




A Network Meta-analysis of Surgery for Chronic Pancreatitis: Impact on Pain and Quality of Life

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Received: 6 April 2020 / Accepted: 27 June 2020 / Published online: 23 July 2020
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Abstract

Background The surgical operation associated with improved pain and quality of life (QoL) in patients with chronic pancreatitis (CP) is unknown.

Method The Scopus, EMBASE, Medline and Cochrane databases were systematically searched until May 2019, and all randomised trials (RCTs) comparing surgical operations for CP pain were included in a network meta-analysis (NMA).

Results Four surgical operations for treating CP were directly compared in eight RCTs including 597 patients. Patients were mainly male (79%, 474/597) with alcoholic CP (85%, 382/452). Surgical operations included were pancreatoduodenectomy (224, 38%), Berne procedure (168, 28%), Beger procedure (133, 22%) and Frey procedure (72, 12%). The NMA revealed that the Beger procedure ranked best for pain relief, whilst the Frey procedure ranked best for postoperative QoL, postoperative pancreatic fistula rate and postoperative exocrine insufficiency rate during a median follow-up of 26 months (reported range 6–58 months). Overall the Frey procedure ranked best for the combination of primary outcome measures based on surface under cumulative ranking curve scores.

Conclusions Overall the Frey procedure may perform the best for both pain relief and postoperative QoL in patients with CP. Further trials are warranted in defining the role of surgery in relation to endotherapy.

Keywords Chronic pancreatitis · Pancreatectomy · Pain · Quality of life

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s11605-020-04718-z>) contains supplementary material, which is available to authorized users.

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Introduction

Chronic refractory pain is the most challenging aspect to managing patients with chronic pancreatitis (CP), and it severely impacts quality of life (QoL) ¹. Surgery has often been considered the treatment of last resort and offered only after multiple attempts at endotherapy. However, 60–80% of patients fail endotherapy, reporting poor long-term relief from symptoms ^{2–5}. Recent evidence suggests that surgery should be offered earlier and may be even more effective compared with endotherapy ⁶. This is plausible due to the preservation of pancreatic parenchyma and function that is associated with early surgery ^{7, 8}. In addition to the treatment of chronic pain, surgery is sometimes indicated for local complications of CP including biliary and duodenal stenosis, inflammatory mass, complex pseudocyst, and venous compression/thrombosis/portal venous hypertension ^{6, 9, 10}.

Many different surgical operations have been described for the management of CP ¹¹, including drainage procedures (e.g. Puestow ¹², Partington-Rochelle ¹³), resection procedures (e.g.

Whipple procedure, duodenum preserving pancreatic head resection¹⁴) and hybrid procedures (e.g. Frey¹⁵, Berne¹⁶, and Beger¹⁷ procedures). Not only are there many operations, there are also many variations in the way these are performed and described. Further, there is no consensus regarding the best operation in regard to durable pain relief and improved QoL¹⁸. Although level one evidence is available, it is limited to pairwise comparisons^{19–21}. This limitation can be overcome by network meta-analysis (NMA) which allows multiple simultaneous comparisons (whilst maintaining randomisation) of more than two different treatment arms using Bayesian modelling²².

The aim of this study is to compare surgical operations for CP, using only data from randomised controlled trials (RCTs) and NMA to determine which is most effective for pain relief and improved QoL.

Methodology

The review protocol is available on PROSPERO (ID: CRD42019152027).

Literature Search

A systematic search of all major literature databases was performed observing validated PRISMA methodology²³ in May of 2019. SCOPUS, Medline, EMBASE and the Cochrane Library were interrogated with the literature search strategy reported in Appendix 1. Reference lists of all articles that satisfied the inclusion criteria were then manually reviewed to identify additional RCTs.

Data Selection, Extraction and Quality Assessment

Articles were included if they were RCTs comparing two or more surgical operations of CP management. Exclusion criteria were as follows: (i) non-randomised datasets or conference abstracts, (ii) non-surgical management, (iii) follow-up studies of previous original trials, (iv) study protocols and (v) non-CP pathologies. Two authors independently screened the articles (CBBR and SKK), and data was extracted following corroboration of potentially relevant studies and further reviewed by a third author (SP). Arms were categorised as per the surgical description in the methodology or on review of the cited operation. Primary outcome data was extracted and included the following: complete resolution of pain and European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ) scores. Baseline clinical data including gender, age, aetiology and time from symptoms to operation, and secondary outcome data including postoperative pancreatic fistula (POPF) rates, overall complications rates, readmission rates, new onset postoperative

endocrine insufficiency, new onset postoperative exocrine dysfunction, and overall survival were also extracted. The risk of bias within the study methodology was assessed using the Cochrane risk of bias tool²⁴.

