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 in patients with obstructive chronic pancreatitis. Physicians face the decision between endoscopy and surgery for this group of patients, without clear consensus.

Objectives

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

Search methods

We searched *The Cochrane Library*, MEDLINE, EMBASE and the Conference Proceedings Citation Index; and performed a cross-reference search. Two review authors performed the selection of trials independently.

Selection criteria

All randomised controlled trials (RCTs) investigating endoscopic or surgical interventions for obstructive chronic pancreatitis. All trials were included irrespective of blinding, number of patients randomised and language of the article.

Data collection and analysis

Two authors independently extracted data from the articles. The methodological quality of included trials was evaluated. Authors were requested additional information in the case of missing data.

Main results

We screened 2082 publications and identified three eligible trials. Two trials compared endoscopic intervention to surgical intervention. These included a total of 111 patients, 55 in the endoscopic group and 56 in the surgical group. A higher proportion of patients with pain relief was found in the surgical group compared to the endoscopic group (partial or complete pain relief: RR 1.62, 95% confidence

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interval (CI) 1.11 to 2.37; complete pain relief: RR 2.45, 95% CI 1.18 to 5.09). Surgical intervention resulted in improved quality of life and improved preservation of exocrine pancreatic function in one trial. The number of patients did not allow for a reliable evaluation of morbidity and mortality between the two treatment modalities. One trial compared surgical intervention to conservative treatment. It included 32 patients: 17 in the surgical group and 15 in the conservative group. The trial showed that surgical intervention resulted in a higher percentage of patients with pain relief and better preservation of pancreatic function. The trial had methodological limitations and the number of patients was relatively small.

Authors' conclusions

For patients with obstructive chronic pancreatitis and dilated pancreatic duct, this review showed that surgery is superior to endoscopy in terms of pain control. Morbidity and mortality seemed 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 seems to be a promising approach in terms of pain control and pancreatic function. Confirmation of these results is needed in other trials due to the methodological limitations and limited number of patients of the present evidence.

PLAIN LANGUAGE SUMMARY

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

Endoscopy and surgery are the treatments of choice in patients with chronic pancreatitis and a dilated pancreatic duct. In this review we compared these two intervention modalities. We found that surgery achieved pain relief in a higher proportion of patients than with endoscopy. Surgery also had other advantages like improved quality of life and reduced risk of developing exocrine pancreatic insufficiency. The studies seemingly showed no difference in complications after intervention between endoscopy and surgery, but lacked the power to establish this with sufficient reliability. We also compared surgery to conservative treatment. Results of one trial suggested that surgery early in the disease achieved better pain relief and preservation of pancreatic function. The trial, however, was small, which precluded drawing reliable conclusions.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [\[Explanation\]](#)

Endoscopy compared to surgery for painful obstructive chronic pancreatitis						
Patient or population: patients with painful obstructive chronic pancreatitis Settings: 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 Follow-up: 2-3 years	509 per 1000	825 per 1000 (621 to 1000)	RR 1.62 (1.22 to 2.15)	111 (2 studies)	⊕⊕⊕○ moderate ¹	
Major complications	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. No significant differences were observed. Observed outcome rates were: Endoscopy 0/19 (0%) vs Surgery 1/20 (5%) (CaHEN 2007), and 5/64 (8%) and 3/76 (4%) (Dite 2003) (Table 1). ²
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. No significant differences were

				observed. Observed outcome rates were: Endoscopy 1/19 (5%) vs Surgery 0/20 (0%) (Cahen 2007), 0% in both arms (Dite 2003) (Table 1). ²
Quality of life SF-36 - Physical health. Scale from: 0 to 100. Follow-up: median 24 months	The mean quality of life in the control groups was 38 points	The mean Quality of life in the intervention groups was 9.00 higher (3.92 to 14.08 higher)	39 (1 study ⁴)	⊕⊕⊕○ moderate ³
Quality of life SF-36 - Mental health. Scale from: 0 to 100. Follow-up: median 24 months	The mean quality of life in the control groups was 40 points	The mean Quality of life in the intervention groups was 5.00 higher (0.65 lower to 10.65 higher)	39 (1 study ⁴)	⊕⊕⊕○ moderate ³
Endocrine pancreatic insufficiency (new onset) Follow-up: 2-3 years	300 per 1000	294 per 1000 (165 to 528)	102 (2 studies)	⊕⊕○○ low ^{1,3}
		RR 0.98 (0.55 to 1.76)		Only patients without endocrine pancreatic insufficiency at baseline (new onset insufficiency) are included in the analysis (Table 1).
Exocrine pancreatic insufficiency (new onset) Follow-up: 2-3 years	1000 per 1000	320 per 1000 (80 to 1000)	10 (1 study ⁴)	⊕⊕⊕○ moderate ^{1,3}
		RR 0.32 (0.08 to 1.25)		Only patients 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 ([Dite 2003](#)) had some serious methodological limitations. The second trial ([Cahen 2007](#)), however, was a well conducted trial. Results were consistent and evident both trials.

