

REVIEW ARTICLE

Short and long-term post-operative outcomes of duodenum preserving pancreatic head resection for chronic pancreatitis affecting the head of pancreas: a systematic review and meta-analysis

Zaynab A.R. Jawad¹, Nicole Tsim¹, Madhava Pai¹, Dev Bansi², David Westaby², Panagiotis Vlavianos² & Long R. Jiao¹

¹Hepato-Pancreato-Biliary Surgical Unit, Department of Surgery and Cancer Imperial College, Hammersmith Hospital Campus, and

²Department of Gastroenterology, Hammersmith Hospital, Du Cane Road, London, W12 0HS, UK

Abstract

Background: To evaluate the short and long term outcomes of duodenum preserving pancreatic head resection (DPPHR) procedures in the treatment of painful chronic pancreatitis.

Methods: A systematic literature search was performed to identify all comparative studies evaluating long and short term postoperative outcomes (pain relief, morbidity and mortality, pancreatic exocrine and endocrine function).

Results: Five published studies fulfilled the inclusion criteria including 1 randomized controlled trial comparing the Beger and Frey procedure. In total, 323 patients underwent surgical procedures for chronic pancreatitis, including Beger (n = 138) and Frey (n = 99), minimal Frey (n = 32), modified Frey (n = 25) and Berne's modification (n = 29). Two studies comparing the Beger and Frey procedure were entered into a meta-analysis and showed no difference in post-operative pain (RD = -0.06; CI -0.21 to 0.09), mortality (RD = 0.01; CI -0.03 to 0.05), morbidity (RD = 0.12; CI -0.00 to 0.24), exocrine insufficiency (RD = 0.04; CI -0.10 to 0.18) and endocrine insufficiency (RD = -0.14 CI -0.28 to 0.01).

Conclusion: All procedures are equally effective for the management of pain for chronic pancreatitis. The choice of procedure should be determined by other factors including the presence of secondary complications of pancreatitis and intra-operative findings. Registration number CRD42015019275. Centre for Reviews and Dissemination, University of York, 2009.

Received 19 October 2015; accepted 21 October 2015

Correspondence

Long R. Jiao, General and HPB Surgery, Hepatopancreatobiliary Surgical Unit, Department of Surgery and Cancer, Imperial College, Hammersmith Hospital Campus, Du Cane Road, London, W12 0HS, UK. Tel: +44 (0) 20 8383 3937. Fax: +44 (0) 20 8383 3212. E-mail: l.jiao@imperial.ac.uk

Introduction

Chronic pancreatitis (CP) is a chronic inflammatory disease characterized by irreversible parenchymal fibrosis and progressive destruction of endocrine and exocrine components.¹ The treatment of CP can be divided into three categories: pain management; management of complications such as pseudocysts; and correction of pancreatic insufficiency.² Pain is the most frequent symptom and achieving adequate analgesia is often extremely difficult. Although medical treatment has been the

mainstay of therapeutic modalities,³ endoscopic and surgical management have increasingly become the mainstream in patients with intractable pain or complications. In a recent Cochrane review surgery was superior to endoscopy for pain relief in chronic pancreatitis.⁴ In one trial surgery improved quality of life and resulted in better preservation of exocrine pancreatic function.⁵ Choosing the surgical approach is rarely straightforward and is often determined by factors such as disease location (head, body, tail of the pancreas or diffuse disease)

or the suspicion of cancer. When the distal pancreas is affected and pancreatic duct dilated, longitudinal pancreaticojejunostomy (LPJ) is usually the most effective procedure. For ducts less than 5 mm the anastomosis can be difficult and resection of the distal pancreas is more appropriate.⁶ When the disease is characterized by a mass in the head of pancreas, the aim of surgery is to excise the head which is the thought to act as a pacemaker of the disease. Available surgical interventions in patients with CP affecting the head of pancreas can be divided into 2 groups: complete pancreatic head resection (PHR) procedures and duodenum preserving pancreatic head resection (DPPHR) procedures. A number of procedures in the DPPHR group have been reported as well as modifications of the original techniques (Table 1). Total pancreatectomy and islet autotransplantation (TPIAT) has also been proposed as an effective intervention for managing the complications of chronic pancreatitis.¹² However, this still needs to undergo further evaluation before it is routinely adopted.