Terminology and Definitions

The *Beger* procedure was defined as a duodenum preserving pancreatic head resection characterised by a subtotal resection of the pancreatic head with a divided pancreatic neck or body¹⁷. *Frey procedure* included coring out of the head of the pancreas with an additional longitudinal pancreaticojejunostomy¹⁵. The *Berne* is another modification of the duodenum preserving pancreatic head resection but without division of the pancreas¹⁶. A *pancreaticoduodenectomy* (PD) included both a conventional Whipple procedure and a pylorus preserving PD (PPPD).

Study Endpoints

Primary Endpoints Pain relief was determined as the number with complete resolution of pain on normal activities of daily living at the end of the postoperative follow-up interval defined by each study. QoL was determined through the EORTC QLQ C30 global score. The overall physical functioning score was used if a global score was unavailable.

Secondary Endpoints

The definition of *POPF* was rarely reported in the included articles. *New onset endocrine insufficiency* was defined as the diagnosis of diabetes in the postoperative period by meeting the World Health Organisation (WHO) definition²⁵ in patients without pre-existing diabetes prior to surgery. *Readmissions* were defined as the number of patients readmitted to hospital due to their CP following surgery. *Postoperative exocrine insufficiency* also described the new diagnosis of exocrine insufficiency postoperatively through stool chymotrypsin, pancreolauryl test, presence of steatorrhea and/or the need for oral pancreatic enzyme supplementation that was not observed preoperatively^{26, 27}.

Statistical Analysis

A NMA with a Bayesian framework was conducted in R²⁸ (R Foundation for Statistical Computing, Austria 2014) using the *gemtc* package. Odds ratio (OR) outputs for dichotomous data and mean difference outputs (MD) for continuous data were presented with their respective 95% credible intervals (CrI). Wan et al.'s²⁹ method was utilised to provide mean and standard deviation estimates from median and ranges. A graphical summary of the direct comparisons was reported in the form of network maps, where the line thickness correlates with the

number of direct comparisons and the node size with the population available for comparison. Comparisons between operations were made by three methods, analysis of NMA outputs (odds ratios and mean differences), the relative rankings on plotted rankograms corresponding to the treatment rank probabilities and manually calculating the surface under the cumulative ranking curve (SUCRA) scores. Odds ratios and mean differences were compared for each operation in the NMA output, and any statistically significant differences or consistently higher operation specific odds ratios or mean differences were identified³⁰. This guided the assessment of the best and worst ranked technique which was then confirmed by the order of rankogram and SUCRA rankings³⁰. A clustered ranking plot was drawn to determine the best overall surgical operation for CP management for pain and QoL. A random effects standard deviation was calculated to make a heterogeneity assessment, and a node-splitting analysis was conducted to determine inconsistency in the indirect comparison outputs. Publication bias was visually determined by constructed comparison adjusted funnel plots. If a study reported on more than a single operation in a single arm, the study arm was allocated to the surgical operation arm that was most prevalent within that same study. A NMA was only conducted on outcomes reported in four or more articles with an incidence of > 0 in both arms to maintain power.

Results

The literature search identified 449 articles and eight RCTs were included in this NMA (Fig. 1). Four different surgical operations for CP management were compared (Table 1). Patient recruitment occurred from 1984 to 2013 and the RCTs were published from 1994 to 2017, in Germany ($n = 5$)^{16, 27, 31–33}, Hungary ($n = 1$)³⁴ and multinationally ($n = 2$)^{14, 16}. Overall, 597 patients were randomised to different arms: PD (224, 38%) of which PPPD was the most common (78%, 172/224), Berne procedure (168, 28%), Beger procedure (133, 22%) and Frey procedure (72, 12%). The recruited patients were predominantly male (79%, 474/597). The aetiology of the CP was reported in five studies^{14, 26, 27, 31, 32} and was most commonly due to alcohol (85%, 382/452), the remainder being idiopathic (7%, 32/452) and not reported (8%, 38/452). The estimated mean age of the population was 48 years (SD 35.07) (Supplementary Fig. S1), and the time from symptom onset to surgery was a mean of 4.7 years (see Supplementary Table S1 for details). Age and pre-operative symptom duration did not differ between treatment arms in all included articles.

