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REVIEW ARTICLE

Pain relief in chronic pancreatitis: endoscopic or surgical treatment? a systematic review with meta-analysis

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Abstract

Background and aims Pain is one of the consequences of chronic pancreatitis (CP) that has the greatest impact on the quality of life of patients.

Endoscopic and surgical interventions, by producing a decrease in intraductal pancreatic pressure, can provide pain relief. This is the first systematic review that includes only randomized clinical trials (RTCs) comparing outcomes in the short-term (less than 2 years) and long-term (more than 2 years) between these two types of interventions.

Material and methods A comprehensive search of multiple electronic databases to identify RTCs comparing short and long-term pain relief, procedural complications, and days of hospitalization between endoscopic and surgical interventions was performed following the PRISMA guidelines.

Results Three RCTs evaluating a total of 199 patients (99 in the endoscopy group and 100 in the surgery group) were included in this study. Surgical interventions provided complete pain relief, with statistical difference, in the long-term (16,4% vs 35.7%; RD 0.19; 95% CI 0.03–0.35; $p=0.02$; I2 = 0%), without significant difference in short-term (17.5% vs 31.2%; RD 0.14; 95% CI −0.01–0.28; $p=0.07$; I2 = 0%) when compared to endoscopy. There was no statistical difference in short-term (17.5% vs 28.1%; RD 0.11; 95% CI −0.04–0.25; $p=0.15$; I2 = 0%) and long-term (34% vs 41.1%; RD 0.07; 95% CI −0.10–0.24; $p=0.42$; I2 0%) in partial relief of pain between both interventions. In the short-term, both complications (34.9% vs 29.7%; RD 0.05; 95% CI −0.10–0.21; $p=0.50$; I2 = 48%) and days of hospitalization (MD −1.02; 95% CI −2.61–0.58; $p=0.21$; I2 = 0%) showed no significant differences.

Conclusion Surgical interventions showed superior results when compared to endoscopy in terms of complete long-term pain relief. The number of complications and length of hospitalization in both groups were similar.

Keywords Chronic pancreatitis (CP) · Endoscopy · Lithotripsy · Surgery · Pain

Chronic pancreatitis (CP) is an irreversible, multifactorial, and fibroinflammatory disease that has a detrimental impact on the quality and life expectancy of affected patients [1]. This is clinically manifested by abdominal pain, malnutrition, and endocrine and exocrine pancreatic insufficiency, whose causative or contributing factor to its progression is categorized by a classification system, depending on whether it is toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, or obstructive (TIGAR-0_V2) [2, 3].

Pain, the most common presenting symptom in CP, has a poorly understood and complex pathophysiology [3–5]. As it is a somewhat subjective symptom, scales have been developed for its measurement, including the Izbicki scale [6], which is specific for chronic pancreatitis, and the Mezlack scale [7] which is more widely used scale. Amongst the complications of CP, strictures, and calcifications in the main pancreatic duct (MPD), by causing obstruction and an increase in MPD pressure, are the main etiology of pain. Nevertheless, neuropathic nerve inflammation, pancreatic cancer, peripancreatic fluid collections, and extra-pancreatic

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complications (peptic ulcer disease and duodenal/bile duct strictures) can contribute or be the etiology for the pain [2].

Both endoscopic and surgical interventions aim at relieving pain and treating local complications [8]. Endoscopic interventions such as pneumatic dilation of MPD strictures, stent placement, and stone removal/lithotripsy via endoscopic retrograde cholangiopancreatography (ERCP) alongside extracorporeal shock wave lithotripsy (ESWL) work by relieving intraductal pressure [4, 9]. Surgical therapies can be classified into decompression, resection, and mixed techniques. These are performed accordingly to the characteristics of the patient, anatomical alterations of the pancreatic gland and its ductal system, and the presence of an associated inflammatory pancreatic head mass [10–12]. Also, local expertise plays a role in ultimately determining the most appropriate surgical intervention.

This study aims to evaluate the impact of endoscopic interventions in comparison with surgical procedures on pain relief, complications, and hospitalization time in patients with chronic obstructive pancreatitis.