Although complete PHR offers long-term pain control by resecting the diseased head with drainage of the duct, it is associated with considerable side effects due to resection of the duodenum, pylorus and bile duct when compared with DPPHR.^{13–15} DPPHR allows incomplete though sufficient

resection of the head of pancreas while preserving the continuity of the upper gastrointestinal tract. At the time of writing three meta-analyses have been published comparing PHR with DPPHR.^{13–15} While these have shown similar improvements in post-operative pain relief, DPPHR has been associated with improved quality of life and exocrine function.

There is no level 1 evidence comparing the different DPPHR procedures used in the management of pain for CP. The aim of this systematic review was to systematically review the literature to identify the most effective DPPHR procedure for pain relief in CP affecting the head of pancreas.

Materials and methods

A study protocol was developed before the conduct of the meta-analysis. The objective, inclusion, and exclusion criteria, outcome parameters, and methods for analysis were predefined. Reporting was in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)¹⁶ and MOOSE (Meta-analysis Of Observational Studies in Epidemiology)¹⁷ statements. The review protocol was registered with the Centre for Reviews and Dissemination, University of York, 2009. Registration number CRD42015019275.

Inclusion and exclusion criteria

Studies were assessed by 2 authors independently (Z.A.R.J. and N.T.) and any conflict was resolved by a 3rd assessor (L.R.J.) until there was consensus. To be included in the analysis, studies had to meet the following criteria: (i) be comparative randomized or non-randomized studies evaluating two or more different DPPHR procedures (ii) the study population consists of patients diagnosed with chronic pancreatitis undergoing planned elective surgery (iii) be a human study, and (iv) be written in English.

Studies were excluded from the analysis for the following reasons: (i) failure to describe the surgical methodology; (ii) the outcomes and variables of interest were not clearly reported (e.g. studies that did not record short-term results, such as mortality and morbidity, or long-term results, such as pain control and pancreatic function); (iii) non-comparative study (iv) less than 12 months follow-up for long term outcomes (v) it was impossible to extract the appropriate data from the published results; (vi) there was overlap between patient cohorts evaluated in the published literature.

Study selection

A systematic literature search of the published studies on management of CP was performed using a PubMed search covering the MEDLINE, EMBASE, Ovid, and Cochrane databases. No time limits were specified up to the date of the search. The following Medical Subject Headings were used for the search: 'chronic pancreatitis', 'surgery', 'Frey*', 'Beger*', 'duodenum-preserving pancreatic head resection', 'Izbicki*', 'Berne*'. These terms, and their combinations were also searched as text words.

Table 1 Main characteristics of DPPHR procedures and their modifications identified in the systematic review

Duodenum preserving pancreatic head resection (DPPHR) procedure	Main characteristics of procedure
Beger procedure ⁷	<ul style="list-style-type: none"> Dissection of pancreatic neck from portal vein and complete transection of neck Subtotal excision of pancreatic head and neck Reconstruction with two anastomoses (pancreaticojejunostomy) with Roux-en-Y jejunal loop
Frey procedure ⁸	<ul style="list-style-type: none"> Longitudinal drainage of pancreatic duct Local resection of pancreatic head
Modified Frey procedure ⁹	<ul style="list-style-type: none"> Mean area of resection of pancreatic head $3.0 \pm 0.4 \text{ cm}^2$
Minimal Frey procedure ⁹	<ul style="list-style-type: none"> Mean area of resection $1.8 \pm 0.3 \text{ cm}^2$
Berne's modification of Beger procedure ¹⁰	<ul style="list-style-type: none"> No dissection from portal vein Partial resection of pancreatic head to leave cavum Single anastomosis (pancreaticojejunostomy) with Roux-en-Y jejunal loop
Izbicki procedure ¹¹	<ul style="list-style-type: none"> Indicated in small duct disease V-shaped excision of ventral pancreas Longitudinal pancreaticojejunostomy to Roux-en-Y jejunal loop

The “related articles” function was used to broaden the search, and all abstracts, studies, and citations retrieved were reviewed. References of the articles acquired were also included. The last search was carried out on the 28th September 2015. Article titles and abstracts were screened for potentially eligible studies. Full articles were obtained for detailed evaluation and eligible studies were included into the systematic review. Missing information such as study methods or results was acquired by contacting the corresponding author of the article.

