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Endoscopic or surgical intervention for painful obstructive chronic pancreatitis (Review)

Ahmed Ali U, Pahlplatz JM, Nealon WH, van Goor H, Gooszen HG, Boermeester MA

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[Intervention Review]

Endoscopic or surgical intervention for painful obstructive chronic pancreatitis

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ABSTRACT

Background

Endoscopy and surgery are the treatment modalities of choice for patients with chronic pancreatitis and dilated pancreatic duct (obstructive chronic pancreatitis). Physicians face, without clear consensus, the choice between endoscopy or surgery for this group of patients.

Objectives

To assess and compare the effects and complications of surgical and endoscopic interventions in the management of pain for obstructive chronic pancreatitis.

Search methods

We searched the following databases in *The Cochrane Library*: CENTRAL (2014, Issue 2), the Cochrane Database of Systematic Reviews (2014, Issue 2), and DARE (2014, Issue 2). We also searched the following databases up to 25 March 2014: MEDLINE (from 1950), Embase (from 1980), and the Conference Proceedings Citation Index - Science (CPCI-S) (from 1990). We performed a cross-reference search. Two review authors independently performed the selection of trials.

Selection criteria

All randomised controlled trials (RCTs) of endoscopic or surgical interventions in obstructive chronic pancreatitis. We included trials comparing endoscopic versus surgical interventions as well as trials comparing either endoscopic or surgical interventions to conservative treatment (i.e. non-invasive treatment modalities). We included relevant trials irrespective of blinding, the number of participants randomised, and the language of the article.

Data collection and analysis

We used standard methodological procedures expected by The Cochrane Collaboration. Two authors independently extracted data from the articles. We evaluated the methodological quality of the included trials and requested additional information from study authors in the case of missing data.

Main results

We identified three eligible trials. Two trials compared endoscopic intervention with surgical intervention and included a total of 111 participants: 55 in the endoscopic group and 56 in the surgical group. Compared with the endoscopic group, the surgical group had a higher proportion of participants with pain relief, both at middle/long-term follow-up (two to five years: risk ratio (RR) 1.62, 95% confidence interval (CI) 1.22 to 2.15) and long-term follow-up (≥ five years, RR 1.56, 95% CI 1.18 to 2.05). Surgical intervention resulted in improved quality of life and improved preservation of exocrine pancreatic function at middle/long-term follow-up (two to five years), but not at long-term follow-up (≥ 5 years). No differences were found in terms of major post-interventional complications or mortality, although the number of participants did not allow for this to be reliably evaluated. One trial, including 32 participants, compared surgical intervention with conservative treatment: 17 in the surgical group and 15 in the conservative group. The trial showed that surgical intervention resulted in a higher percentage of participants with pain relief and better preservation of pancreatic function. The trial had methodological limitations, and the number of participants was relatively small.

Authors' conclusions

For patients with obstructive chronic pancreatitis and dilated pancreatic duct, this review shows that surgery is superior to endoscopy in terms of pain relief. Morbidity and mortality seem not to differ between the two intervention modalities, but the small trials identified do not provide sufficient power to detect the small differences expected in this outcome.

Regarding the comparison of surgical intervention versus conservative treatment, this review has shown that surgical intervention in an early stage of chronic pancreatitis is a promising approach in terms of pain relief and pancreatic function. Other trials need to confirm these results because of the methodological limitations and limited number of participants assessed in the present evidence.

PLAIN LANGUAGE SUMMARY

Endoscopy or surgery for patients with chronic pancreatitis and dilated pancreatic duct

Background

Endoscopy and surgery are the treatments of choice in patients with chronic pancreatitis and a dilated pancreatic duct. Pain is the most important symptom in this disease and can be severely debilitating. In addition, chronic pancreatitis can result in malabsorption and/or diabetes due to failure of the gland function of the pancreas.

Question

In this review, we compare endoscopy versus surgery in terms of pain relief, complications and mortality in patients with chronic pancreatitis with a dilated pancreatic duct.

Study characteristics

We performed a search in March 2014 and found three relevant randomised trials. Two comparing endoscopic versus surgical interventions (111 patients with durations of two and three years), while the third compared surgery to conservative treatment (i.e. no intervention) (32 patients with a duration of 16 months).

Key results

We found that surgery achieved pain relief in a higher proportion of participants than endoscopy. Surgery also had other advantages like improved quality of life for the first two years after intervention, although this difference disappeared with time. Similarly, surgery reduced the risk of developing malabsorption due to failure of the pancreas, but with longer follow-up this advantage became smaller. The studies seemingly showed no difference between endoscopy and surgery in complications after interventions. We also compared surgery with conservative treatment. The results of one trial suggested that surgery early in the condition achieved better pain relief and preservation of pancreatic function.

Quality of evidence

For endoscopy versus surgery, the quality of the evidence for pain relief, quality of life and pancreatic function was moderate (according to GRADE). For both complications and mortality this was low, since the two trials were too small to make reliable conclusions. The quality of evidence regarding surgery versus conservative treatment was low, since the trial was small, which precluded drawing reliable conclusions regarding all outcomes.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Endoscopy compared with surgery for painful obstructive chronic pancreatitis

Endoscopy compared with surgery for painful obstructive chronic pancreatitis

Patient or population: participants with painful obstructive chronic pancreatitis
Settings: tertiary centres in Europe specialized in both endoscopic and surgical treatment of chronic pancreatitis
Intervention: surgery
Comparison: endoscopy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Endoscopy	Surgery				
Pain relief - middle-term Follow up: 2 to 5 years	**509 per 1000**	**825 per 1000** (621 to 1000)	**RR 1.62** (1.22 to 2.15)	111 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	-
Pain relief - long-term Follow up: 5 years	**538 per 1000**	**840 per 1000** (635 to 1000)	**RR 1.56** (1.18 to 2.05)	103 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	-
Major complications and mortality	See comment	See comment	Not estimable	179 (2 studies)	⊕⊕⊖⊖ **low**[2], [3]	We refrained from pooling data, since results are partly based on non-randomised data. Observed outcome rate: endoscopy 7% versus surgery 4% (Table 1)[2]
Quality of life - long-term SF-36 - Physical health at 2 years. Scale from 0 to 100 Follow up: 5 years	The mean quality of life - long-term in the control groups was **43 points**	The mean quality of life - long-term in the intervention groups was **4 higher** (3 lower to 12 higher)	-	31 (1 study[4])	⊕⊕⊕⊖ **moderate**[3]	Difference was not statistically significant (Table 1)
Quality of life - long-term SF-36 - Mental health at 2 years. Scale from 0 to 100 Follow up: 5 years	The mean quality of life - long-term in the control groups was **46 points**	The mean quality of life - long-term in the intervention groups was **2 higher** (4 lower to 9 higher)	-	31 (1 study[4])	⊕⊕⊕⊖ **moderate**[3]	Difference was not statistically significant (Table 1)

Endocrine pancreatic insufficiency (new onset) - long-term Follow up: 5 years	**396 per 1000**	**364 per 1000** (214 to 614)	**RR 0.92** (0.54 to 1.55)	95 (2 studies)	⊕⊕⊖⊖ **low**[1], [3]	Only participants without endocrine pancreatic insufficiency at baseline (new onset insufficiency) are included in the analysis (Table 1)
Exocrine pancreatic insufficiency (new onset) - long-term Follow up: 5 years	**1000 per 1000**	**500 per 1000** (190 to 1000)	**RR 0.5** (0.19 to 1.33)	10 (1 study[4])	⊕⊕⊕⊖ **moderate**[1], [3]	Only participants without exocrine pancreatic insufficiency at baseline (new onset insufficiency) are included in the analysis (Table 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]One of the two trials included (Díte 2003) had some serious methodological limitations. The second trial (Cahen 2007) however was a well-conducted trial. Results were consistent between both trials.
[2]One of the trials (Díte 2003) published data for this outcome for a cohort including randomised and non-randomised participants. We could not obtain the data from the randomised group separately.
[3]The number of participants does not provide enough power to detect differences that could exist between the two groups.
[4]Only one study (Cahen 2007) reported this outcome.
CI = confidence interval.
GRADE = Grading of Recommendations, Assessment, Development and Evaluation.
No. = number.

Summary of findings 2. Surgery compared with conservative treatment for painful obstructive chronic pancreatitis

Surgery compared with conservative treatment for painful obstructive chronic pancreatitis

Patient or population: participants with painful obstructive chronic pancreatitis
Settings: tertiary centre in the United States with large experience in surgical treatment of chronic pancreatitis
Intervention: surgery
Comparison: conservative

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of Participants	Quality of the evidence	Comments

	Assumed risk	Corresponding risk				
	Conservative	Surgery		(studies)	(GRADE)	
Pain relief Follow up: median 10 years	**133 per 1000**	**944 per 1000** (257 to 1000)	**RR 7.1** (1.93 to 25.8)	32 (1 study)	⊕⊕⊝⊝ **low**[1], [2]	-
Major complications - not reported	See comment	See comment	Not estimable	-	See comment	Trial did not report on postoperative complications
Mortality - not reported	See comment	See comment	Not estimable	-	See comment	Trial did not report on mortality
Quality of life - not measured	See comment	See comment	Not estimable	-	See comment	Trial did not measure quality of life
Endocrine pancreatic insufficiency (new onset) Follow up: median 10 years	**833 per 1000**	**192 per 1000** (50 to 725)	**RR 0.23** (0.06 to 0.87)	25 (1 study)	⊕⊕⊝⊝ **low**[1], [2]	Only participants without endocrine pancreatic insufficiency at baseline (new onset insufficiency) were included in analysis (Table 2)
Exocrine pancreatic insufficiency (new onset) Follow up: 2 to 3 years	**786 per 1000**	**63 per 1000** (8 to 448)	**RR 0.08** (0.01 to 0.57)	29 (1 study)	⊕⊕⊝⊝ **low**[1], [2]	Only participants without exocrine pancreatic insufficiency at baseline (new onset insufficiency) were included in analysis (Table 2)

*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]Trials showed some important methodological limitations (see Summary of risk of bias Figure 1).
[2]The number of participants did not fulfil the GRADE guidelines for sufficient precision.
CI = confidence interval.
GRADE = Grading of Recommendations, Assessment, Development and Evaluation.
No. = number.

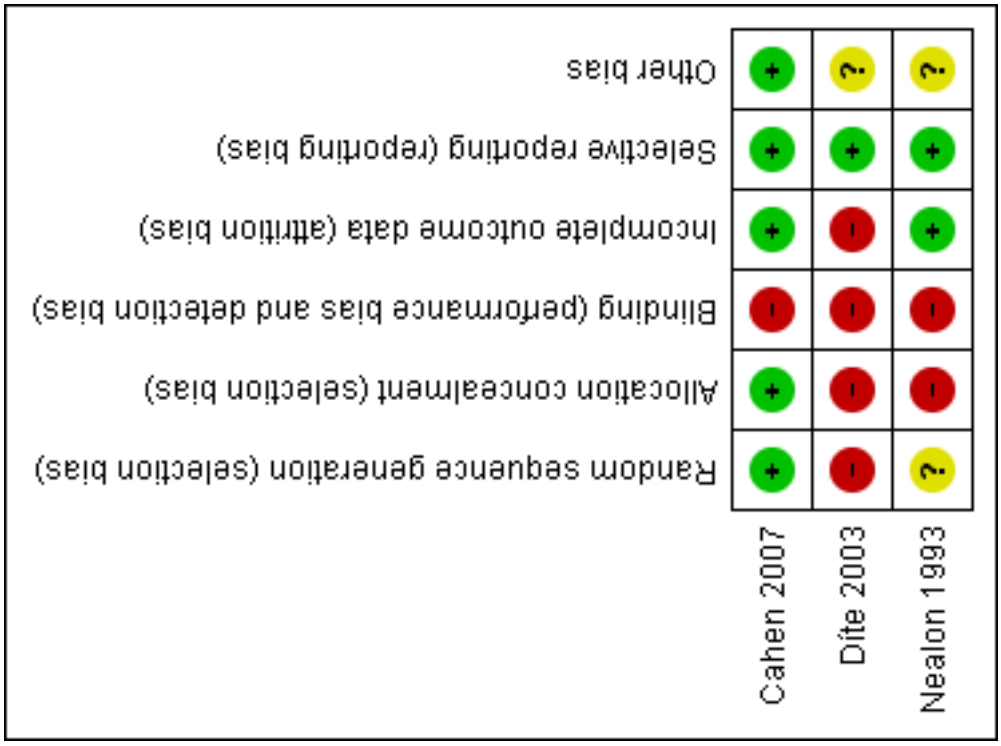


Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for the three included trials

BACKGROUND

Description of the condition

Chronic pancreatitis (CP) is a progressive inflammatory condition of the pancreas, characterised by severe pain and damage to endocrine and exocrine pancreatic tissue. The incidence and prevalence of rates of chronic pancreatitis in western Europe are estimated to be around seven and 26 per 100,000, respectively (Díte 2001; Lévy 2006; Spanier 2008). The etiology of CP is a complex multifactorial process (Witt 2007). In the western world, alcohol is the leading contributing factor. Genetics, auto-immunity, metabolic abnormalities (hypertriglyceridaemia, hypercalcaemia), and anatomical malformations (pancreas divisum) play a role as well in the development of CP (Witt 2007).

Pain is the characteristic clinical symptom of CP. Therefore, management of this disease is mostly focused towards pain alleviation (AGA 1998; van Esch 2006). Long-standing CP is also associated with the development of endocrine and exocrine insufficiency, which may result in diabetes, malabsorption, weight loss, and deterioration of the patient's general condition (Pezzilli 2005; Wehler 2004). Additionally, pancreatic pseudocyst formation, abscess formation, stenosis of the common bile duct, and an increased risk of pancreatic cancer can complicate CP (Lankisch 2001).

Description of the intervention

In patients with obstructive CP (i.e. with presence of pancreatic duct dilatation), it is believed that ductal and parenchymal hypertension, caused by an elevated pressure in the main pancreatic duct, is the source of pain (Fasanella 2007). Fibrosis within the chronically inflamed pancreas is assumed to contribute to elevated pressure by limiting the ability of the gland to expand during periods of exocrine secretion (Fasanella 2007; Gourgiotis 2007). Strictures and elevated pressure are contributing factors to the formation of stones in the pancreatic duct, which may further limit the ability of the gland to excrete its exocrine products normally. Endoscopy and surgery are considered the treatment modalities of choice in the case of painful obstructive pancreatitis. The aim of both modalities is to alleviate the pressure of the pancreatic duct and ensure adequate drainage of pancreatic excretions.