² One of the trials ([Dite 2003](#)) published data for this outcome for a cohort including randomised and non-randomised patients. We could not obtain the data from the randomised group separately.

³ The number of patients does not provide enough power to detect differences that could exist between the two groups.

⁴ Only one study ([Cahen 2007](#)) reported this outcome.

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 chronic pancreatitis in Western Europe are estimated to be around seven and 26 per 100,000, respectively (Dite 2001; Levy 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. Management of this disease is, therefore, mostly focused towards pain alleviation (AGA 1998; van Esch 2006). Longstanding CP is also associated with 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, CP can be complicated by pancreatic pseudocyst formation, abscess formation, stenosis of the common bile duct and an increased risk of pancreatic cancer (Lankisch 2001).

Description of the intervention

In patients with obstructive CP 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) and 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 in some patients subsequent surgery is still needed. 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 Bern operations) (Strate 2005). Patients typically remain hospitalized 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 decision 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 due to the lack of head-to-head comparisons (Gourgiotis 2007; Tringali 2008; van der Gaag 2007). One review of randomised clinical trials on endoscopic versus surgical interventions was published recently, but the methodology was not explicit and the review lacked a clear conclusion (Devriere 2008). We, therefore, aimed to review and summarise the evidence for both treatment modalities.

OBJECTIVES

To assess and compare the effectiveness 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). All trials were included irrespective of blinding, number of patients randomised and 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 were included.

- Endoscopic versus surgical intervention.
- Endoscopic intervention versus conservative treatment.
- 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 one of 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 patients achieving pain relief compared to 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. Partial pain relief was defined as a decrease in pain of at least 50% compared to baseline, without achieving complete pain relief. We conducted analysis for complete and partial pain relief separately, and for total proportion of patients experiencing pain relief (both partial and complete).
- Major post-interventional 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 post-interventional complications: these included 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.

- *The Cochrane Library*, 2011, Issue 4 (search strategy in [Appendix 1](#)):
 - Cochrane Database of Systematic Reviews;
 - Database of Abstracts of Reviews of Effects (DARE);
 - Cochrane Central Register of Controlled Trials (CENTRAL).
- MEDLINE via Ovid (from 1950 to November 2011) ([Appendix 2](#)).
- EMBASE via Ovid (from 1980 to November 2011) ([Appendix 3](#)).
- Conference Proceedings Citation Index - Science (CPCI-S) (from 1990 to February 2010) ([Appendix 4](#)).

We developed the search strategies in cooperation 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) performed the selection of trials independently. 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 consensus was reached by discussion.

Data extraction and management

Two review authors (UAA and JMP) independently extracted all relevant data. For each study the review authors extracted patient characteristics, study characteristics, data needed for the methodological quality assessment of the study and the primary and secondary outcomes, according to availability. Data regarding patient characteristics included number of patients 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. These data are presented in the [Characteristics of included studies](#) table.

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 the allocation sequence was generated by a computer or random number table. Drawing of lots, tossing of a coin, shuffling of cards, or throwing dice was considered 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 patients.

Allocation concealment

- Adequate, if the allocation of patients 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 allocation sequence was known to the investigators who assigned the participants.

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 dropouts did not exceed 20%, and numbers and reasons for dropouts and withdrawals in all intervention groups were described.
- Unclear, if the report gave the impression that there had been no dropouts or withdrawals but this was not specifically stated.
- Inadequate, if the percentage of dropouts exceeded 20%, or the numbers and reasons for dropouts 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 pre-specified.
- Unclear, if insufficient information was provided to permit clear judgement of this aspect.
- Inadequate, if all relevant outcomes and all the study's pre-specified 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 analysis of binary data using risk ratio (RR) as the summary statistic. For continuous outcomes we used mean differences (MD) as the summary statistic.

Assessment of heterogeneity

We calculated the heterogeneity using the Chi^2 test and quantified the inconsistency in study effects by 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

Due to the low number of identified studies, funnel plots were not useful in assessing the presence of publication bias. We, therefore, 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.
- Surgical intervention versus conservative treatment.