The assessments of the primary outcome were made at an estimated median follow-up interval of 26 months (reported range 6–58 months) (Supplementary Table S1). Three studies^{26, 27, 32} reported pain scores using a visual analogue scale. Comparable scores were observed in both arms of each study.

Two studies^{26, 32} also used a pain score based on the visual analogue scale, pain attack frequency, medication requirement and inability to work and found no difference between their respective trial comparisons. One study compared EORTC QLQ-C30 pain scale scores and did not find a difference between the Berne procedures and PD¹⁴. QoL was reported in six studies^{14, 26, 27, 31–33}, and EORTC Q30 scores were reported in five studies^{14, 26, 27, 32, 33}. Of these four studies reported either means and standard deviations^{14, 33} or medians and ranges^{26, 27} allowing comparison in a NMA. A single study reported the number able to pursue daily work as a surrogate for QoL and found no difference between Beger and Frey arms (79%, 15/19 vs 84%, 16/19 respectively $P = 1.000$)¹⁴.

Of the five articles^{14, 16, 26, 27, 31} that reported on the incidence of POPF, a single trial¹⁴ employed the international study group for pancreatic fistula (ISGPF)³⁵ definition. The remaining trials did not state the definition used. Overall complications were reported in three trials^{16, 27, 33} and were similar between trial arms. The presence of new onset endocrine insufficiency did not differ in three trials^{14, 27, 34} reporting this outcome, and although Farkas et al.³⁴ found new onset endocrine insufficiency solely in the PD arm (6%, 3/20) compared with the Beger arm (0%, 0/20), the study was poorly powered to detect a difference ($P = 0.231$). Mortality during follow-up was observed in two trials^{14, 27} but similarly did not differ between the randomised arms in either trial.

Network Meta-analysis

Eight direct comparisons were distributed among the eight trials, and Berne vs PD was the most commonly reported comparison (Supplementary Fig. S1). Five trials satisfied the criteria for inclusion in the NMA with regard to number of articles reporting the outcome and the incidence.

Primary Endpoints: Pain Relief and Quality of Life

Pain relief was reported in five trials^{16, 26, 27, 31, 34} and included 264 patients (Supplementary Table S2). Beger vs PD was the most commonly compared direct comparison (Supplementary Fig. S2A). The NMA output is reported in supplementary figure S2C. The Beger procedure was ranked the best operation in 51% of all direct and indirect comparisons followed by the Frey procedure in 28% of all comparisons (Supplementary Fig. S2B). The SUCRA scores confirmed these rankings (Table 2).

QoL using mean and standard deviations were reported in four trials^{14, 26, 27, 33} with 437 randomised patients available for comparison (Supplementary Table S2). Berne vs PD was the most commonly compared direct comparison (Fig. 2a). The NMA output is reported in Fig. 2c. On the plotted rankogram, the Frey procedure was the best ranked operation in 94% of all direct and indirect comparisons (Fig. 2b); the three alternative

