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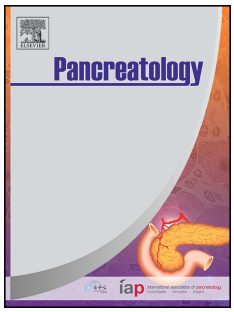

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Endoscopic Ultrasound-guided Celiac Plexus Neurolysis (EUS-CPN) Technique and Analgesic Efficacy in Patients with Pancreatic Cancer: a Systematic Review and Meta-analysis.

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ABSTRACT

Background

Endoscopic Ultrasound-guided Celiac Plexus Neurolysis (EUS-CPN) for the treatment of abdominal pain in pancreatic cancer can be administered in three different ways, depending on the site of needle insertion: central injection (CI), bilateral injection (BI) and celiac ganglia neurolysis (CGN). This meta-analysis aimed to (1) estimate the overall efficacy of the EUS-CPN; (2) compare the efficacy of each of the three techniques; and (3) investigate demographic and disease characteristics as potential predictors of treatment response.

Methods

We searched MEDLINE and EMBASE for studies that reported the proportion of treatment responders to EUS-CPN overall, and according to the technique used. We performed a random effects meta-analysis of proportions, and meta-regression was used to estimate the association between technique and clinical characteristics on treatment response. The safety profile was reviewed through narrative synthesis.

Results

Overall response rate to EUS-CPN was 68% (95% CI 61%-74%) at week two and 53% (95% CI 45%-62%) at week four. There was no evidence of a significant difference in the response rates between the three techniques. Demographics and disease characteristics were not associated with treatment response. Serious complications have been reported for BI and CGN but not for CI. Moderate to high risk of bias was observed.

Discussion

EUS-CPN is a useful adjunct to opioids in the management of pain. There is no evidence of a difference in the efficacy among the three techniques, however, CI is the only one for which serious complications have not been reported. Future research should focus on the appropriate timing of EUS-CPN (early versus on demand) and randomised comparison to establish the comparative efficacy of each technique.

INTRODUCTION

Nearly 80% of patients with pancreatic cancer suffer from abdominal pain [1]. The management of pain relies mainly on the prescription of opioid analgesics. However, those are frequently poorly tolerated due to debilitating side-effects such as reduced energy levels, constipation, confusion and delayed gastric emptying [2]. Endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN) causes irreversible ablation of the celiac plexus and can be used as an alternative or adjunct to opioids [3].

Several variations of the EUS-CPN technique are reported in the literature. The central injection (CI) technique for EUS-CPN involves injection of absolute alcohol into the peritoneal space, immediately anteriorly to the root of the celiac artery. The bilateral injection (BI) technique involves administration of the same volume of injectate, divided in two and injected bilaterally at the root of the celiac artery [4]. Further reports describe advancement of the tip of the needle deep into the middle of the celiac ganglia and injection until resistance is felt on the syringe. This procedure is usually referred to as Celiac Ganglia Neurolysis (CGN). This can be combined with an extra injection in the free retroperitoneal space (Combined CGN). Injection at the area of the superior mesenteric ganglion, at the root of the superior mesenteric artery is a fourth technique frequently refer to as Broad Plexus Neurolysis (BPN) but this has only been examined in one pilot study [5].

A series of clinical studies have assessed the analgesic efficacy and safety profile of EUS-CPN approaches in patients with pancreatic cancer; however considerable uncertainties remain. The comparative effectiveness and safety of each injection techniques is unknown. There are only two randomised clinical trials comparing directly different techniques and their findings are conflicting [6, 7]. Previous meta-analyses comparing CI versus BI reported contradictory results with one finding no difference [8] whilst the other reporting substantially higher efficacy of the BI technique [9]. The efficacy of EUS-CGN has not been assessed in any meta-analysis. It is also not clear whether clinical characteristics influence analgesic response. Therefore, this systematic review aimed to determine (i) the comparative analgesic efficacy of each technique; (ii) the independent clinical predictors of treatment response; (iii) the safety profile of each approach; and (iv) the risk of bias of included clinical studies.

METHODS

Eligibility Criteria

The eligibility criteria for the meta-analysis of the efficacy of the EUS-CPN were: (1) studies treating patients with pancreatic cancer; (2) studies using EUS-guided methods; (3) Clinical trials of any design, including randomised, non-randomised or single-arm trials. The exclusion criteria were: (1) method of guidance other than EUS (percutaneous ultrasound, CT, surgical or fluoroscopic); and (2) studies investigating a mixture of painful abdominal conditions alongside pancreatic cancer such as chronic pancreatitis, or other upper gastrointestinal cancers. We propose such conditions have different biological behaviour and analgesic treatment responses, hence should be studied separately.