How the intervention might work

Endoscopic therapy attempts to relieve the pressure in the pancreatic duct by ensuring good drainage of pancreatic juices into the intestines. This is typically done by means of endoscopic retrograde cholangiopancreatography (ERCP). Endoscopic treatment may involve papillotomy of the papilla of Vater, dilation of strictures, removal of stones (with or without lithotripsy), or placement of stents in the pancreatic duct (Rösch 2002). Endoscopic intervention is less invasive than surgery, and patients can usually be discharged in about one to two days. Usually, however, more than one endoscopic intervention is needed to achieve satisfactory results, and some patients still need subsequent surgery. Overall, endoscopic treatment achieves complete or partial pain relief in approximately 74% of patients (van der Gaag 2007).

Surgical interventions for CP can be classified into resection and drainage procedures (Gourgiotis 2007; van der Gaag 2007). In a drainage procedure, the pancreatic duct is opened over its full length, and subsequently, a side-to-side anastomosis with the jejunum is performed (that is, pancreaticojejunostomy). In resection procedures, the affected head or tail of the pancreas is resected. After duodenum-preserving pancreatic head (Beger) resection or pancreaticoduodenectomy, the open end of the remnant pancreatic duct is connected to the small bowel. For distal pancreatic (pancreatic tail) resections, a bowel connection for drainage is not routinely needed. There are also mixed drainage and resection procedures, in which a local pancreatic resection (mostly of the pancreatic head) is combined with a partial drainage procedure (for example, Frey or Berne operations) (Strate 2005). Patients typically remain hospitalised for one to two weeks after surgery (Cahen 2007). Surgical interventions accomplish partial or complete pain relief in approximately 80% of patients (van der Gaag 2007).

Why it is important to do this review

There is no clear consensus regarding the best choice between endoscopy and surgery for patients with painful obstructive CP. Several reviews describe results of endoscopic and surgical procedures separately, but inference from these reports is difficult because of the lack of head-to-head comparisons (Gourgiotis 2007; Tringali 2008; van der Gaag 2007). One review of randomised clinical trials of endoscopic versus surgical interventions was found (Devière 2008), but the methodology was not explicit and the review lacked a clear conclusion. We therefore aimed to review and summarise the evidence for both treatment modalities.

OBJECTIVES

To assess and compare the effects and complications of surgical and endoscopic interventions in the management of pain for obstructive chronic pancreatitis.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) investigating endoscopic or surgical interventions for obstructive chronic pancreatitis (that is, with a dilated pancreatic duct). We included all trials, irrespective of blinding, the number of participants randomised, and the language of the article.

Types of participants

Trials including adults with confirmed chronic pancreatitis (CP), pancreatic duct dilation, and pain were eligible for this review. Pain was the primary indication for the interventions.

Types of interventions

Studies with any of the following comparisons:

- endoscopic versus surgical intervention;
- endoscopic intervention versus conservative treatment; or
- surgical intervention versus conservative treatment.

We used the following definitions for the different treatment modalities.

- Endoscopic intervention: an endoscopic retrograde cholangiopancreatography (ERCP) performed with therapeutic intent and in which either papillotomy, dilation of the pancreatic duct, or placement of a pancreatic ductal stent was performed.
- Surgical intervention: any surgical procedure used for the treatment of obstructive CP, including pancreaticojejunostomy (PJ), resection-drainage procedures (e.g., Frey, Beger), or a (pylorus-preserving) pancreaticoduodenectomy.
- Conservative treatment: non-invasive therapy, mainly medical treatment for pain and nutritional supportive treatment.

Types of outcome measures

Primary outcomes

- Pain relief: proportion of participants achieving pain relief compared with the situation prior to intervention. Since pain is a subjective outcome and many different scores are used, we did not use a strict definition of pain relief. We classified the observed pain relief as either complete or partial, defining partial pain relief as a decrease in pain of at least 50% compared with baseline, without achieving complete pain relief. We conducted analyses for complete and partial pain relief separately and for total proportion of participants experiencing pain relief (both partial and complete).
- Major postinterventional complications, including intra-abdominal abscess, ileus-necessitating surgery, pancreatitis flare-up, bleeding, anastomotic leakage, sepsis, abdominal fascial dehiscence (Platzbauch), and myocardial infarction.
- Mortality.

Secondary outcomes

- Quality of life.
- Minor postinterventional complications, including wound infections, pneumonia, cholecystitis, prolonged ileus (not necessitating intervention), fistulas, urinary tract infections, urinary retention, and deep venous thrombosis.
- New onset endocrine and exocrine pancreatic insufficiency.
- Number of endoscopic and surgical procedures related to the treatment of CP.
- Change in nutritional status (body weight or body mass index (BMI)) after intervention.
- Duration of hospital stay.

Search methods for identification of studies

Electronic searches

We searched the following databases in *The Cochrane Library*, using the search strategy in Appendix 1:

- the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 2);
- the Cochrane Database of Systematic Reviews (2014, Issue 2); and
- the Database of Abstracts of Reviews of Effects (DARE) (2014, Issue 2).

We searched the following databases up to 25 March 2014:

- MEDLINE via Ovid (from 1950) (using the search strategy in Appendix 2);
- Embase via Ovid (from 1980) (using the search strategy in Appendix 3); and
- Conference Proceedings Citation Index - Science (CPCI-S) (from 1990) (using the search strategy in Appendix 4).

We developed the search strategies in co-operation with the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group (see Acknowledgements).

Searching other resources

We performed a cross-reference search of all included randomised trials and relevant reviews identified during the search process. We also requested additional information, by letter or e-mail, from all authors of included trials, on any published, unpublished, or ongoing trials.

Data collection and analysis

We conducted this review according to the recommendations of the *Cochrane Handbook for Systematic Review of Interventions* (Higgins 2008).

Selection of studies

Two review authors (UAA and JMP) independently performed the selection of trials. First, they screened titles and abstracts and selected all potentially relevant publications, including those where the relevance was uncertain. Subsequently, they reviewed the full text of all selected publications and selected trials meeting the selection criteria. In the case of disagreements, we reached consensus by discussion.

Data extraction and management

Two review authors (UAA and JMP) independently extracted all relevant data. For each study, the review authors extracted participant characteristics; study characteristics; data needed for the methodological quality assessment of the study; and the primary and secondary outcomes, according to availability. Data regarding participant characteristics included number of participants in each group, age, gender, BMI, and type of pain (A or B) according to the Ammann classification (Ammann 1999). Data regarding study characteristics included study design, sample size information, inclusion and exclusion criteria of the study, follow-up period, loss to follow up, surgical and endoscopic experience, and information regarding surgical and endoscopic techniques. We present these data in the 'Characteristics of included studies' tables.

Assessment of risk of bias in included studies

Based on the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* and available literature, we assessed the methodological quality of RCTs by using the tool for assessing risk of bias (Higgins 2008; Kjaergard 2001; Moher 1998; Schulz 1995). We used the following definitions of the items in this tool.

Sequence allocation

- Adequate, if a computer or random number table generated the allocation sequence. We considered drawing of lots, the tossing of a coin, shuffling of cards, or throwing dice as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.

- Unclear, if the trial was described as randomised, but the method used for generation of the allocation sequence was not described.
- Inadequate, if a system involving dates, names, or alternating allocation was used for the allocation of participants.

Allocation concealment

- Adequate, if the allocation of participants involved a central independent unit, on-site locked computer, or sealed envelopes.
- Unclear, if the trial was described as randomised, but the method used to conceal the allocation was not described.
- Inadequate, if the investigators who assigned the participants knew the allocation sequence.

Blinding

- Adequate, if the trial was described as blind to participants or assessors, and the method of blinding was described. We are well aware that it is very difficult to properly blind trials comparing endoscopic or surgical treatments.
- Unclear, if the trial was described as (double-) blind, but the method of blinding was not described.
- Inadequate, if the trial was not blinded.

Incomplete data outcome

- Adequate, if the percentage of drop-outs did not exceed 20%, and numbers and reasons for drop-outs and withdrawals in all intervention groups were described.
- Unclear, if the report gave the impression that there had been no drop-outs or withdrawals but this was not specifically stated.
- Inadequate, if the percentage of drop-outs exceeded 20%, or the numbers and reasons for drop-outs and withdrawals were not described.

Selective outcome reporting

- Adequate, when it was clear that the published reports included all expected outcomes, including those that were prespecified.
- Unclear, if insufficient information was provided to permit clear judgement of this aspect.
- Inadequate, if all relevant outcomes and all the study's prespecified outcomes were not reported, or if they were incompletely reported.

Other sources of bias

- Adequate, if the study appeared to be free of other sources of bias.
- Unclear, if a risk of potentially important bias existed, but sufficient information to assess this bias was lacking.
- Inadequate, if one or more sources of potentially important biases could be identified in the study (e.g., extreme baseline imbalances or other imbalances in study design).

Measures of treatment effect

We conducted statistical analyses of dichotomous data using the risk ratio (RR) as the summary statistic. For continuous outcomes, we used mean differences (MD) as the summary statistic.

Assessment of heterogeneity

We calculated heterogeneity using the Chi^2 test and quantified inconsistency in study effects using the I^2 statistic (Higgins 2002). We considered a Chi^2 test with a P value of < 0.10 to indicate the presence of heterogeneity and an I^2 statistic > 50% to suggest a marked inconsistency in effect between studies.

Assessment of reporting biases

Because of the low number of identified studies, funnel plots were not useful in assessing the presence of publication bias. Therefore, we refrained from using them.

Data synthesis

Depending on the availability of appropriate evidence, we conducted the following comparisons in this review:

- endoscopic intervention versus surgical intervention;
- endoscopic intervention versus conservative treatment; and
- surgical intervention versus conservative treatment.

If appropriate data were available, we conducted meta-analysis. Otherwise, we conducted a narrative review of the identified evidence. For the meta-analysis, we used the fixed-effect model if no heterogeneity was present (Chi^2 test P > 0.1 and I^2 statistic < 50%). In all other cases, we used the random-effects model.

Because of the insufficient numbers of trials, we were not able to perform a subgroup analysis according to the methodological quality of the included trials. We have presented the methodological quality of trials using the criteria of the 'Risk of bias' assessment tool described earlier, and we took this into consideration when discussing the results of the review.

We conducted statistical analysis using the statistical package Review Manager (RevMan 2012), provided by The Cochrane Collaboration.

RESULTS

Description of studies

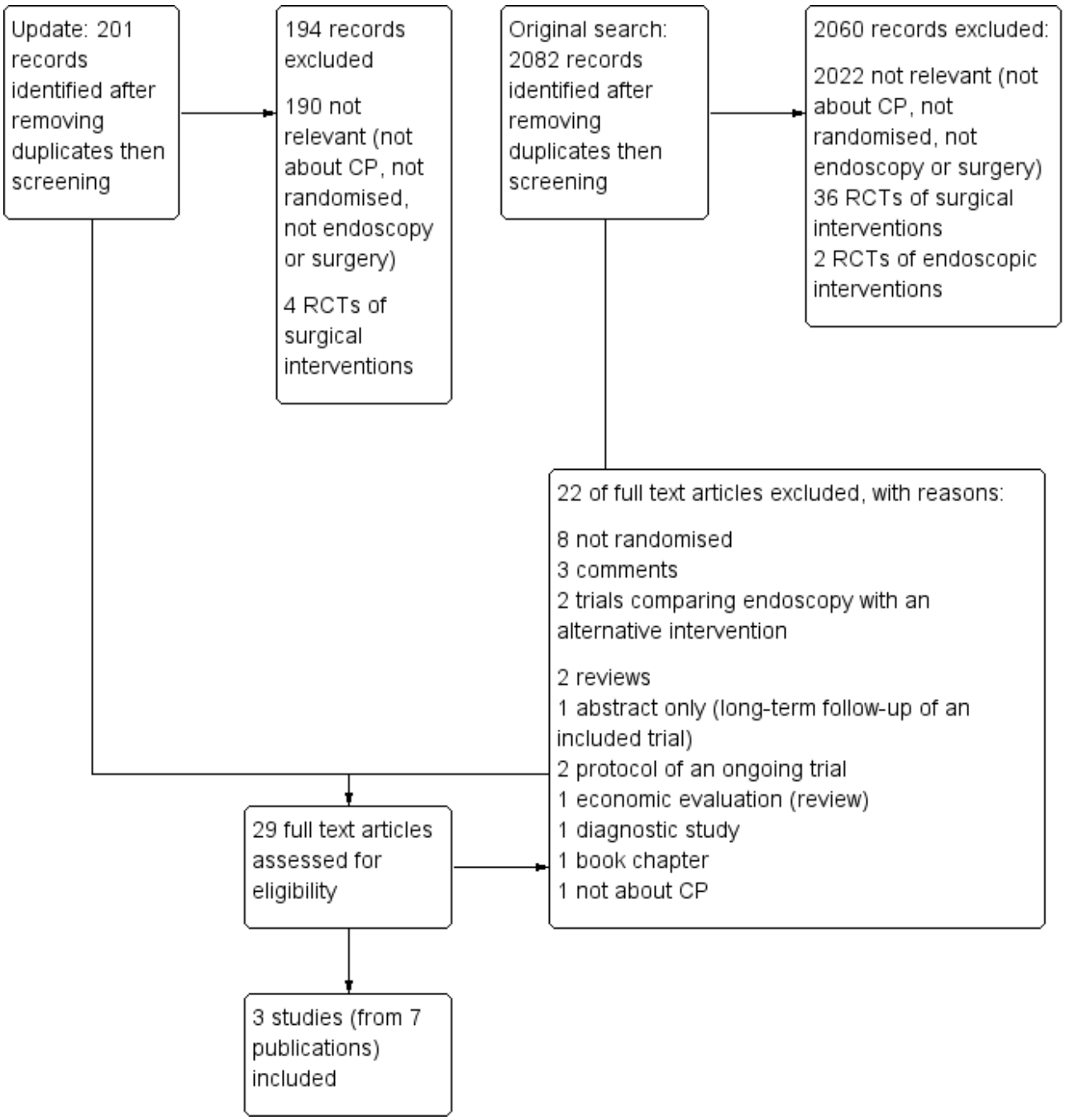
Results of the search

We performed the original search on 3 November 2011 and the update on 25 March 2014 and obtained a total of 2082 and 201 publications, respectively. We screened the titles and abstracts of all publications and selected a total of 29 potentially relevant publications for full text reviewing. Two publications were study protocols of ongoing trials (see the 'Characteristics of ongoing studies' tables). Two publications described a randomised trial of endoscopy versus extracorporeal shock wave lithotripsy (ESWL). Since ESWL cannot be considered as conservative treatment, this trial did not fulfil our inclusion criteria and was excluded (see the 'Characteristics of excluded studies' tables). Fifteen publications were excluded for other reasons (see the 'Characteristics of excluded studies' tables).