Data collection

Data was collected from the eligible studies on a computerized data collection proforma by one author. This was checked by a second author. Disagreements were resolved by a third author. In three of the studies^{18–20} it was not clear whether the data had come from the same group of patients. The corresponding author of one of the studies was therefore contacted who verified the duplication of the patient cohort in these three separate publications.^{18–20} This was handled by extracting short term data (morbidity and mortality) from the earlier study¹⁸ and long term data (pain relief and pancreatic insufficiency) from the study at 8 year follow up.¹⁹ The third paper²⁰ on this cohort gave 16 year follow up data from the same patient group but the mortality rate at this stage had increased to 36% which meant the number of patients remaining at the follow-up was very small and it was felt that this may have a clinically relevant impact on the intervention effect estimate. Therefore long term data was taken from the 8 year follow up study. The author of another study²¹ was contacted to confirm the group allocation of one postoperative mortality as this was not specified in the paper.

The following data was collected: (i) characteristics of patients (including age, gender, indication for surgery, cause of pancreatitis, duration of symptoms) (ii) surgical intervention (procedure type, duration of surgery, length of hospital stay) (iii) outcome measures (follow up time, patients achieving complete pain relief, method of pain assessment, pain scores according to chosen method of pain assessment, morbidity, complication type, mortality, exocrine and endocrine function).

Variables and outcomes of interest

The primary outcome parameter was relief of abdominal pain. Quantification of pain relief had to be based either on validated and comparable reliable methods (e.g. visual analogue scale) or on ratios of pain-free patients postoperatively. Secondary outcome parameters included overall morbidity, mortality and deterioration in exocrine function or endocrine function as defined by a worsening in the preoperative status.

Risk of bias assessment

To ascertain the validity of the included studies a risk of bias assessment was carried out by 2 authors. The Downs and Black tool²² was used for both randomized and non-randomized

studies. This is a validated tool for risk of bias assessment and is based on a 27 item checklist. Scores of 20 or more are considered good studies, 15–19 are fair and 14 or less are poor studies.

Statistical analysis

The results were pooled as estimates of overall treatment effects in a meta-analysis and presented as the risk difference for dichotomous outcomes, with the corresponding 95% confidence intervals (CI). Risk difference was chosen due to the presence of zero counts in some of the study results which makes the calculation of ratios inappropriate. The weight of each study was related to its sample size. The point estimate of the risk difference was considered statistically significant at $P < 0.05$ if the 95% CI did not include 1. Mantel-Haenszel method was used to combine the OR for the outcomes of interest using a random-effect meta-analytical technique (Review Manager, Version 5.3 for Windows, The Cochrane Collaboration, 2014). This is a more conservative method than a fixed effects model but takes into account clinical heterogeneity (varying or missing definitions of outcome parameters). The data is presented as forest plots. The vertical line represents the odds ratio (OR) which is the line of equivalence between the methods being compared. Individual trials are presented horizontally; the squares for each trial represent the point estimate with the area of the square being proportional to the sample size and the line represents the 95% CI. Summary measures are presented by diamonds, where the width of the diamond corresponds to the 95% CI. Two-sided p-values were used throughout. All results were investigated for statistical heterogeneity. Statistical heterogeneity was explored by inspection of the forest plot and I_2 statistic²³ which reveals no observed heterogeneity across the studies when the value is close to 0%. Publication bias was also assessed by graphical exploration with funnel plots.^{24,25}

Results

Description of studies

Following the search strategy (Fig. 1) a total of 5 studies were identified for inclusion in the review.^{9–11,19,21} These studies included a total of 323 patients. Patient and study characteristics are shown in Table 2. Two of these studies were included in a meta-analysis.^{19,21} The third study was excluded as it was found to be of low quality in the risk of bias assessment.²⁶ At sensitivity analysis the results of this study significantly altered the results of the meta-analysis. This is described in more detail below. Of the remaining 2 studies one was a cohort study comparing a modified Frey procedure ($n = 25$) with a minimal Frey procedure⁹ ($n = 32$) to determine whether a reduction in the amount of excised tissue has a bearing on pain scores, exocrine and endocrine function as well as the mortality, morbidity and reoperation rates. The authors compared the minimum Frey

