Endoscopic and Surgical Treatments for Painful Chronic Pancreatitis: A Scoping Review of Pain Assessment Tools and Meta-analysis of Outcomes

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Objective: Managing painful chronic pancreatitis (CP) often involves invasive treatments, but success rates are variable. We aimed to describe the pain assessment tools used to measure the efficacy of endotherapy and surgery for painful CP and perform a meta-analysis of outcomes.

Design: PubMed, Embase, and Scopus databases were searched for published studies through April 1, 2023. Full papers in English that assessed pain outcomes among adults with painful CP undergoing invasive interventions were included.

Results: There were 413 out of 1,282 studies that underwent full-text review, and 279 studies were selected for the scoping review. Most commonly used pain assessment tools included symptom description (n = 68 studies), numeric pain rating scales (NRS) or visual analog scales (VAS) (n = 52), binary pain relief (yes or no) (n = 27), and the pancreatitis-specific 4-item Izbicki score (n = 28). In a meta-analysis of studies reporting preintervention and postintervention NRS or VAS (0–100), the mean decrease in pain after endoscopic intervention (n = 9 studies) was 40.3 (95% CI: 27–53.6, $P < 0.001$) and after surgical intervention (n = 12 studies) it was 43.2 (95% CI: 31.5–54.9, $P < 0.001$). A separate meta-analysis of studies reporting the preintervention and postintervention Izbicki score (n = 5) showed similar findings. There was no difference in the change in pain scores between endotherapy and surgical cohorts in studies using NRS/VAS or Izbicki scores.

Conclusions: Pain outcomes were similar between endotherapy and surgery for painful CP based on the use of simple and highly variable pain assessment tools. Referral bias and sham effects need to be considered in future trials.

Key Words: chronic pancreatitis, abdominal pain, meta-analysis, pain assessment tools, patient-reported outcome measure

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Abdominal pain is the primary symptom of chronic pancreatitis (CP) and is present in a majority of patients during the course of disease.[1] The management of painful CP remains challenging to clinicians. A failure of preventive measures (ie, smoking cessation and alcohol abstinence) and failure of medical management are reasons to consider invasive interventions, including endoscopic treatment (with stenting, stone removal ± extracorporeal shockwave lithotripsy)[2] and surgical treatment (with ductal decompression, resections, or combinations).[3] The risk of morbidity and mortality associated with invasive procedures necessitates an accurate selection of patients with an acceptable chance of clinical benefit.[4,5] However, there is a ongoing debate, in the face of insufficient evidence, as to the relative indications and roles of invasive treatments.[4]

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Comparing studies examining the outcomes of endoscopic and surgical treatments is challenging due to the heterogeneity of assessment tools for painful CP. Because the criteria used to define "pain relief" vary widely, the interpretation and application of the findings to clinical practice are often challanging.[6] For example, many series report the percentage of patients achieving pain relief at the first postoperative visit. Still, they neglect to measure the duration of pain, baseline pain scores, or analgesic use at either time point. Thus, these reports may display a successful outcome but cannot inform expectations for pain relief for a patient with mild or severe pain who may or may not be using analgesics (such as opioids) already. Furthermore, patients in clinical practice will undoubtedly have questions about their quality of life following an intervention, the chance for reintervention, and the ability to return to work.[7] It is now accepted that the assessment of pain outcome (ie, the primary endpoint), should take into account multiple domains to capture the complex nature of the pain experience (ie, psychological, physical, and social), including patient-reported outcomes[8] and be done before and after invasive interventions to be clinically meaningful.[9] Hence, there is an unmet need for better pain assessment tools to select patients for invasive treatments and to monitor their response.[9–12] In addition to the heterogeneity of pain assessment tools, the published studies evaluating the impact of interventions on pain display significant heterogeneity in regard to the patient populations, pain characteristics, indication criteria for intervention, treatment protocols, study designs, and secondary outcome measures. Therefore, previous studies are difficult to compare, leaving the clinician uncertain and reliant on local guidelines and established practices when invasive management of painful CP is considered.

The aims of this study were to first systematically review the pain assessment tools used in studies of invasive interventions for pain in CP patients and second, to conduct meta-analyses of studies that used the same pain assessment tools to compare the effect of endoscopic and surgical treatments on pain.

MATERIALS AND METHODS

The first step was to conduct a scoping review based on the methodological framework established by Arksey and O'Malley.[13] Then, a systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and checklist.[14] The protocol for this review has not been published elsewhere.

Search Strategy

A comprehensive literature search of the PubMed, Embase, and Scopus databases was conducted, aiming to include all studies reporting on invasive interventions in patients with CP (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/MPA/B364). The search was implemented on April 1, 2023, and included all possible studies without limitation to time period or language. The reference lists of identified studies were secondarily searched for additional articles not identified by the primary search strategy.