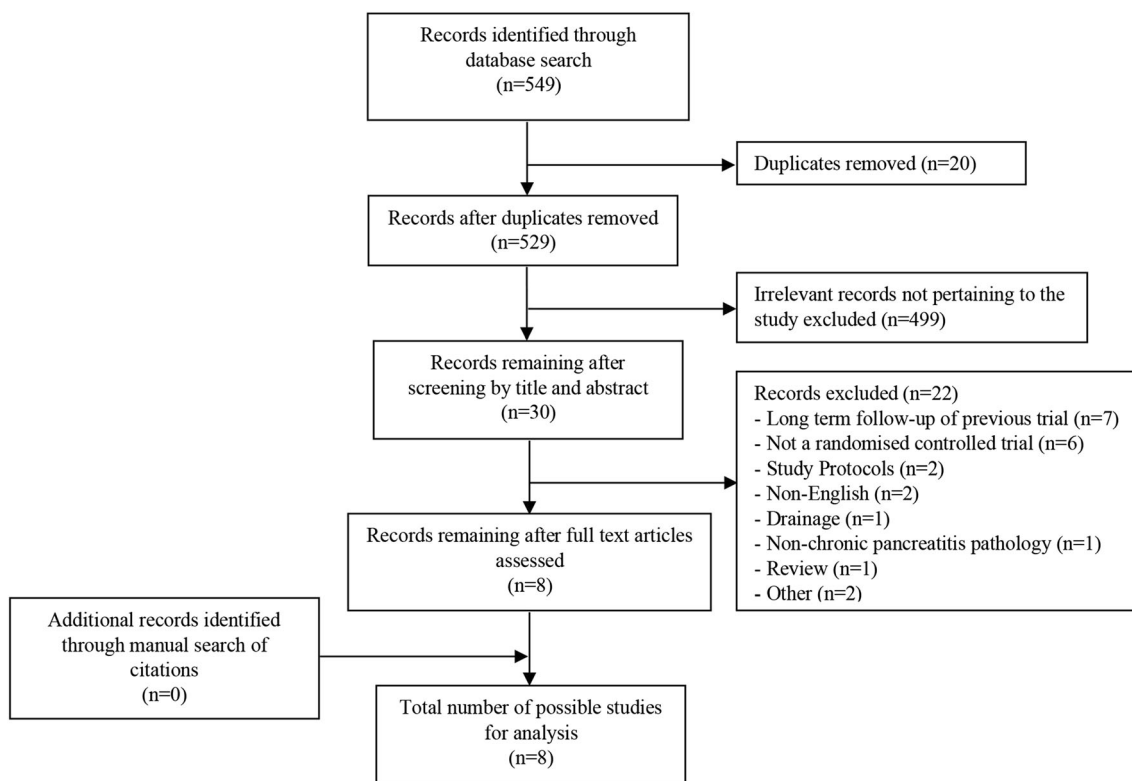


Fig. 1 Prisma flow chart of literature search strategy

operations scored similarly. The SUCRA scores confirmed the rankings. The clustered ranking plot of the SUCRA scores for pain relief plotted against QoL is shown in Fig. 3. Here, the Frey procedure performed the best overall in achieving both durable pain relief and improving postoperative QoL.

Postoperative Pancreatic Fistula

POPF was reported in five studies ^{14, 16, 26, 27, 31} comprising 450 patients randomised to all four operations (Supplementary Table S2). Beger vs PD was the most commonly reported

Table 1 Characteristics of included trials within the network meta-analysis.

Author	Country	Trial comparison	Follow-up	No. of patients	Network meta-analysis Outcomes reported
Diener et al. 2017 ¹⁴	Germany, Slovenia and UK	<i>Berne</i> * vs <i>Partial PD</i>	-	226	QoL, POPF, readmissions, and postoperative exocrine dysfunction
Keck et al. 2012 ²⁷	Germany	<i>PPPD</i> vs <i>Beger</i> *	3, 6, 12, and 24 months	85	QoL, pain relief, POPF, and postoperative exocrine dysfunction
Koninger et al. 2008 ³³	Germany	<i>Beger</i> vs <i>Berne</i>	-	65	QoL, POPF and readmissions
Farkas et al. 2006 ³⁴	Hungary	<i>Berne</i> vs <i>PPPD</i>	1 year	40	Pain relief and readmissions
Izbicki et al. 1998 ²⁶	Germany	<i>Frey</i> vs <i>PPPD</i>	24 (12–36) months	61	QoL, pain relief, POPF and postoperative exocrine dysfunction
Buchler et al. 1995 ¹⁶	Germany and Switzerland	<i>Beger</i> [‡] vs <i>PD</i>	12 to 35 months	40	Pain relief, POPF and readmissions
Izbicki et al. 1995 ³²	Germany	<i>Beger</i> vs <i>Frey</i>	1.5 (6–24) years	42	QoL [¥] , pain relief [¥] and postoperative exocrine dysfunction
Izbicki et al. 1994 ³¹	Germany	<i>Beger</i> vs <i>Frey</i>	-	38	QoL [¥] , pain relief and POPF

*The most common operation, [‡] as per the reference to which they describe their surgical operation, [¥] insufficient data to be included in the analysis. -, not reported. *POPF*, postoperative pancreatic fistula; *PD*, pancreaticoduodenectomy; *PPPD*, pylorus preserving PD; *QoL*, quality of life; postoperative pancreatic fistula. All reference numbers correlate to the bibliography