Finally, we included seven publications describing three distinct trials; one trial was described in three publications (Cahen 2007), and its long-term follow-up was described in two publications (see the 'Characteristics of included studies' tables).

A cross-reference search of included trials and three additional reviews (Devière 2008; Gourgiotis 2007; van der Gaag 2007) yielded no new eligible publications. Figure 2 is a flow diagram depicting the flow of the selection process.

Figure 2. Flow diagram of selection process



Included studies

Two trials compared endoscopic intervention with surgical intervention (Cahen 2007; Díte 2003). One trial compared surgical intervention with conservative treatment (Nealon 1993). We did not identify any trials comparing endoscopic intervention with conservative treatment. We describe the characteristics of the included trials in the 'Characteristics of included studies' tables, but we summarise the most important characteristics below.

Studies comparing endoscopic with surgical intervention

The two trials comparing endoscopic with surgical intervention (Cahen 2007; Díte 2003) included a total of 111 participants, of whom 55 were in the endoscopic group, and 56 were in the surgical group.

Cahen 2007 randomised 39 participants with advanced CP (all participants needed opioid analgesics before study inclusion), a dilated pancreatic duct (> 5 mm), and without pancreatic head

enlargement between endoscopy (19 participants) and surgery (20 participants). The endoscopic intervention consisted of drainage of the pancreatic duct by ERCP, with dilatation of strictures and stent placement in the pancreatic duct, as necessary. In the case of persistent strictures of the pancreatic duct, repeated dilation and stenting were performed until patency of the duct was achieved. Participants with large stones in the pancreatic duct (> 7 mm) underwent extracorporeal shock wave lithotripsy (ESWL) before drainage. The surgical group underwent surgical drainage of the pancreatic duct by a longitudinal pancreaticojejunostomy as the intended treatment. In one participant, a Whipple procedure was performed because of peripancreatic inflammation. In another participant, stone extraction required a Frey procedure. The primary outcome was pain as assessed by the Izbicki pain score (Izbicki 1998). Secondary outcomes were proportion of participants with pain relief, quality of life (SF-36), complications, mortality, duration of hospital stay, number of hospital re-admittances, number of performed procedures, change in pancreatic function, rate of conversion from endoscopic treatment to surgery, and technical success of the intervention. Follow-up was two years. The safety committee prematurely terminated the study on the basis of the significant difference in outcome favouring the surgical group, with a P value of less than 0.001 for the primary outcome (pain on the Izbicki pain score). In 2012, the long-term results of this trial after a minimal follow-up period of five years were published separately. Results from the original publication are reported under the heading 'middle/long-term' (two to five years), and results from the follow-up publication are reported under the heading 'long-term' (≥ 5 years).

Díte 2003 included 140 participants in the study but only randomised 72. The other 68 participants refused randomisation in the trial because of an outspoken preference for one of the treatment modalities. Díte 2003 reported some outcomes for the randomised group separately, yet only reported baseline characteristics and other outcomes (for example, complications) for the complete cohort.

In the randomised group, 36 participants were allocated to each of the two groups. All participants had advanced CP (at least three years of failed medical management) and obstruction of the pancreatic duct. Participants with enlargement of the pancreatic head were also included. Endoscopic treatment consisted of drainage of the pancreatic duct by ERCP, with dilatation of strictures and stent placement in the pancreatic duct, as necessary. In the case of persistent strictures of the pancreatic duct, repeated dilation and stenting were performed until patency of the duct was achieved. ESWL was not performed as part of the endoscopic treatment. The surgical group underwent any type of drainage or resection procedure considered appropriate by the surgeon. The study only reported data on the specific operation for the complete cohort (80% resection procedures and 20% drainage procedures). Primary outcomes were pain relief and necessity for further intervention. Secondary outcomes were change in body weight, presence of diabetes, complications, and mortality. Follow-up was five years.

Studies comparing surgical intervention with conservative treatment

Nealon 1993 was primarily a report of a cohort of 143 participants with CP followed prospectively for 47.3 months. Within this cohort, a small pilot trial was conducted comparing surgical treatment with conservative treatment. In this review, we only included data from the randomised trial.

In the published version of the trial, 17 participants with mild to moderate CP (graded using a self-developed grading system; see the 'Characteristics of included studies' tables) and a dilated pancreatic duct were randomised. Nine and eight participants were allocated to the surgical group and the conservative group, respectively. The only outcome reported was the change in CP grade during follow-up. We contacted an author for additional data, and he provided us with an update of the trial including data concerning an additional 15 participants that had been included since the publication.

The trial therefore included 32 participants with mild to moderate (early-stage) CP and dilated pancreatic duct, allocated to either early surgical treatment (17 participants) or conservative treatment (15 participants). The surgical group was treated with surgical drainage of the pancreatic duct by a longitudinal pancreaticojejunostomy. The conservative group was kept on non-invasive treatment (specific treatment modalities unspecified). Pain and endocrine and exocrine pancreatic function were reported as outcomes. The median follow-up period was 124 months.

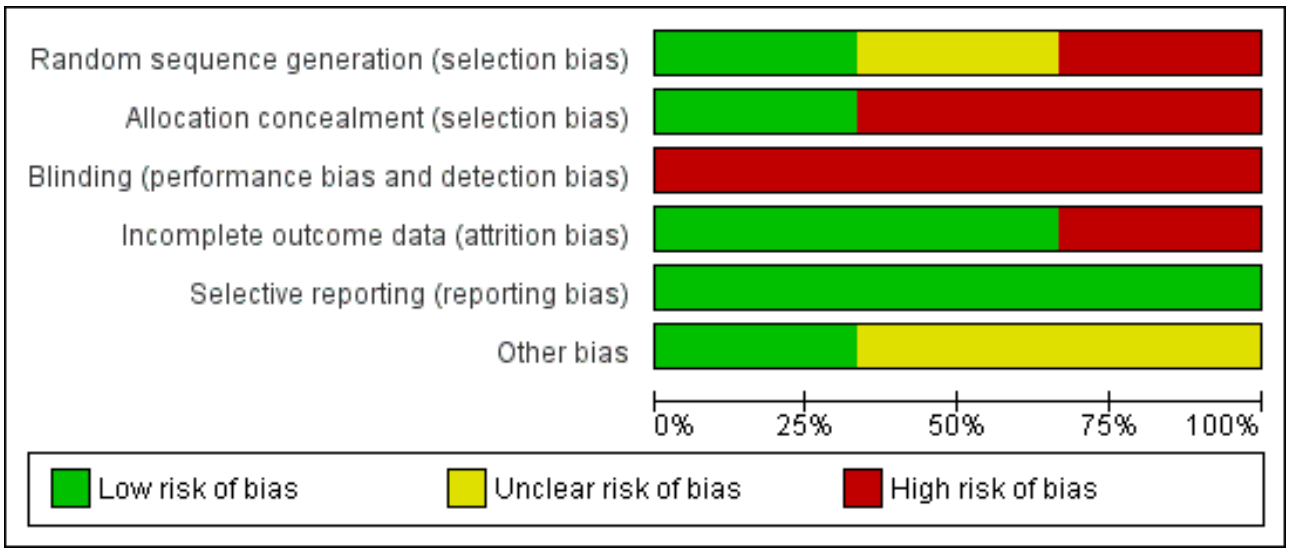
Excluded studies

We listed all excluded publications that were not obviously excluded based on title and abstract alone (that is, full text reviewing was necessary for exclusion), with the reason for exclusion, in the 'Characteristics of excluded studies' tables.

Risk of bias in included studies

Risk of bias varied considerably between the three included trials. Figure 3 and Figure 1 illustrate an overview of the different aspects of the risk of bias in the 'Risk of bias' summary figures. We provide a detailed description of the 'Risk of bias' assessment in the 'Characteristics of included studies' tables.

Figure 3. 'Risk of bias graph': review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies



Cahen 2007 was a well-performed study with low risk of bias. Díte 2001 had many methodological short-comings, including pseudo-randomisation (allocation by alternation), unconcealed allocation, a lack of baseline characteristics, and the lack of an intention-to-treat analysis (only a per-protocol analysis was performed). Nealon 1993 did not report satisfactorily on methodological quality. Therefore, important aspects remained unclear.

Effects of interventions

See: **Summary of findings for the main comparison** Endoscopy compared with surgery for painful obstructive chronic pancreatitis; **Summary of findings 2** Surgery compared with conservative treatment for painful obstructive chronic pancreatitis

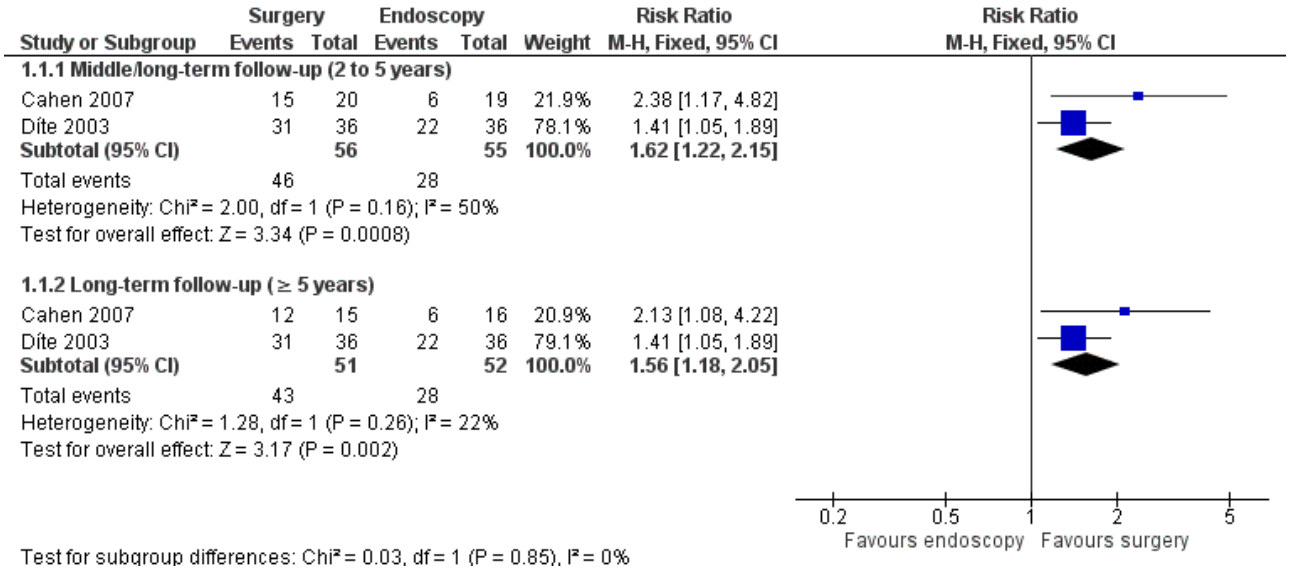
Endoscopic versus surgical intervention

We identified two studies comparing endoscopic with surgical intervention (Cahen 2007; Díte 2003); they mostly reported different outcomes. Pooling of data was only possible with regard to two outcomes: pain relief and new onset endocrine pancreatic insufficiency. We provide a narrative review for other outcomes. We summarised results of all outcomes considered to be of critical importance according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology (scored seven or higher on a nine-point score) in the Summary of findings for the main comparison. These outcomes were pain relief, major complications and mortality, quality of life, and endocrine and exocrine pancreatic insufficiency.

Pain relief

Both studies reported a higher proportion of participants with pain relief (partial or complete) in the surgical group compared with the endoscopic group after middle/long-term follow-up (RR 1.62, 95% CI 1.22 to 2.15) and long-term follow-up (RR 1.56, 95% CI 1.18 to 2.05) (Analysis 1.1; Figure 4). The proportion of participants with complete pain relief was higher in the surgical group, but there was no difference in the proportion of participants with partial pain relief (Analysis 1.2 and Analysis 1.3).

Figure 4. Forest plot of comparison: 1 Endoscopy versus surgery, outcome: 1.1 Pain relief



Major postinterventional complications

Both studies reported on major complications associated with the study interventions (Table 1). There was no evidence of a difference between the surgical and endoscopic interventions.

Mortality

Both studies reported on mortality. The endoscopic group included one death (Table 1). Therefore, there was no evidence of a difference between the two groups.

Quality of life

Cahen 2007 reported the quality of life in both groups using the SF-36 quality of life instrument (Brazier 1992) (Table 1). The study showed that participants undergoing surgery scored higher (better) on the physical health component of the SF-36 quality of life scale in the middle/long-term. However, this difference became less in the long-term and was no longer significant at five-year follow up. No difference was observed in the mental health component of the same instrument.