Material and methods

Protocol registration

This study was performed in conformity with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, and it was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under the file number CRD42020200449. The study was approved by the Ethics Committee of Hospital das Clínicas, Faculty of Medicine at The University of São Paulo.

Eligibility criteria

Data search was made without limitations of language or publication date. The eligibility criteria were randomized clinical trials (RCTs) comparing endoscopic therapy (associated or not with lithotripsy) versus surgery for the treatment of chronic pancreatitis in patients over 18 years of age, with dilation in the main pancreatic duct, associated with proximal stenosis, or the presence of stones in it, with or without increased pancreatic head volume. The exclusion criteria were studies that compared another type of therapy different from those mentioned in the inclusion criteria, or studies that included neoplastic pathologies.

Information sources

We performed a search in electronic databases MEDLINE, Embase, Cochrane, LILACS, and a cross-reference search, from their inception until November 2020. The search strategy is described in supplementary Appendix 1.

Study selection and data collection process

Two researchers reviewed the title and abstract of each article after the removal of duplicated articles. Articles that were found to be relevant were selected for full-text review. The final decision on the selection of the studies was based on predetermined inclusion and exclusion criteria. Any disagreement on the selection of the studies was resolved by consensus with a third experienced researcher. The primary outcome was complete and partial pain relief. The secondary outcomes were complications and hospital stay.

Due to the variability of follow-up time between studies, we grouped them according to the time of evaluation of their results, in short-term follow-up (less than 2 years) and long-term follow-up (more than two years).

Data items

The following data were extracted: name of the first author, year of publication, type of study, population (characteristics and number of patients), intervention or test (characteristics and number of patients), comparison (characteristics and number of patients), follow-up time, and outcomes (number of events) (Table 1).

Evaluation of biases and quality of studies

The selected studies were all RCTs and the risks of bias were defined by version 2 of the Cochrane Risk-of-Bias tool for Randomized Trials (RoB2) [13] (Table 2). The quality of evidence, expressed in high, moderate, low, and very low, was assessed utilizing the objective criteria from GRADE (Grading Recommendations Assessment, Development, and Evaluation) for each of the pre-specified results and outcomes using GRADEpro—Guideline Development Tool software (McMaster University, 2015; Evidence Prime, Inc., Ontario, Canada).

Data analysis

The data of interest extracted from the selected studies were meta-analyzed using RevMan software (Review Manager Software version 5.4—Cochrane Collaboration Copyright© 2020).

For dichotomous variables, the risk difference was determined by calculating the number of events and the sample size using the Mantel Haenszel test with a 95% confidence interval. For continuous variables the mean or median with standard deviation and the total number of patients were used, employing the inverse variance test with a 95% confidence interval. When the results were not presented with standard deviation, the estimation of a sample's mean and

Table 1 Characteristics of included studies

Autor	Year	Study design	Follow-up time	Patient	Intervention/comparison	ESWL	Pain measurement instruments	Outcomes				
								Pain relief		Technical success	Complications	Days of hospitalization
								Complete	Partial			
Issa Y	2020	RCT	18 months	88	44 ENDOSCOPY	Yes	Melzack score	8	8		11	10 + −4.91
					44 SURGERY	No		12	11		12	11 + −2.32
Cahen	2011	RCT	2 years	39	19 ENDOSCOPY	Yes	Izbicki score	3	3	10	11	8 + −36.98
					20 SURGERY	No		8	7	20	7	11 + −15.61
			7 years	39	19 ENDOSCOPY	Yes		4	2	6	9	13 + −67.87
					20 SURGERY	No		8	4	18	1	11 + −98.18
Dité	2003	RCT	5 years	72	36 ENDOSCOPY	No	Izbicki score	5	17			
					36 SURGERY	No		12	19			

RCT Randomized clinical trial, *ESWL* Extracorporeal shock wave lithotripsy

variance from its median and range using the Hozo test [14] was performed.

In both dichotomous and continuous variables, a fixed effect was used when the heterogeneity was <50% and a random effect when >50%. Values of $p < 0.05$ were considered statistically significant. Heterogeneity was calculated using the Higgins test (I2), ranging from 0% to 100%. I2 values higher than 50% were considered substantial heterogeneity [14, 15].

Due to the low number of identified clinical trials and the low heterogeneity between them, funnel plots were not useful to assess the presence of publication bias. Therefore, it was not necessary to use them.

Results

Literature search results and characteristics of included studies

The initial search strategy identified 15,327 records. After the removal of duplicates, evaluation of the titles and abstracts, and a full reading of 13 studies, three studies were selected [16–18]. Figure 1 shows the selection process.

The selected studies compared endoscopic therapy versus surgical procedures for the management of chronic pancreatitis, with some variations regarding the technique performed, patient characteristics, and follow-up time. Three RCTs [16–18] evaluated a total of 199 patients, with 99 in the intervention group (endoscopy) and 100 in the comparison group (surgery). One of the RCTs [18] included both patients who accepted and did not accept randomization, and to maintain the quality of the evidence, only data from randomized patients were extracted for the analysis. Another author evaluates the same population in two different publications, one with a 2-year follow-up [19] and the other five years after the end of the first evaluation [17]. We extracted the data from both publications (Table 1).

Results

Pain relief

Complete pain relief

After the subgroup analysis, 2 RCTs [17, 18], with a total of 111 patients (55 in the endoscopy group and 56 in the surgery group), showed a significant difference in long-term pain relief in favor of surgery group (RD 0.19; 95% CI 0.03, 0.35; $p = 0.02$; $I^2 = 0\%$). High quality of evidence (Table 3). No significant difference was observed in the short term (RD 0.14; 95% CI −0.01, 0.28; $p = 0.07$; $I^2 = 0\%$ (Fig. 2). High quality of evidence (Table 3).

Table 2 Rob 2 Risk of bias assessment

Study ID	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall			
Issa 2020	+	+	+	+	?	!		+	Low risk
Cahen 2011	+	+	+	+	+	+		?	Some concerns
Cahen 2007	+	+	+	+	+	+		−	High risk
Dité 2003	−	?	+	?	+	−			

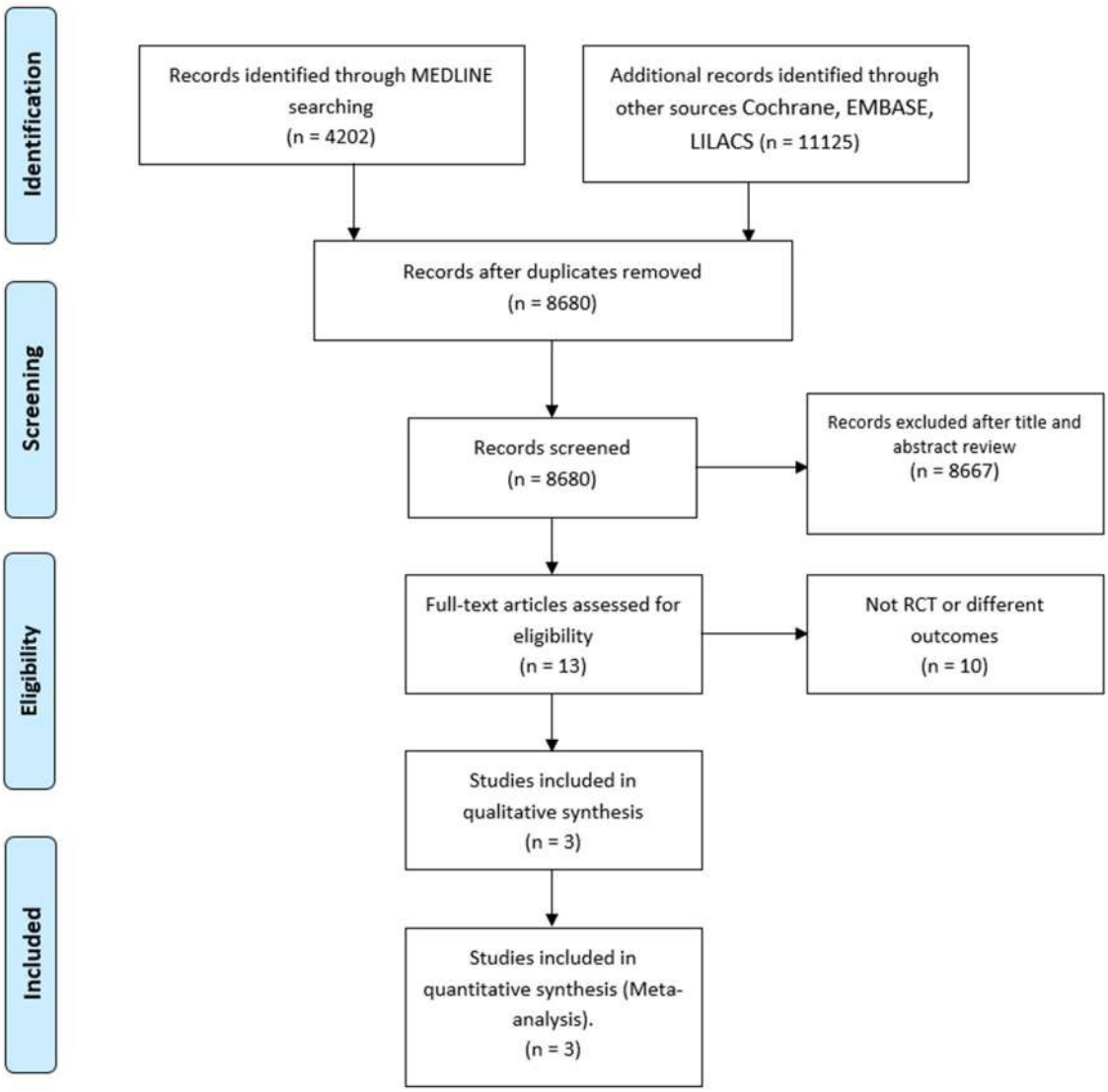

Fig. 1 Flow diagram showing study selection process for meta-analysis

Table 3 Grading recommendations assessment, development, and evaluation (GRADE)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endoscopy	Surgery	Relative (95% CI)	Absolute (95% CI)		
Complete pain relief—Middle term												
2	Randomized trials	Not serious[a]	Not serious	Not serious	Not serious	None	11/63 (17.5%)	20/64 (31.3%)	Not estimable	**140 fewer per 1.000** (from 280 fewer to 10 more)	⨁⨁⨁⨁ HIGH	
Complete pain relief—long term												
2	Randomized trials	Not serious[b]	Not serious	Not serious	Not serious	None	9/55 (16.4%)	20/56 (35.7%)	Not estimable	**190 fewer per 1.000** (from 350 to 30 fewer)	⨁⨁⨁⨁ HIGH	
Partial pain relief—Middle term												
2	Randomized trials	Not serious[a]	Not serious	Not serious	Serious[c]	None	11/63 (17.5%)	18/64 (28.1%)	Not estimable	**110 fewer per 1.000** (from 250 fewer to 40 more)	⨁⨁⨁◯ MODERATE	
Partial pain relief—Long term												
2	Randomized trials	Not serious[b]	Not serious	Not serious	Very serious[c]	None	19/55 (34.5%)	23/56 (41.1%)	Not estimable	**70 fewer per 1.000** (from 240 fewer to 100 more)	⨁⨁◯◯ LOW	
Complications—Middle term												
2	Randomized trials	Not serious[a]	Not serious	Not serious	Very serious[c]	None	22/63 (34.9%)	19/64 (29.7%)	Not estimable	**50 fewer per 1.000** (from 210 fewer to 100 more)	⨁⨁◯◯ LOW	
Days of hospitalization—Middle term												
2	Randomized trials	Not serious[a]	Not serious	Not serious	Not serious	None	63	64	–	MD 1.02 lower (2.61 lower to 0.58 higher)	⨁⨁⨁◯ HIGH	

CI Confidence interval, *MD* Mean difference

[a]Bias in selection of the reported result

[b]Bias in randomization

[c]Wide confidence interval

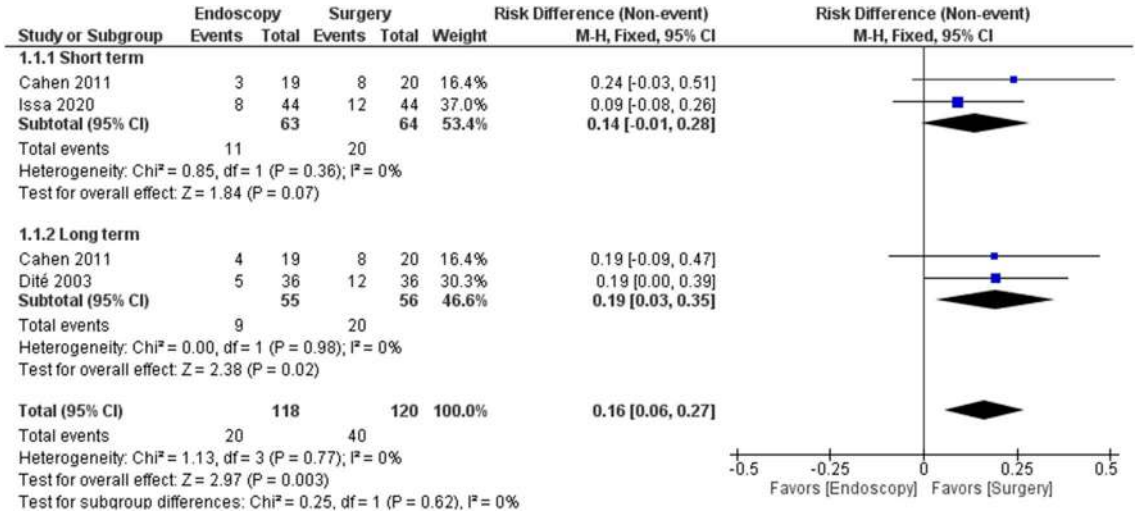

Fig. 2 Forest plot of complete pain relief:Overall

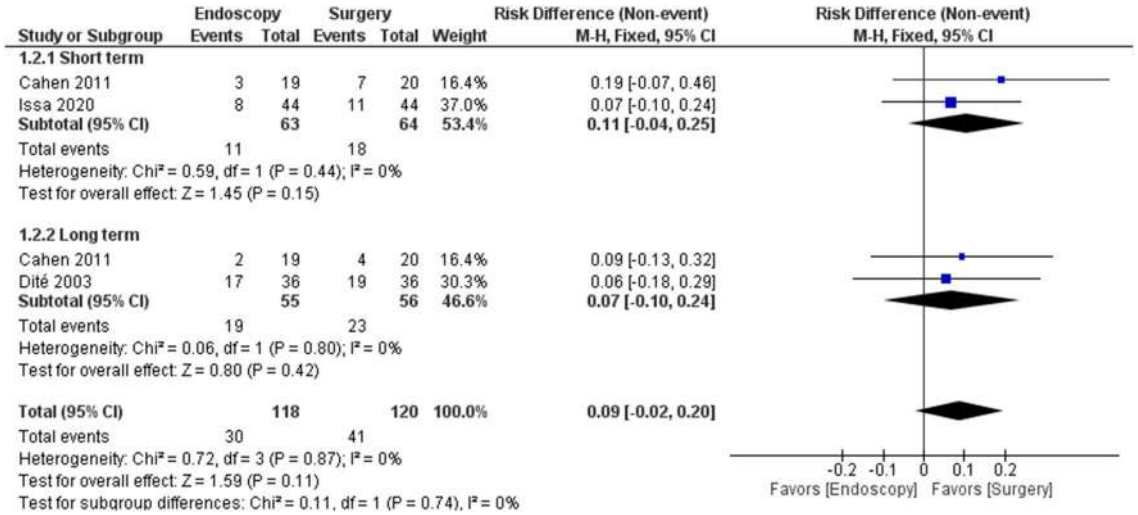

Fig. 3 Forest plot of partial pain relief

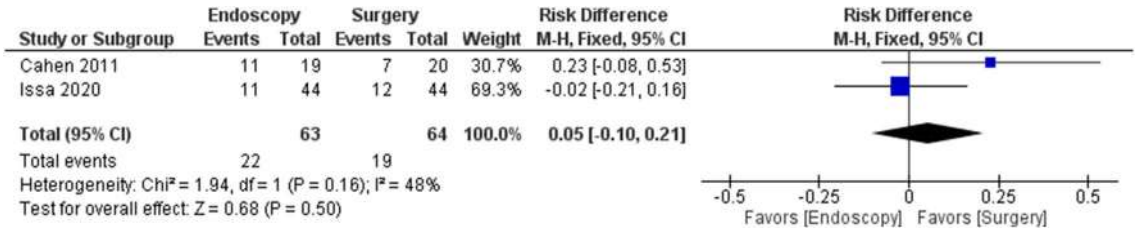

Fig. 4 Forest plot of complications

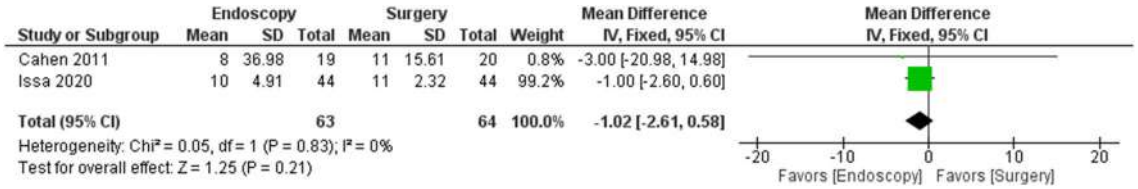

Fig. 5 Forest plot of days of hospitalization

Partial pain relief

No statistical difference was observed in the subgroup analysis. Two RCTs [16, 19] evaluated partial pain relief in the short term, with a total of 127 patients (63 in the endoscopy group and 64 in the surgery group) (RD 0.11; 95% CI −0.04, 0.25; $p=0.15$; $I^2=0\%$) (Fig. 3). Moderate quality of evidence (Table 3). Two RCTs [17, 18] evaluated long-term partial relief in 111 patients (55 in the endoscopy group and 56 in the surgery group) (RD 0.07; 95% CI −0.10, 0.24; $p=0.42$; $I^2=0\%$) (Fig. 3). Low quality of evidence (Table 3).

Complications

Two RCTs [16, 19], with a total of 127 patients (63 in the endoscopy group and 64 in the surgery group), were compared regarding the post-procedure complications in the short term, without a significant difference (RD 0.05; 95% CI −0.10, 0.21; $p=0.50$; $I^2=48\%$) between them (Fig. 4). Low quality of evidence (Table 3).

Days of hospitalization

Two RCTs [16, 19], with a total of 127 patients (63 in the endoscopy group and 64 in the surgery group), were compared regarding the days of hospitalization in the short term, with no significant difference (MD −1.02; 95% CI −2.61, 0.58; $p=0.21$; $I^2=0\%$) between them (Fig. 5). High quality of evidence (Table 3).

Discussion

Endoscopic therapy-associated or not with ESWL- and surgical interventions are widely used options for the treatment of patients with pain caused by chronic pancreatitis. Both treatments focus on relieving pancreatic intraductal pressure without taking into account other possible mechanisms that could account for this symptom [20], which could explain the number of patients who do not achieve complete or partial relief of pain in both types of therapies.

Other meta-analyses have evaluated comparative studies between surgery and endoscopy. One of them [21] evaluated pain relief in middle and long-term subgroups, showing a significant difference in both in favor of the surgical intervention group. However, they used the same population of one of the randomized studies for the analysis of both subgroups [18]. Also, the follow-up time of the results shows a very wide difference (2 compared to 5 years). The other meta-analysis [22] showed a significant difference in complete long-term pain relief in favor of surgery. However, it included randomized and non-randomized patients from one of their studies [18] which decreases the quality of the evidence.

In our meta-analysis, randomized studies showed that surgical interventions had better results than endoscopy, with a significant difference regarding complete pain relief when their long-term results were compared. We found no statistical difference in the short-term, which is partially consistent with the aforementioned meta-analyses [21, 22]. This could be mainly due to the long-term recurrences of pain observed in part of the cases undergoing endoscopic therapy. Unlikely surgery, in which there is a permanent anatomical alteration that allows decompression of the gland via a wide anastomosis with the intestinal loop that significantly reduces the likelihood of recurrent strictures or stone impactions.

Although it was not the reason for the analysis of the present study, one clinical trial reports similar rates of pain relief when a complete clearance was achieved via endoscopic therapy, either with or without the application of ESWL [16]. We thus believe that endoscopic interventions can be considered in the first instance in selected cases (those that have the possibility of reaching clearance or relief of obstruction) since a decompression surgery would not achieve additional benefit for this symptom if it does not improve after endoscopic therapy. Surgery could then be performed when there is a recurrence of a stricture or pancreatolithiasis, or in the event of a failure with endoscopic treatment. We find this approach to be recommended in different guidelines [23–25], amongst these, the European Society of Gastrointestinal Endoscopy (ESGE) which recommends endoscopic therapy and ESWL as the first treatment option in obstructions at the level of the head or body of the pancreas, followed by a reevaluation of the response 6 to 8 weeks later.

Regarding complications, no statistical difference was found in the short-term. Because only one randomized study reported long-term data, this comparison was not possible [17]. Although surgical interventions are more invasive and more complications are expected (wound infection, dehiscence, or fistulas), this generally requires a single-stage procedure. On the opposite side, endoscopic therapy requires multiple sessions, leading to a higher chance of complications (cholecystitis, bleeding, or cholangitis) or exacerbations of pancreatitis. Only one of the studies reports an early death, four days after ESWL, caused by a perforated duodenal ulcer in a patient using non-steroidal anti-inflammatory drugs (NSAIDs) [19].

There was no statistical difference in the average days of hospitalization in the short-term, and it was not possible to meta-analyze this result in the long-term. Even though endoscopic therapies are an outpatient procedure, in some cases, the hospitalizations were related to post-procedural complications. We must also mention that one of the studies [16] reported in the endoscopy arm -in addition to hospitalizations secondary to endoscopic complications-, hospitalizations for surgical procedures that were performed in the event of failure of the endoscopic treatment.

This study has some limitations such as the low number of identified clinical trials, the differences in terms of follow-up time, patient characteristics, pain measurement scales used and time interval for evaluating them, and types of treatments performed across studies (Table 2). One study excluded patients with an increased volume of the head of the pancreas [17]. There are also differences regarding the type of lithotripsy. In one study, ESWL was not offered in any case of lithiasis of the main pancreatic duct, and instead, mechanical lithotripsy was performed [18]. Extracorporeal shock wave lithotripsy can be performed on an outpatient basis, and in addition to relieving the stone obstruction, some of its effects on pain could be related to changes in nociception via some effects on the intra-pancreatic nerves [26]. Despite this, surgical interventions (particularly resection techniques) continue to be superior to ERCP even when associated with ESWL. Nevertheless, CP is a complex, multifactorial, and difficult-to-treat disease, with different responses to each type of intervention. Also, each study individually shows homogeneous populations between groups, observing high-quality evidence in three randomized clinical trials.

In conclusion, in the treatment of chronic obstructive pancreatitis, surgical interventions showed superior benefits to endoscopic therapies in terms of pain relief in the long-term. The number of complications and length of hospitalization in both groups were similar.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00464-021-08515-w.

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Declarations

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Ethical approval The study was approved by the Research Ethics Committee of the University of São Paulo School of Medicine Hospital das Clínicas.

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