If appropriate data were available, meta-analysis was conducted. 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 $I^2 < 50\%$). In all other cases we used the random-effects model.

Due to insufficient numbers of trials, we were not able to perform a subgroup analysis according to the methodological quality of the included trials. The methodological quality of trials has been presented using the criteria of the risk of bias assessment tool described earlier, and has been taken into consideration when discussing the results of the review.

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

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

Results of the search

We performed the search on 3 November 2011 and obtained a total of 2082 publications. We screened titles and abstract of all publications and excluded 2060 publications. Twenty-two potentially relevant publications remained for full-text reviewing. One publication was a study protocol of an ongoing trial (see [Characteristics of ongoing studies](#)). Two publications described a randomised trial of endoscopy versus extracorporeal shock-wave lithotripsy (ESWL). Since ESWL can not be considered as conservative treatment, this trial did not fulfil our inclusion criteria and was excluded (see [Characteristics of excluded studies](#)). Eleven publications were excluded for other reason (see [Characteristics of excluded studies](#)). Finally, we included five publications describing three distinct trials; one trial was described in three publications ([Cahen 2007](#)) (see [Characteristics of included studies](#)).

A cross-reference search of included trials and three additional reviews ([Deviere 2008](#); [Gourgiotis 2007](#); [van der Gaag 2007](#)) yielded no new eligible publications. [Figure 1](#) is a flow-chart depicting the flow of the selection process.

Figure 1. Study flow diagram.

Included studies

Two trials compared endoscopic intervention to surgical intervention (Cahen 2007; Dite 2003). One compared surgical intervention to conservative treatment (Nealon 1993). We did not identify any trials comparing endoscopic intervention to conservative treatment. We did encounter one ongoing trial comparing endoscopic intervention to sham endoscopy (Characteristics of ongoing studies). The characteristics of the included trials are described in the table 'Characteristics of included studies'. A brief summary of the most important characteristics is found below.

Studies comparing endoscopic versus surgical intervention

The two trials (Cahen 2007; Dite 2003) included a total of 111 patients, of whom 55 were in the endoscopic group and 56 in the surgical group.

Cahen 2007 randomised 39 patients with advanced CP (all patients needed opioid analgesics before study inclusion), a dilated pancreatic duct (> 5 mm) and without pancreatic head enlargement between endoscopy (19 patients) and surgery (20 patients). 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. Patients 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 patient, a Whipple procedure was performed because of peripancreatic inflammation. In another patient, 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 patients with pain relief, quality of life (SF-36), complications, mortality, duration of hospital stay, number of hospital readmittances, 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 study was prematurely terminated by the safety committee on the bases of the 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).

Dite 2003 included 140 patients in the study but only randomised 72 patients. The other 68 patients refused to be randomised in the trial due to an outspoken preference for one of the treatment modalities. Dite 2003 reported some outcomes for the randomised group separately. However, baseline characteristics and other out-

comes (for example complications) were only reported for the complete cohort.

In the randomised group 36 patients were allocated to each of the two groups. All patients had advanced CP (at least three years of failed medical management) and obstruction of the pancreatic duct. Patients 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. Data on the specific operation were only reported 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 versus conservative treatment

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

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

The trial, therefore, included 32 patients with mild to moderate (early stage) CP and dilated pancreatic duct, allocated to either early surgical treatment (17 patients) or conservative treatment (15 patients). 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

All excluded publications that were not obviously excluded based on title and abstract alone (that is full-text reviewing was necessary for exclusion) are listed with the reason for exclusion in the table 'Characteristics of excluded studies'. Reasons for exclusion of these studies were: non-randomised trial (five publications), comment (two publications), study not about CP (one publication) and a book chapter (one publication).

Risk of bias in included studies

Risk of bias varied considerably between the three included trials. An overview of the different aspects of the risk of bias are illustrated in the risk of bias summary figures (Figure 2; Figure 3). A detailed description of the risk of bias assessment can be found in the 'Characteristics of included studies' table.