Table 2 Rank probability of being the best ranked operation for chronic pancreatitis management in all direct and indirect comparison within the network meta-analysis

Operation	Rank probability of coming the first ranked operation for chronic pancreatitis management (SUCRA score)				
	QoL	Pain relief	POPF	Readmissions	Postoperative exocrine dysfunction
<i>Beger</i>	0.017 (0.17)	<i>0.514*</i> (0.77)	0.057 (0.26)	0.346 (0.56)	0.360* (0.53)
<i>Berne</i>	0.036 (0.38)	0.155 (0.28)	0.139 (0.46)	0.072 (0.20)	0.338 (0.56)
<i>Frey</i>	<i>0.935*</i> (0.96)	0.275 (0.53)	<i>0.749*</i> (0.85)		0.257 (0.61)
<i>PD</i>	0.013 (0.48)	0.056 (0.41)	0.055 (0.44)	<i>0.583*</i> (0.75)	0.045 (0.30)

Asterisk and italics indicate the operation for chronic pancreatitis management with the highest probability of ranking first and the best operation as per the respective SUCRA score respectively. The grey box denotes the analysis did not have an output specific to that procedure. *PD*, pancreaticoduodenectomy; *QoL*, quality of life; *POPF*, postoperative pancreatic fistula; *SUCRA*, surface under the cumulative ranking curve score whereby a value of 1 represents 100% chance of being the best operation