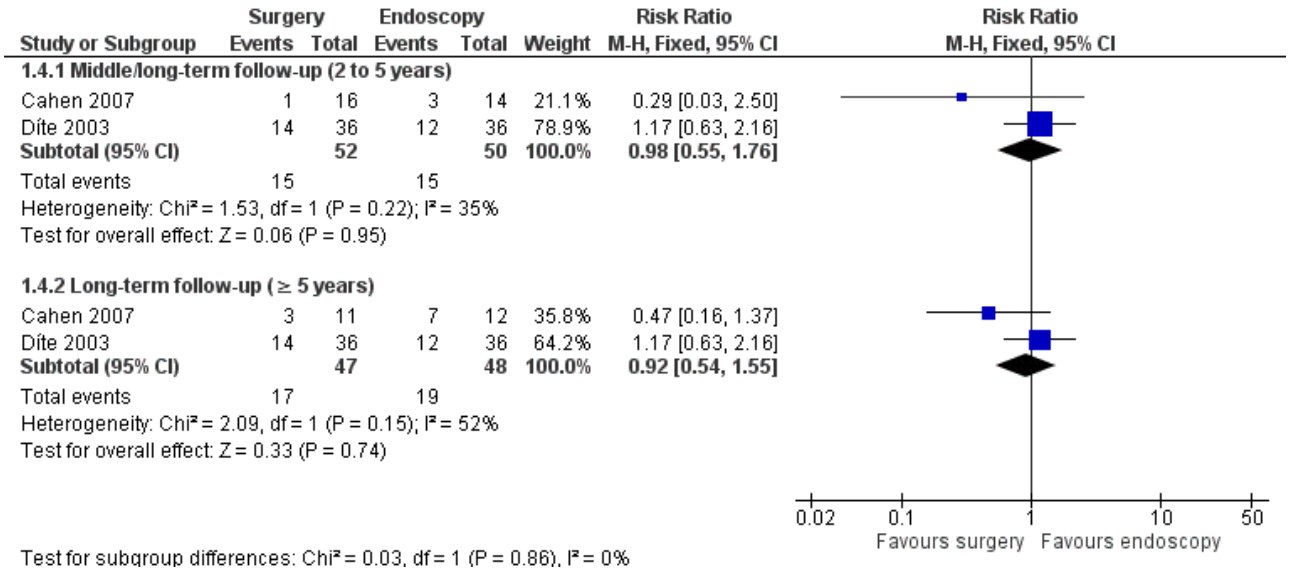
Minor postinterventional complications

Both studies reported on minor complications associated with the study interventions (Table 1). There was no evidence of a difference between the surgical and endoscopic interventions in terms of these complications.

Pancreatic function

Both studies reported endocrine pancreatic function. We pooled the proportion of participants with new onset endocrine pancreatic insufficiency (Analysis 1.4; Figure 5). There was no evidence of a difference between the two groups.

Figure 5. Forest plot of comparison: 1 Endoscopy versus surgery, outcome: 1.4 Endocrine pancreatic insufficiency (new onset)



Cahen 2007 only reported exocrine pancreatic function. In the endoscopic group, exocrine pancreatic insufficiency developed in six out of six participants (100%) with intact exocrine pancreatic function at baseline, compared with one out of four participants (25%) in the surgical group in the middle/long-term (P = 0.03) and two out of four (50%) in the long-term (not significant) (Table 1).

Number of endoscopic and surgical procedures needed

Both studies reported on this outcome, but the data were not suitable for pooling. Cahen 2007 showed that participants in the surgical group underwent significantly fewer procedures than participants in the endoscopic group (Table 1). Díte 2003 only reported this outcome for the complete cohort (both randomised and non-randomised participants). Participants in the surgical group required fewer procedures compared with the endoscopic group (with a mean of six procedures in the endoscopic group versus one procedure in the surgical group).

Change in nutritional status

Díte 2003 reported a higher proportion of participants with increases in body weight at the end of the follow-up period in the surgical group compared with the endoscopic group (10 out of 36 (28%) for the endoscopic group versus 17 out of 36 (47%) for the surgical group) (Table 1). Although the study claimed that this difference was statistically significant, we could not reproduce the reported P value.

Duration of hospital stay

Cahen 2007 reported on this outcome (Table 1). There was no evidence of a difference between the two groups.

Surgical intervention versus conservative treatment

We identified one trial (Nealon 1993) comparing surgical intervention with conservative treatment for CP. We summarise the findings of this study in Table 2. In summary, this study showed a highly significant difference in favour of early surgical intervention compared with conservative treatment with regard to pain relief and pancreatic function. The study observed partial or complete pain relief in 16 out of 17 (94%) participants in the surgical group versus two out of 15 (13%) in the conservative group. The proportion of participants developing new onset endocrine and exocrine pancreatic insufficiency was respectively two out of 13 participants (15%) and one out of 15 (7%) participants in the surgical group versus 10 out of 12 participants (83%) and 11 out of 14 (79%) participants in the conservative group.

We summarised the results of all outcomes considered to be of critical importance according to the GRADE guideline (that is, pain relief, major complications and mortality, quality of life, and endocrine and exocrine pancreatic insufficiency) in the Summary of findings 2.

DISCUSSION

Summary of main results

Endoscopic versus surgical intervention

The main finding of this review is that surgery achieves pain relief in a higher proportion of patients compared with endoscopic treatment for patients with obstructive CP. This finding was consistent in the two included RCTs and also with a longer duration of follow up (Cahen 2007; Díte 2003). The observed difference had an evident clinical importance and was long-lasting. Additional benefits of surgery compared with endoscopy were reported as well, mainly, improved quality of life in the middle/long-term and a lower risk of developing exocrine pancreatic insufficiency. The available evidence could not identify differences between endoscopy and surgery in terms of morbidity or mortality, mainly, because of the small size of the trials.

Surgical intervention versus conservative treatment

This review identified one trial (Nealon 1993) comparing surgical intervention with conservative treatment. This trial observed important differences in terms of pain relief and preservation of pancreatic function in favour of the surgical group. Several

methodological and clinical factors however impede drawing reliable conclusions from this trial (see the next sections: Overall completeness and applicability of evidence and Quality of the evidence). Therefore, the main finding of this review regarding this comparison is that in an early stage of CP, surgery rather than conservative treatment seems to be associated with potential benefits, which merit further investigation.

Overall completeness and applicability of evidence

Endoscopic versus surgical intervention

Cahen 2007 offered a complete comparison of both treatment modalities with reporting of most outcomes that were of interest to this review. On the contrary, Díte 2003 reported only a limited set of outcomes.

Regarding the applicability of the results, it should be noted that both trials included only participants with severe-stage (i.e., late) CP (opioid dependency in Cahen 2007 and a period of > five years from diagnosis and three years of failed medical management in Díte 2003). Therefore, the results of these trials can only be generalised in patients with similar severity.

Two concerns could be raised regarding the applicability of the results of Díte 2003. First, the study did not exclude participants with an inflammatory mass in the pancreas. The problem is that endoscopy cannot fairly compete with surgery if such masses are present since surgical resection (with or without pancreatic duct drainage) is the treatment of choice in this case (van der Gaag 2007), especially since it was observed that 80% of the participants in the surgical arm had some type of surgical resection procedure. Secondly, the endoscopic intervention did not include the use of ESWL. Experts consider this modality to be an important component of optimal endoscopic management (Dumonceau 2007).

The impact of these concerns on the applicability of the study is difficult to assess. It seems acceptable that this could have led to an unbalanced comparison, possibly leading to unjustly favouring surgery over endoscopy. Regarding the first concern, however, the authors did explicitly specify that they only included participants if the surgeon and the gastroenterologist established a consensus that both endoscopy and surgery were feasible therapeutic alternatives. Therefore, the population of this trial may more accurately resemble the population expected in the real clinical situation. The authors would thereby have avoided a too narrow participant selection that could compromise external validity (Yusuf 1990). Regarding the lack of ESWL in the endoscopic group, it could be argued that in many centres, ESWL is simply not (yet) used as a routine treatment modality for this group of participants. Therefore, Díte 2003 may more accurately resemble the current situation in many hospitals.

Surgical intervention versus conservative treatment

Nealon 1993 only reported on two outcomes (pain relief and pancreatic function), and the authors especially did not report on potential harms associated with either treatment. This trial thereby only answered one part of the objective of the review. An important point regarding the applicability of the results is that the conservative treatment was not explicitly specified in the report. Also, the report did not clearly list the exclusion criteria. This limits our ability to draw conclusions regarding the generalisability of the results. We did not identify any studies comparing endoscopic to conservative treatment.

Quality of the evidence

Endoscopic versus surgical intervention

This review included two RCTs for this comparison, with a total of 111 participants.

Cahen 2007, despite its small sample size, is a high quality trial with low risk of bias. The results, especially regarding the benefits of surgery in terms of pain relief, are convincing both statistically and clinically. The only remark that could be made about the trial is that it was terminated at an unplanned interim analysis: at 80% of the planned inclusion, because of significant results of benefit. Termination of trials before full inclusion because of benefit carries the risk of overestimating the treatment effect (Montori 2005; Pocock 1999). However, both the observed effect as well as the P value have been corrected for this early termination. Moreover, the observed P value ($P < 0.001$) and the application of an independent safety commission to take the decision of trial termination give more confidence in the correctness of the decision.

Díte 2003 had several methodological flaws. First, allocation was performed by alternation rather than true randomisation. This method has two problems: The generated allocation is not random, and it makes allocation concealment impossible (Randelli 2008). Absence of allocation concealment has been shown to significantly overestimate the treatment effects in RCTs by up to 40% (Schulz 1995). In the study's defence, Díte 2003 did specify that they only included participants if a consulting gastroenterologist and surgeon established a consensus regarding the inclusion of participants. While this is by no means a substitution of proper randomisation and allocation concealment, reaching consensus by physicians of two different specialities with competing interests may have reduced the selection bias associated with unconcealed allocation. Further limitations of the study were the exclusion of participants who were non-compliant to follow up (per-protocol analysis rather than an intention-to-treat analysis) and the lack of baseline characteristics.

In general, the overall quality and quantity of the available evidence is, in our opinion, of moderate quality (Summary of findings for the main comparison) and is sufficient to draw conclusions about benefits of both interventions, especially regarding pain relief. The fact that the two RCTs showed consistent results and that the observed differences were more evident (both statistically and clinically) in the study with low risk of bias, increases the reliability of the observed differences. On the other hand, the small size of the trials makes drawing conclusions regarding outcomes with potentially a small difference between the interventions (for example, complications and mortality) beyond reach. Also, the lack of evidence of benefit regarding other more objective outcomes (for example, pancreatic function) is a drawback in the quality of the evidence.

Surgical intervention versus conservative treatment

As stated earlier, we identified one trial (Nealon 1993) including 32 participants for this comparison. This trial had limitations as the trial had a small sample size and lacked a formal sample size calculation; the conservative arm was not clearly defined; the inclusion of participants was conducted over a long period of

time; and the methodology was not clearly reported. Therefore, the quality of evidence was considered to be low (Summary of findings 2). This could be partly explained by the study being a pilot RCT intended to generate a hypothesis to be tested in a larger randomised trial. Another potential explanation is that the study was set up about 18 years ago, in a period when knowledge of the methodology of RCTs was not commonly available.

With this in mind, it seems best to consider this trial as a hypothesis-generating pilot trial, which should lead to further study of the promising results before conclusions can be drawn for current practice.

Potential biases in the review process

Obtaining all relevant data was the most challenging aspect of this review. For all included studies, some potentially relevant data were missing in the original reports. We were able to obtain some of these data by contacting the authors of the trials, but despite repeated contacting of authors, some data remained missing. Nonetheless, it is not likely that these data would have changed the conclusions of the review, especially since most concerned secondary outcomes.

Finally, this review once again shows that reporting of several aspects in trials, including essential aspects like baseline characteristics, is still inadequate in many cases. This clearly illustrates the need to adhere to guidelines for reporting research to make the validity of studies more assessable. Caution should be applied however in critically appraising poorly reported trials since evidence showed that this is not always interchangeable with bad methodology (Soares 2004).

Agreements and disagreements with other studies or reviews

Endoscopic versus surgical intervention

A review by Devière 2008 comparing endoscopic with surgical treatment for CP and including the same two RCTs as in our review concluded that the low number of participants in the trials and the differences in methodology did not allow for drawing any conclusions about the choice between endoscopy and surgery. Devière 2008 stated that "because of paucity in the available RCTs, physicians and surgeons must rely on their own experience".

We do not entirely agree with these conclusions. Choosing individual experiences and preferences (level V evidence) as a basis for decision-making, despite the availability of two RCTs (level one evidence) showing consistent results in favour of one treatment, is - in our opinion - too conservative. This is especially so since one of these studies is a well-conducted study with low risk of bias, and the endoscopic treatment in this trial was performed in centres with high expertise and performing of ESWL for large pancreatic duct stones (Cahen 2007). We think that serious efforts should be made to interpret the available evidence in a way that is most beneficial to patients, taking into account the limitations regarding the generalisability and validity of this evidence.

Surgical intervention versus conservative treatment

Although Nealon 1993 is the only RCT that compared surgical intervention at an early stage of CP with conservative intervention, the results are in agreement with other non-randomised studies. Clinically, two non-randomised cohort studies have shown that surgical interventions, especially drainage procedures, have the potential to delay the progressive loss of pancreatic function in CP patients (Maartense 2004; Nealon 1993). This is in line with findings from experimental studies. An experimental model of early versus late surgical drainage for CP in piglets observed that the histology of the pancreas and exocrine pancreatic function were significantly better in the early surgical group compared with the late surgical group (Lamme 2007).

AUTHORS' CONCLUSIONS

Implications for practice

Endoscopic versus surgical intervention

For patients with severe CP (that is, with pain intractable to opioid medication) and a dilated pancreatic duct, this review shows that surgery is superior to endoscopy in terms of pain relief. However, when it comes to morbidity and mortality, this review is not able to draw reliable conclusions. Decisions for either intervention should be made after informing patients about risks associated with both treatments and openly discussing the gaps in current knowledge.

Surgical intervention versus conservative treatment

Regarding this comparison, this review cannot draw reliable conclusions for clinical practice. Surgery rather than conservative treatment at an early stage of CP seems a promising approach, but more evidence is needed.

Implications for research

Endoscopic versus surgical intervention

This review identified two aspects regarding the comparison of endoscopic versus surgical intervention for CP, which need further investigation. First, endoscopic and surgical interventions should be compared with regard to morbidity and mortality, preferably in a large well-conducted trial. Secondly, the effectiveness and complications of endoscopic versus surgical intervention for patients with early-stage CP (rather than late-stage CP) should be investigated. Combining these two aspects by conducting a large RCT in participants with early-stage CP could be an efficient way to answer both questions simultaneously. Future trials should focus on objective outcomes as well as those that are reported by patients to provide a more complete picture of benefits and harms.

Surgical intervention versus conservative treatment

This review identified one pilot trial showing that surgery rather than conservative treatment for early CP may bring important benefits to patients in terms of pain relief and preservation of pancreatic function. We recommend investigating these results in a large well-conducted RCT, with attention to benefit, harm, and cost-effectiveness of both interventions. Similarly, no trials were identified comparing endoscopic to conservative treatments. Further research on this topic is recommended.

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REFERENCES

References to studies included in this review

Cahen 2007 *{published data only}*

Cahen DL, Gouma DJ, Laramee P, Nio CY, Rauws E, Boermeester MA, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis: long-term outcome. Gastroenterology. Presetend at: Digestive Disease Week 2011, Chicago, USA, 2011; Vol. 140, Page S69.