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

Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for the three included trials.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cahen 2007						
Dite 2003						
Nealon 1993						

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

Effects of interventions

See: [Summary of findings for the main comparison](#) Endoscopy compared to surgery for painful obstructive chronic pancreatitis; [Summary of findings 2](#) Surgery compared to conservative treatment for painful obstructive chronic pancreatitis

Endoscopic versus surgical intervention

Two studies comparing endoscopic versus surgical treatment were identified ([Cahen 2007](#); [Dite 2003](#)). The two studies mostly reported different outcomes. Pooling of data was only possible in regard to two outcomes: pain relief and new onset endocrine pancreatic insufficiency. A narrative review is provided for other outcomes. Results of all outcomes considered to be of critical importance according to the GRADE guideline (scored 7 or higher on a 9-point score) were summarised 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 patients with pain relief (partial or complete) in the surgical group compared to the endoscopic group (RR 1.62, 95% confidence interval (CI) 1.22 to 2.15) (Analysis 1.1; Figure 4). The proportion of patients with complete pain relief was higher in the surgical group (RR 2.45, 95% CI 1.18 to 5.09) but there was no difference in the proportion of patients with partial pain relief (Analysis 1.2; Figure 5).

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

Figure 5. Forest plot of comparison: 1 Endoscopy versus surgery, outcome: 1.2 Complete and partial pain relief.

Major post-interventional complications

Both studies reported on major complications associated with study interventions (Table 1). There was no evidence for a differ-

ence between the surgical and endoscopic interventions.

Mortality

Both studies reported on mortality. One death was reported in the endoscopic group (Table 1). There was, therefore, no evidence for 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 patients undergoing surgery scored higher (better) on the physical health component of the SF-36 quality of life scale. No difference was observed in the mental health component of the same instrument.

Minor post-interventional complications

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

Pancreatic function

Endocrine pancreatic function was reported by both studies. The proportion of new onset endocrine pancreatic insufficiency was pooled (Analysis 1.3; Figure 6). There was no evidence for a difference between the two groups.

Figure 6. Forest plot of comparison: 1 Endoscopy versus surgery, outcome: 1.3 Endocrine pancreatic insufficiency (new onset).

Exocrine pancreatic function was reported by Cahen 2007. In the endoscopic group, exocrine pancreatic insufficiency developed in six out of six patients (100%) with intact exocrine pancreatic function at baseline, compared to one out of four patients (25%) in the surgical group. The difference was statistically significant (Table 1).

Number of needed endoscopic and surgical procedures

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

Change in nutritional status

Dite 2003 reported a higher proportion of patients with increases in body weight at the end of the follow-up period in the surgical

group compared to 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 for a difference between the two groups.

Surgical intervention versus conservative treatment

We identified one trial (Nealon 1993) comparing surgical intervention to conservative treatment for CP. We summarised the findings of this study in Table 2. In summary, this study showed a highly significant difference in favour of early surgical intervention compared to conservative treatment in regard to pain relief and pancreatic function. Partial or complete pain relief was observed in 16 out of 17 (94%) patients in the surgical group versus 2 out of 15 (13%) in the conservative group. The proportion of patients developing new onset endocrine and exocrine pancreatic

insufficiency was, respectively, 2 out of 13 (15%) and 1 out of 15 (7%) patients in the surgical group versus 10 out of 12 (83%) and 11 out of 14 (79%) patients in the conservative group.

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) were summarised in the [Summary of findings 2](#).

ADDITIONAL SUMMARY OF FINDINGS [\[Explanation\]](#)

Surgery compared to conservative treatment for painful obstructive chronic pancreatitis						
Patient or population: patients with painful obstructive chronic pancreatitis						
Settings:						
Intervention: surgery						
Comparison: conservative						
Outcomes	Illustrative comparative risks * (95% CI)			Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk				
	Conservative	Surgery				
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
Mortality - not reported	See comment	See comment		Not estimable	-	See comment
Quality of life - not measured	See comment	See comment		Not estimable	-	See comment
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 patients without endocrine pancreatic insufficiency at baseline (new onset insufficiency) were included in analysis (Table 2). 						

Exocrine pancreatic insufficiency (new onset) Follow-up: 2-3 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 patients without exocrine pancreatic insufficiency at baseline (new onset insufficiency) were included in analysis (Table 2)
<p>*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).</p> <p>CI: confidence interval; RR: risk ratio;</p> <p>GRADE Working Group grades of evidence</p> <p>High quality: Further research is very unlikely to change our confidence in the estimate of effect.</p> <p>Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p>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.</p> <p>Very low quality: We are very uncertain about the estimate.</p>						

¹ Trials showed some important methodological limitations (see Summary of risk of bias Figure 3).

² The number of patients did not fulfil the GRADE guidelines for sufficient precision.