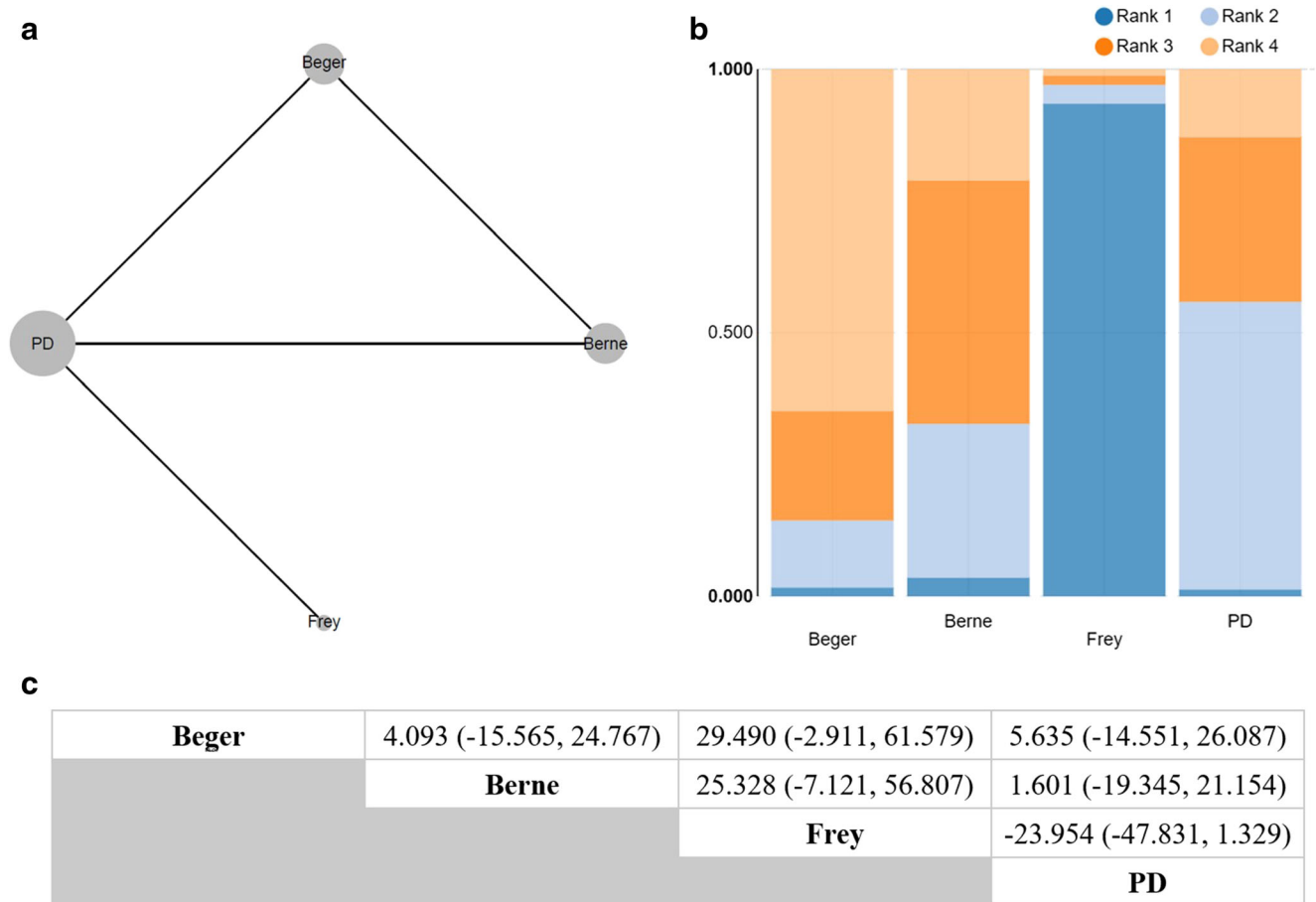


Fig. 2 Summary for the outcome quality of life. **a** Network map showing all direct comparisons. The thickness of the line correlates with the number of comparisons made and the size of the node represents the population available for that arm. **b** Rankogram. Rank 1 correlates with the highest quality of life scores. **c** Table of network meta-analysis output. Values are expressed as mean differences (95% credible intervals). Each

cell gives the effect of the column-defining intervention relative to the row-defining intervention. Values > 1 indicate that operation for chronic pancreatitis management in the corresponding column has a lower quality of life score than those in the corresponding rows and values < 1 indicate a higher score. PD, pancreaticoduodenectomy

direct comparison (Supplementary Fig. S3A). The NMA output is reported in supplementary figure S3C. The plotted rankogram identified the Frey procedure was the best operation in 75% of all direct and indirect comparisons (Supplementary Figure S3B and Table 2), the rankings corresponding to those observed by comparing the SUCRA scores.

Readmissions

Three operations were compared for the outcome of re-admissions in four trials^{14, 16, 33, 34} and 371 patients were randomised (Supplementary Table S2). Berne vs PD was the most commonly compared direct comparison (Supplementary Fig. S4A). The output from the NMA is reported in Supplementary Fig. S4C. PD was the best ranked operation in 58% of all comparisons and Beger followed with the best ranking in 35% of all comparison in regard to re-admission (Supplementary Fig. S4B). The SUCRA scores were consistent with this finding.

Postoperative Exocrine Dysfunction

Exocrine dysfunction was reported in four trials^{14, 26, 27, 32} comparing all four operations with 414 patients available for comparison (Supplementary Table S2). Frey vs PD was the most commonly compared direct comparison (Supplementary Fig. S5A). The NMA output reported similar comparative odds ratios and CrI between operations (Supplementary Fig. S5B). Although Beger was most frequently ranked first (36%)

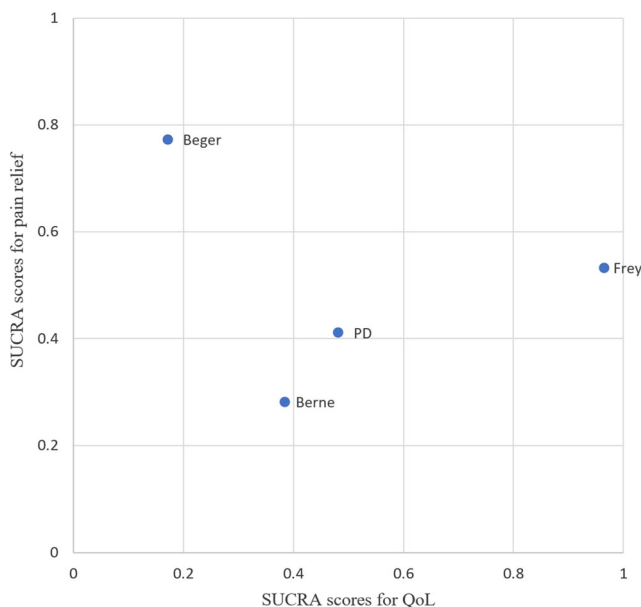


Fig. 3 Clustered ranking plot for operations for chronic pancreatitis management according to quality of life and pain relief rankings. The SUCRA score value of 1 indicates a 100% probability of ranking first and 0 indicating a 100% probability of ranking last. These are derived from the ranking for each outcome. SUCRA, surface under cumulative ranking curve score; PD, pancreaticoduodenectomy; QoL, quality of life

followed closely by Berne (34%) and Frey (26%) (Supplementary Fig. S5C), the Frey procedure was best on analysis of SUCRA scores (Table 2).