procedure which entails a small spindle shaped anterior resection of the pancreatic head compared to a slightly wider excision offered by the modified Frey procedure. The study showed similar or better pain scores in those patients undergoing the minimum Frey procedure although this was not significant. Similarly there was no significant difference in endocrine function, morbidity or mortality. Overall, lesser excision did not compromise patient outcomes. The final study¹⁰ was an RCT

comparing the Berne modification with the Beger procedure. The Berne modification refers to a variation of the classical Beger procedure whereby rather than division of the pancreatic neck anterior to the portal vein, the pancreatic head is resected partially to leave a single cavum which is anastomosed end-to-side with a Roux-en-Y jejunal loop. It avoids the delicate dissection of the neck from the portal vein, but similarly to the Beger procedure there is no longitudinal drainage of the pancreatic duct. There was no mortality in either group and no significant difference in morbidity ($p > 0.99$). Post-operative quality of life scores ($p = 0.371$) and Hba1c ($p = 0.990$) were also similar in the two groups.

Risk of bias assessment

The Downs and Black scores of the included studies showed a variation in the study quality with the RCT¹⁹ being the highest quality study. There was good inter-rater reliability when scoring the studies.

Meta-analysis results

Two of the 5 studies were considered to be eligible for inclusion in a meta-analysis^{19,21} (Fig. 2). These were long term comparative studies that compared the Beger and Frey procedure. In Keck *et al.*, 2010,²¹ patient characteristics in the Beger and Frey groups were similar despite no randomization. It was therefore felt appropriate to include this in the meta-analysis. To compare the amount of pain relief, the number of patients that were pain free as a proportion of the total number at follow up were entered into the meta-analysis. In one study¹⁹ the pain outcomes were recorded as the visual analogue score. This score was converted to a positive outcome by subtracting from 100 and multiplying by the number of patients in the group. Keleman and Horvath, 2002²⁶ was excluded from the meta-analysis as it was assessed to be of poor quality. Furthermore, following sensitivity analysis as described below it was decided that it should be excluded. The meta-analysis showed no difference in post-operative pain, mortality, morbidity, exocrine or endocrine insufficiency (Fig. 2).

Sensitivity analyses

Due to the range in the quality of the studies included in the meta-analysis, a sensitivity analysis was carried out to test the robustness of methodology. The meta-analysis was undertaken before and after exclusion of Keleman and Horvath, 2002²⁶ as this was assessed to be of poor quality. Exclusion of this study resulted in a change in two of the outcomes. Morbidity was significantly higher after the Beger procedure whereas endocrine insufficiency were significantly higher following the Frey procedure when this study was included ($p = 0.002$ and $p = 0.02$ respectively). The significance of all other outcomes was not affected by exclusion. Based on the results of this sensitivity analysis the study was excluded from the meta-analysis.