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 to endoscopic treatment, for patients with obstructive CP. This finding was consistent in the two RCTs included (Cahen 2007; Dite 2003). The observed difference had an evident clinical importance and was long lasting. Additional benefits of surgery compared to endoscopy were reported as well, mainly improved quality of life 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 due to the small size of the trials.

Surgical intervention to conservative treatment

This review identified one trial (Nealon 1993) comparing surgical intervention to 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). The main finding of this review regarding this topic is, therefore, that in an early stage of CP surgery rather than conservative treatment seems to be associated with potential benefits, which merits 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. The study of Dite 2003, on the other hand, reported only a limited set of outcomes.

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

Two concerns could be raised regarding the applicability of the results of Dite 2003. First, the study did not exclude patients 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 patients in the surgical arm had some type of surgical resection procedure. Secondly, the endoscopic intervention did not include the use of ESWL. This modality is considered by experts 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 patients were only included if a consensus between the surgeon and the gastroenterologist was established 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 patient selection that could compromise external validity (Yusuf 1990). Regarding the lack of ESWL in the endoscopic group, it could be argued that in many centers ESWL is simply not (yet) used as a routine treatment modality for this group of patients. Dite 2003 may, therefore, 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 exclusion criteria are not clearly listed in the report. This limits the ability to draw conclusions regarding the generalizability of the results.

Quality of the evidence

Endoscopic versus surgical intervention

This review included two RCTs with a total of 111 patients. 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 and quality of life, 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, due to significant results of benefit. Termination of trials before full inclusion due to 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.

[Dite 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, to up to 40% ([Schulz 1995](#)). In its defence, [Dite 2003](#) did specify that patients were only included if a consensus was established by a consulting gastroenterologist and surgeon regarding the inclusion of patients. 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 patients 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, sufficient to draw conclusions about benefits of both interventions, especially regarding pain relief. The fact that the two RCTs show consistent results and that the observed differences are more evident (both statistically and clinically) in the study with low risk of bias, increase 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, one trial [Nealon 1993](#) including 32 patients was identified for this comparison. This trial has 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 patients was conducted over a long period of time and the methodology was not clearly reported. 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 ([Nealon 1993](#)). 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.

Taking the above mentioned in mind, this trial is best considered as a hypothesis-generating pilot trial that should lead to further studying of the promising results shown by this trial 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 studies included, 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 [Deviere 2008](#) comparing endoscopic to surgical treatment for CP and including the same two RCTs as in our review concluded that the low number of patients in the trials and the differences in methodology did not allow for drawing any conclusions about the choice between endoscopy and surgery. [Deviere 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 1 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 generalizability and validity of this evidence.

Surgical intervention versus conservative treatment

Although [Nealon 1993](#) is the only RCT that has compared surgical intervention at an early stage of CP to 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. In an experimental model of early versus late surgical drainage for CP in piglets, it was observed that the histology of the pancreas and exocrine pancreatic function were significantly better in the early surgical group compared to 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 term of benefits (that is pain control and quality of life). However, when it comes to morbidity and mortality, this review is not able to draw reliable conclusions. Therefore, we believe that surgery should be considered the treatment of choice for patients with severe CP, but 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 can not 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 in 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 patients 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. Investigating these results in a large well conducted RCT, with attention to benefit, harm and cost-effectiveness of both interventions, is recommended.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Cahen 2007

Methods	<p>Study design: randomised controlled trial</p> <p>Setting of study: single center, AMC Amsterdam, the Netherlands</p> <p>Follow-up period: 24 months</p> <p>Loss to follow-up: one patient in the surgical group</p> <p>Type of analysis: intention-to-treat analysis</p> <p>Sample size calculations: yes, a sample size of 50 patients was calculated</p>
Participants	<p>Number of participants: 39 (19 in the endoscopy group, 20 in the surgical group)</p> <p>Gender: endoscopy group: 11 males, 8 females; surgery group: 15 males, 5 females</p> <p>Age [mean (SD)]: endoscopy group: 52 years (9); surgery group: 46 years (12)</p> <p>BMI [mean (SD)]: endoscopy group: 21 kg (4. 1); surgery group: 21 kg (3. 7)</p> <p>Type of pain:</p> <ul style="list-style-type: none"> endoscopy group: 7 patients with intermittent pain (type A), 12 patients with continuous pain (type B) surgery group: 9 patients with intermittent pain (type A), 11 patients with continuous pain (type B) <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Established CP Obstruction of pancreatic duct (>5 mm) No pancreatic head enlargement Severe recurrent pancreatic pain intractable to non-narcotic analgesics <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Age <18 or > 80 years Enlargement of pancreatic head > 4 cm Contra-indications to surgery or endoscopic interventions Previous pancreatic surgery Suspected pancreatic malignancy, or life expectancy < 2 years Pregnancy <p>Duration of symptoms: endoscopy group: 16 months (SD 14); surgery group 21 months (SD 19)</p> <p>Ongoing alcohol abuse at randomisation: endoscopy group: 0 patients; surgical group: 5 patients</p> <p>Ongoing smoking at randomisation: endoscopy group: 15 patients; surgical group: 17 patients</p>
Interventions	<p>Endoscopic drainage versus surgical drainage:</p> <ul style="list-style-type: none"> Endoscopic drainage: endoscopic drainage of the pancreatic duct by ERCP with (repeated) dilatation and stent placement if required. Patients with large stones in the pancreatic duct (>7mm) 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 one patient, a Whipple procedure was performed because of peripancreatic inflammation. In another patient, stone extraction required a Frey procedure.

