (Tilidine or tilidate or Valoron or Valtran or Tilidin).mp.
54. exp Tramadol/
55. (Tramadol or 'k-315' or ralivia or ryzolt or tramahexal or tramake insts or tramal$ or tramedo or ultram or zamadol or zydol).mp.
56. (Dezocine or Dalgan or 'WY-16225').mp.
57. exp Meptazinol/
58. (Meptazinol or Meptid).mp.
59. (Tapentadol or cg5503 or nucynta).mp.
60. (Remifentanil or 'gi 87084b' or remifentanyl or ultiva).mp.
61. exp Procaine/
62. (Procaine or allocaine or anuject or gerokit or mericaine or novocaine or procaina serra).mp.
63. or/9-62
64. 8 and 63
65. Clinical trial/
66. Randomized controlled trial/
67. Randomization/
68. Single-Blind Method/
69. Double-Blind Method/
70. Cross-Over Studies/
71. Random Allocation/
72. Placebo/
73. Randomi?ed controlled trial$.tw.
74. Rct.tw.
75. Random allocation.tw.
76. Randomly allocated.tw.
77. Allocated randomly.tw.
78. (allocated adj2 random).tw.

79.Single blind$.tw.
80.Double blind$.tw.
81.((treble or triple) adj blind$).tw.
82.Placebo$.tw.
83.Prospective study/
84.or/65-83
85.Case study/
86.Case report.tw.
87.Abstract report/ or letter/
88.or/85-87
89.84 not 88
90.64 and 89

CONTRIBUTIONS OF AUTHORS

Draft the protocol: All authors and M. Roqué (Iberoamerican Cochrane Center Statistician)
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Search for trials: X Basurto
Obtain copies of trials: X Basurto
Select which trials to include: X Basurto and D Rigau
Extract data from trials (2 people): X Basurto and D Rigau (G Urrutia as arbiter)
Enter data into Review Manager 5: X Basurto
Carry out the analysis: X Basurto
Interpret the analysis: all authors
Draft the final review: all authors
Update the review: all authors

DECLARATIONS OF INTEREST

None known.

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the effect of the intervention related to number of participants demanding supplementary analgesia, we compared opioids versus non-opioids combining the results of three RCTs (Jakobs 2000; Kahl 2004; Peiro 2008), which demonstrated substantial heterogeneity (I^2 = 64%). We decided to do a post hoc sensitivity analysis not planned at the protocol stage, to test the origin of the heterogeneity. We excluded Jakobs 2000 because the effect size was so different from the two others RCTs, and this was attributed to its continuous intravenous infusion of opioids compared to Kahl 2004 and Peiro 2008, in which opioids were administered every six and four hours respectively. The conclusions derived from this post hoc sensitivity analysis should be interpreted with caution for clinical practice, but may be of use for the generation of new hypotheses.

INDEX TERMS

Medical Subject Headings (MeSH)

Abdominal Pain [*drug therapy] [etiology]; Acute Disease; Analgesics, Opioid [*administration & dosage]; Buprenorphine [administration & dosage]; Fentanyl [administration & dosage]; Meperidine [administration & dosage]; Morphine [administration & dosage]; Pancreatitis [*complications]; Pentazocine [administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Humans