Study Selection Criteria

All studies that performed invasive interventions for humans with painful CP and reported baseline and postprocedural pain outcomes were considered (Fig. 1). The selected studies were published as original, peer-reviewed manuscripts in English. Review papers, conference abstracts, duplicate reports, and studies, including patients with disease entities other than CP (eg, pancreatic cyst or neoplasm), were excluded from the analysis. Studies were imported into the Covidence web-based software (Covidence, Melbourne, Australia) and were reviewed in a series of steps. First, the titles and abstracts were reviewed for study design, population, intervention, and outcome to assess inclusion and exclusion criteria. Second, full-text articles were reviewed, and those reporting baseline and postintervention quantitative pain assessments were selected for inclusion. At this step, studies were selected for meta-analysis if the preintervention and postintervention pain rating scores were numerically reported. Scores derived from numeric rating scales (NRS) or visual analog scale (VAS) were converted to a 0- to 100-point scale, where 0 indicated no pain, and 100 indicated severe pain. The Izbicki score was also included, which incorporates pain frequency and intensity, analgesic use, and disease-related disability weighted equally on a 0–100 scale.[15,16] The corresponding authors of studies with incomplete data reporting were contacted by email to request the missing data. Studies were

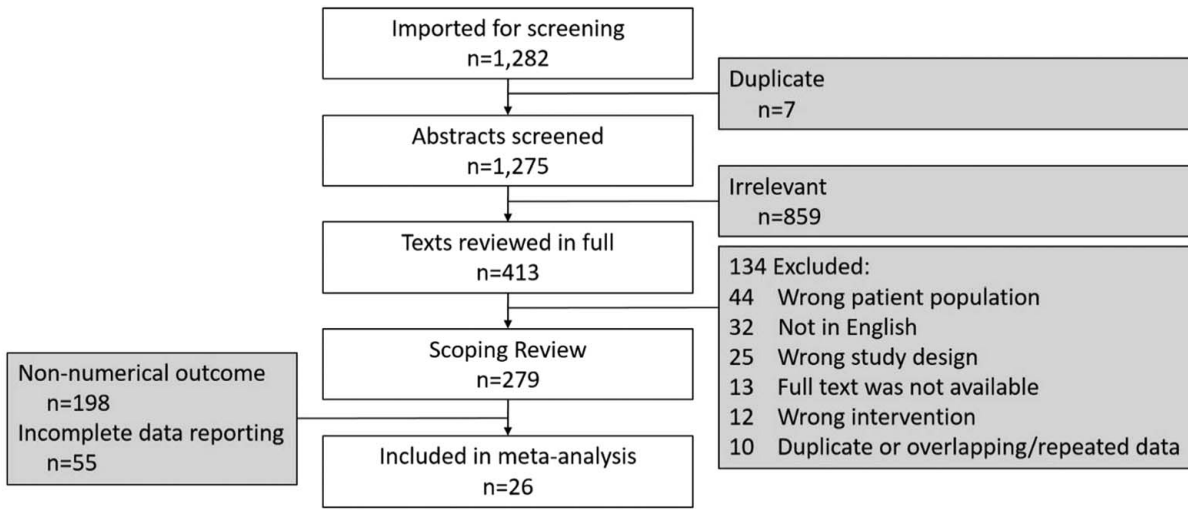

FIGURE 1. PRISMA flow diagram illustrating the selection process for studies included in the scoping review and meta-analysis

screened by 2 independent reviewers (M.F. and M.R.) who were blinded to the other's responses, and disagreement was adjudicated by an additional independent reviewer (A.E.P.). Reviewers were not masked to authors, journals, or interventions assessed.

Risk of Bias in Individual Studies

Risk of bias assessment was performed for each study in the meta-analysis using the risk of bias in randomized trials, version 2.0 (ROB 2), and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tools (Supplemental Fig. 1, Supplemental Digital Content 2, http://links.lww.com/MPA/B365).[17,18] All studies were independently assessed by 2 reviewers (M.F. and M.R.).

Data Extraction and Qualitative Analysis

Specific study-related, patient-related, and treatment-related characteristics, including first author, year of publication, number of enrolling centers, projected sample size, disease characteristics, method of pain assessment, specific aspects of pain assessed, intervention(s) used to treat pain, and the outcomes of the interventions on pain, were extracted by 2 independent reviewers (M.F. and M.R.).

Data Analysis

All papers that included adult subjects with CP were eligible for inclusion in the scoping review. Two reviewers (M.F. and M.R.) independently reviewed the studies to determine the method used for pain assessment. These were first recorded based on the authors' description and were subsequently grouped into broader categories such as "clinical success," which incorporated studies with similar definitions for responders and nonresponders. Subsequently, pain assessment tools were classified into 3 groups unidimensional when the assessment tool measured a single aspect of pain (eg, VAS, pain relief, opioid use), bidimensional when the tool measured 2 different aspects of pain (eg, pain intensity and opioid use), and multidimensional when more than 2 aspects of pain were measured (eg, Izbicki score, quality of life surveys).[6] Data are reported descriptively. Mortality within 3 months after the intervention was used for pooled mortality analysis.