	Endoscopic experience: study interventions were performed by experienced endoscopists (performed > 1000 ERCPs) Surgical experience: surgical procedures were performed by experienced pancreatic surgeons (no specific criteria stated)
Outcomes	<p>Primary outcome (prespecified in method section):</p> <ul style="list-style-type: none"> • Pain score (Izbicki questionnaire) <p>Secondary outcomes (prespecified in method section):</p> <ul style="list-style-type: none"> • Pain relief (defined by Izbicki score) • Physical and mental health (SF-36 questionnaires) • Post-interventional complications • Length of hospital stay • Number of performed procedures • Change in pancreatic function • Mortality <p>Other outcomes (results reported, but not specified in method section):</p> <ul style="list-style-type: none"> • Conversion to surgery • Technical success of intervention • Hospital re-admittance <p>Time points of outcomes: 6 weeks and 3, 6, 12, 18 and 24 months</p>
Notes	<ul style="list-style-type: none"> • Study was terminated prematurely by the safety committee on the bases 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). • Author provided us with additional methodological information and data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Automated assignment system.
Allocation concealment (selection bias)	Low risk	Specifically stated.
Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Proportion of loss to follow-up did not exceed 20%.
Selective reporting (reporting bias)	Low risk	All relevant and pre-specified outcomes reported.
Other bias	Low risk	Study terminated prematurely, but authors performed adequate adjustment for treatment effect and P value for early termination

Methods	<p>Study design: pseudo-randomised controlled trial (alternating allocation)</p> <p>Setting of study: single center, University Hospital Brno, Czech Republic</p> <p>Follow-up period: 5 years</p> <p>Loss to follow up: patients not compliant to follow-up were excluded</p> <p>Type of analysis: per protocol analysis</p> <p>Sample size calculation: yes, a sample size of 140 patients was calculated</p>
Participants	<p>Number of randomised participants: 72 (36 in the endoscopy group, 36 in the surgical group). The population of the RCT is part of a larger prospective cohort reported in the same publication. The total sample of the cohort is 140</p> <p>Gender: not specified for the randomised group (only for the complete cohort, with 119 males and 21 females)</p> <p>Age: not specified for the randomised group (only for the complete cohort with a mean age of 41.7 years ranging between 26-53)</p> <p>BMI: not specified</p> <p>Type of pain (continuous vs recurrent flairs ups): not specified</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Established CP • Obstruction of pancreatic duct (dilated pancreatic duct) • Painful CP (pain score > 3 on the Melzack's pain score) • Failure of conservative management in the previous 3 years • Duration clinical CP for more than 5 years • Consensus of surgeon and gastroenterologist regarding suitability of patient for both endoscopy and surgery <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • 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 <p>Duration of symptoms: > 5 years (inclusion criteria)</p> <p>Ongoing alcohol abuse and/or smoking at randomisation: not reported</p>
Interventions	<p>Endoscopic drainage versus surgical intervention (drainage and resection):</p> <ul style="list-style-type: none"> • Endoscopic drainage: endoscopic drainage of the pancreatic duct by ERCP with pancreatic sphincterotomy, stone extraction, 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 pre-operative imaging. Pancreaticojejunostomy was performed in patients with absence of focal pancreatic enlargement. In patients 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. <p>Endoscopic experience: study interventions were performed by two experienced endoscopists (performed > 200 drainage procedures)</p> <p>Surgical experience: surgical procedures was performed by one abdominal surgeon (performed 90 pancreatic operations before the start of the study)</p>

