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REVIEW ARTICLE

Surgery remains the best option for the management of pain in patients with chronic pancreatitis: A systematic review and meta-analysis

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Summary Controversy related to endoscopic or surgical management of pain in patients with chronic pancreatitis remains. Despite improvement in endoscopic treatments, surgery remains the best option for pain management in these patients.

1. Introduction

Chronic pancreatitis (CP) is a major cause of morbidity, accounting for 7400 hospital admissions in the United Kingdom during the period 2011/2012. The mainstay of treatment is to avoid precipitating causes, such as alcohol. Pain is the most debilitating symptom and the symptom most resistant to treatment, with patients often becoming reliant on long-term analgesia leading to drug dependency.

The etiology of pain in CP is not completely understood, though it has been studied extensively. Currently its origin

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is thought to be due to increased pressure within the pancreatic duct (PD) which leads to intraductal and interstitial hypertension. An inflammatory response occurs in the pancreatic tissue mediated by the neuron-specific proteinase-activated receptor 2 (PAR-2), substance P, neurokinin A, and calcitonin-gene related peptide (CGRP), or a combination.[1] The resulting fibrosis further contributes to pain as the pancreas parenchyma loses its ability to distend during its excretory function.[2] This is exacerbated by the presence of strictures and stones which affect the ability of the gland to drain. Other factors affecting pain have also been advocated. Centrally mediated pancreas-independent pain is a possible contributor and this is due to chronic visceral input leading to plastic changes in the brain, which in turn cause a self-perpetuating and sustained pain.[3,4]

Treatment has traditionally been medical with analgesics and enzyme supplementation, while surgical management has been reserved for patients with intractable pain or complications.[5] The aim of surgical procedures is to decompress the and/or resect the nidus of inflammation. Surgical denervation strategies are ineffective and not appropriate as a first-line treatment.[1,6,7] Recently, combination procedures of drainage and local resection have been increasingly used as an alternative to major resection, with good success in symptom alleviation and low morbidity and mortality.[8]

Endoscopy has had an increasing role in the treatment of CP. The development of new techniques (PD stenting, stone removal and sphincterotomy) in combination with better patient selection has led to an increasing number of patients being managed without surgery.[9–11] However, there are only a few, small studies available that evaluate the outcomes of these interventions. While current studies suggest that surgery is better than endoscopy in the short term, it is not clear whether these benefits are sustained. Endoscopic treatments are becoming more complex, for example, the use of lithotripsy which has not been evaluated in earlier studies. The aim of this study is to provide an update on evidence evaluating the outcomes of surgery versus endoscopy for pain control in CP.

2. Methods

2.1. Study selection

A systematic literature search of the published studies comparing the outcomes of endoscopic or surgical treatment for CP was performed using a PubMed search covering the MEDLINE, EMBASE, Ovid, and Cochrane databases. Publications from January 1994 to October 2014 were reviewed. The following medical subject headings were used for the search: *chronic pancreatitis*, *surgery, endoscopic, stent, resection, and drainage*. These terms, and their combinations, were also searched as text words. The "related articles" function was used to broaden the search, and all abstracts, studies, and citations retrieved were reviewed. Relevant references of the articles acquired were also included.

2.2. Inclusion and exclusion criteria

Studies were independently assessed by two authors; conflicts were resolved by a third assessor until consensus was reached. Included studies were: (1) human; (2) reported the indication for surgery; and (3) were written in English.

Excluded studies had failed to: (1) describe their methods for treatment options; (2) clearly report the outcomes and variables of interest; (3) data extraction was impossible or not quantifiable; or (4) there was overlap between authors and centres. Figure 1 shows the flow chart of publication selection.

2.3. Variables and outcomes of interest

These include indication for surgery for CP, surgical methods, result of treatment measured by pain control, postoperative morbidity and mortality, and recurrent symptoms. The main focus during the selection process was the presence of data on pain relief and adequate follow up.

2.4. Statistical analysis

The meta-analysis was performed in line with recommendations from the Cochrane Collaboration.[12] Statistical analysis of dichotomous variables was performed using the odds ratio (OR) as the summary statistic. Postprocedural morbidity and mortality after surgery and endoscopy were analyzed, and the results were compared. Both were reported with 95% confidence intervals (CIs). An OR of <1 favored the particular type of procedure. The point estimate of the OR was considered statistically significant at $p < 0.05$ if the 95% CI did not include 1. In the tabulation of the results (Figure 2), squares indicate the point estimates of the treatment effect (OR or weighted mean difference), with 95% CIs indicated by horizontal bars. The diamond represents the summary estimate from the pooled studies with 95% CIs. The Mantel–Haenszel method was used to combine the OR for the outcomes of interest using a "random-effect" meta-analytical technique. This is a more conservative method than a fixed effects model and takes into account clinical heterogeneity. Statistical heterogeneity, by inspection of the I^2 statistic, reveals no observed heterogeneity across the studies when the value is close to 0%. Heterogeneity was also assessed by graphical exploration with funnel plots to evaluate publication bias. Statistical analysis was performed using Review Manager for Windows, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, England, UK) and SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed using the Fischer's exact test.

3. Results

3.1. Description of studies

The systematic literature search initially identified 1733 potential articles. After irrelevant citations were excluded

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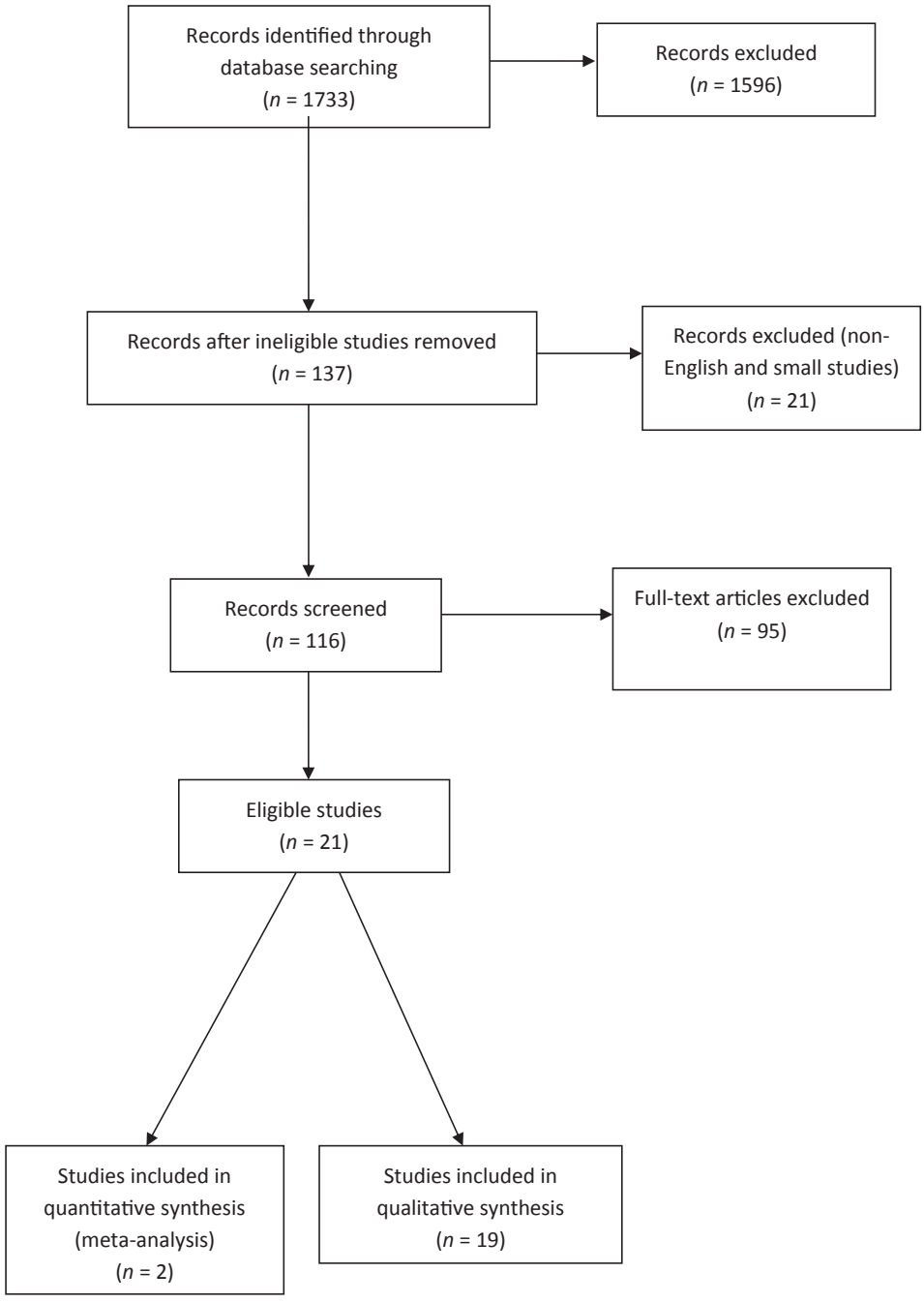

Figure 1 Study selection flow-chart.

the remaining 137 articles were retrieved in full and reviewed for further assessment (Figure 1). The titles and abstracts were first reviewed eliminating non-English ones (7 articles), as well as case reports and small volume trials or series, as defined by patient numbers of <15 (14 articles). A further 95 articles were excluded because of insufficient data on pain relief, including those with follow up of <6 months.

Only three of the 21 studies eventually selected were randomized control trials (RCTs).[13–15] One of these was a report of longer-term data from the same group.[15] The latest paper from this group was included in the meta-analysis to avoid duplication of results.

A total of 2754 patients were included in the 21 studies finally selected (Table 1). Of these, 1602 underwent surgery, including resection, drainage, and combination procedures (i.e., Whipple's resection, distal resection, Frey's procedure). The remaining 1152 patients were treated endoscopically.

Analysis of the two RCTs strongly supports the superiority of surgical treatment when complete pain relief is the outcome under consideration. Figure 2 depicts the forest-

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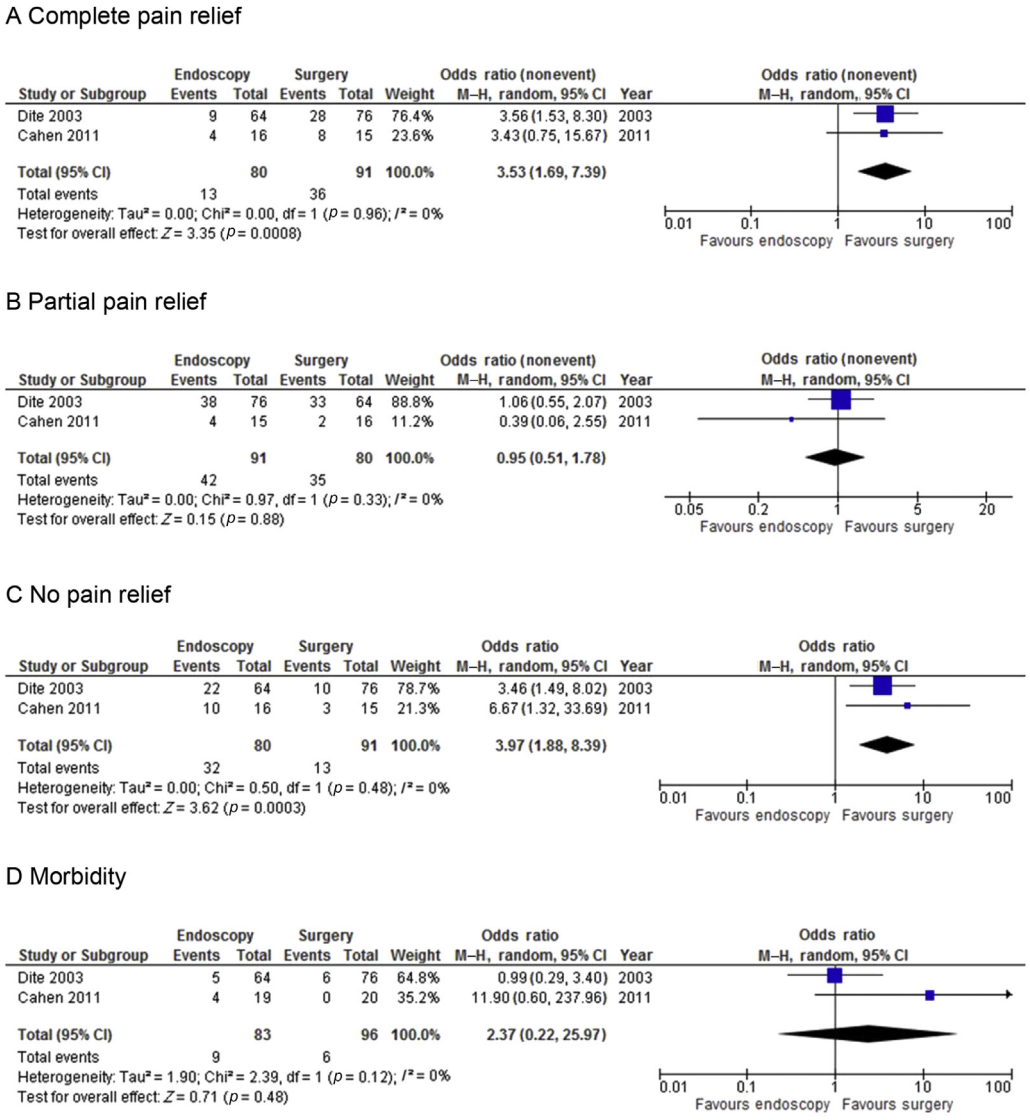

Figure 2 Meta-analysis of two RCTs. (A) Complete pain relief. (B) Partial pain relief. (C) No pain relief. (D) Morbidity. M—H = Mantel—Haenszel method.

plot of patients who had complete resolution of symptoms (OR, 3.53; $p = 0.0008$). When partial pain relief is considered, there was no statistical significance between surgery and endoscopy (OR, 0.95; $p = 0.88$). However, when comparing the outcome of no pain relief, there is again a significant difference in favor of surgery (OR, 3.97; $p = 0.0003$). Similarly, there were no major differences in morbidity ($p = 0.48$) or mortality ($p = 0.47$) between the two groups. One death was observed in Cahen's original study[14] in the endoscopic group, attributed to a perforated duodenal ulcer 4 days post extracorporeal shockwave lithotripsy (ESWL). During their 5-year follow-up period a further six patients died of unrelated causes, two in the endoscopy group and four in the surgical group. These were excluded from the meta-analysis for pain outcomes due to lack of data for these patients. There were a further four morbidities in the endoscopy group, two ruptured PDs and two pancreatic stent occlusions. Table 2 summarizes the complications in the two RCTs.

The remaining 19 articles reviewed were systematically analyzed[16—34] Specifically, surgical treatment was effective in alleviating pain symptoms completely in 58.4% of patients, partially effective in 22.0%, and completely failed in 19.4% of cases. Endoscopic treatment was effective in 64.0%, partially effective in 8.5%, and failed in 27.5%. The ability for a treatment to give any pain relief was significantly better after surgery (80.4%) compared with endoscopy (72.6%; $p < 0.0001$).

Morbidity was higher in the surgical group (12.7%) compared with the endoscopy group (10.1%). Mortality was also higher at 0.6% ($n = 13$), with no deaths occurring following endoscopy.

4. Discussion

The progressive nature of CP leads to at least 50% of patients developing intractable symptoms (i.e., endocrine

Table 1 Characteristics of studies in the review.

Study	Patient age (y), mean	Patients treated (n = 2754)	
		Surgery (n = 1602)	Endoscopy (n = 1152)
Dite 2003[13]	41.7	76	64
Cahen 2011[15]	41.7	20	19
Adams 1994[16]	43.6	62	0
Strate 2005[17]	N/A	51	0
Berney 2000[18]	44	67	0
Dumonceau 2007[19]	49	0	24
Farkas 2003[20]	44	30	0
Frey 1994[21]	47	47	0
Izbicki 1998[22]	43.8	61	0
Mobius 2007[23]	N/A	51	0
Nealon 2001[24]	43	185	0
Rosch 2002[25]	50	0	1018
Sakorafas 2001[26]	47	31	0
Schlosser 2002[27]	44.7	219	0
Schlosser 2005[28]	45.8	55	0
Schnelldorfer 2007[29]	46	368	0
Stapleton 1996[30]	42.2	52	0
Lucas 1999[31]	34	124	0
Byrne 1997[32]	47	51	0
Vasile 2013[33]	51	17	0
Hong 2011[34]	52	35	27

N/A = not available.

Table 2 Complication types in the two randomized control trials.

Complications	Dite et al[13], 2003		Cahen et al[15], 2011	
	Surgery	Endoscopy	Surgery	Endoscopy
Morbidity	6	5	7 (4)	18 (6)
Acute pancreatitis	2	2	0	4
Bleeding	0	2	2	0
Cholecystitis	0	0	0	1
Pancreatic abscess	0	1	0	0
Fistula	2	0	0	0
Anastomotic leak	1	0	1	n/a
Ileus	1	0	0	n/a
Wound infection	0	0	3	1
Cardiopulmonary	0	0	1	0
Stent related	0	0	n/a	5 (2)
Ruptured pancreatic duct	0	0	0	(2)
Other minor complications	0	0	0	7
Mortality	0	0	0 (4)	1 (2)

Numbers in brackets show additional complications at 5-year follow up.
n/a = not available.

and/or exocrine insufficiency and pain). During its natural course, traditional medical treatment is usually the first to fail in controlling the symptoms leaving endoscopic and surgical management as the only alternatives.[35,36]

Endoscopy for CP usually involves a combination of pancreatic sphincterotomy, ESWL, and PD stenting. This, however, involves multiple procedures due to stent occlusion or displacement and carries a fourfold increased risk of associated acute pancreatitis. Radiological changes in ductal and parenchymal morphology that are indistinguishable from those in CP after PD stenting have been reported in up to 50% of patients, which supports a possible causative association between the two.[37–39] A further downside of endoscopy is the need for compliance in patients to sustain repeated procedures, which may be another obstacle to its success.[40]

Surgical treatment for CP traditionally consisted of pancreatic head resection (e.g., Whipple's resection) or drainage procedures (e.g., Partington–Rochelle).[41,42] A shift towards more conservative, less aggressive treatment however has led to the development of pylorus preserving pancreaticoduodenectomy and duodenum preserving pancreatic head resection procedures as well as combination procedures (e.g., Frey's procedure) which have been increasingly performed successfully with minimal morbidity and mortality.[43–46] The results of the reviewed publications show a significantly better response to surgical treatment, with good long-term results.

However, a major limitation in this review is the lack of randomized studies which include a relatively small number of patients. Furthermore, in the two RCTs identified there are some important differences to note. Firstly, in Dite et al's[13] study only 72 of 140 patients agreed to be randomised, with the majority of the remaining patients opting for surgery. The data in the randomised group was analyzed individually as well as for the entire patient group, with no significant differences. Dite et al's[13] study included a higher number of participants (72 vs. 39), more surgical resections than drainage procedures (80% vs. 10%), as well as a lower number of patients with intraductal stones (23% vs. 95%) when compared with Cahen et al's[14,15] study. Moreover, lithotripsy was not available, unlike in Cahen's series were 88% of patients in the endoscopic group underwent ESWL. ESWL is an important component of endoscopic treatment, and the lack of it in the endoscopy arm may reduce its efficacy when comparing it to surgery.

The endoscopy protocol in the Cahen study involves repeated endoscopy as required, whereas Dite reserves repeat only under certain circumstances such as stent occlusion. Despite this, 47% of patients in Cahen's group eventually required surgery due to recurrent PD stenosis. In these patients, only two of nine achieved complete pain relief which suggests that delay in surgical treatment may reduce its efficacy. Dite et al[13] demonstrated the same initial success rate in both the endoscopic and the surgical groups, in contrast to Cahen et al[14,15] who showed an average difference of 24 points on the Izbicki score (0–100) between the two groups, which was consistent during the entire follow-up period. Therefore Dite's study only favors surgery in the long-term management.

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While endoscopy can achieve improvement in the management of pain, the benefit is usually short lived and the need to repeat the procedure is frequent.[47–49] Furthermore, an overall mortality rate of 0.6% following 1622 pancreatic operations is quite remarkable and evidence that as surgical techniques evolve, risk is further minimized.[50] Again a lack of properly designed, multicenter RCTs is a limiting factor in evaluating current practice and assessing the different modalities for treating CP, and it is important to discuss these limitations with the patient. It may be useful to design studies that classify different anomalies seen at endoscopic retrograde cholangiopancreatography (ERCP) or endoscopic ultrasound and study the effect of treatment accordingly with the aim of tailoring treatment to individuals. Another avenue to evaluate is whether early surgery is more effective rather than leaving this as a last resort. This is being evaluated in the ESCAPE trial by the Dutch Pancreatitis Study Group.[51] It may also be useful to define suitable treatments for low and high risk groups. However, at present, analysis of the existing studies can provide evidence that continues to support the superiority of surgical treatment in CP.

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