Cahen DL, Gouma DJ, Laramée P, Nio Y, Rauws EA, Boermeester MA, et al. Long-term outcomes of endoscopic vs surgical drainage of the pancreatic duct in patients with chronic pancreatitis. *Gastroenterology* 2011;**141**(5):1690-5. [PUBMED: 21843494]

* Cahen DL, Gouma DJ, Nio Y, Rauws EA, Boermeester MA, Busch OR, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. *The New England Journal of Medicine* 2007;**356**(7):676-84. [PUBMED: 17301298]

Cahen DL, Gouma DJ, Nio Y, Rauws EA, Boermeester MA, Busch OR, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis: a prospective randomized trial. *Gastrointestinal Endoscopy* 2005;**61**:AB99.

Cahen DL, Gouma DJ, Nio Y, Rauws EA, Boermeester MA, Busch OR, et al. [Surgical drainage of the pancreatic duct in patients with chronic pancreatitis is more effective than endoscopic drainage: randomized trial]. *Nederlands Tijdschrift voor Geneeskunde* 2007;**151**(47):2624-30. [PUBMED: 18161265]

Díte 2003 *{published data only}*

Díte P, Ruzicka M, Zboril V, Novotný I. A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. *Endoscopy* 2003;**35**(7):553-8. [PUBMED: 12822088]

Nealon 1993 *{published data only}*

Nealon WH, Thompson JC. Progressive loss of pancreatic function in chronic pancreatitis is delayed by main pancreatic duct decompression. A longitudinal prospective analysis of the modified puestow procedure. *Annals of Surgery* 1993;**217**(5):458-66. [PUBMED: 8489308]

References to studies excluded from this review

Alexakis 2005 *{published data only}*

Alexakis N, Neoptolemos JP. Chronic pancreatitis: Endoscopic versus surgical procedures for pain relief. Pancreatitis: Advances in Pathobiology, Diagnosis and Treatment. Springer, 2005:190-205.

Cahen 2011 *{published data only}*

Cahen DL, Gouma DJ, Laramee P, Nio CY, Rauws E, Boermeester MA, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis: long-term outcome. Digestive Disease Week. Chicago, 2011.

Ceppa 2013 *{published data only}*

Ceppa EP, Pitt HA, Hunter JL, Leys CM, Zyromski NJ, Rescorla FJ, et al. Hereditary pancreatitis: endoscopic and surgical management. *Journal of Gastrointestinal Surgery* 2013;**17**(5):847-56. [PUBMED: 23435738]

Chang 2010 *{published data only}*

Chang KJ, Erickson RA, Chak A, Lightdale C, Chen YK, Binmoeller KF, et al. EUS compared with endoscopy plus transabdominal US in the initial diagnostic evaluation of patients with upper abdominal pain. *Gastrointestinal Endoscopy* 2010;**72**(5):967-74. [PUBMED: 20650452]

Connors 1993 *{published data only}*

Connors PJ, Friedman LS. Pancreas divisum: to stent or not to stent. *Gastroenterology* 1993;**104**(4):1226-8. [PUBMED: 8462814]

Dumonceau 2007 *{published data only}*

* Dumonceau JM, Costamagna G, Tringali A, Vahedi K, Delhaye M, Hittelet A, et al. Treatment for painful calcified chronic pancreatitis: extracorporeal shock wave lithotripsy versus endoscopic treatment: a randomised controlled trial. *Gut* 2007;**56**(4):545-52. [PUBMED: 17047101]

Dumonceau JM, Vahedi K, Delhaye M, Morales A, Vandermeeren A, Le Moine O, et al. Extracorporeal shock-wave lithotripsy (ESWL) alone compared with ESWL plus endoscopic pancreatic drainage in chronic pancreatitis associated with ductal stones. *Gastrointestinal Endoscopy* 2003;**57**:AB87.

Glass 2012 *{published data only}*

Glass LM, Yadav D, Kennard E, Romagnuolo J, Anderson MA, Whitcomb DC, et al. Spectrum of use and perceived effectiveness of endoscopic and surgical therapies for chronic pancreatitis in the United States. *Gastroenterology* 2012;**142**:S459.

Hirota 2011 *{published data only}*

Hirota M, Asakura T, Kanno A, Kikuta K, Kume K, Hamada S, et al. Long-period pancreatic stenting for painful chronic calcified pancreatitis required higher medical costs and frequent hospitalizations compared with surgery. *Pancreas* 2011;**40**(6):946-50. [PUBMED: 21747315]

Iqbal 2009 *{published data only}*

Iqbal CW, Moir CR, Ishitani MB. Management of chronic pancreatitis in the pediatric patient: endoscopic retrograde cholangiopancreatography vs operative therapy. *Journal of Pediatric Surgery* 2009;**44**(1):139-43. [PUBMED: 19159731]

Knoefel 1997 *{published data only}*

Knoefel WT, Bloechle C, Izbicki JR. [Decompression of the main pancreatic duct can delay progressive loss of pancreatic function in chronic pancreatitis]. *Zeitschrift für Gastroenterologie* 1997;**35**(4):301-3. [PUBMED: 9221614]

Laramee 2010 *{published data only}*

Laramee P, Wonderling D, Cahen DL, Bruno MJ, Dijkgraa MG, Gouma DJ, et al. Surgical versus endoscopic drainage in obstructive chronic pancreatitis: a cost-effectiveness analysis. Gastroenterology. Proceedings of Digestive Disease Week; 2010

May 1-5; New Orleans (LA). 2010; Vol. 138 (5 Suppl 1):475r. [DOI: 10.1016/S0016-5085(10)60301-0]

Lee 2005 *{published data only}*

Lee SS, Kim MH, Lee SK, Seo DW, Han JM, Bang SJ. The outcome and prognostic factors of endoscopic pancreatic stent insertion in chronic pancreatitis with pancreatic duct stricture. *Gastrointestinal Endoscopy* 2005;**61**(5):AB194. [DOI: http://dx.doi.org/10.1016/S0016-5107(05)01048-5]

Levy 1989 *{published data only}*

Levy P, Bernades P, Belghiti J, Fekete F. Does elective pancreatic surgery modify the long-term mortality of patients with chronic pancreatitis? Comparison of operated and non-operated patients. *Gastroentérologie Clinique et Biologique* 1989;**13**:A5.

Lipsky 1993 *{published data only}*

Lipsky H, Barkin JS. Balloon dilation versus Eder-Puestow: bigger and better?. *The American Journal of Gastroenterology* 1993;**88**(4):609-10. [PUBMED: 8470649]

Noda 2004 *{published data only}*

Noda A. Availability of oral litholysis therapy and its combination with ESWL and endoscopic treatment in chronic pancreatitis. *Gastroenterology* 2004;**126**:A230-1.

Regimbeau 2012 *{published data only}*

Regimbeau JM, Fuks D, Bartoli E, Fumery M, Hanes A, Yzet T, et al. A comparative study of surgery and endoscopy for the treatment of bile duct stricture in patients with chronic pancreatitis. *Surgical Endoscopy* 2012;**26**(10):2902-8. [PUBMED: 22580872]

Sauer 2008 *{published data only}*

Sauer B, Talreja JP, Ellen K, Ku J, Shami VM, Kahaleh M. Temporary placement, of covered self-expandable metal stent (CSEMS) in the pancreatic duct for management of painful chronic pancreatitis: preliminary data. *Gastrointestinal Endoscopy* 2008;**67**:AB327.

Seiler 2009 *{published data only}*

Seiler CM. Prospective randomized single-blinded trial of endoscopic stenting for chronic pancreatitis. *Clinical Trials* 2009;**6**(5):464. [PUBMED: 19846898]

Wagh 2008 *{published data only}*

Wagh M, McHenry L, Watkins J, Fogel E, Sherman S, Lehman G. Extracorporeal ShockWave lithotripsy (ESWL) with ERCP for management of chronic pancreatitis with pancreatic duct calculi. *American Journal of Gastroenterology* 2008;**103**:1267.

References to ongoing studies

Ahmed Ali 2013 *{published data only}*

Ahmed Ali U, Issa Y, Bruno MJ, van Goor H, van Santvoort H, Busch OR, et al. Early surgery versus optimal current step-up practice for chronic pancreatitis (ESCAPE): design and rationale of a randomized trial. *BMC Gastroenterology* 2013;**13**:49. [DOI: 10.1186/1471-230X-13-49; PUBMED: 23506415]

Wilcox 2009 *{published data only}*

Wilcox CM, Lopes TL. A randomized trial comparing endoscopic stenting to a sham procedure for chronic pancreatitis. *Clinical Trials* 2009;**6**(5):455-63. [PUBMED: 19737848]

Additional references

AGA 1998

No authors listed. American Gastroenterological Association Medical Position Statement: treatment of pain in chronic pancreatitis. *Gastroenterology* 1998;**115**(3):763-4. [PUBMED: 9721174]

Ammann 1999

Ammann RW, Meullhaupt B. The natural history of pain in alcoholic chronic pancreatitis. *Gastroenterology* 1999;**116**(5):1132-40. [PUBMED: 10220505]

Brazier 1992

Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992;**305**(18):160-4. [PUBMED: 1285753]

Devière 2008

Devière J, Bell RH Jr, Beger HG, Traverso LW. Treatment of chronic pancreatitis with endotherapy or surgery: critical review of randomized control trials. *Journal of Gastrointestinal Surgery* 2008;**12**(4):640-4. [PUBMED: 18247099]

Díte 2001

Díte P, Starý K, Novotný I, Precechtelová M, Dolina J, Lata J, et al. Incidence of chronic pancreatitis in the Czech Republic. *European Journal of Gastroenterology and Hepatology* 2001;**13**(6):749-50. [PUBMED: 11434607]

Fasanella 2007

Fasanella KE, Davis B, Lyons J, Chen Z, Lee KK, Slivka A, et al. Pain in chronic pancreatitis and pancreatic cancer. *Gastroenterology Clinics of North America* 2007;**36**(2):335-64. [PUBMED: 17533083]

Gourgiotis 2007

Gourgiotis S, Germanos S, Ridolfini MP. Surgical management of chronic pancreatitis. *Hepatobiliary and Pancreatic Diseases International* 2007;**6**(2):121-33. [PUBMED: 17374569]

Higgins 2002

Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**(11):1539-58. [PUBMED: 12111919]

Higgins 2008

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Chichester: John Wiley & Sons, 2008.

Izbicki 1998

Izbicki JR, Bloechle C, Broering DC, Knoefel WT, Kuechler T, Broelsch CE. Extended drainage versus resection in surgery for

chronic pancreatitis: a prospective randomized trial comparing the longitudinal pancreaticojejunostomy combined with local pancreatic head excision with the pylorus-preserving pancreatoduodenectomy. *Annals of Surgery* 1998;**228**(6):771-9. [PUBMED: 9860476]

Kjaergard 2001

Kjaergard LL, Villumsen J, Gluud C. Reported methodological quality and discrepancies between large and small randomised trials in meta-analyses. *Annals of Internal Medicine* 2001;**135**(11):982-9.

Lamme 2007

Lamme B, Boermeester MA, Straatsburg IH, van Buijtenen JM, Boerma D, Offerhaus GJ, et al. Early versus late surgical drainage for obstructive pancreatitis in an experimental model. *The British Journal of Surgery* 2007;**94**(7):849-54. [PUBMED: 17335122]

Lankisch 2001

Lankisch PG. Natural course of chronic pancreatitis. *Pancreatology* 2001;**1**(1):3-14. [PUBMED: 12120264]

Lévy 2006

Lévy P, Barthet M, Mollard BR, Amouretti M, Marion-Audibert AM, Dyard F. Estimation of the prevalence and incidence of chronic pancreatitis and its complications. *Gastroentérologie Clinique et Biologique* 2006;**30**(6-7):838-44. [PUBMED: 16885867]

Maartense 2004

Maartense S, Ledeboer M, Bemelman WA, Ringers J, Frolich M, Masclee AA. Effect of surgery for chronic pancreatitis on pancreatic function: pancreatico-jejunostomy and duodenum-preserving resection of the head of the pancreas. *Surgery* 2004;**135**(2):125-30. [PUBMED: 14739846]

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?. *Lancet* 1998;**352**(9128):609-13. [PUBMED: 9746022]

Montori 2005

Montori VM, Devereaux PJ, Adhikari NK, Burns KE, Eggert CH, Briel M, et al. Randomized trials stopped early for benefit: a systematic review. *JAMA* 2005;**294**(17):2203-9. [PUBMED: 16264162]

Pezzilli 2005

Pezzilli R, Morselli Labate AM, Ceciliato R, Frulloni L, Cavestro GM, Comparato G, et al. Quality of life in patients with chronic pancreatitis. *Digestive and Liver Disease* 2005;**37**(3):181-9. [PUBMED: 15888283]

Pocock 1999

Pocock S, White I. Trials stopped early: too good to be true?. *Lancet* 1999;**353**(9157):943-4. [PUBMED: 10459899]

Randelli 2008

Randelli P, Arrigoni P, Lubowitz JH, Cabitza P, Denti M. Randomisation procedures in orthopaedic trials. *Arthroscopy* 2008;**24**(7):834-8.

RevMan 2012 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.2.10. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Rösch 2002

Rösch T, Daniel S, Scholz M, Huilbregtse K, Smits M, Schneider T, et al. Endoscopic treatment of chronic pancreatitis: a multicenter study of 1000 patients with long-term follow up. *Endoscopy* 2002;**34**(10):765-71. [PUBMED: 12244496]

Schulz 1995

Schulz KF, Chalmers I, Hayer R, Altman D. Empirical evidence of bias. *JAMA* 1995;**273**(5):408-12.