Outcomes	Primary outcome (prespecified in method section): <ul style="list-style-type: none">● Pain relief (defined by Melzack score)● Necessity for further interventions Secondary outcomes (prespecified in method section): <ul style="list-style-type: none">● Change in body weight● Presence of diabetes Other outcomes (results reported, but not specified in method section): <ul style="list-style-type: none">● Complications● Mortality Time points of outcomes: 6 months and 1, 3 and 5 years	
Notes	<ul style="list-style-type: none">● The population of the RCT is part of a larger prospective cohort reported in the same publication.● Author provided us with additional information regarding methodology of the study, but not with additional data regarding missing baseline characteristics and outcomes.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Allocation 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	Patients not compliant to follow-up were excluded.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported.
Other bias	Unclear risk	<ul style="list-style-type: none">● The study did not present a baseline table with relevant patient characteristics and potential confounders (e.g. smoking, alcohol use, pre-operative pain, etc).● Study allowed for inclusion of patients with enlarged pancreatic head. These patients 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 center, The University of Texas Medical Branch, Galveston, Texas Follow-up period: median 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 patients (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: <ul style="list-style-type: none">Established CPDilation of pancreatic ductMild, non-debilitating painMild 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) . Patients were categorized as mild/moderate (3 or less points) or severe CP (more than 3 points). Exclusion criteria: not specified Duration of symptoms: not specified Ongoing alcohol abuse at randomisation: not specified for patients within the RCT Ongoing smoking at randomisation: not specified	
Interventions	Surgical drainage versus conservative treatment <ul style="list-style-type: none">Surgical drainage: surgical drainage of the pancreatic duct by means of a longitudinal pancreaticojejunostomy. With choledochenterostomy and pseudocyst drainage when deemed necessary. In patients with duodenum obstruction a gastrojejunostomy was performed as well.Conservative treatment: not specified. Surgical experience: not specified	
Outcomes	Primary and secondary outcomes (prespecified in method section): not specified as such Outcomes (specified in method section): <ul style="list-style-type: none">Presence of abdominal painGrade of CP (using the self developed grading system described above) Other outcomes (results reported, but not specified in method section): <ul style="list-style-type: none">Exocrine and endocrine pancreatic function Time points of outcomes: standardised follow-up each 14 to 16 months	
Notes	<ul style="list-style-type: none">The population of the RCT is part of a larger prospective cohort reported in the same publication.The author only published the results of the first 17 patients. Other data were provided to us by the author for the purpose of this review.	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Nealon 1993 (Continued)

Random sequence generation (selection bias)	Unclear risk	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	Proportion of losses to follow-up did not exceed 20%.
Selective reporting (reporting bias)	Low risk	All specified data were reported.
Other bias	Unclear risk	The study did not present a baseline table with relevant patient characteristics and potential confounders

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Alexakis 2005	Abstract was not electronically available. Publication appeared to be a book chapter. Not an original publication
Cahen 2011	Report is only available in abstract form. This is a long-term report of one of the included trials. Final report will be added to the review when published
Chang 2010	Diagnostic study comparing endoscopic ultrasound with transabdominal ultrasound for upper abdominal pain
Connors 1993	Abstract was not electronically available. Publication is a comment on another study regarding use of stents in acute recurrent pancreatitis. Chronic pancreatitis patients were excluded
Dumonceau 2007	Randomised trial comparing endoscopic intervention to an alternative treatment, i.e. extracorporeal shock-wave lithotripsy (ESWL)
Iqbal 2009	Non-randomised trial comparing endoscopic intervention to surgical intervention in pediatric patients
Knoefel 1997	Abstract was not electronically available. Publication only provides comment on the Nealon 1993 study. No original data.
Laramée 2010	Publication (only in abstract form) is a report of an economic evaluation based on a review of literature

(Continued)

Lee 2005	Abstract was not electronically available. Publication (only in abstract form) is a report of a non-randomised series
Levy 1989	Abstract was not electronically available. Publication (only in abstract form) is a report of a non-randomised comparison
Lipsky 1993	Abstract was not electronically available. Study compares two techniques for treatment of oesophageal strictures
Noda 2004	Abstract was not electronically available. Publication (only in abstract form) is a report of a non-randomised comparison of different methods of litholysis
Sauer 2008	Abstract was not electronically available. Publication (only in abstract form) is a report of a non-randomised comparison
Seiler 2009	No abstract. Publication is a commentary on a protocol of a randomised trial comparing endoscopic intervention to sham intervention (Wilcox 2009)
Wagh 2008	Abstract was not electronically available. Publication (only in abstract form) describes a cohort of patients, without comparison