Literature Search

The literature search was conducted in the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, ClinicalTrials.gov and Google Scholar, from their establishment until December 6th 2020. Search terms were: “pancreatic cancer”, “endoscopic ultrasound”, “celiac plexus neurolysis”, “celiac ganglia neurolysis”, and “broad plexus neurolysis”. A detailed search strategy on OVID MEDLINE is displayed in Appendix 1. A manual search for additional articles was conducted by reviewing the reference lists of the retrieved publications. The number of identified, screened, included and excluded studies is illustrated on the PRISMA flow diagram.

Statistical Analysis

For each trial arm, data on the number of the treatment responders and total number of participants were pooled. Treatment responders were classed as those with at least a 3-point drop in their 0-10 visual analogue scale (VAS). The primary outcome was the summary proportion of treatment responders to endoscopic neurolysis, regardless of the performed endoscopic technique. Subsequently, a meta-analysis stratified by the type of the performed technique (CI, BI and CGN) was conducted and pooled proportions of treatment responders were calculated for each technique. We used *metaprop*[10], to perform a meta-analysis of proportions extracted from each study. Presented confidence intervals for individual studies were calculated using the binomial exact method[11]. Proportions were transformed to stabilize their variances using Freeman-Tukey double arcsine transformation[12], prior to calculation of pooled estimates using the random effects model proposed by DeSimonian and Laird[13]. Confidence intervals for the pooled estimates were calculated using the Wald method.

Heterogeneity between studies was assessed with x^2 test (Cochrane Q statistic) and quantified with the I^2 statistic. Heterogeneity was classified as low, moderate and high with cut-off values of 25%, 50% and 75%. Publication bias was assessed, firstly by examining the visual symmetry of funnel plots, and secondly with the Egger regression test and the "Trim and Fill Method" [14]],[15].

A meta-regression analysis investigated the association between each technique and overall treatment response, and estimated the relative efficacy of each technique[16]. The outcome variable was the probability of treatment response, the performed technique was the categorical moderator variable and the CI group was the reference category. The relative effect of the one technique over the others was reported as difference in the proportion of pain responders. In addition, the relationship of treatment response with other explanatory variables: age, gender, tumour located in the head of pancreas, stage IV disease and baseline pain score, was examined with the same methodology. A sensitivity analysis excluding studies with definition of pain response other than the 30% drop in the VAS was performed. In contrast, sensitivity analysis based on the quality of studies was not possible due to their small number. The analysis was conducted on the STATA 16.0 software [17, 18] (StataCorp LP, College Station, Texas, USA).

Adverse Events

Adverse events were assessed through a systematic review of the published clinical trials. However, as the most serious events have been described in case reports, a narrative synthesis of those is provided.

Risk of Bias Assessment and GRADE Quality of Evidence Assessment

Risk of bias assessment was carried out using the Cochrane's Collaboration Tool for randomised clinical trials and the Risk of Bias Assessment Tool for Non-Randomized Studies (RoBANS) [19], [20]. The quality of the evidence was assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach [21].

RESULTS

In total, 136 reports were identified through the database searches. After removal of duplicates, there were 54 remaining records. Based on their titles and abstracts, 28 publications were removed as not relevant. The remaining 26 reports underwent a full-text review. Eight reports were excluded based on the eligibility criteria (five were abstracts, some of which were included in later reports [22-27], two offered EUS-CPN for chronic pancreatitis [28, 29]). One study administered two different EUS techniques, however, the pain responses were reported cumulatively [30]. In total, sixteen studies of 727 patients were included in the meta-analysis. These consisted of: five two-arm randomised trials [4, 6, 7, 31, 32], three two-arm non-randomised trials [5, 33, 34] and eight single

arm trials [35-41]. Four studies were included in the narrative synthesis but not the quantitative because they did not report proportion of treatment responders. Instead, their outcome was reported as mean difference only [4, 5, 31, 32].

Proportion of Treatment Responders

The estimated summary proportion of treatment responders to endoscopic neurolysis, regardless of the exact technique, was 68% (95% CI 61%-74%) (I^2 = 68%, P=0.01) at week two, and 53% (95% CI 45-62%) (I^2 = 60.3%, P=0.01) at week four (*Figure 4*).