Soares 2004

Soares HP, Daniels S, Kumar A, Clarke M, Scott C, Swann S, et al. Bad reporting does not mean bad methods for randomised trials: observational study of randomised controlled trials performed by the Radiation Therapy Oncology Group. *BMJ* 2004;**328**(7430):22-4. [PUBMED: 14703540]

Spanier 2008

Spanier BW, Dijkgraaf MG, Bruno MJ. Epidemiology, aetiology and outcome of acute and chronic pancreatitis: an update. *Best Practice & Research. Clinical Gastroenterology* 2008;**22**(1):45-63. [PUBMED: 18206812]

Strate 2005

Strate T, Taherpour Z, Bloechle C, Mann O, Bruhn JP, Schneider C, et al. Long-term follow-up of a randomized trial comparing the beger and frey procedures for patients suffering from chronic pancreatitis. *Annals of Surgery* 2005;**241**(4):591-8. [PUBMED: 15798460]

Tringali 2008

Tringali A, Boskoski I, Costamagna G. The role of endoscopy in the therapy of chronic pancreatitis. *Best Practice & Research. Clinical Gastroenterology* 2008;**22**(1):145-65. [PUBMED: 18206819]

van der Gaag 2007

van der Gaag NA, Gouma DJ, van Gulik TM, Busch ORC, Boermeester MA. Surgical management of chronic pancreatitis. *Alimentary Pharmacology and Therapeutics* 2007;**26 Suppl 2**:221-32.

van Esch 2006

van Esch AA, Wilder-Smith OH, Jansen JB, van Goor H, Drenth JP. Pharmacological management of pain in chronic pancreatitis. *Digestive Liver Disease* 2006;**38**(7):518-26. [PUBMED: 16627019]

Wehler 2004

Wehler M, Nichterlein R, Fischer B, Farnbacher M, Reulbach U, Hahn EG, et al. Factors associated with health-related

quality of life in chronic pancreatitis. *The American Journal of Gastroenterology* 2004;**99**(1):138-46. [PUBMED: 14687155]

Witt 2007

Witt H, Apte MV, Keim V, Wilson JS. Chronic pancreatitis: challenges and advances in pathogenesis, genetics, diagnosis, and therapy. *Gastroenterology* 2007;**132**(4):1557-73. [PUBMED: 17466744]

Yusuf 1990

Yusuf S, Held P, Teo KK, Toretsky ER. Selection of patients for randomized controlled trials: implications of wide or narrow eligibility criteria. *Statistics in Medicine* 1990;**9**(1-2):73-83; discussion 83-6. [PUBMED: 2345840]

CHARACTERISTICS OF STUDIES

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

Cahen 2007

Methods	Study design: randomised controlled trial Setting of study: single centre (Academic Medical Center, Amsterdam, the Netherlands) Follow-up period: 24 months, with a second long-term publication after minimal follow up of 5 years Loss to follow up at 2 years' follow up: 1 participant in the surgical group Loss to follow up at 5 years' follow up: 3 participants in the endoscopy group and 5 participants in the surgery group Type of analysis: intention-to-treat analysis Sample size calculations: yes, a sample size of 50 participants was calculated
Participants	Number of participants: 39 (19 in the endoscopy group, 20 in the surgical group) Gender: 11 men and 8 women in the endoscopy group, 15 men and 5 women in the surgery group Age (mean (SD)): 52 years (9) in the endoscopy group, 46 years (12) in the surgery group BMI (mean (SD)): 21 kg (4.1) in the endoscopy group, 21 kg (3.7) surgery group Type of pain: • endoscopy group: 7 participants with intermittent pain (type A), 12 participants with continuous pain (type B) • surgery group: 9 participants with intermittent pain (type A), 11 participants with continuous pain (type B) Inclusion criteria: • Established CP • Obstruction of pancreatic duct (> 5 mm) • No pancreatic head enlargement • Severe recurrent pancreatic pain intractable to non-narcotic analgesics Exclusion criteria: • Age < 18 or > 80 years • Enlargement of pancreatic head > 4 cm • Contraindications to surgery or endoscopic interventions

References to other published versions of this review

Ahmed Ali 2012

Ahmed Ali U, Pahlplatz JM, Nealon WH, van Goor H, Gooszen HG, Boermeester MA. Endoscopic or surgical intervention for painful obstructive chronic pancreatitis. *Cochrane Database of Systematic Reviews* 2012, Issue 1. [DOI: 10.1002/14651858.CD007884.pub2]

* Indicates the major publication for the study

Cahen 2007 *(Continued)*

	• Previous pancreatic surgery • Suspected pancreatic malignancy or life expectancy < 2 years • Pregnancy Duration of symptoms: 16 months in the endoscopy group (SD 14), 21 months in the surgery group (SD 19) Ongoing alcohol abuse at randomisation: 0 participants in the endoscopy group, 5 participants in the surgical group Ongoing smoking at randomisation: 15 participants in the endoscopy group, 17 participants in the surgical group
Interventions	Endoscopic drainage versus surgical drainage: • Endoscopic drainage: endoscopic drainage of the pancreatic duct by ERCP with (repeated) dilatation and stent placement if required. Participants with large stones in the pancreatic duct (> 7 mm) underwent extracorporeal shock wave lithotripsy (ESWL) before drainage • Surgical drainage: surgical drainage of the pancreatic duct by means of a longitudinal pancreaticojejunostomy as intended treatment. In 1 participant, a Whipple procedure was performed because of peripancreatic inflammation. In another participant, stone extraction required a Frey procedure Endoscopic experience: Experienced endoscopists performed study interventions (performed > 1000 ERCPs) Surgical experience: Experienced pancreatic surgeons performed surgical procedures (no specific criteria stated)
Outcomes	Primary outcome (prespecified in the methods section): • Pain score (Izbicki questionnaire) Secondary outcomes (prespecified in the methods section): • Pain relief (defined by Izbicki score) • Physical and mental health (SF-36 questionnaires) • Postinterventional complications • Length of hospital stay • Number of performed procedures • Change in pancreatic function • Mortality Other outcomes (results reported, but not specified in the methods section): • Conversion to surgery • Technical success of intervention • Hospital re-admittance Time points of outcomes: 6 weeks and 3, 6, 12, 18, and 24 months Long-term follow-up: minimum of 5 years (mean follow up was 85 months in the endoscopy and 92 months in the surgery group)
Notes	• The safety committee terminated the study prematurely on the basis of significant difference in outcome favouring the surgical group with a P value of less than 0.001 regarding the primary outcome (pain on the Izbicki pain score) • An author provided us with additional methodological information and data

Risk of bias

Cahen 2007 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study used an automated assignment system
Allocation concealment (selection bias)	Low risk	This was specifically stated
Blinding (performance bias and detection bias) All outcomes	High risk	-
Incomplete outcome data (attrition bias) All outcomes	Low risk	The proportion of loss to follow up did not exceed 20%
Selective reporting (reporting bias)	Low risk	The study reported all relevant and prespecified outcomes
Other bias	Low risk	The study terminated prematurely, but the authors performed adequate adjustment for treatment effect and P value for early termination

Díte 2003

Methods	Study design: pseudo-randomised controlled trial (alternating allocation) Setting of study: single centre (University Hospital Brno, Czech Republic) Follow-up period: 5 years Loss to up: Participants not compliant to follow up were excluded Type of analysis: per-protocol analysis Sample size calculation: yes, a sample size of 140 participants was calculated
Participants	Number of randomised participants: 72 (36 in the endoscopy group, 36 in the surgical group). The population of the RCT was part of a larger prospective cohort reported in the same publication. The total sample of the cohort was 140 Gender: not specified for the randomised group (only for the complete cohort, which had 119 men and 21 women) Age: not specified for the randomised group (only for the complete cohort, which had mean age of 41.7 years, ranging between 26 to 53) BMI: not specified Type of pain (continuous vs recurrent flare-ups): not specified Inclusion criteria: • Established CP • Obstruction of pancreatic duct (dilated pancreatic duct) • Painful CP (pain score > 3 on the Melzack pain score) • Failure of conservative management in the previous 3 years • Duration of clinical CP for more than 5 years

Díte 2003 *(Continued)*

	• Consensus of surgeon and gastroenterologist regarding suitability of participant for both endoscopy and surgery Exclusion criteria: • Age < 18 or > 70 years • Previous interventional therapy for CP (surgery, endoscopy, or nerve block) • Suspected pancreatic malignancy • Non-compliance to follow-up examinations • Pregnancy Duration of symptoms: > 5 years (inclusion criteria) Ongoing alcohol abuse at randomisation: not reported Ongoing smoking at randomisation: not reported
Interventions	Endoscopic drainage versus surgical intervention (drainage and resection): • Endoscopic drainage: endoscopic drainage of the pancreatic duct by ERCP with pancreatic sphincterotomy, stone extraction, or dilation of strictures and stenting, as appropriate. ESWL was not applied as part of the endoscopic intervention • Surgical intervention: choice of operation was dependent on the morphology of the pancreas on preoperative imaging. Pancreaticojejunostomy was performed in participants with absence of focal pancreatic enlargement. In participants in whom disease was limited predominantly to the pancreatic head, either duodenum-preserving pancreatic head resection or pancreatoduodenectomy (Whipple resection) were performed. CP predominantly affecting the pancreatic tail was treated by left pancreatic resection Endoscopic experience: 2 experienced endoscopists performed study interventions (performed > 200 drainage procedures) Surgical experience: 1 abdominal surgeon performed surgical procedures (performed 90 pancreatic operations before the start of the study)
Outcomes	Primary outcome (prespecified in the methods section): • Pain relief (defined by Melzack score) • Necessity for further interventions Secondary outcomes (prespecified in the methods section): • Change in body weight • Presence of diabetes Other outcomes (results reported, but not specified in the methods section): • Complcations • Mortality Time points of outcomes: 6 months and 1, 3, and 5 years
Notes	The population of the RCT was part of a larger prospective cohort reported in the same publication An author provided us with additional information regarding the methodology of the study, but not with additional data regarding missing baseline characteristics and outcomes

Risk of bias

Bias	Authors' judgement	Support for judgement

Díte 2003 *(Continued)*

Random sequence generation (selection bias)	High risk	Allocation was by alternation
Allocation concealment (selection bias)	High risk	-
Blinding (performance bias and detection bias) All outcomes	High risk	-
Incomplete outcome data (attrition bias) All outcomes	High risk	The study excluded participants not compliant to follow up
Selective reporting (reporting bias)	Low risk	The paper reported all prespecified data
Other bias	Unclear risk	The study did not present a baseline table with relevant participant characteristics and potential confounders (e.g., smoking, alcohol use, preoperative pain, etc.) The study allowed for inclusion of participants with enlarged pancreatic head; these participants potentially benefit more from surgery than endoscopy, since surgery allows for resection of the inflamed mass while endoscopy does not

Nealon 1993

Methods	Study design: randomised controlled trial Setting of study: single centre (The University of Texas Medical Branch, Galveston, Texas, USA) Follow-up period: median of 124 months Loss to follow up: no Type of analysis: intention-to-treat analysis Sample size calculations: no (pilot study)
Participants	Number of participants: 32 participants (17 in the surgical group, 15 in the conservative group) Gender: not specified Age (mean): 41.7 years in the surgical group, 44.6 in the conservative group Inclusion criteria: • Established CP • Dilation of pancreatic duct • Mild, non-debilitating pain • Mild to moderate grade of CP: using a self-developed grading system (1 point for morphology on ERCP, 2 points for exocrine function, 2 points for endocrine function). Participants were categorised as mild/moderate (3 or less points) or severe CP (more then 3 points) Exclusion criteria: not specified Duration of symptoms: not specified

Nealon 1993 *(Continued)*

	Ongoing alcohol abuse at randomisation: not specified for participants within the RCT Ongoing smoking at randomisation: not specified
Interventions	Surgical drainage versus conservative treatment: • Surgical drainage: surgical drainage of the pancreatic duct by means of a longitudinal pancreaticojejunostomy, with choledochoenterostomy and pseudocyst drainage when deemed necessary. In participants with duodenum obstruction, a gastrojejunostomy was performed as well • Conservative treatment: not specified Surgical experience: not specified
Outcomes	Primary and secondary outcomes (prespecified in the methods section): not specified as such Outcomes (specified in the methods section): • Presence of abdominal pain • Grade of CP (using the self-developed grading system described above) Other outcomes (results reported, but not specified in the methods section): • Exocrine and endocrine pancreatic function Time points of outcomes: standardised follow up, each 14 to 16 months
Notes	The population of the RCT was part of a larger prospective cohort reported in the same publication The study only published the results of the first 17 participants. An author provided us with other data for the purpose of this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The last digit of the MRI number was used (odd versus even digits). It is unclear if the numbers generated by such a mechanism are truly random
Allocation concealment (selection bias)	High risk	-
Blinding (performance bias and detection bias) All outcomes	High risk	-
Incomplete outcome data (attrition bias) All outcomes	Low risk	The proportion of losses to follow up did not exceed 20%
Selective reporting (reporting bias)	Low risk	The paper reported all specified data
Other bias	Unclear risk	The study did not present a baseline table with relevant participant characteristics and potential confounders

CP = chronic pancreatitis.
ERCP = endoscopic retrograde cholangiopancreatography.
MRI = magnetic resonance imaging.
RCT = randomised controlled trial.
SD = standard deviation.

vs = versus.