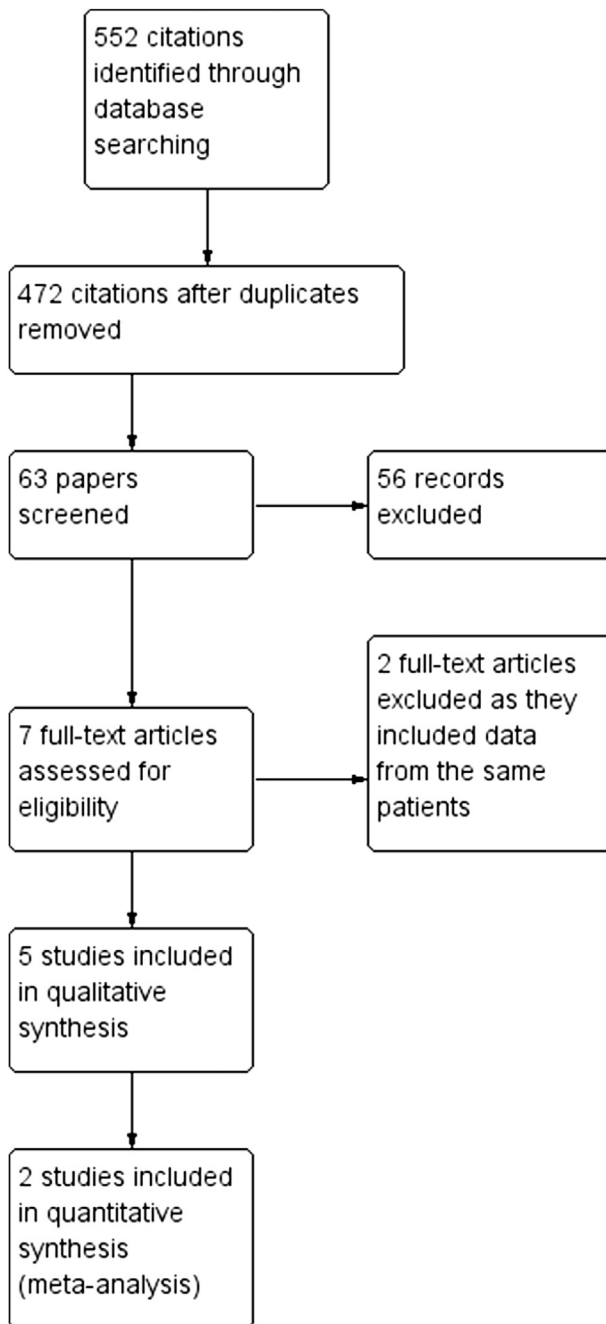


Figure 1 Flow diagram for study selection process

Table 2 Characteristics of studies included in the systematic review and meta-analysis

Study	Izbicki <i>et al.</i> , 1995	Keleman and Horvath, 2002	Strate <i>et al.</i> , 2005	Koninger <i>et al.</i> , 2008	Sakata <i>et al.</i> , 2009	Keck <i>et al.</i> , 2010
Comparators	Beger and Frey	Beger and Frey	Beger and Frey	Beger and Berne modification	Modified and minimal Frey	Beger and Frey
Total patients (n)	20:22	32:13	38:36	26:29	25:32	42:50
Age, years ^b	45:44	45:45	NS	48:46	49:49	41:45
Male gender (n)	15:16	26:13	NS	20:25	25:29	36:39
Indication for surgery pain (n)	20:22	31:12	NS	NS	NS	35:45
Alcoholic pancreatitis (n)	13:17	29:13	NS	NS	21:25	33:38
Duration of symptoms (months) ^b	71:77	37:57	61 ^a	36:43	36 ^a	48:59
Study design	RCT	Cohort	RCT	RCT	Cohort	Cohort
Follow-up (months) ^b	18 ^a	41:20	102 ^a	24 ^a	60 ^a	62:43
Duration of surgery (mins) ^b	325 ^a	360:288	NS	369:323	NS	415:360
Length of hospital stay (days) ^b	NS	9:7	NS	15:11	NS	13:13

NS, not specified.

^a Data given for both groups combined.

^b Mean or median values given n = number of patients.

Heterogeneity

There was no significant statistical heterogeneity across the 2 studies included in the meta-analysis. With all outcomes the I_2 statistic remained at 0%. This remained to be the case when the excluded study²⁶ was entered into the meta-analysis.

Discussion

The current study identified 5 published studies assessing the outcomes of patients with CP undergoing DPPHR. Comparing the Beger procedure to the Frey procedure showed there was no significant difference in short or long term post-operative outcomes.

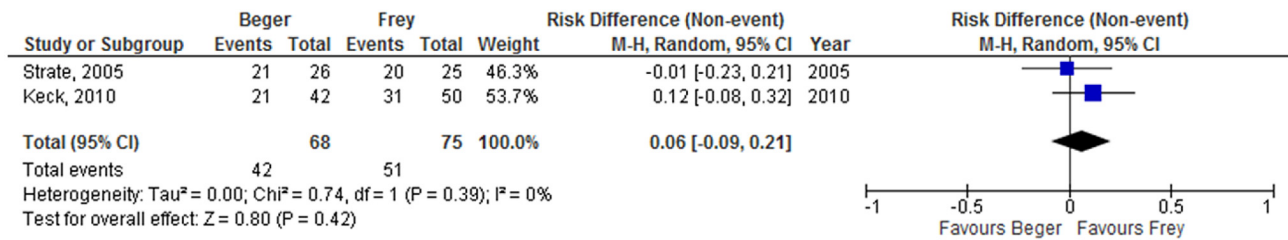
While there are several RCTs comparing pancreaticoduodenectomy with DPPHR, this review identified only 2 RCTs comparing different DPPHR procedures.^{10,19} The results of the current study highlight several points regarding the management of pancreatitis. Despite considering only those patients with chronic pancreatitis affecting the head of pancreas there are a number of effective procedures reported and it is possible that a flexible approach may be required for this heterogeneous disease. For example Koninger *et al.*¹⁰ report 3 patients randomized to the Beger procedure that were converted to the Berne technique to avoid dissection around a thrombosed portal vein and associated varices. Three patients in the Berne group were converted to the Beger procedure due to anticipated difficulties with formation of the pancreaticojejunostomy. Despite using intention to treat analysis the similar outcomes particularly with regards to pain relief suggests that this interchangeability is acceptable. In