Risk of Bias, Heterogeneity and Consistency

A summary of the overall Cochrane's risk of bias analysis is reported in Supplementary Fig. S6. Overall, there was moderate to high risk of bias among all included trials (Supplementary Fig. S6). Due to the nature of the operations and the trial designs, it was not surprising that there was no blinding of the surgeons. There was also a consistent lack of blinding of patients and outcome assessment. Failure to use validated and consistent outcomes in the reporting of primary outcomes (pain) was also a source of potential bias. No obvious publication bias was observed on visual inspection of all comparison adjusted funnel plots for each outcome (Supplementary Fig. S7). Similarly, the random effects standard deviations are reported in Appendix 2 and no heterogeneity was identified in all reported outcome measures. Node splitting consistency models revealed no evidence of inconsistency in the networks devised for each outcome measure; however, due to the nature of the network map node splitting was unable to be performed on the outcome postoperative exocrine insufficiency (Appendix 2).

Discussion

The Frey procedure was ranked best of the operations for CP in this NMA of eight RCTs with regard to postoperative QoL, rates of readmission and exocrine insufficiency. The Frey procedure was also ranked best for the combined primary outcomes of pain relief and QoL. For pain relief alone, without consideration of QoL, the Beger procedure had the highest ranking. There remains a wide variation in publication date, study design, inclusion criteria and endpoints, and the trials comprised predominantly of middle-aged, male patients with alcohol-induced pancreatitis largely limited to European populations. Although no statistically significant differences were identified comparing odds ratios, trends were confirmed by rankograms and SUCRA scores.

Although previous pairwise comparisons of various proposed operations of surgical management of CP have been published³⁶, there remains significant controversy regarding the recommended operation. Particularly among early reports, reviews consistently reported comparable QoL and pain relief outcomes between duodenum preserving pancreatic head resection (DPPHR) and PD where non-randomised data were commonly included in view of the scarcity of randomised trials^{37, 38}. A 2016 Cochrane review published the first meta-analysis of solely RCTs (five trials), and concluded that the lack of high-powered multicentre trials limited the validity

of recommendations formulated from meta-analyses at the time²⁰. Similarly, a single explorative NMA on the topic was previously published on RCTs published until 2015¹⁸. Although potential advantages of the DPPHR were identified through a pairwise comparison, the relative benefit of specific DPPHR modalities NMA was uncertain due to poor comparative power. The present NMA reports a higher powered, more comprehensive outcome analysis with the reporting of clustered ranking plots and NMA outputs thereby providing a valid comparative assessment of specific DPPHR modalities for the first time. The advantage of performing a NMA over conventional pairwise comparisons is that it allows comparison of multiple operations simultaneously through Bayesian modelling whilst maintaining the randomisation for each trial arm. This allows a validated assessment of the relative benefit of each operation and provides a global assessment with greater confidence than pairwise comparisons.

It is only recently that variation in CP pain severity and frequency has been correlated with varying QoL outcomes. Indeed, following a review of CP patients in 27 centres in the USA in a large multi-centre prospective cohort, the authors found constant mild-moderate pain with episodes of more severe pain or constant severe pain to be major predictors of poor mental and physical QoL scores³⁹. Furthermore, intermittent severe pain did not correlate with poor mental QoL scoring and the study observed only a borderline correlation with poor physical QoL scoring. The study used the short form 12 questionnaire in contrast to the EORTC QLQ C30 questionnaire utilised in trials published in this review. Although our NMA was unable to perform a quantitative comparison of each component of the EORTC QLQ C30 questionnaire to validate these physical and mental domain specific findings, this observation suggests a need for targeted patient selection to identify patients who may experience the greatest benefit from surgical intervention. It is important to note that the Beger procedure was ranked the best with regard to pain relief, but performed poorly with respect to postoperative QoL. This is a finding suggesting that QoL may not solely depend on pain relief.

The original construct of CP pain secondary to a localised pathology such as a duct obstruction or inflammatory focus has been largely replaced due to a failure to correlate pancreatic morphological changes and the experience of pain^{40, 41}. The primarily neuropathic element in chronic pain secondary to CP may be a contributor to this finding⁴², and central sensitisation that is perpetuated by recurrent pancreatitis may result in a pain experience that is independent of nociceptive stimuli^{43, 44}. At all stages, the experience of pain differs considerably between individuals and steps have been taken to fully characterise pain and the impact of activities of daily living. There remain inconsistent and inadequate methods by which authors assess pain from CP⁴⁵. As evidenced by a previous review on the topic, studies investigating CP pain

employ tools that universally failed to address all relevant components of CP pain few were CP specific and none validated in that context⁴⁵. The recently developed comprehensive pain assessment tool (COMPAT) is associated with promising early validity data and aims to address the concern about inconsistent pain reporting in future trials⁴⁶. Formal prospective validation is eagerly awaited along with the development of a shorter form. Consistent reporting in CP surgery must also be established. The International Study Group of Pancreatic Surgery aims to publish on standards for reporting minimum clinical baseline and outcome data, morphology of the diseased gland and accurate description of the operations.

There is increasing evidence that early surgery for CP is more effective^{47–50}. Risk factors for a failure of surgery included narcotic dependence and more than five endoscopic treatments. The preliminary data from the Dutch ESCAPE trial (ISRCTN number: ISRCTN45877994) indicates that those who underwent early surgical therapy had an increased likelihood of complete postoperative pain relief and a reduced risk of pancreatic insufficiency when compared with those who had delayed surgery. This is particularly relevant to the trials included in this NMA, which were from an era before this evidence was available. Therefore, there may have been a more pronounced impact of operations on durable pain relief and QoL if surgery had been offered at an earlier stage in the disease course. Furthermore, there are situations where endotherapy appears to be more effective than surgery, indicating that the respective roles of surgery and endotherapy in CP management still require further elucidation⁵¹. Total pancreatectomy and auto-islet cell transplantation (TPAIT) has a role to play in management strategy for CP pain, but this also requires further study⁵². Trials comparing TPAIT and other operations for CP are required.

There are several limitations to this NMA. The quality of this analysis directly reflects the quality of the trials available for inclusion, which is especially important in regard to the relatively crude methods used to assess pain relief. The included studies were commonly published in the late 1990s and early 2000s which may not reflect current practice in terms of case selection or perioperative management. Only eight RCTs met the inclusion criteria and limited outcome data meant that in only five were outcomes compared quantitatively. The included trials were also generally low-powered potentially explaining the lack of statistically significant NMA outputs. Interpretations of specific rankings are therefore limited in that rankograms and SUCRA scores only confirm trends in the NMA outputs. Data on POPF rates were only available for three operations. Some trials included more than one operation in a single trial arm. This NMA is further limited by its ability to determine the relative efficacy of the Puestow procedure. Pain assessment was also rudimentary, and the trials did not employ comprehensive and validated

pain assessment tools⁴⁵. This study only includes RCTs comparing surgical techniques and not those comparing surgery with endoscopic or medical management. Therefore, the larger question of the relative roles of surgical and endoscopic treatment has not been addressed in this study but remains an important priority^{51,53}. The extracted data was also limited in that known prognostic factors such as smoking⁵⁴ or continuing alcohol consumption⁵⁵ were not investigated. Differences in patient characteristics between RCTs that may have contributed to the efficacy and suitability of surgery were also unexplored. Future RCTs exploring surgical techniques should ensure comparable patient selection criteria to address this limitation. Nevertheless, this review is confined to RCT datasets and employs a sound NMA methodology and provides the best available data for comparing the efficacy of operations for CP in terms of pain relief and QoL impact.

Conclusion

This NMA demonstrated that the Frey procedure may be the best operation for patients with CP in regard to postoperative QoL, risk of POPF and PEI, and was ranked second for pain relief. CP pain is complex and the identification of subset of patients for whom early surgery should be offered remains a work in progress. New validated tools to assess CP pain and the influence of various types of pain patterns on QoL will allow future trials to better stratify patients. Given the different inclusion criteria, pain and QoL assessment and duration of symptoms, further trials are required to investigate the role of surgery for different CP phenotypes, timing of surgery and in defining the role of surgery in relation to endotherapy.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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