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

Study	Reason for exclusion
Alexakis 2005	The abstract was not electronically available. Publication appeared to be a book chapter. This was not an original publication
Cahen 2011	The report was only available in abstract form. This is a long-term report of 1 of the included trials. We will add the final report to the review when it is published
Ceppa 2013	This was a review article
Chang 2010	This was a diagnostic study comparing endoscopic ultrasound with transabdominal ultrasound for upper abdominal pain
Connors 1993	The abstract was not electronically available. The publication was a comment on another study regarding use of stents in acute recurrent pancreatitis; the study excluded participants with chronic pancreatitis
Dumonceau 2007	This was a randomised trial comparing endoscopic intervention with an alternative treatment, i.e., extracorporeal shock wave lithotripsy (ESWL)
Glass 2012	This was a review article
Hirota 2011	This was a non-randomised comparison of endoscopic versus surgical intervention
Iqbal 2009	This was a non-randomised trial comparing endoscopic intervention with surgical intervention in paediatric participants
Knoefel 1997	The abstract was not electronically available. Publication only provides comment on the Nealon 1993 study. There were no original data
Laramee 2010	The publication (only in abstract form) was a report of an economic evaluation based on a review of literature
Lee 2005	The abstract was not electronically available. The publication (only in abstract form) was a report of a non-randomised series
Levy 1989	The abstract was not electronically available. The publication (only in abstract form) was a report of a non-randomised comparison
Lipsky 1993	The abstract was not electronically available. The study compared 2 techniques for treatment of oesophageal strictures
Noda 2004	The abstract was not electronically available. The publication (only in abstract form) was a report of a non-randomised comparison of different methods of litholysis
Regimbeau 2012	This was a non-randomised comparison of endoscopic versus surgical interventions
Sauer 2008	The abstract was not electronically available. The publication (only in abstract form) was a report of a non-randomised comparison
Seiler 2009	There was no abstract. The publication was a commentary on a protocol of a randomised trial comparing endoscopic intervention to sham intervention (Wilcox 2009)

Study	Reason for exclusion
Wagh 2008	The abstract was not electronically available. The publication (only in abstract form) describes a cohort of participants, without comparison

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

Ahmed Ali 2013

Trial name or title	Early surgery versus optimal current step-up practice for chronic pancreatitis (ESCAPE)
Methods	Randomised controlled, parallel, superiority multicentre trial
Participants	Participants with chronic pancreatitis, a dilated pancreatic duct (≥ 5 mm), and either moderate pain or frequent flare-ups that require opioid for pain management
Interventions	Early surgical intervention within 2 months of randomisation, by either a pancreaticojejunostomy or a duodenum-preserving head resection (according to Frey) if pancreatic head was enlarged
Outcomes	Primary outcome: pain (Izbicki pain score) during an 18-month follow-up period Secondary outcomes: complications, mortality, total direct and indirect costs, quality of life, pancreatic insufficiency, alternative pain scales, length of hospital admission, number of interventions, and pancreatitis flare-ups
Starting date	April 2011
Contact information	U Ahmed Ali and MA Boermeester, Department of Surgery, Academic Medical Center Amsterdam, PO 22660, 1100 DD, Amsterdam, the Netherlands
Notes	-

Wilcox 2009

Trial name or title	A randomised trial comparing endoscopic stenting to a sham procedure for chronic pancreatitis
Methods	Randomised controlled trial
Participants	Participants with typical abdominal pain, imaging confirmation of chronic pancreatitis, and endoscopic retrograde cholangiopancreatography (ERCP) confirmation of pancreatic duct stricture
Interventions	ERCP with sphincterotomy and pancreatic duct stenting versus sham procedure
Outcomes	Primary end point: reduction in abdominal pain Secondary end points: reduction in narcotic use as documented by pill counts, improvement in quality of life as assessed by the quality of life instruments, reduction in healthcare utilisation (emergency room, clinic visits, or hospitalisations), weight gain, return to employment, and reduction in number of missed days from work
Starting date	Not stated
Contact information	Dr C Mel Wilcox, University of Alabama at Birmingham, Division of Gastroenterology & Hepatology, 703 19th Street South, ZRB Room 633, Birmingham, AL 35294-0007, USA Telephone: +1 (205) 975 4958

Wilcox 2009 *(Continued)*

Fax: +1 (205) 934 1546
E-mail: melw@uab.edu

Notes	-

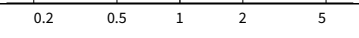
DATA AND ANALYSES

Comparison 1. Endoscopy versus surgery

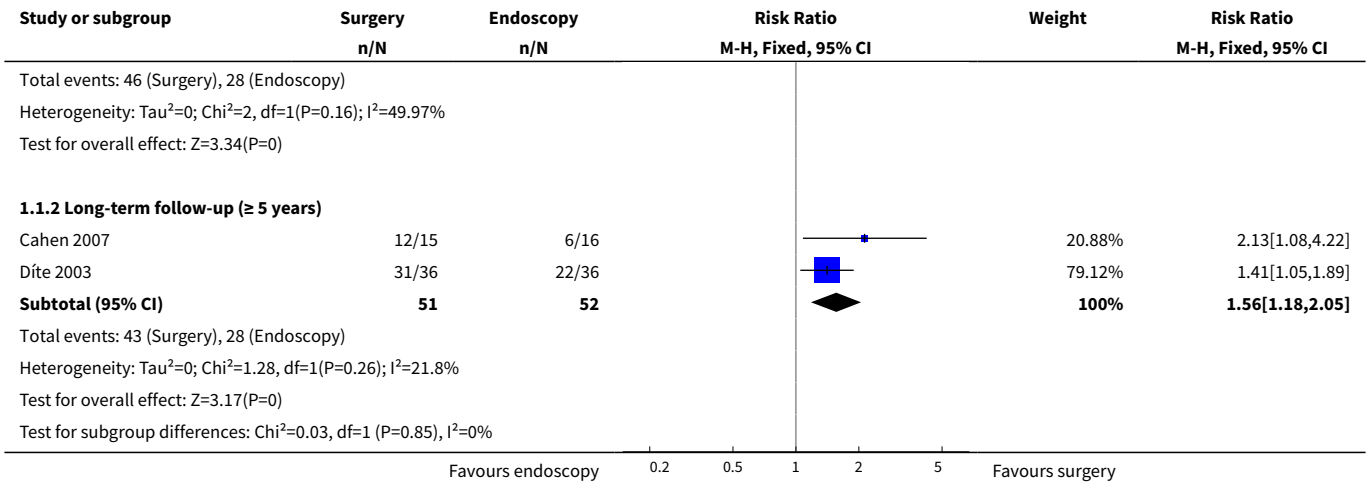
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain relief	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Middle/long-term follow-up (2 to 5 years)	2	111	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.22, 2.15]
1.2 Long-term follow-up (≥ 5 years)	2	103	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.18, 2.05]
2 Complete pain relief	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Middle/long-term follow-up (2 to 5 years)	2	111	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [1.18, 5.09]
2.2 Long-term follow-up (≥ 5 years)	2	103	Risk Ratio (M-H, Fixed, 95% CI)	2.28 [1.16, 4.50]
3 Partial pain relief	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Middle/long-term follow-up (2 to 5 years)	2	111	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.83, 1.99]
3.2 Long-term follow-up (≥ 5 years)	2	103	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.78, 1.91]
4 Endocrine pancreatic insufficiency (new onset)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Middle/long-term follow-up (2 to 5 years)	2	102	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.55, 1.76]
4.2 Long-term follow-up (≥ 5 years)	2	95	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.54, 1.55]

Analysis 1.1. Comparison 1 Endoscopy versus surgery, Outcome 1 Pain relief.

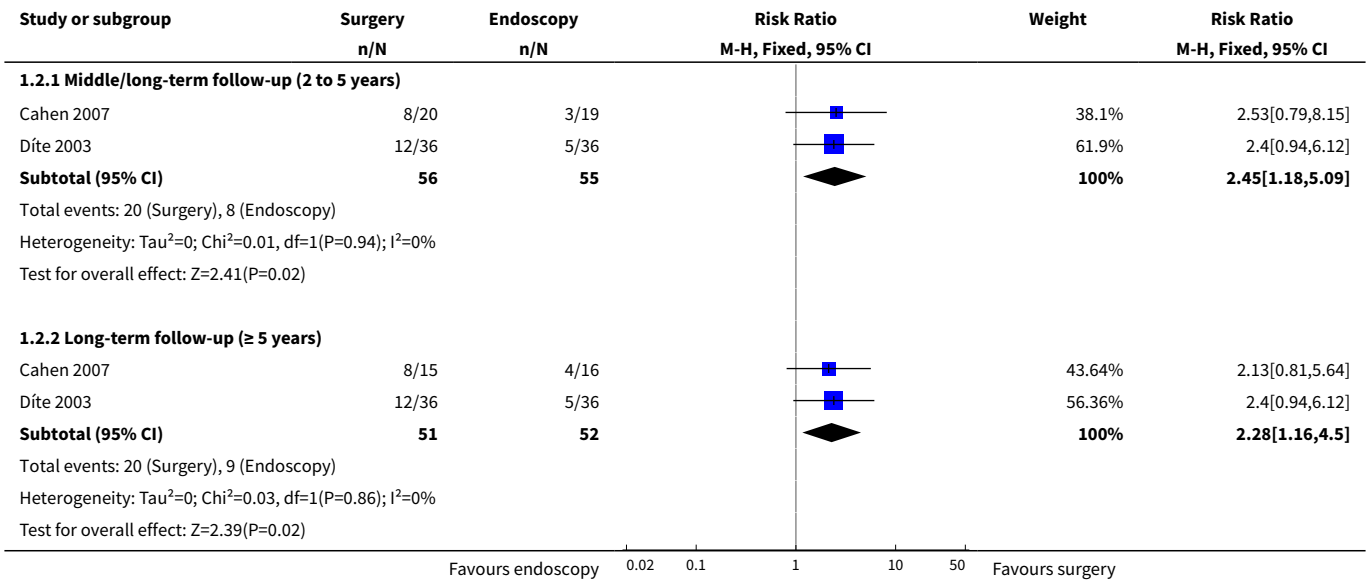
Study or subgroup	Surgery n/N	Endoscopy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Middle/long-term follow-up (2 to 5 years)					
Cahen 2007	15/20	6/19		21.86%	2.38[1.17,4.82]
Díte 2003	31/36	22/36		78.14%	1.41[1.05,1.89]
Subtotal (95% CI)	**56**	**55**		**100%**	**1.62[1.22,2.15]**



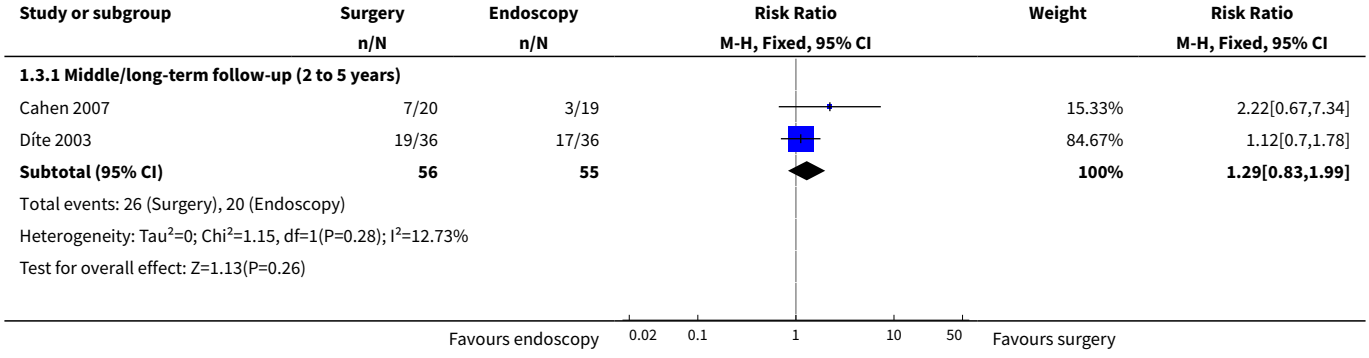
Favours endoscopy — Favours surgery

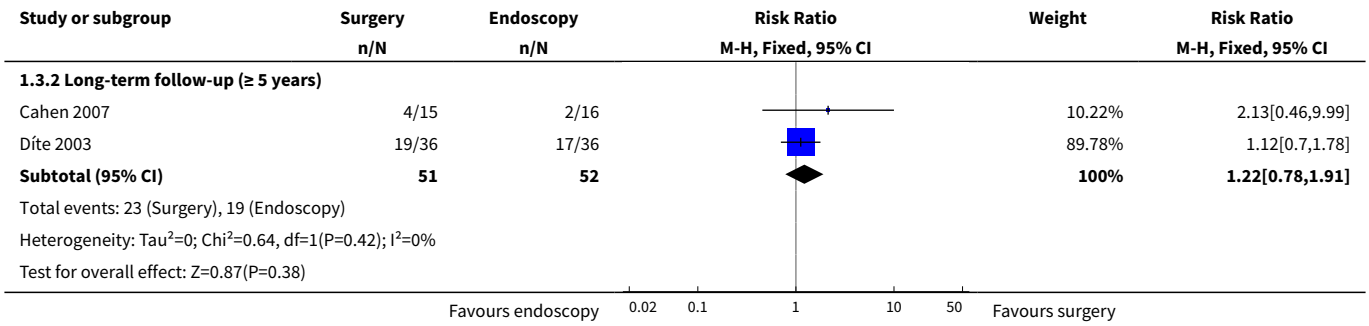


Analysis 1.2. Comparison 1 Endoscopy versus surgery, Outcome 2 Complete pain relief.

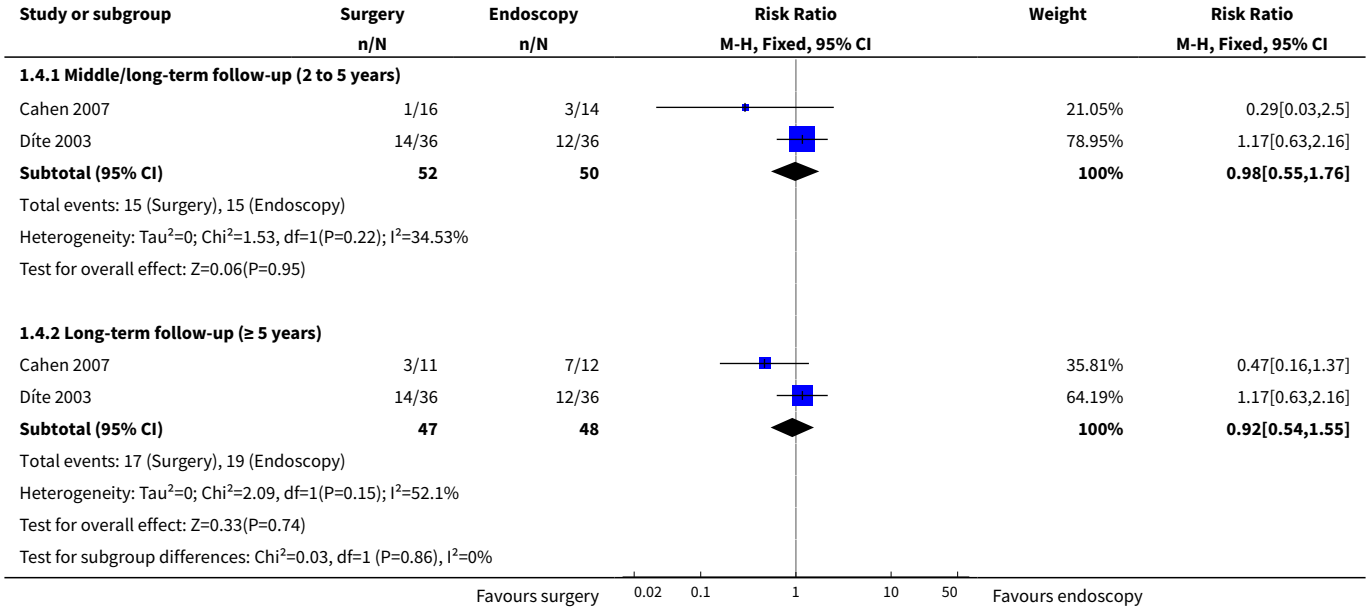


Analysis 1.3. Comparison 1 Endoscopy versus surgery, Outcome 3 Partial pain relief.