the study by Keck *et al.*, 2010,²¹ though patient characteristics were similar, there was a bias for those patients having biliary stenosis and pre-operative biliary drainage procedures to undergo the Beger procedure. 67% of patients in the Beger group had radiological evidence of common bile duct stenosis compared to 28% in the Frey group. Table 3.

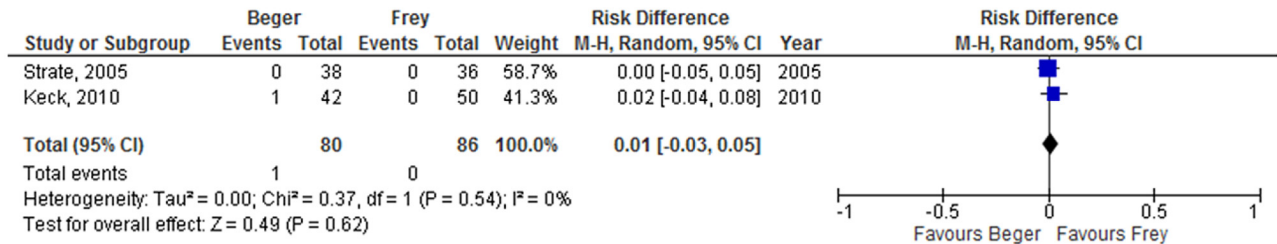
Another issue highlighted by this review is that Surgeons appear to be searching for a procedure that is technically less demanding than the Beger procedure as highlighted by the number of modifications in use. Although the results of the current meta-analysis showed a higher morbidity associated with the Beger procedure it did not reach statistical significance ($p = 0.06$). Examining the complications in more detail, one of the studies¹⁸ shows more significant complications in the Beger group which include pancreatic fistula and jejunal perforation. Similarly in Keck *et al.*, 2010, there is a higher rate of pancreatic fistula and abdominal abscess in the Beger group than the Frey group (9 versus 5 in total). However the re-operation rate was similar (3 versus 3) as was the length of ITU stay across two of the studies where this data was provided.^{18,26} Clearly this needs to be evaluated further in larger studies.

While the number of studies included in the meta-analysis were small in number, they were good quality studies demonstrated by risk of bias assessment and also low statistical heterogeneity ($I_2 = 0\%$). Even so, the authors acknowledge that there is potential for bias due to clinical heterogeneity. The series included had different patient populations and therefore different thresholds and indications for performing the surgical procedures described. Pain is a subjective symptom and heterogeneity in the

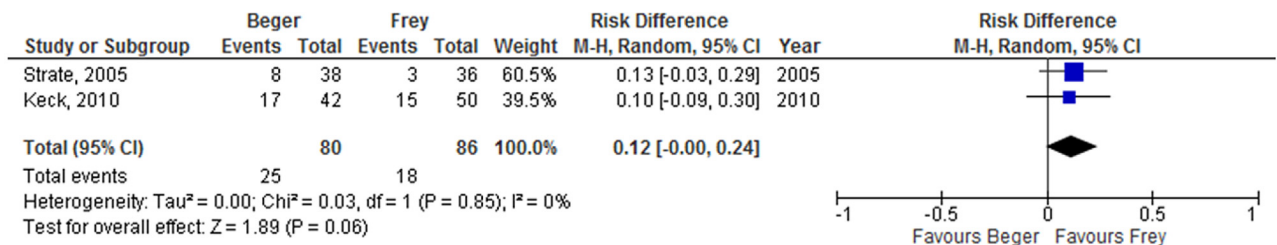
(a)