Central Injection Technique

At week two and four, the proportions reporting analgesic response were 67% (95% CI 56%-79%) (I^2= 72.4%, P<0.05) and 46% (95% CI 36%-55%) (I^2=0.00) (P<0.05) respectively (Figures 2 and 3). Three parallel group RCTs provided direct comparison between central and bilateral injection techniques [25, 33, 34]. All of them showed higher response rates in their bilateral injection groups but none of them reached statistical significance. Only one used a double-blind randomised design [25]. Two randomised trials directly compared between Central Injection EUS-CPN to EUS-CGN [6, 7]. The one trial delivered EUS-CGN as an endoscopic monotherapy, showing higher response rates in the EUS-CGN group compared to CI (73.5% vs 45.5%, p=0.03) [6]. The second trial administered CGN and when resistance was felt on the syringe the left over volume of the neurolytic agent was injected in the free peritoneal space anteriorly to the root of the celiac trunk, in a Central Injection EUS-CPN fashion. The difference in the proportion of pain responders was only marginal between the two trial arms at month one, two and three in favour of the CGN and the difference, in contrast to the previous trial, was not statistically significant (46.2% vs 40.4% at 12 weeks, p>0.05) [7].

Bilateral Injection Technique

At week two the proportion reporting analgesic response after BI was 68% (95% CI: 55%-82%). However, this result suffers moderate level of heterogeneity (I^2=74.8%)(P=0.02) (*Figure 2*). A meta-analysis of the BI Technique was not possible for other follow up time-points due to insufficient data. Two randomised clinical trials investigated the effect of the BI technique versus opioids alone, both of which reported a higher drop in mean pain scores in the EUS-CPN groups [4, 32]. The one with the greatest methodological rigor reported 60.7% greater reduction in the EUS-CPN group (95% CI, 25.5%-86.6%, p= 0.01) at 12 weeks [4]. The other randomised trial showed higher drop in the pain scores in the EUS-CPN group at week four, too, but the difference was not statistically significant [32].

Celiac Ganglia Neurolysis (CGN)

At week two and four the proportion reporting analgesic response after EUS-CGN was 76% (95% CI, 71%- 82%) (I^2= 0.01%) (P=0.38) and 58% (95% CI, 48%- 69%; I^2 = 64.9%), respectively. Only two studies were randomised trials, comparing central injection EUS-CPN versus EUS-CGN and reported respond rates between 46.2% and 73.5% in their CGN arms, respectively [6],[7]. Three delivered EUS-CPN as main therapy, and CGN was performed as an additional manoeuvre, if ganglia were identifiable endosonographically [35, 37, 41]. The group of patients who received CGN was not reported separately.

Putative Predictors of Treatment Response

The meta-regression analysis using the individual technique as moderator variable, showed that there was no evidence of difference in the efficacy of the three techniques at week two and week 4 (Error! Reference source not found.). In addition, there was no evidence that age, male gender, tumour located in the head of pancreas, TNM stage IV disease and baseline pain score are associated with the efficacy of the EUS-CPN (Table 2).

Sensitivity Analysis

The analysis was repeated excluding the studies with definition of treatment response other than >3 point drop in the VAS. In a total of 298 patients the response rate remained comparable to the original analysis; response rates 70% (95% CI 61% – 80%) (I^2= 79.9, P= 0.02) and 54.5% (95%CI 45.2% -63.8%) (I^2= 62.07%, P = 0.01), at weeks two and four respectively.

Adverse Events of EUS-CPN

A systematic search revealed a total of 16 studies (871 participants) which reported adverse events (Table 3). Four of those did not report any incidences of benign, spontaneously resolving side effects but stated that no EUS-CPN-related mortality or morbidity was observed [4, 25, 32, 36, 42]. In the remaining 12 studies, diarrhoea (9%), temporary pain exacerbation (8%) and hypotension (6%) were the most commonly observed. Their frequencies were comparable among the three techniques. Inebriation was specific only to Japanese studies. One patient who was anticoagulated and received EUS-CGN, developed gastric bleeding at the puncture site which was terminated with endoscopic clipping [6].

Spinal stroke was observed in two patients (0.2%) in the EUS-CGN group given in the context of a trial (although one technically had a failed CGN which was converted into EUS-BPN intra-procedurally) [7, 41]. Another three case-reports have documented similar events, however, some of these are potentially duplicates considering the clinical details, location, authorship and year of publication (two patients have been reported by Minaga et al in 2016 [41, 43], Mittal [44] Fuji [45] and Levy all reported in Mayo Clinic, Rochester, Minesota, with overlapping dates (2010-2014)) (Table 4). One of those used epinephrine alongside alcohol and local anaesthetic [44]. Importantly, these patients received either EUS-CGN combined with injection in the free retroperitoneal space, BI or EUS-BPN and the dose of injected alcohol was 20ml or above.

Gastric ischaemia in pancreatic cancer has been reported only once [46]. This patient had undergone ERCP and stent exchange during the same time of the EUS-CPN which was complicated by gastric bleeding. Another patient who underwent EUS-FNA and EUS-CPN for mass-forming chronic pancreatitis pain developed extensive (hepatic, renal, pancreatic) visceral ischaemia within 24 hours [47]. This patient had undergone EUS-CPN 13 times in total. Of relevance, is that this patient had retroperitoneal fibrosis involving segments of his aorta. This may be due to be the long-term sclerotic effect of alcohol. A third case report described a patient with alcohol-related chronic pancreatitis who was admitted with abdominal pain and received EUS-CPN [48]. Four days later a CT showed splenic infarcts. A fourth case-report described the case of a 57 year old patient with idiopathic recurrent acute pancreatitis who developed complete thrombotic occlusion of the celiac artery post EUS-CPN [49].

Heterogeneity

The following methodological and clinical sources of diversity were detected, which may account for the observed heterogeneity (**Table 5**) definition of “treatment response” was variable, as the volume of the neurolytic agent and the proportion of patients with concurrent opioid and chemoradiotherapy treatments; in some CGN studies, the ganglia injection was combined with injection of neurolytic agent at the free retroperitoneal space; the pre-treatment mean pain scores ranged between 3.6 and 9.5; In addition, some clinical heterogeneity should inherently be attributed to the fact that pain scores are self-reported outcomes, therefore influenced by ethnicity, gender, co-morbidities, psychosocial factors, as well as access to social support and palliative care networks which vary among regions, countries and health systems.

Risk of Bias Assessment

The following sources of bias were classified as "high risk" in non-randomised trials: (1) recruitment of non-consecutive cases; (2) co-variates, especially chemotherapy treatment and dose of opioid analgesic drugs, not being considered (except two single arm trials [38, 39]); (3) imputation methods to address missing values (it is likely that patients do not complete follow-up assessments due to their declining health status, who may plausibly have higher pain levels); and (4) selective reporting arising from the use of a single cut-off value in the definition of treatment response. Instead, proportions at several cut-off points (3, 4 and 5 point drop from baseline) as well as mean differences in VAS scores before and after the procedure should have been reported. Regarding randomised trials, three of them met good quality standards [4, 7, 31]. In two [6, 25] we detected selective reporting of moderate significance. At week two, the high-risk studies contributing to the summary result with a total weight of 61.3%, affected mainly the studies in the CGN group (CGN 30.07%, BI 19.47% and CI 11.80%). Similarly, at week four effect sizes of high risk studies contributed with 44.76% weight to the summary result, with most of them belonging to the CGN group (35.47%).

Publication Bias

Review of the grey literature revealed 16 unpublished studies. Of these, 10 were published as conference proceedings and 6 were registered with ClinicalTrials.gov (Appendix 3 & 4). Funnel plots for weeks 2 and 4 were constructed, plotting effect sizes, expressed as logit proportions on the horizontal axis and standard error on the vertical. Subjective visual assessment of the plots showed symmetrical distribution of the effect sizes of the included studies. The Egger's regression test did not detect evidence of publication bias either at week two (p=0.17) or four (p=0.16). The application of the "Trim and Fill" method demonstrated that a small degree of asymmetry was attributed to two studies at week 2 which were removed and replaced by their counterparts and the modified summary effect size remained almost the same (68%, 95% CI 60-74%, I^2=58.9%, p=0.02)]. Similarly, there was one study "trimmed and filled" at week four with no effect on the summary effect size (53%, 95% CI 45-64%, I^2= 54.2%, p=0.032). Based on the above assessments, we concluded that, although unpublished studies exist, there are unlikely to have affected our results.

The GRADE quality of the evidence is summarised in the figure 6.

DISCUSSION

This systematic review and meta-analysis demonstrated that endoscopic denervation therapies, using either CI, BI or CGN technique, reduce pain scores by approximately 30% in two thirds of patients with pancreatic cancer at week two. This pain remission is sustained by week four in approximately half of those patients. The pain control outcomes were not dissimilar among the three techniques at week two, however, CI is the only one linked to serious adverse events. Moreover, demographics (age, gender) and disease characteristics (cancer stage, tumour at the head of pancreas and pain score at baseline) are not associated with treatment response.

This systematic review has several strengths, including a systematic search strategy, strict eligibility criteria which focused on only those with PC, appropriate methods of pooling proportions and comprehensive risk of bias assessment. However, it is also impacted by several weaknesses which may have affected our assessment of the treatment efficacy. Firstly, the only a few of the primary studies were randomised trials, therefore the comparison between the techniques provided in here is not randomised. Secondly, due to inherent limitations of the included studies, it was not possible to stratify treatment response meta-estimates by opiate use or receipt of chemo- and/or radio-therapy. Thirdly, the definition of treatment response varied between the studies, ranging from 3 to 5 point drop in VAS. This may have introduced a misclassification of cases as "successes" or "failures", however, the therapeutic effect did not change upon the relevant sensitivity analysis. Our risk of bias assessment demonstrated that all three study subgroups are subjected to biases.

Previous meta-analyses report conflicting results. The first published in 2009[9], reported overall treatment response in 63.31% (95%CI: 57.75%-68.72%) in a total of 283 patients who were treated with EUS-CPN regardless the technique, whilst for those treated with central injection it was 45.99% (95% CI: 37.33- 54.78) and bilateral injection was 84.54% (95%CI: 72.15- 93.77%). However, this meta-analysis combined pain outcomes measured at different time-points post-procedure, which is arguably inappropriate, as we have shown analgesic effect of the EUS-CPN declines over time. Another previous meta-analysis of 437 patients, comparing CI versus BI technique reported no difference between them. This reported a Standardised Mean Difference (SMD) of the VAS pain scores between these two techniques of 0.31 (95% CI: -0.20 to 0.81, p=0.97) [8]. However, several limitations should be noted: the two largest studies, weighting 24.7% and 19.9%, treated patients with chronic pancreatitis [28, 29, 50]; one study, weighing 25.9%, used percutaneous EUS-guidance [50]; and another one administered CGN, if ganglia were visible [35]. Nagels et al (2013) [51] conducted a meta-analysis of studies reporting difference in the mean pain scores before and after EUS-CPN and showed that patients with baseline VAS pain score of 6-7 have on average a 4-point reduction sustained until week eight (p<0.001). However, it did not provide comparisons between the techniques.

Sufficient data exists demonstrating the safety of EUS-CPN. The only established major complication being spinal stroke. However, this occurs very rarely (0.2%) and it is associated with the more invasive forms of neurolysis; BI, CGN and the combined CGN, but not with the CI. Moreover, the incident cases received high doses of absolute alcohol, varying from 20 to 40 ml. Even more scarce is the evidence in visceral ischaemia, with case-reports providing very limited information on the exact circumstances leading to this event. Overall, ischaemic events either in the spinal cord or other internal organs, although not implausible, are highly unlikely to occur for two reasons; firstly, most of these organs have dual vascular supply and secondly, the alcohol can only cause a very local effect which does not affect this dual supply. The lumbar portion of the spinal cord is supplied by one anterior and two posterolateral arterial branches [52]. Previous experiments in mammals whose had one of their three spinal arteries clamped at a time did not detect neurological deficits [53]. Appropriate patient selection and technique selection and peri-procedural care should be considered to minimise the risk of ischaemia. Any evidence of arteriopathy and endothelial damage, such as history of heavy smoking, previous thromboembolic events, ischaemic strokes, peripheral vascular disease, uncontrolled diabetes with end-organ damage or excessive calcifications in the aorta should be regarded as a relative contraindications and the CI should be the technique of choice in those cases. Pre-hydration and continuous blood pressure monitoring during the procedure to ensure euvolaemia is maintained throughout is advisable. Sedation should be preferred over general anaesthesia as the latter may mask neurological events occurring intra-procedurally. Instillation of the alcohol shoould be given in small increments of 1-2 ml with pauses in between to permit detection of early neurological signs and discontinuation of the procedure.

Our findings suggest overall that EUS-CPN is a useful and safe adjunct to analgesics when patients are carefully selected. CI is probably the most attractive option considering that it has similar efficacy to the other two and it is not linked with ischaemic events. Further clinical questions remain regarding the application and relative efficacy of EUS-CPN. Further research should focus on disease characteristics predisposing to success or failure. In addition, the exact timing of EUS-CPN should be explored; it is unknown if it should be given as a first line treatment before opioids, if it should be reserved as a rescue therapy or if it could be given preventatively; and finally whether it is cost effective in comparison to other analgesic treatments such as the stereotactic radiotherapy.

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Figure 1. PRISMA Flow Chart for the meta-analysis of the efficacy of the EUS-CPN

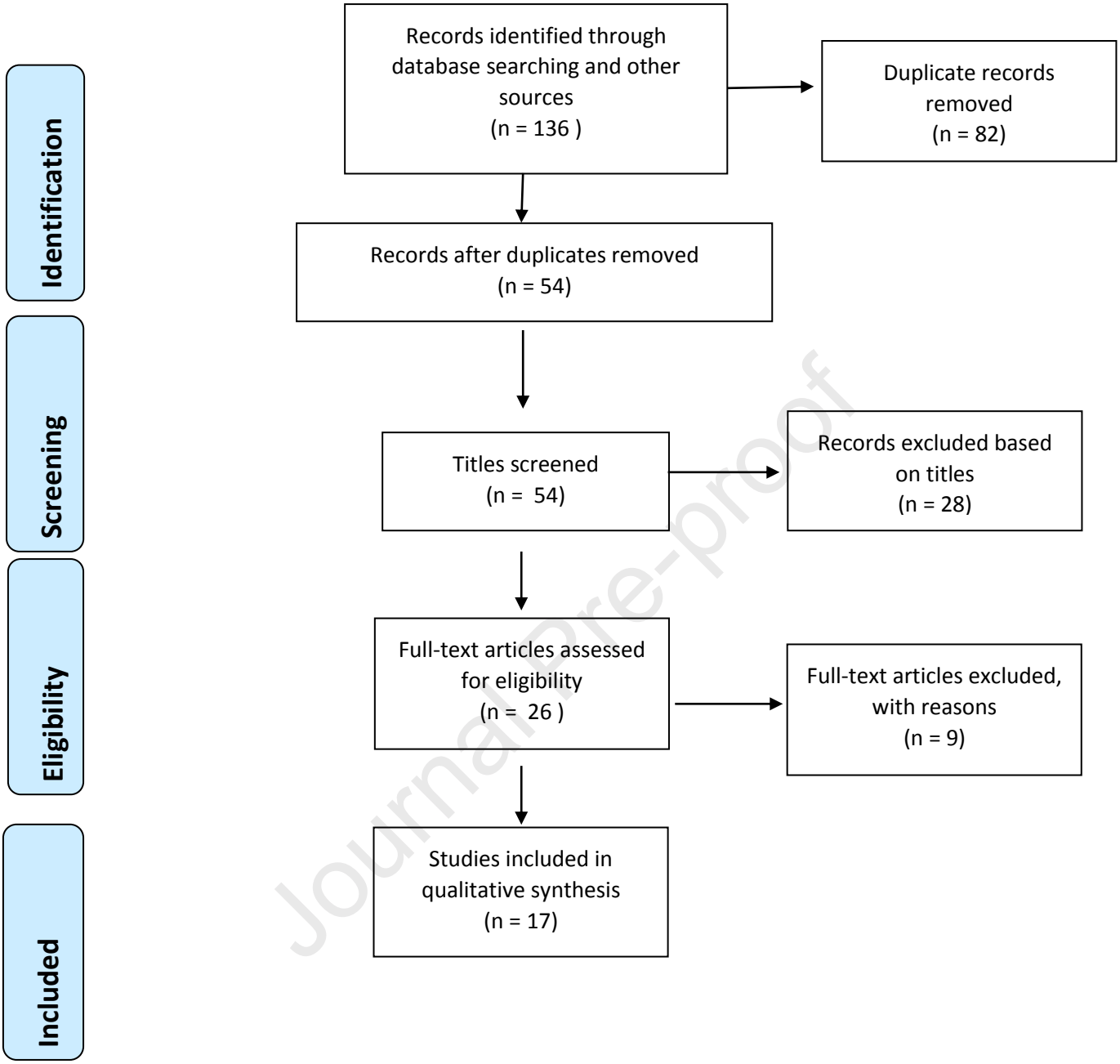


Figure 2. PRISMA flow chart for the systematic review of adverse events to EUS-CPN

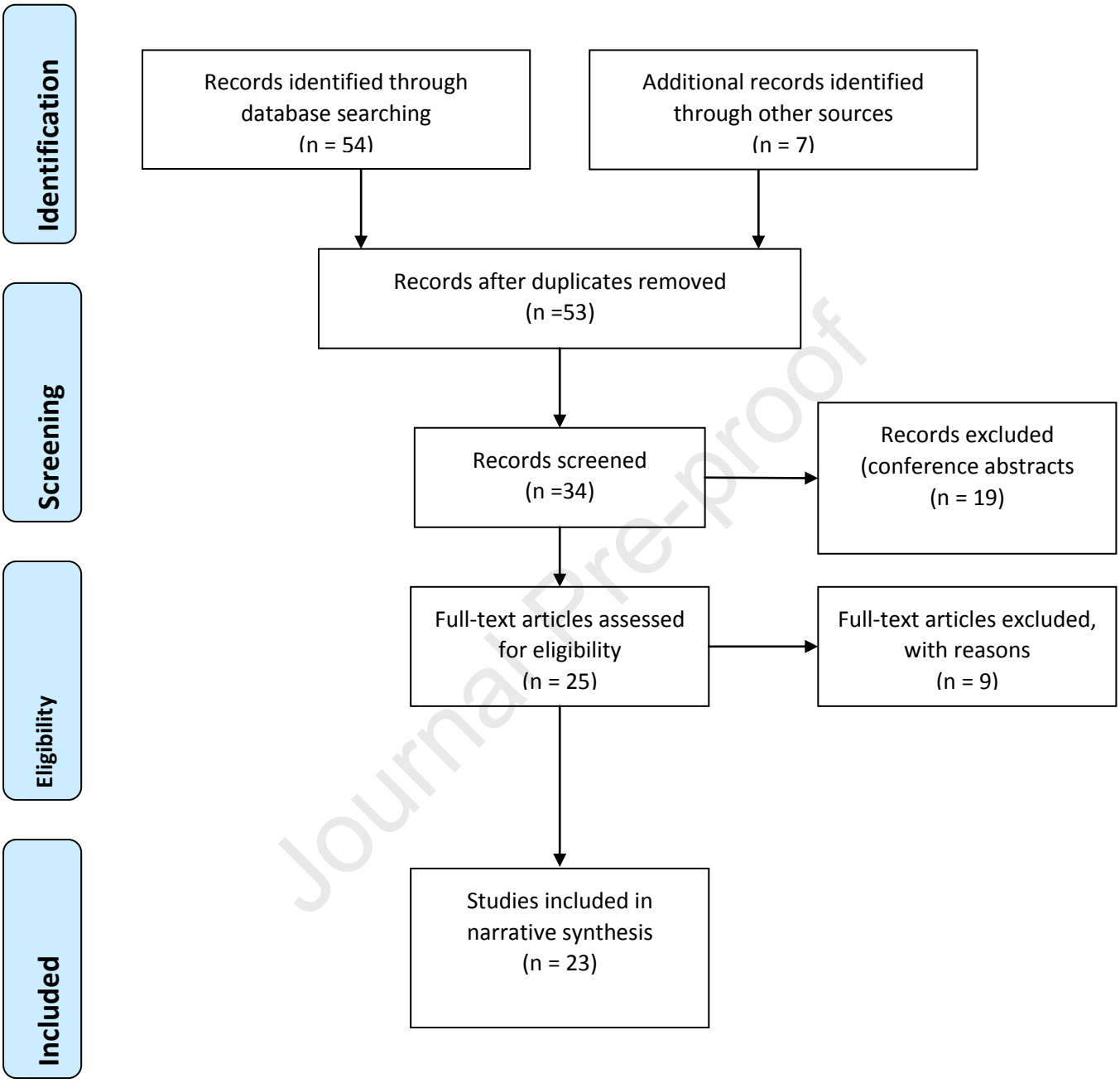


Table 1. Effect sizes of the reporting "proportion of pain responders" post- EUS-guided neurolysis".

Author	Number of participants per trial arm	Week 1-2	Week 4	Week 8	Week 12
Central Injection Technique					
LeBlanc et al [25]	21	69.0%	-	-	-
Tellez-Avila et al [33]	21	62.0%	47.6%	-	-
Doi et al [6]	33	45.5%	39.2%	33.3%	33.3%
Levy et al [7]	60	-	48.1%	39.6%	40.4%
Iwata et al [36]	47	61.8%	-	-	-
Facciorusso et al [55]	58	70.7%	-	-	-
Seican et al [42]	32	87.5%	-	-	-
Bilateral Injection Technique					
LeBlanc et al [25]	29	81%	-	-	-
Tellez-Avila et al [23]	32	59.4%	56.3%	-	-
Wiechovwska et al [40]	29	59.0%	-	56%	-
Wieserma et al [38]	29	54.0%	-	-	-
Gunaratnam et al [39]	58	54.0%			
Celiac Ganglia Neurolysis					
Minanga et al [41]	112	77.7%	67.9%	-	-
Doi et al [6]	34	73.5%	64.7%	58.8%	47.0%
Levy et al [7]	50	-	52.3%	55.9%	46.2%
Si-Jie et al [37]	42	80.4%	-	-	60.9%
Ascuse et al [35]	40	65.0%	50.0%	-	-

Figure 3. Summary proportion of Treatment Responders at the first two weeks post-EUS-guided neurolysis and individual pooled proportions for: a. Central Injection, b. Bilateral Injection and c. Celiac Ganglia Neurolysis.