Analysis 1.4. Comparison 1 Endoscopy versus surgery, Outcome 4 Endocrine pancreatic insufficiency (new onset).



ADDITIONAL TABLES

Table 1. Results of studies comparing endoscopic with surgical treatment

	Cahen 2007			Díte 2003		
Outcome	**Endoscopy (N = 19)**	**Surgery (N = 20)**	**P value**	**Endoscopy (N = 36)**	**Surgery (N = 36)**	**P value**
Major complications (N (%))	0 (0%)	1 (5%)	NS	5 (8%)*	3 (4%)*	NS
Mortality (N (%))	1 (5%)	0 (0%)	NS	0 (0%)	0 (0%)	NS
Quality of life score (SF-36) (mean (SD))	-	-	-	-	-	-
- Physical health component (2 years)	38 (9)	47 (7)	0.003	-	-	-

Table 1. Results of studies comparing endoscopic with surgical treatment *(Continued)*

- Physical health component (5 years)	43 (11)	48 (9)				
- Mental health component (2 years)	40 (9)	45 (9)	NS	-	-	-
- Mental health component (5 years)	46 (9)	48 (10)				
Minor complications (N (%))	11 (58%)	6 (30%)	NS	0 (0%)*	3 (4%)*	-
Number of interventions (2 years) (mean (range))	9 (1 to 21)	3 (1 to 9)	< 0.001	-	-	N/A
Number of interventions (5 years) (mean (range))	12 (1 to 59)	4 (1 to 25)	0.001	6 (4 to 9)*	1 (1 to 3)*	
Change in nutritional status (N (%))	-	-	-	-	-	-
- Increase from baseline	-	-	-	10 (28%)	17 (47%)	NS
- Unchanged from baseline	-	-	-	9 (25%)	9 (25%)	NS
- Decrese from baseline	-	-	-	17 (47%)	10 (28%)	NS
Duration of hospital stay (2 years) (median (range))	8 (0 to 128)	11 (5 to 59)	NS	-	-	-
Duration of hospital stay (5 years) (median (range))	13 (2 to 237)	11 (5 to 345)				
	Endoscopy (N = 6)**	**Surgery (N = 4)****	**P value**	**Endoscopy (N = 36)**	**Surgery (N = 36)**	**P value**
Exocrine pancreatic insufficiency (new onset at 2 years) (N (%))	6 (100%)	1 (25%)	0.03	-	-	-
Exocrine pancreatic insufficiency (new onset at 5 years) (N (%))	6 (100%)	2 (50%)	NS			

*For this outcome, Díte 2003 only reported the result for the complete cohort (140 participants: 64 in the endoscopic group and 76 in the surgical group). Only a portion of the total number of participants were randomised (72 randomised and 68 non-randomised participants).
**N consists of all participants without exocrine pancreatic insufficiency at baseline.
N/A = not available.
NS = not significant.

Table 2. Results of Nealon 1993

Outcome	**Surgery (N = 17) N (%)**	**Conservative (N = 15) N (%)**	**P value**
Pain relief (partial or complete)	16 (94%)	2 (13%)	< 0.001
- Complete pain relief	14 (82%)	0 (0%)	< 0.001
- Partial pain relief	2 (12%)	2 (13%)	NS
	Surgery	**Conservative**	**P value**

Table 2. Results of Nealon 1993 *(Continued)*

	(N = 13)*	**(N = 12)***	
New onset endocrine pancreatic insufficiency	2 (15%)	10 (83%)	0.001
	Surgery (N = 15)*	**Conservative (N = 14)***	**P value**
New onset exocrine pancreatic insufficiency	1 (7%)	11 (79%)	< 0.001

*N represents the number of participants without exocrine pancreatic insufficiency at baseline.
NS = not significant.

APPENDICES

Appendix 1. CENTRAL search strategy

1. exp Pancreatitis, Chronic/
2. chronic pancreatitis.mp.
3. 1 or 2
4. ((autoimmun$ or auto-immun$ or Tropical or hereditar$ or familiar$) and pancreatitis).mp.
5. exp Pancreatitis, Alcoholic/
6. exp Pancreatic Ducts/
7. obstruction.mp.
8. 6 and 7
9. (Pancrea$ adj2 Duct$ adj2 obstruction$).mp.
10. 8 or 9
11. alcohol intoxicat$.mp.
12. (autoimmunity$ or auto-immunity$).mp.
13. Hypertriglyceridemia/
14. Hypercalcemia/
15. 12 or 11 or 14 or 13
16. Pancreas/
17. 15 and 16
18. 3 or 4 or 5 or 10 or 17
19. Cholangiopancreatography, Endoscopic Retrograde/ or Drainage/ or Endoscopy/ or Endoscopy, Digestive System/
20. ERCP.mp.
21. Decompression/
22. Sphincterotomy, Endoscopic/
23. Dilatation/
24. Stents/
25. or/19-24
26. 16 and 25
27. Surgery/
28. Surgical Procedures, Operative/
29. 27 or 28
30. 29 and 16
31. Pancreaticojejunostomy/
32. beger.mp.
33. Frey.mp.
34. (puestow or Partington-Rochelle).mp.
35. Pancreatectomy/

36.((left or tail or distal or caudal) and (resection or pancreatectomy)).mp.
37.Pancreaticoduodenectomy/ or whipple.mp.
38.(dilation adj2 pancrea$).mp.
39.or/31-38
40.18 or 26 or 30 or 39

Appendix 2. MEDLINE search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10.(animals not (humans and animals)).sh.
11.9 not 10
12.exp Pancreatitis, Chronic/
13.chronic pancreatitis.mp.
14.12 or 13
15.((autoimmun$ or auto-immun$ or Tropical or hereditar$ or familiar$) and pancreatitis).mp.
16.exp Pancreatitis, Alcoholic/
17.exp Pancreatic Ducts/
18.obstruction.mp.
19.17 and 18
20.(Pancrea$ adj2 Duct$ adj2 obstruction$).mp.
21.19 or 20
22.alcohol intoxicat$.mp.
23.(autoimmunity$ or auto-immunity$).mp.
24.Hypertriglyceridemia/
25.Hypercalcemia/
26.23 or 22 or 25 or 24
27.Pancreas/
28.26 and 27
29.14 or 15 or 16 or 21 or 28
30.Cholangiopancreatography, Endoscopic Retrograde/ or Drainage/ or Endoscopy/ or Endoscopy, Digestive System/
31.ERCP.mp.
32.Decompression/
33.Sphincterotomy, Endoscopic/
34.Dilatation/
35.Stents/
36.or/30-35
37.Surgery/
38.Surgical Procedures, Operative/
39.37 or 38
40.39 and (14 or 27)
41.Pancreaticojejunostomy/
42.beger.mp.
43.Frey.mp.
44.(puestow or Partington-Rochelle).mp.
45.Pancreatectomy/

46.((left or tail or distal or caudal) and (resection or pancreatectomy)).mp.
47.Pancreaticoduodenectomy/ or whipple.mp.
48.(dilation adj2 pancrea$).mp.
49.or/41-48
50.36 or 40 or 49
51.11 and 29 and 50

Appendix 3. Embase search strategy

1. (random$ or placebo$).ti,ab.
2. ((single$ or double$ or triple$ or treble$) and (blind$ or mask$)).ti,ab.
3. controlled clinical trial$.ti,ab.
4. RETRACTED ARTICLE/
5. or/1-4
6. (animal$ not human$).sh,hw.
7. 5 not 6
8. exp Pancreatitis, Chronic/
9. chronic pancreatitis.mp.
10.8 or 9
11.((autoimmun$ or auto-immun$ or Tropical or hereditar$ or familiar$) and pancreatitis).mp.
12.exp Pancreatitis, Alcoholic/
13.exp Pancreatic Ducts/
14.obstruction.mp.
15.13 and 14
16.(Pancrea$ adj2 Duct$ adj2 obstruction$).mp.
17.15 or 16
18.alcohol intoxicat$.mp.
19.(autoimmunit$ or auto-immunit$).mp.
20.Hypertriglyceridemia/
21.Hypercalcemia/
22.19 or 18 or 21 or 20
23.Pancreas/
24.22 and 23
25.10 or 11 or 12 or 17 or 24
26.Cholangiopancreatography, Endoscopic Retrograde/ or Drainage/ or Endoscopy/ or Endoscopy, Digestive System/
27.ERCP.mp.
28.Decompression/
29.Sphincterotomy, Endoscopic/
30.Dilatation/
31.Stents/
32.or/26-31
33.Surgery/
34.Surgical Procedures, Operative/
35.33 or 34
36.35 and (10 or 23)
37.Pancreaticojejunostomy/
38.beger.mp.
39.Frey.mp.
40.(puestow or Partington-Rochelle).mp.
41.Pancreatectomy/
42.((left or tail or distal or caudal) and (resection or pancreatectomy)).mp.
43.Pancreaticoduodenectomy/ or Whipple.mp.
44.(dilation adj2 pancrea$).mp.

45.or/37-44
46.32 or 36 or 45
47.7 and 25 and 46

Appendix 4. Conference Proceeding Index - Science search strategy

#1 Topic=(chronic pancreatitis) OR Title=(chronic AND pancreatitis)

#2 Topic=((autoimmun* OR auto-immun* OR tropical OR hereditar* OR familiar*) AND (pancreatitis))

#3 Title=((autoimmun* OR auto-immun* OR tropical OR hereditar* OR familiar*) AND (pancreatitis))

#4 Topic=((pancrea*) AND (obstruction OR "alcohol intox*" OR autoimmune* OR auto-immun* OR Hypertriglyceridem* OR Hypercalcem*))

#5 Title=((pancrea*) AND (obstruction OR "alcohol intox*" OR autoimmune* OR auto-immun* OR Hypertriglyceridem* OR Hypercalcem*))

#6 #1 OR #2 OR #3 OR #4 OR #5

#7 Topic=((endosc* OR ERCP OR decompression OR drainage OR sphincterotomy OR dilatation OR stent* OR surg* OR beger OR frey OR PJ OR pancreaticojejunostomy OR puestow OR partington-rochelle OR PD OR Pancreaticoduodenectomy OR PPPD OR whipple))

#8 Title=((endosc* OR ERCP OR decompression OR drainage OR sphincterotomy OR dilatation OR stent* OR surg* OR beger OR frey OR PJ OR pancreaticojejunostomy OR puestow OR partington-rochelle OR PD OR Pancreaticoduodenectomy OR PPPD OR whipple))

#9 Topic=((left OR tail OR distal OR caudal) AND (resection OR pancreatectomy))

#10 Title=((left OR tail OR distal OR caudal) AND (resection OR pancreatectomy))

#11 #7 OR #8 OR #9 OR #10

#12 #6 AND #11

Appendix 5. Glossary

Anastomosis: a connection made surgically between adjacent blood vessels, parts of the intestines or other channels of the body.

Cholecystitis: inflammation of the gallbladder.

Fascial dehiscence (Platzbauch): a postoperative rupture of the abdominal wall, when the skin has not healed.

Hypercalcaemia: elevated levels of calcium in the blood.

Hypertriglyceridaemia: elevated levels of triglycerides (a type of lipids) in the blood.

Ileus: disruption of the normal mobility of the contents of the intestines, either due to decrease motility of the bowels or obstruction of the bowels.

Jejunum: middle part of the small intestines.

Lithotripsy: procedure in which sounds waves are used to break up stones in a hollow organ in the body.

Pancreaticoduodenectomy: a procedure in which the pancreas along with a part of the duodenum (first part of the small intestines) are surgically resected.

Pancreas divisum: a congenital abnormality of the pancreatic duct, in which a single duct is not formed, but rather remains as two distinct smaller ducts.

Papilla of Vater: the opening of the joined pancreatic duct and bile duct into the small intestines.

Papillotomy: an endoscopic procedure in which a cut is place into the Papilla of Vater to make it wider, and facilitate drainage of pancreatic excretions and bile.

Parenchymal hypertension: elevated pressure into the tissue (parenchyma) of the pancreas.

Pseudocyst: a collection of fluid (like a cyst) with a distinct epithelial lining (i.e. fluid is kept together by surrounding tissue).

Pylorus: the final part of the stomach that connects it to the duodenum (first part of the small intestines).

WHAT'S NEW

Date	Event	Description
7 June 2014	New citation required but conclusions have not changed	No new studies were identified for inclusion in the review
7 June 2014	New search has been performed	Search updated and results incorporated in the review

CONTRIBUTIONS OF AUTHORS

U Ahmed Ali, JM Pahlplatz, HG Gooszen, and MA Boermeester participated in the design of this review and drafting of the protocol.
U Ahmed Ali and JM Pahlplatz participated in the literature search, extraction of data, and methodological quality assessment of the studies.
U Ahmed Ali, H van Goor, HG Gooszen, and MA Boermeester participated in the statistical analysis and interpretation of results.
WH Nealon provided data and reviewed the protocol and final manuscript.
U Ahmed Ali and JM Pahlplatz drafted the review.
All authors co-authored the writing of the review and read and approved the final manuscript.

DECLARATIONS OF INTEREST

Usama Ahmed Ali: nothing to declare.
Johanna M Pahlplatz: nothing to declare.
Wiliam H Nealon: nothing to declare. He is a co-author of one of the included studies, which was not commercially funded. He did not not participate in the appraising of this study for inclusion or risk of bias, and was not responsible for data extraction.
Harry van Goor: Grants received regard innovative medical therapy to reduce pain and normalize pain processing in opioid dependent patients with chronic pancreatitis, which are outside of the scope of this review.
Hein G Gooszen: nothing to declare.
Marja A Boermeester: nothing to declare. She is a co-author of one of the included studies, which was not commercially funded. She did not not participate in the appraising of this study for inclusion or risk of bias, and was not responsible for data extraction.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We conducted this review in accordance with the published protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Constriction, Pathologic [complications]; Endoscopy, Gastrointestinal [adverse effects] [*methods]; Humans; Pain [etiology] [*surgery]; Pain Management [*methods]; Pancreatic Ducts; Pancreatitis, Chronic [*surgery]; Pressure [adverse effects]; Randomized Controlled Trials as Topic