For the meta-analyses, a random-effects model using maximum likelihood estimation was chosen. The random-effects model was selected to account for unmeasured confounders. Heterogeneity was quantified using the Q statistic (calculated with 21 degrees of freedom), the between-study variance (τ^2), and the heterogeneity statistic (I^2) for each study.[19,20] Heterogeneity was assessed via the calculation of "I" for each analysis. Values of $I^2 > 50\%$ and/or $P < 0.1$ were considered significant. Differences between interventions were assessed using meta-regression, with surgery versus endotherapy added to the meta-analysis model as a moderator variable. By deleting each study in turn, the sensitivity analysis was performed to evaluate the stability of this systematic analysis. Assessment of publication bias was quantitatively assessed via Egger test, and by visual inspection of the funnel plot.[21] A 2-sided P-value < 0.05 was considered evidence of significant publication bias.

RESULTS

Search Results and Selection of Studies

The search yielded 1282 publications (Fig. 1). A total of 413 publications underwent full-text review, among which 279 were included in the scoping review. Following the scoping review, 198 studies were excluded due to the use of non-numerical outcome measures, and 55 studies were excluded due to incomplete data reporting. Ultimately, 26 studies used quantitative reporting of pain scores before and after invasive intervention and were included in the NRS/VAS meta-analysis (n = 20), Izbicki score meta-analysis (n = 5), or both (n = 1).

Pain Assessment Tools Scoping Review

Among the 279 studies investigating painful CP, there was a range of reported pain assessment tools (Fig. 2, Supplemental Table 2, Supplemental Digital Content 3, http://links.lww.com/MPA/B366). There were 205 (73.5%) studies that used a unidimensional pain assessment tool, 49 (17.5%) bidimensional, and 25 (9%) multidimensional. A large number of studies used either a subjective assessment of pain relief (eg, including a binary approach of "yes" or "no") or retrospective objective measure (eg, narcotic use or number of hospitalizations per year). In these studies, preoperative pain intensity was rarely recorded. Finally, there were other poorly defined measures of pain relief, such as "total relief of the symptoms,"[22] "no pain or rare occurrences,"[23] or "alleviated pain."[24]

Pain Assessment Tools Included in Meta-analyses

There was a total of 25 studies included. Pain assessment by a VAS was used in 16 studies, an NRS in 5 studies and one study used both. These were combined for the first meta-analysis. In addition, pain assessment by the Izbicki score was used in 6 studies. One study used both Izbicki and VAS scores and was included in both meta-analyses. One study was excluded during the sensitivity analysis, leaving 5 studies in the Izbicki meta-analysis. Pain assessment as the primary outcome was made at an estimated mean follow-up interval of 51.6 months (range 3–360 mo) from the time of intervention.

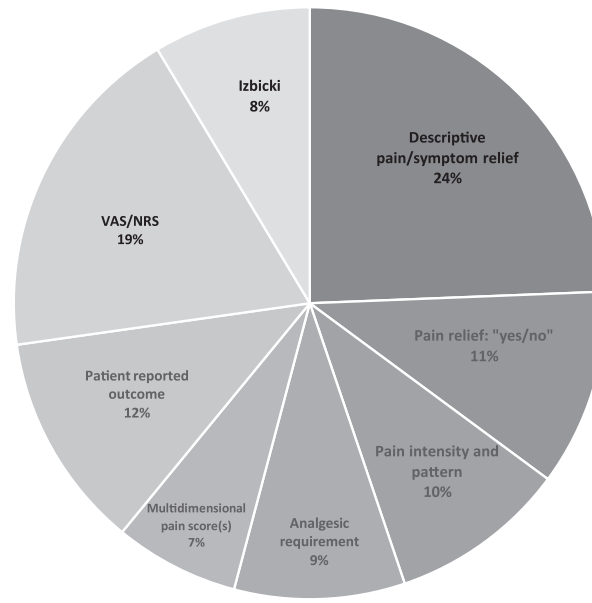

FIGURE 2. Frequency of pain assessment tools reported across studies evaluating endoscopic and surgical treatments for painful chronic pancreatitis.

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Study and Subject Characteristics in Studies for Meta-analyses

The characteristics of the 25 studies included in the meta-analyses are provided in Table 1 and Supplemental Tables 3, Supplemental Digital Content 4, http://links.lww.com/MPA/B367 and 4, Supplemental Digital Content 5, http://links.lww.com/MPA/B368.

Patient recruitment occurred from 1976 to 2019 in Europe (9 studies), North America (7 studies), Asia (8 studies), and Africa (1 study). There were 13 observational studies, 4 prospective studies, 4 retrospective reviews, 2 randomized controlled trials (RCTs), 1 retrospective review of prospectively collected data, and 1 observational follow-up of an RCT.

Overall, 1821 subjects (824 subjects in surgery and 997 in endotherapy groups) were recruited for individual studies, and 1139 (62%) completed follow-up visits. Patients were predominantly male (n = 1095, 65.3%). The mean age of the study population was 47.2 years (SD 11.5). The etiology of CP was most frequently due to alcohol (n = 661, 59.8%, reported in 23 studies) followed by idiopathic (n = 226, 35%, reported in 13 studies). Age and symptom duration did not differ between surgical and endoscopic groups. Pancreatic morphology was reported in 8 studies (377 subjects) in the surgery group and 8 studies (896 subjects) in the endoscopic group. Among the surgery group, 65 (17%) subjects had small-duct disease (2 studies), 108 (28%) had large-duct disease (5 studies), 63 (17%) had calcification(s) (2 studies) and 49 (15%) had pseudocyst(s) (1 study). Among the endoscopic group, 732 (81%) subjects had calcification(s) (4 studies), 72 (8%) had stricture(s) (5 studies), and 89 (9%) subjects reported morphology using the Cambridge classification (2 studies).

A small number of studies had active comparator arms: 7 compared different surgical approaches, 3 reported pain outcomes after ESWL with or without ERCP, 6 reported various endotherapy approaches, and 6 studies reported surgical approaches.

The pooled mortality from all studies was 2%, representing 21 deaths (among 918 subjects) reported in 15 studies (10 in surgery, 4 in endotherapy, and 1 RCT of surgery vs. endotherapy).

Meta-analysis of Studies Using VAS/NRS

There were 21 studies that reported pain using VAS or NRS. Overall, the standardized mean difference (SMD) in pain was 42.03 (95% CI: 33.4–50.6, $P < 0.001$) (Fig. 3). The SMD in pain was not significantly different between the endoscopic group (40.3, 95% CI: 27.1–53.6) and surgical group (43.2, 95% CI: 31.5–54.9)

TABLE 1. Characteristics of Studies Included in the Meta-analysis

	Intervention group	Analgesics reported	Number at baseline	Number at follow-up	Baseline score*	Follow-up score*	Follow-up time†
Studies that reported VAS/NRS							
Benzing et al[25]	Surgery	No	145	65	53.5 (23.2)	35.9 (23.4)	12
Croome et al[26]	Surgery	Yes	166	54	79 (35)	16 (26)	180 (6–360)
Dumonceau et al[27]	Endotherapy	No	55	55	72.53 (18.3)	57 (17.1)	53.1 (21.5)
Farnbacher et al[28]	Endotherapy	No	98	29	88 (18)	10.6 (10.8)	35 (28)
Heise et al[29]	Surgery	No	126	89	84 (26.4)	20.28 (25.6)	62.4‡
Howard et al[30]	Surgery	Yes	55	38	73.84 (14.3)	39.13 (14.0)	32 (6–48)
Jeppe et al[31]	Surgery	No	45	32	85 (13)	38 (32)	25 (1–83)
Kahaleh et al[32]	Endotherapy	No	13	10	73 (19)	36 (37)	14
Kozarek et al[33]	Endotherapy	Yes	40	28	69 (13)	29 (11)	29 (7)
Maher et al[34]	Surgery	Yes	15	15	72 (24)	45 (38)	69 (50–73)
Mokadem et al[35]	Surgery	Yes	57	27	80 (17)	27 (29)	36 (6–120)
Oh et al[36]	Endotherapy	Yes	25	25	59.1 (18.8)	10 (12)	221.1 d (190.48)
Pakosz-Golanowska et al[37]	Surgery	No	17	9	89 (11)	27 (12)	28 (13–60)
Pessaux et al[38]	Surgery	Yes	34	34	34 (12)	29 (12)	15 (3–37)
Pothula-Rajendra et al[39]	Surgery	No	25	24	82.1 (16.4)	15.8 (14.1)	12
Rath et al[40]	Surgery	No	35	33	81.5 (10)	51.5 (65)	12
Sah et al[41]	Surgery	No	26	25	70 (15.8)	24.4 (14.1)	17
Sauer et al[42]	Endotherapy	No	6	6	64 (20)	16 (18)	3
Tandan et al[5]	Endotherapy	Yes	636	272	64 (10)	37 (12)	> 5 y
Weber et al[43]	Endotherapy	Yes	19	17	70 (18)	18 (24)	12
Zheng et al[44]	Endotherapy	No	22	21	56 (33)	39 (18)	3
Studies that reported Izbicki Score							
Cahen et al[45]	Endotherapy	No	19	16	73 (12)	51 (23)	24
	Surgery	No	20	15	69 (18)	25 (15)	24
He et al[46]	Endotherapy	No	89	83	33.1 (3.1)	14.5 (6.9)	24
Issa et al[47]	Endotherapy	Yes	44	44	64 (16)	36 (17)	18
	Surgery	Yes	44	43	63 (19)	28 (22)	18
Chen et al[48]	Surgery	No	15	15	82 (17)	25 (10)	3
Sah et al[41]	Surgery	No	26	25	53.4 (18)	10.7 (11.4)	17

*Pain scores are transformed from Numeric rating scale (NRS) or Visual analog scale (VAS) to a 100-point scale from 0 (no pain) to 100 (worst imaginable pain). Data is reported as mean (SD).