Characteristics of ongoing studies [ordered by study ID]

Wilcox 2009

Trial name or title	A randomised trial comparing endoscopic stenting to a sham procedure for chronic pancreatitis
Methods	Randomised controlled trial
Participants	Patients with typical abdominal pain, imaging confirmation of CP and endoscopic retrograde cholangiopancreatography (ERCP) confirmation of PD stricture
Interventions	ERCP with sphincterotomy and PD stenting versus sham procedure
Outcomes	Primary endpoint: reduction in abdominal pain. Secondary endpoints: 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 utilization (emergency room, clinic visits, or hospitalizations); 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. Tel: (205) 975-4958, Fax: (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	111	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.22, 2.15]
2 Complete and partial pain relief	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Complete pain relief	2	111	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [1.18, 5.09]
2.2 Partial pain relief	2	111	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.83, 1.99]
3 Endocrine pancreatic insufficiency (new onset)	2	102	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.55, 1.76]

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

Review: Endoscopic or surgical intervention for painful obstructive chronic pancreatitis

Comparison: 1 Endoscopy versus surgery

Outcome: 1 Pain relief

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

Review: Endoscopic or surgical intervention for painful obstructive chronic pancreatitis

Comparison: 1 Endoscopy versus surgery

Outcome: 2 Complete and partial pain relief

Analysis 1.3. Comparison 1 Endoscopy versus surgery, Outcome 3 Endocrine pancreatic insufficiency (new onset).

Review: Endoscopic or surgical intervention for painful obstructive chronic pancreatitis

Comparison: 1 Endoscopy versus surgery

Outcome: 3 Endocrine pancreatic insufficiency (new onset)

ADDITIONAL TABLES

Table 1. Results of studies comparing endoscopic to surgical treatment

	Cahen 2007			Dite 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	38 (9)	47 (7)	0.003	-	-	-
- Mental health component	40 (9)	45 (9)	NS	-	-	-

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

Minor complications [N (%)]	11 (58%)	6 (30%)	NS	0 (0%)*	3 (4%)*	
Number of interventions [mean (range)]	9 (1 to 21)	3 (1 to 9)	< 0.001	6 (4 to 9)*	1 (1 to 3)*	N/A
Change in nutritional status [N (%)]						
- Increase from baseline	-	-	-	10 (28%)	17 (47%)	NS
- Unchanged from baseline	-	-	-	9 (25%)	9 (25%)	NS
- Decrease from baseline	-	-	-	17 (47%)	10 (28%)	NS
Duration of hospital stay [median (range)]	8 (0 to 128)	11 (5 to 59)	NS	-	-	
	Endoscopy (N=6)**	Surgery (N=4)**	P value	Endoscopy (N=36)	Surgery (N=36)	P value
Exocrine pancreatic insufficiency (new onset) [N (%)]	6 (100%)	1 (25%)	0.03	-	-	-

* For this outcome [Dite 2003](#) only reported the result for the complete cohort (140 patients, 64 in the endoscopic group and 76 in the surgical group. Only part of the patients were randomised (72 randomised and 68 non-randomised patients).

** N consists of all patients without exocrine pancreatic insufficiency at baseline.

NS = not significant; N/A = not available.

Table 2. Results of Nealon 1993

Outcome	Surgery (N=17)	Conservative (N=15)	P value
Pain relief (partial or complete) [N (%)]	16 (94%)	2 (13%)	< 0.001

Table 2. Results of Nealon 1993 (Continued)

- Complete pain relief [N (%)]	14 (82%)	0 (0%)	< 0.001
- Partial pain relief [N (%)]	2 (12%)	2 (13%)	NS
	Surgery (N=13)*	Conservative (N=12)*	P value
New onset endocrine pancreatic insufficiency [N (%)]	2 (15%)	10 (83%)	0.001
	Surgery (N=15)*	Conservative (N=14)*	P value
New onset exocrine pancreatic insufficiency [N (%)]	1 (7%)	11 (79%)	< 0.001

* N represents the number of patients without exocrine pancreatic insufficiency at baseline.

NS=not significant.

APPENDICES

Appendix I. 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. (Pancreas\$ 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

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 1, 2012

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, JM Pahlplatz participated in the literature search, extraction of data and methodological quality assessment of 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, read and approved the final manuscript.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review has been conducted in accordance with the published protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans