J Gastrointest Surg
DOI 10.1007/s11605-014-2571-8

REVIEW ARTICLE

Systematic Review of Early Surgery for Chronic Pancreatitis: Impact on Pain, Pancreatic Function, and Re-intervention

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Received: 23 April 2014 / Accepted: 6 June 2014

Abstract
Background Surgical intervention has traditionally been reserved as the last management option for pain in chronic pancreatitis. Recently, there has been a call for surgery to be offered earlier in the disease process. The objectives of this review were to evaluate the effect of early surgery on postoperative pain, pancreatic function, and re-intervention rates in chronic pancreatitis.
Methods A systematic literature search through EMBASE, Cochrane Review, and PubMed from January 1950 to January 2014 was conducted. Citations found in relevant papers are hand-searched. Data which could be pooled were analyzed using Revman (v5.2). Risk of bias analysis was conducted.
Results Of the 2,886 potentially eligible studies identified, 11 studies met the inclusion criteria. There was large heterogeneity in the study designs, and studies were conducted over a lengthy time span. Seven studies examined pain, three studies examined pancreatic function, and three studies examined rates of re-intervention. Meta-analysis of the three studies with comparative raw data regarding complete pain relief showed that early surgery was associated with an increased likelihood of complete postoperative pain relief (RR=1.67, 95 % CI 1.09–2.56, p=0.02). Early surgery was also associated with reduced risk of pancreatic insufficiency and low re-intervention rates.
Conclusions Data from this study supports considering early surgery for pain management in patients with chronic pancreatitis, with the potential of a reduced risk of pancreatic insufficiency and the need for further intervention. Further prospective randomized studies are warranted comparing early surgery against conservative step-up approaches.

Keywords Surgery · Surgical management · Chronic pancreatitis · Pain · Pain management · Pancreatic function · Diabetes · Steatorrhea · Re-intervention

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Introduction

Chronic pancreatitis (CP) is a debilitating inflammatory disease characterized by recurrent episodes of pain, progression to pancreatic insufficiency, and increased risk of pancreatic cancer.[1,2] Most patients are eventually incapacitated by unrelenting pain and become heavy opioid users without satisfactory pain relief.[3] Achieving satisfactory pain relief in patients with chronic pancreatitis remains a challenge.[4]

Current management strategies have been based on a step-up approach, where conservative management, lifestyle modifications, and endoscopy are offered prior to surgery. Surgery, which has recognized morbidity and mortality, has been reserved as a last resort in this schema. Several, newer recent theories have been proposed describing the mechanisms of pain in chronic pancreatitis. These include ductal hypertension and the ensuing changes to peripancreatic nerves and cortical

Published online: 19 June 2014

plasticity secondary to chronic inflammation.[2,3,5] Ductal hypertension may be caused by chronic inflammation which leads to fibrosis and stricture of ducts, progressing to ductal obstruction which in turn further exacerbates the ductal hypertension.[6] Compartment syndrome, abnormal proliferation of peripancreatic nerves, activation of neurons containing pro-inflammatory peptides, and hypersensitization of these nerve endings further contribute to the intractable pain.[3]

In light of these scientific developments and growing clinical evidence, there has been a push for definitive surgical therapy early in the disease process.[7–9] There remains significant debates as to whether early surgery mitigates disease progression, preserving pancreatic function and reducing the risk of long-term opioid dependency.[9–12] The aim of this review was to examine the available evidence regarding the impact of early surgery on postoperative pain, pancreatic function, and need for re-intervention in chronic pancreatitis.

Methods

Study Identification

A systematic literature search was conducted through EMBASE, Cochrane Review, and PubMed from January 1950 to January 2014 inclusively. The search string included "chronic pancreatitis" and surgery.mp or surgical.mp or operative.mp or surgical treatment.mp or resection.mp. Studies were limited to humans and adults (defined as≥18 years old). Language restrictions were not applied. Studies written in languages other than English were translated by a native speaker of that language who also holds a medical degree and with familiarity in surgery or in gastroenterology. Secondary searching was performed in which citations found in relevant papers were hand-searched for additional papers not captured by the above searches.

Inclusion Criteria

Inclusion criteria were human, adults defined as aged 18 years or older. Comparisons were performed between patients in the early course of their disease who received surgery against those who did not and patients who received surgery early in their disease against those who received surgery later in the disease process, including studies in which initial management with surgery was compared with initial management of endoscopy or with conservative therapy. These studies listed subsequent surgical operations performed on the patients during the follow-up period, and those who initially received non-surgical intervention and then went on to have surgical intervention were used as the comparison group.

Exclusion Criteria

Studies including patients who had surgery for indications other than CP including hepatopancreatobiliary malignancy, pancreas divisum, pancreatic hemorrhage or pancreatic infection, or had previous definitive pancreatic surgery were excluded. Studies pertaining only to drainage of cysts or pseudocysts and pancreatic transplant were excluded. Review papers were also excluded.

Definitions

Re-intervention after surgery was defined as any surgical or endoscopic procedure to relieve pain after initial surgery. All-cause mortality was defined as any mortality during the follow-up period.

Statistical Analysis

Data were analysed using RevMan version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). Studies reporting numerical values were aggregated to give pooled relative risks (RRs) and odds ratios (ORs) with 95 % confidence intervals (CI).

Results

Of the 2,886 potentially eligible studies identified, 11 studies met the inclusion criteria. Figure 1 outlines the selection process using a PRISMA diagram. There were eight prospective and three retrospective studies. Table 1 presents key characteristics of each study. Two studies examined outcomes after surgery early and late in the course of the disease.[17,20] One study used preoperative opioid use as a proxy for symptom duration prior to surgery.[16] Five studies compared initial treatment with surgery against treatment with endoscopy and/or conservative therapy.[14,15,18,22,23] Three studies followed patients after surgery and identified risk factors for not attaining postoperative pain relief using multivariable regression analysis.[1,13,21] Table 2 outlines key design features of each study. Table 3 shows the follow-up times for each study, proportion of patients who attained pain relief after surgery, re-intervention rate after surgery, and proportion of all-cause mortality during the follow-up period.

Postoperative Pain Relief

Raw individual patient (n=406) data were available from three papers allowing a meta-analysis with regard in determining complete postoperative pain relief at follow-up. The included papers described single-center experiences in both observational and randomized patient populations. Follow-up

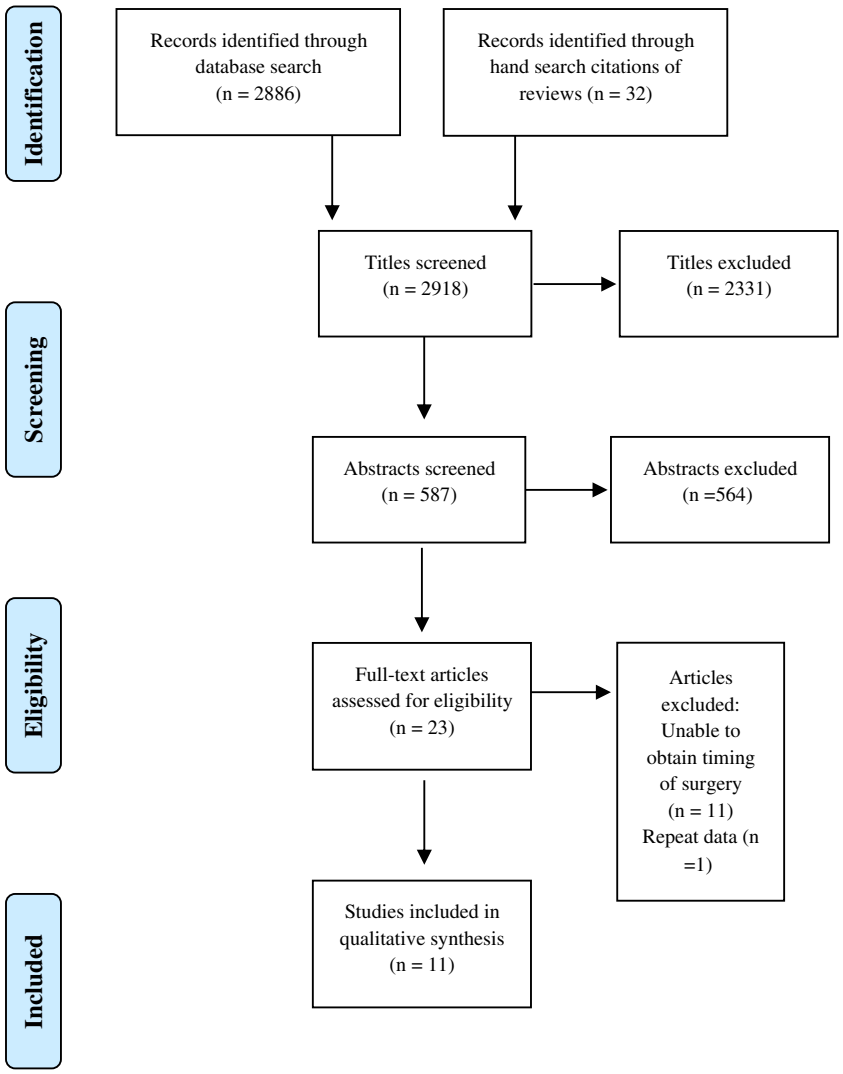

Fig. 1 PRISMA diagram for study selection

periods are listed in Table 3. For meta-analysis of complete postoperative pain relief, two papers with raw data included for complete pain relief for a total of 406 patients were analyzed.[14,23] Early surgery was associated with an increased

Table 1 Characteristics of included studies

Paper	Year	Country	Study design	Risk of bias
Mannell et al.[13]	1988	USA	Prospective observational	High risk of bias
Dite et al.[14]	2003	Czech Republic	Prospective RCT	Unclear risk of bias
Maartense et al.[15]	2004	Netherlands	Prospective observational	High risk of bias
Alexakis et al.[16]	2004	UK.	Retrospective	Unclear risk of bias
Riediger et al.[17]	2007	Germany	Prospective observational	Low risk of bias
Rutter et al.[18]	2010	Austria	Retrospective	High risk of bias
Cahen et al.[19]	2011	Netherlands	Prospective RCT	Low risk of bias
Ahmed Ali et al.[20]	2012	Netherlands	Prospective observational	Unclear risk of bias
van der Gaag et al.[1]	2012	Netherlands	Prospective observational	Unclear risk of bias
Clarke et al.[21]	2012	USA	Retrospective	High risk of bias
Negi et al.[22]	2012	India	Prospective observational	Unclear risk of bias

RCT randomized controlled trial, *USA* United States of America, *UK* United Kingdom

Table 2 Designs of included studies

Paper	Comparison	Control	Numbers		
			Intervention	Control	Total
Riediger et al.[17]	Duration of CP ≤3 years	Duration of CP >3 years	102	122	224
Ahmed Ali et al.[20]	Duration of CP ≤3 years	Duration of CP >3 years	121	124	245
Cahen et al.[19]	Endoscopy	Surgery	19	20	39
Maartense et al.[15]	Conservative treatment	PJ and DPPHR	18	39	57
Dite et al.[14]	Endoscopy	Surgery	64	76	140
Mannell et al.[13]	N/A	Surgery	N/A	141	141
Alexakis et al.[16]	Preoperative opioid use	No preoperative opioid use	46	66	112
Rutter et al.[18]	1. Endoscopy 2. Conservative therapy	Surgery	1. 150 2. 43	99	292
van der Gaag et al.[1]	N/A	Surgery	N/A	223	223
Clarke et al.[21]	N/A	Surgery	N/A	24	24
Negi et al.[22]	N/A	Surgery	N/A	60	60

CP chronic pancreatitis, *PJ* pancreatojejunostomy, *DPPHR* duodenum-preserving pancreatic head resection, *N/A* not applicable

likelihood of complete postoperative pain relief (RR=1.67, 95 % CI 1.09–2.56, p=0.02). Figure 2 presents a forest plot showing the distribution of relative risks. For analysis of partial or complete postoperative pain relief, one paper with 245 patients was analyzed. Early surgery was associated with an increased likelihood of partial or complete postoperative pain relief (RR=1.32, 95 % CI 1.06–1.66, p=0.01).[20]

Four other papers reported postoperative pain relief in ways which could not be incorporated into the meta-analysis, as they did not provide raw individual patient data or did not assess complete pain relief as outcome. A study based at the Mayo Clinic examined outcomes in patients operated on between 1958 and 1979.[13] This study found no statistical significance in length of preoperative history, but did not give any more detail.[13] A study describing a single institution experience of 11 years including 224 patients found a higher proportion of pain relief with early surgery (66 of 102) compared with late surgery (57 of 122). Another retrospective analysis of patients receiving surgery, this time after failed endoscopy, found that a shorter duration of CP (54 vs. 87 months) trended towards better rates of pain relief though this did not reach statistical significance (p=0.19).[21]

The other, more contemporary study conducted in the UK used preoperative opioid use as a risk factor for outcomes.[16] Patients who used opioids prior to surgery had statistically longer duration of preoperative symptoms (mean, 2.0 vs. 5.9 years) and larger number of hospitalizations prior to surgery (mean, 3 vs. 10).[16] The postoperative pain scores on the Visual Analogue Scale (VAS) was significantly higher in the patients with preoperative opioid use (9 vs. 8, p=0.001).[16]

Pancreatic Function

Three papers studied the influence of early surgery on post-operative pancreatic insufficiency.[15,17,20] One study found on

Table 3 Outcomes of included studies

Paper	Follow-up (months)	Attained pain relief after surgery (%)	Re-intervention rate after surgery (%)	All-cause mortality (%)
Riediger et al.[17]	Median 56.3	87	7	14
Ahmed Ali et al.[20]	Median 62.0	58	12	0
Cahen et al.[19]	All 60.0	80	5	18
Maartense et al.[15]	All 18.0	NS	NS	0
Dite et al.[14]	All 60.0	86	2.6	0
Mannell et al.[13]	Mean 102.0	NS	NS	1
Alexakis et al.[16]	Median 16.9	86	24	6
Rutter et al.[18]	Mean 58.0	NS	22	5
van der Gaag et al.[1]	Mean 63.0	68	12	20
Clarke et al.[21]	Mean 51.6	50	NS	NS
Negi et al.[22]	Median 76.8	75	NS	3

NS not stated

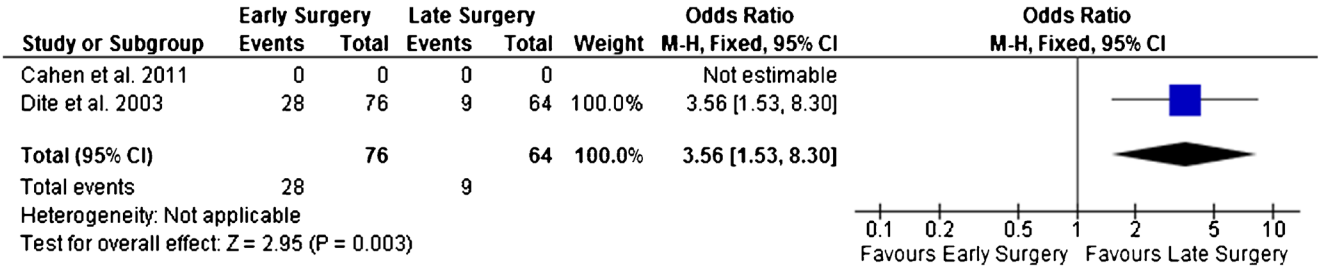

Fig. 2 Relative risk of attaining complete postoperative pain relief

multivariate regression that early surgery lowered the odds of developing de novo pancreatic endocrine insufficiency (adjusted OR 0.57, 95 % CI, 0.33–0.96), but did not report its effect on exocrine insufficiency.[20] Another study found, after multivariate regression, that late surgery was associated with a higher likelihood of de novo postoperative exocrine pancreatic insufficiency (OR 2.47, p=0.002).[17] In the same study, there was a trend towards a higher rate of de novo diabetes mellitus after late surgery, but this was not a significant finding (21 vs. 30 %, p=0.12). The third study compared surgery with conservative therapy in patients with a comparable duration of CP[15] reported an improvement in endocrine function, but not exocrine function measured by fecal fat and urinary p-aminobenzoic acid (PABA) recovery 18 months after surgery.

Re-intervention Rates

Four of the 11 studies reported on re-intervention rates on 583 patients. In the long-term follow-up of a randomized controlled trial, there was a significant difference in re-intervention rates after initial endoscopy compared with initial surgical treatment (68 vs. 5 %).[19] These findings are consistent with an earlier randomized study that compared initial endoscopic to surgical treatment in terms of re-intervention rates (52 vs. 0 %) during the 5-year follow-up.[14] In contrast, only two (2.6 %) of the 76 patients who initially received surgery required further intervention during this time period, both for complications related to the operation.[14]

A study comparing surgery, endoscopy, or conservative management showed patients who initially received surgery had significantly less re-interventions than those who received endoscopy or conservative treatment to begin with (p<0.05) despite the longest follow-up period for the surgery group (mean follow-up in months: surgery 98.1, endoscopy 33.3, conservative management 51.6).[18]

In the study using preoperative opioid use as a marker for duration of chronic pancreatitis, the opioid use group had higher preoperative symptom duration (87 vs. 54 months) than the non-opioid use group. The opioid use group demonstrated an over threefold increase in reoperation rate (11 vs. 3 %, p=0.003).[16]

Discussion

This review suggests that early surgery may increase the likelihood of achieving postoperative pain relief and may prevent the development of pancreatic insufficiency. Further, early surgery appears to reduce the risk of repeated intervention. Nearly half of patients who undergo initial endoscopy in this series received further intervention, and almost half eventually required surgery.[14,19]

This has important clinical implications. Patients should be informed about the risk of re-intervention with both endoscopic and surgical approaches including cumulative risk.[20] There have been significant recent developments in the endoscopic management of CP, including the introduction of more effective extracorporeal shockwave lithotripsy for calculi and multiple plastic stents and removable self-expanding stents for strictures.[24] There is also literature to suggest that an increasing number of endoscopic procedures are being performed in lieu of surgery.[2,19] Higher powered, longer duration, well-timed prospective randomized controlled trials comparing state-of-the-art endoscopic and surgical treatment in well-selected patients are necessary.

The literature suggests that 40–75 % patients will eventually require surgery for painful CP.[2] Thirty-four to fifty-two percent patients attain pain relief after resection.[25] The ultimate goal of surgery is to resolve the intractable pain, restore patients' quality of lives and independence, retain as much endocrine and exocrine pancreatic function as possible, and prevent further hypersensitization and damage to structures surrounding the pancreas.[12] Thus, definitive surgery focuses on ductal decompression to alleviate pain from obstruction and to prevent inflammatory consequences on surrounding tissues.[26–28] These can be broadly classified as either resection procedures, especially for disease involving the head of the pancreas (including Whipple procedure and pylorus-preserving pancreatoduodenectomy, and distal and total pancreatectomy), drainage procedures (including Puestow procedure), and/or resection with drainage including Frey and Beger procedures. Studies, thus, far have focused on comparing the efficacy of these procedures, but the optimal timing to definitive surgery still remains elusive.[2] This study did not specifically compare the effects of early surgery by type of procedure as studies either did not list procedures performed

or classified procedures into groups which could not be compared with other groupings.

Extensive decompression of the ductal system with preservation of parenchyma is likely to be effective due to its timing prior to the progression of fibrosis and atrophy with progression of disease. As early as 1993, there was a realization that drainage should be performed prior to progression to irreversible dysfunction.[9] In this regard, early surgery may be regarded as prophylactic: simultaneously removing the cause of pain and ongoing injury. The fibrotic and damaged parenchyma is removed, along with intra-pancreatic and peripancreatic nociceptive stimuli and its associated pancreatic tachykinins which trigger pain.[29] Animal studies have demonstrated clear benefits of early surgery. Pancreatic exocrine function could be restored in 14 dogs if obstruction was reversed within a short duration.[30] Longitudinal pancreaticojejunostomy in 21 piglets demonstrated surgery at 3 weeks led to restoration of pancreatic secretion of lipase and amylase, while surgery at 6 weeks did not.[8] Histopathology showed reversal of fibrosis, inflammatory cell infiltration, and destruction of acinar organization in the group operated on earlier.

There are several limitations to this study. The quality of studies, heterogeneity of endpoints, and study design and the wide time span of the studies precluded formal meta-analysis. While it would have been useful to include quality of life data, it was not possible for similar reasons. However, there is a close correlation between pain and quality of life and it is reasonable to expect that quality of life measures will track the response to pain. Other areas that warrant study is the impact of alcohol abstinence and smoking cessation on the efficacy of early surgery. This review included several non-randomized controlled trials. In this setting, the benefits seen in patients undergoing early surgery may merely reflect patient selection biases.

Another aspect not covered by this review is the surgical option of total pancreatectomy (with or without autoislet transplantation). It is now becoming a more viable option, at least in North America, for both the adult and pediatric populations.[31] Although further studies are required to better define the optimal timing and the subgroup for whom this is best indicated,[31] it is an attractive option because it removes the pancreas as the local source of the pain and addresses the functional consequences by providing autoislet transplantation and pancreatic enzyme replacement therapy. If TP/AIT is a potential option, then it should be considered before alternative surgical approaches since prior surgery has been shown to reduce islet cell yield and increase post-transplantation insulin requirements[30,32–34] and increase postoperative pain scores.[31]

This literature review is the first, to our knowledge, that specifically examines the impact of early surgical treatment for CP on pain, pancreatic function, and re-intervention rates. While the limitations of the available literature reduce the strength of the conclusions, there is sufficient evidence to say that early surgery appears to be effective in reducing postoperative pain, maintaining pancreatic function, and reducing the need for further intervention when compared with other conservative and/or endoscopic treatments. This review also highlights the importance of undertaking further prospective studies that may resurrect surgery from a last resort option to one that has important prophylactic benefits if offered early in the disease course. The results of the ESCAPE trial (ISRCT N45877994) that compares early surgery with a step-up approach are eagerly awaited.[20]

Funding Catherine Yang received a fund from Fulbright New Zealand Scholarship, Lindsay Bliss was funded by the Pyrtek Fund Research Scholarship, and Jennifer Tseng was funded by Howard Hughes Medical Institute Early Career Grant.

Conflict of interest The authors declare no conflicts of interest.

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