†Follow-up time is reported as mean (SD), median (range), or a single date if follow-up was completed at a single interval. Data are reported in months unless otherwise noted.

‡Follow-up SD was not reported.

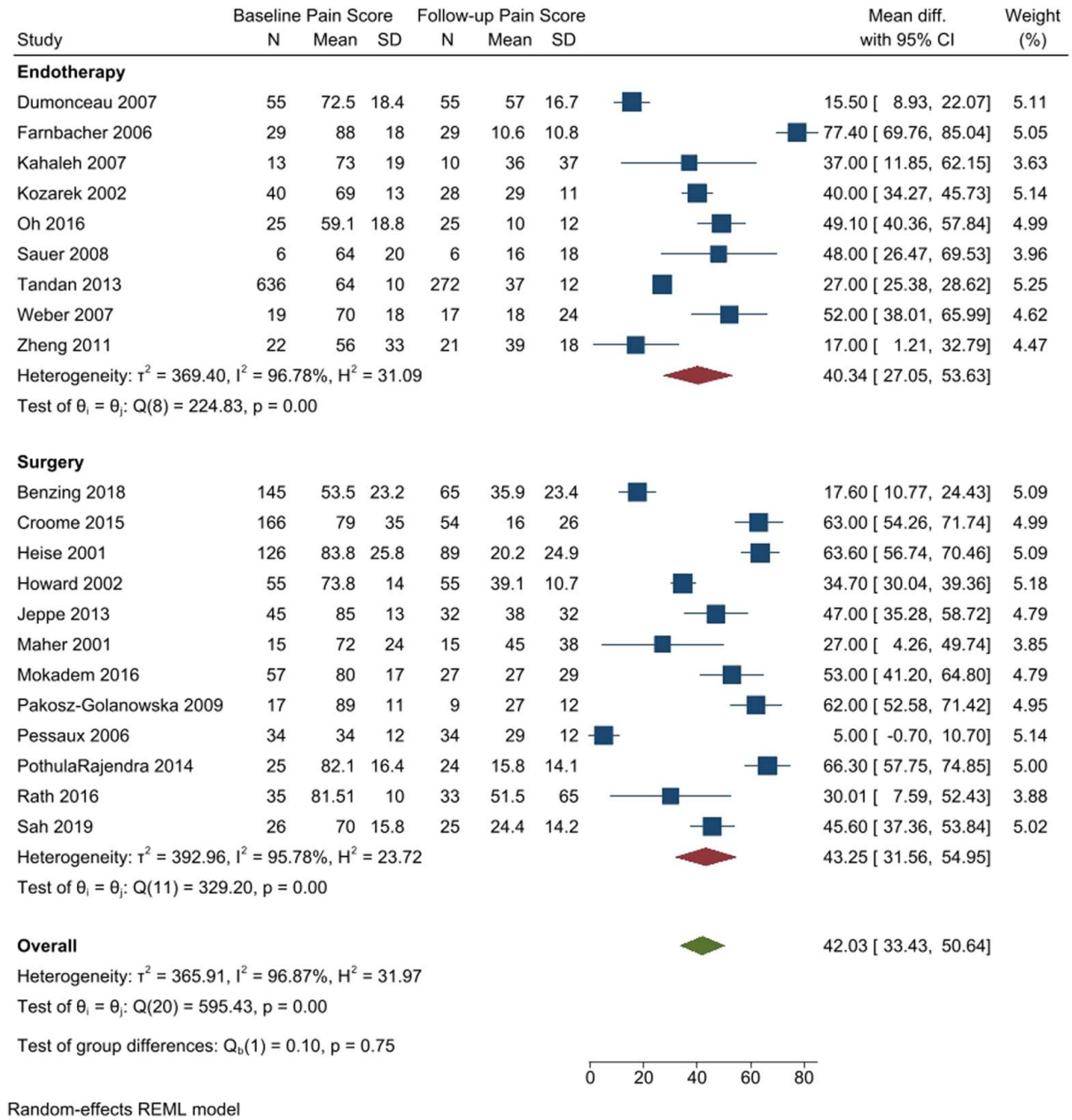

FIGURE 3. Forest plot summarizing pain reductions using Visual Analog Scale (VAS) or Numeric Rating Scale (NRS) from 21 studies. Overall standardized mean difference (SMD) was 42.03 (95% CI: 33.4–50.6, P < 0.001). Pain improvement did not significantly differ between endoscopic (SMD 40.3, 95% CI: 27.1–53.6) and surgical treatments (SMD 43.2, 95% CI: 31.5–54.9; P = 0.75). No publication bias was detected.