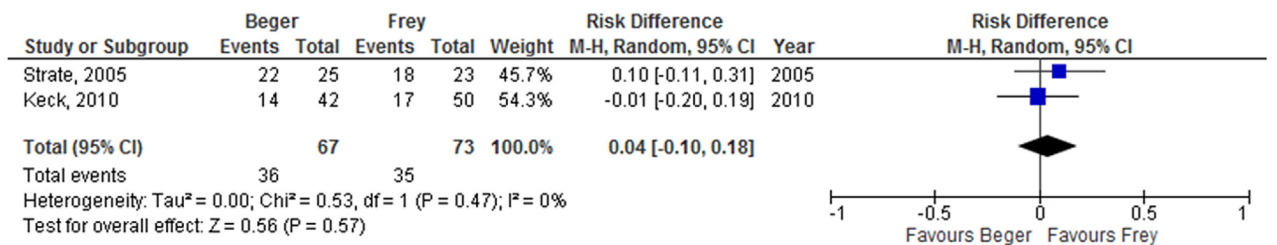
(b)



(c)



(d)



(e)

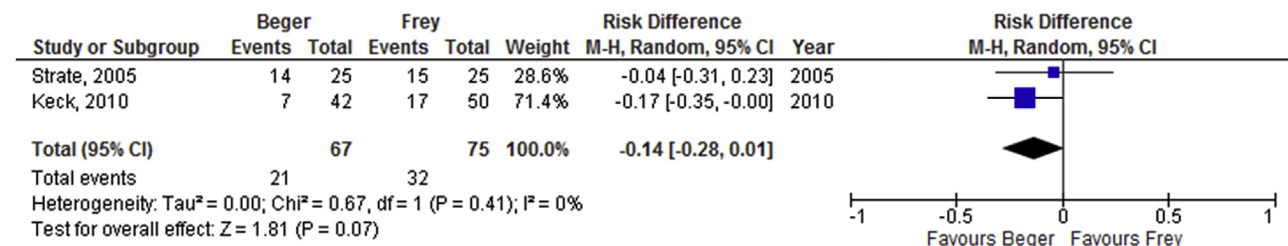


Figure 2 Forest plot comparing outcomes of Beger and Frey procedure. (a) pain relief (b) post-operative mortality (c) post-operative morbidity (d) exocrine insufficiency (e) endocrine insufficiency (CI indicates confidence interval; OR, odds ratio; PPPD, pylorus-preserving pancreaticoduodenectomy; n, number of events; N, number of patients in treatment group)

Table 3 Primary and secondary outcomes for studies included in the systematic review

Study	Keleman and Horvath, 2002 Frey:Beger	Strate <i>et al.</i> , 2005 Frey:Beger	Koninger <i>et al.</i> , 2008 Beger:Berne	Sakata <i>et al.</i> , 2009 Mod.:Min. Frey	Keck <i>et al.</i> , 2010 Frey:Beger
Pain relief	7/12:17/27	20/25:21/26	n/a	21/25:28/32 ^a	31/50:21/42
Mortality	0/13:0/32	0:0	0/26:0/29	0/25:0/32	0/50:1/42
Morbidity	0/13:8/32	3/36:8/38	6/26:7/29	5/25:3/32	15/50:17/42
Exocrine insufficiency	10/12:23/27	18/23:22/25	NS	NS	17/50:14/42
Endocrine insufficiency	3/12:1/27	15/25:14/25	NS	4/25:2/32	17/50:7/42

^a At time of discharge.

measurement of pain across the included studies may introduce bias. Furthermore, pain is a frequently used outcome measure for chronic pancreatitis but does not address other aspects of the disease covered by quality of life scores such as the SF-36²⁷ and use of these alternatives should be encouraged. In the study protocol 12 months was used as a minimum follow period so as not to limit the yield of studies. While this may not have revealed longer term decrease in pancreatic function, in fact both of the studies included in the meta-analysis had follow-up that far exceeded this with the lowest being 43 months.²¹

Conclusion

This study is the first to evaluate DPPHR for the management of chronic pancreatitis in the head of the pancreas. The results of the meta-analysis show no difference in post-operative outcomes between the Beger and Frey procedure. However, these results are based on a limited number of patients and needs further evaluation in larger studies.

Source of funding

Alliance Family Foundation.

Conflicts of interest

None to declare.

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