($P = 0.75$). There was no evidence of publication bias in either group (Supplemental Fig. 2A, Supplemental Digital Content 6, http://links.lww.com/MPA/B369).

Meta-analysis of Studies Using Comprehensive Izbicki Score

There were 6 studies that reported pain using the comprehensive Izbicki score (Table 1). There was no significant difference in the SMD for pain between the endoscopic and surgical groups ($P = 0.53$) (Fig. 4). For both groups, a difference in score was found between baseline and at the time of follow-up (endoscopy group Hedges's g = 2.28, 95% CI: 1.04–3.51 and surgery group Hedges g = 2.86, 95% CI: 1.51–4.21). Study heterogeneity was high for both groups [endoscopy group $I^2 = 96.8\%$, Q ($df = 8$) = 226.2 and surgery group $I^2 = 95.5\%$, Q ($df = 12$) = 337.4]. There was no evidence of publication bias in either group (Supplemental Fig. 2b, Supplemental Digital Content 7, http://links.lww.com/MPA/B370).

Additional Reported Outcomes

Several studies reported adverse events, technical success rates, postintervention analgesic use, and conversion rates to surgery (Supplemental Tables 4, Supplemental

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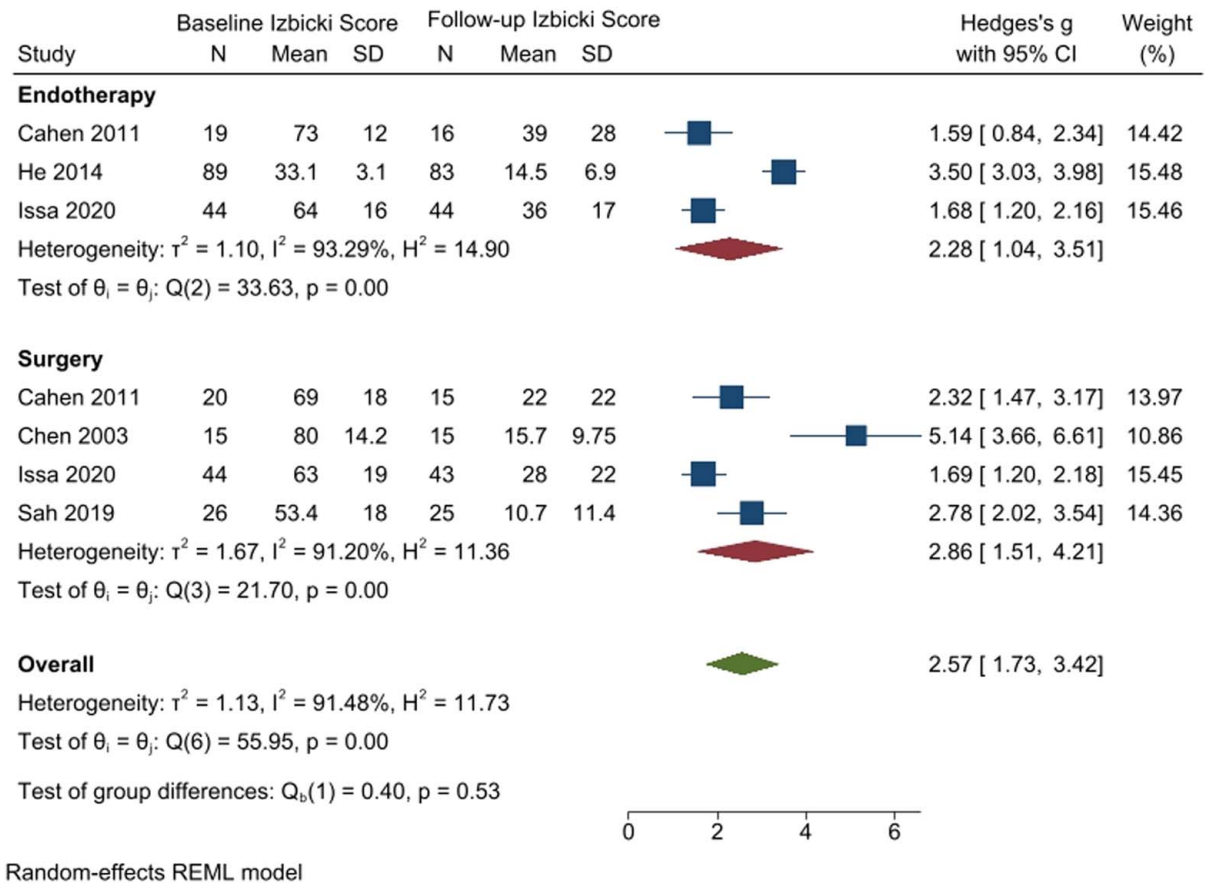

FIGURE 4. Forest plot of pain reductions using the Izbicki score from 6 studies. No significant difference between endoscopic and surgical groups (P = 0.53). Both showed significant improvement (endoscopy: Hedges's g = 2.28, 95% CI: 1.04–3.51; surgery: Hedges's g = 2.86, 95% CI: 1.51–4.21).

Digital Content 8, http://links.lww.com/MPA/B371 and 5, Supplemental Digital Content 9, http://links.lww.com/MPA/B372). However, inconsistent reporting and variability in definitions and follow-up durations limited pooled analysis. Similarly, conversion rates varied widely in follow-up duration and criteria. Due to these inconsistencies, no pooled analysis was performed.

Subgroup Analysis by Study Period

To assess the impact of evolving techniques, studies were categorized into 2 time frames. No significant differences in clinical outcomes were observed between earlier and more recent studies. The meta-regression analysis (Supplemental Fig. 3, Supplemental Digital Content 10, http://links.lww.com/MPA/B373) showed that publication year had no significant impact on pain reduction outcomes for surgery ($P = 0.720$) and endoscopy ($P = 0.583$).

Sensitivity Analyses

These results did not change during the sensitivity analysis when each study was sequentially removed, and analyses were repeated (Supplemental Figs. 4A, Supplemental Digital Content 11, http://links.lww.com/MPA/B374, 4B, and Supplemental Digital Content 12, http://links.lww.com/MPA/B375). The omission of studies that reported VAS/NRS had no influence on the overall SMD for pain. However, among the studies that reported the Izbicki score, the Chiang et al study had a relatively large influence on the overall effect size estimate and was excluded.

Risk of Bias

The risk of bias was high in nearly all included studies (Supplemental Fig. 1, Supplemental Digital Content 2, http://links.lww.com/MPA/B365). Important potential confounders such as ongoing smoking or alcohol use, anatomic features, duration of disease, and analgesic use were infrequently reported. The risk of bias was also increased because of unblinded assessments of pain using poorly defined, subjective outcome measures.

DISCUSSION

This study highlights the variability with which pain outcomes are reported in the CP literature and addresses the ongoing discussion about the efficacy of endoscopy and surgery for treating painful CP. We report data from a systematic review of the literature that summarizes and integrates the results of endoscopy and surgery on post-intervention pain scores. Although the majority of the studies were single-arm studies, a meta-analysis was subsequently performed on 25 studies. This demonstrated an overall reduction of pain scores of about 40%, with no difference between the endoscopic and surgery groups. Similar findings were seen using the more extensive Izbicki

score. Our study highlights the paucity of high-quality publications in this field with very heterogeneous instruments used for pain assessment. There are significant opportunities to improve the reporting of pain by agreeing on a standardized approach that incorporates multidimensional, CP-specific pain assessment tools that cover important outcome domains. This will improve the quality of research and, ultimately, clinical practice.

Comparison Between Studies

Very few manuscripts were encountered that reported numerical pain scores and compared one treatment to another. The most studied intervention encountered in this systematic review was the duodenum-preserving pancreatic head resection (Beger procedure) and the head coring with duct decompression procedure (Frey procedure). While several studies compared the pylorus-preserving pancreaticoduodenectomy (Whipple) operation to the Frey or Beger operation, it was not possible to complete a meaningful network meta-analysis among studies that reported preintervention and postintervention numerical pain assessments.[29,49–54] For example, one group utilized a proprietary pain score that incorporated VAS, pain frequency, analgesic use, and ability to work, but the resulting score (scaled from 0 to 100) was not comparable to any other study in this review.[49]

Tools for Pain Assessment

The assessment and measurement of pain in CP has been a longstanding challenge in the field. Previously, painful CP has been categorized according to pain frequency as Ammann type A (intermittent) or B (constant).[55] Pain frequency, rather than pain intensity, was subsequently shown to be a more important predictor of health-related quality of life and resource utilization,[56] but pain frequency has not been shown to predict response to invasive intervention. Additional pain assessment instruments include the multidimensional Izbicki score, that includes pain severity (VAS), pain frequency, use of analgesic medications, and disease-related inability to work.[15,16] Several groups have established additional CP-specific symptom assessment scores, including the Pancreatitis Quality of Life Instrument (PANQOLI) and the Comprehensive Pain Assessment Tool for Chronic Pancreatitis (COMPAT and COMPAT-SF).[11,12,57] Although PANQOLI was proposed in 2016 and COMPAT in 2017, these outcome measures have not yet appeared in the published literature at this time of the search (April 2023). Lastly, pancreatic quantitative sensory testing (P-QST) is the most recent addition to the pain assessment field. P-QST aims to categorize subjects according to the mechanism of pain being predominantly of peripheral or central origin.[10] This represents a unique direction for pain assessment in CP, because P-QST seeks to determine the mechanism of pain to apply directed interventions, such as pregabalin for central sensitization.[58–60] It remains to be seen whether P-QST can fulfill the need for a clinical assessment tool capable of predicting the outcome of invasive interventions.

Outcomes From Endotherapy and Surgery

On the basis of the available data, it is not possible to show a difference between the outcomes of endotherapy and surgery for patients with painful CP. The outcomes are similar whether a unidimensional pain assessment tool (NRS or VAS) or a multidimensional pain assessment instrument (Izbicki score) is used. There were no publications that used more comprehensive, multidimensional, and CP-specific pain assessment tools, such as COMPAT and PANQOLI. It should also be noted that no studies included a placebo/sham arm, and the effect size we report is within the expected level of placebo effect.[3,61] While the SCHOKE trial (published after our analysis was completed) was not included in this study, its findings further highlight the significant placebo effect in endoscopic treatment, demonstrating that sham procedures alone can provide meaningful pain relief.[62] This highlights the need for randomized, sham-controlled trials to accurately assess the true efficacy of invasive interventions. Yet, there are many confounding variables, such as variation in patient morphology, comorbidities, patients' pain perception, and medication use, which make designing the ideal study challenging. Given these complexities, there remains insufficient evidence to favor surgery or endotherapy when pain relief is the primary treatment goal. This study also highlights the variability in reporting clinically relevant outcomes, including adverse events, technical success rates, and conversion from endoscopic to surgical treatment. While some studies provided data on these measures, definitions and follow-up durations varied significantly, preventing pooled analysis.

The reporting of postintervention analgesic use was remarkably inconsistent, limiting conclusions on the impact of endoscopic or surgical treatments on opioid dependence. Standardizing the definition and reporting of these outcomes is essential to improve comparability across future studies.

Limitations and Strengths

There are a few limitations to the present study. There is a considerable risk of selection bias in these studies, which cannot be corrected retrospectively. For example, endotherapy is usually offered with a lower threshold rather early in the disease course, whereas surgery is often considered a "last resort" in patients with longer-lasting pain complicated with psychological and social consequences as well as central sensitization.[7] Furthermore, selection for surgery versus endotherapy may also be influenced by morphology, etiology, local expertise, and patient preference. Although analgesics are the first-line therapies for pain management in CP, we did not include medication in this review and recognize there is a bias toward intervention in most Western countries. This was to limit the heterogeneity of the included studies, and because systematic reviews have been completed for common medical interventions such as antioxidants[63] and pancreas enzyme replacement therapy.[64] By limiting the outcome measures to include VAS or NRS for the first meta-analysis and Izbicki score for the second meta-analysis, we excluded the majority of published studies in the field. This was necessary to limit heterogeneity and improve the precision of measuring the effect size. However, heterogeneity in our study was attributed to a variety of factors. First, the diverse patient population and disease severity across studies can be major contributors to the reported heterogeneity. CP is a complex disease with patients presenting varying degrees of symptoms, complications, and psychosocial comorbidities, which may affect the pain outcome and effectiveness of different interventions. Second, the included study utilized an extensive variety of interventions. This variation may lead to the observed heterogeneity in our meta-analysis. Advancements in endoscopic and surgical techniques prompted a subgroup analysis by study period, but many studies included patients

treated over extended time frames (eg, Benzing 2018: 1995–2013), making direct comparisons difficult. No significant differences in outcomes were observed, suggesting that patient selection and disease severity may play a more significant role than technological advancements. Standardized cohorts and follow-up protocols are needed for future research. In addition, methodological discrepancies between the studies, such as research design, follow-up periods, and outcome assessments, contributed to the high degree of heterogeneity. It should also be noted that we were not able to assess the temporal pattern of pain, etiology of CP, or effects of pancreatic morphology as these important variables were not consistently reported. It is now accepted that these variables are important predictors of response to invasive interventions. For example, early invasive interventions may improve pain management with the rationale that treatment is needed before irreversible changes in the central nervous system appear.[65,66] In future studies, CP-specific outcome measures such as COMPAT-SF should be incorporated, and time from symptom onset to invasive intervention should also be reported in order to address these limitations.

The study also has several strengths. It represents the most up-to-date, systematic assessment of pain outcomes in CP, and was not limited to only RCTs but included all study types. Although RCTs produce the most rigorous data, a recent review[67] identified only 8 RCTs on this topic, so we elected to include other study designs in order to comprehensively understand outcomes reported in all studies. Furthermore, we included all invasive interventions, including various approaches to surgery and endotherapy, that are routinely used in clinical practice. Lastly, we completed a meta-analysis to increase the precision of individual study effect sizes and included only studies with the most complete outcome data. In this effort, we were able to compare outcomes between surgical and endotherapy groups.

CONCLUSIONS

Although many studies have been completed to improve the management of pain in CP, the vast majority of published studies used nonspecific outcomes for pain relief. When strictly looking at studies using preprocedural and postprocedural assessment of pain intensity, no differences in pain outcomes between endoscopy and surgery were seen, and the effect sizes were not much higher than can be ascribed to placebo. However, as pain is a multidimensional experience including affective, cognitive, and social aspects, our study highlights the need to adhere to recent international guidelines to incorporate multidimensional, CP-specific pain assessment tools[9] so that future studies can better address the problem of pain in CP.

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