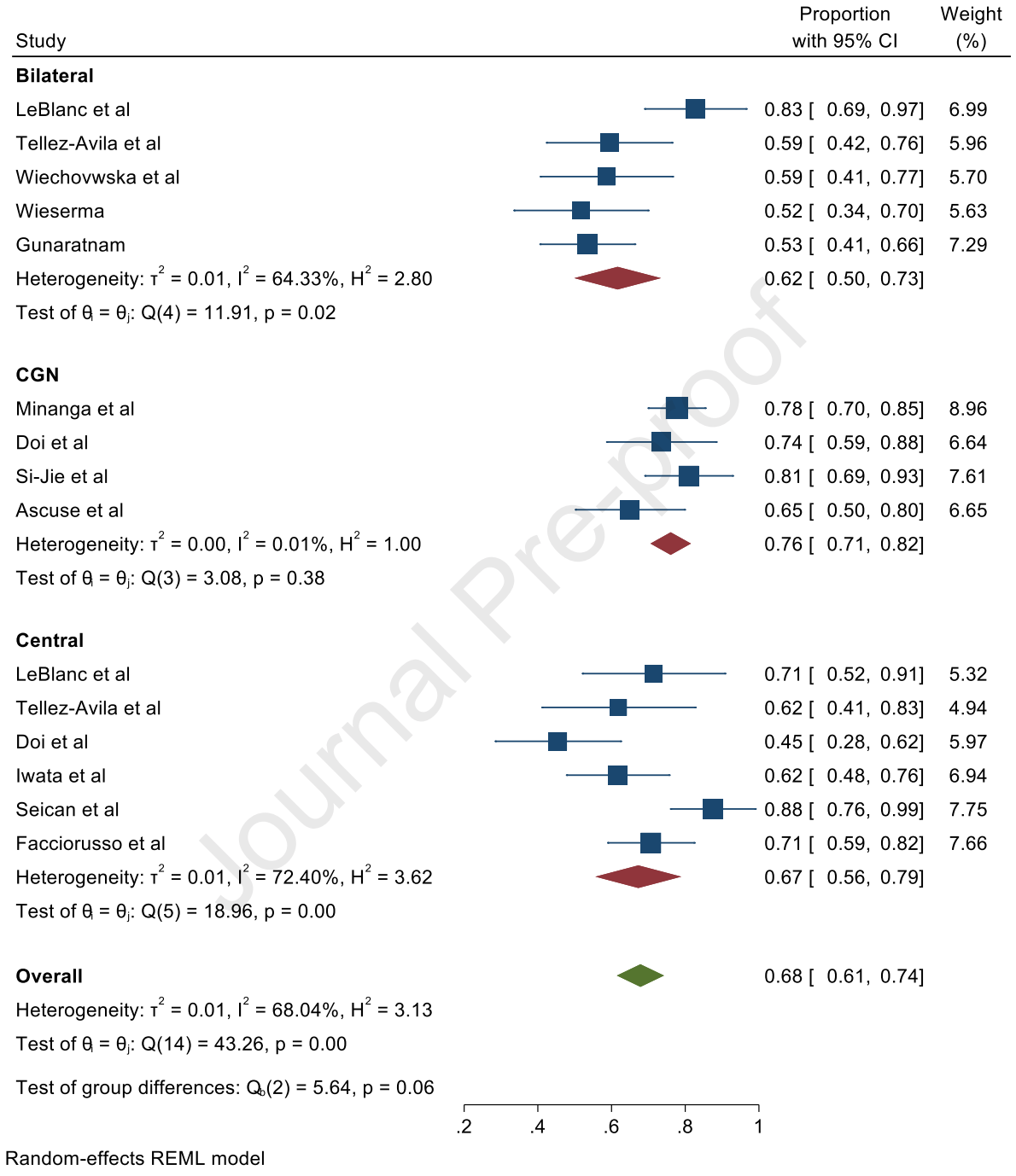


Figure 4. Summary pooled proportion of Pain Responders at week four post-EUS-guided neurolysis and individual pooled proportions for: a. Central Injection and b. Celiac Ganglia Neurolysis. Pooled proportion for Bilateral Injection was not possible due to insufficient data.

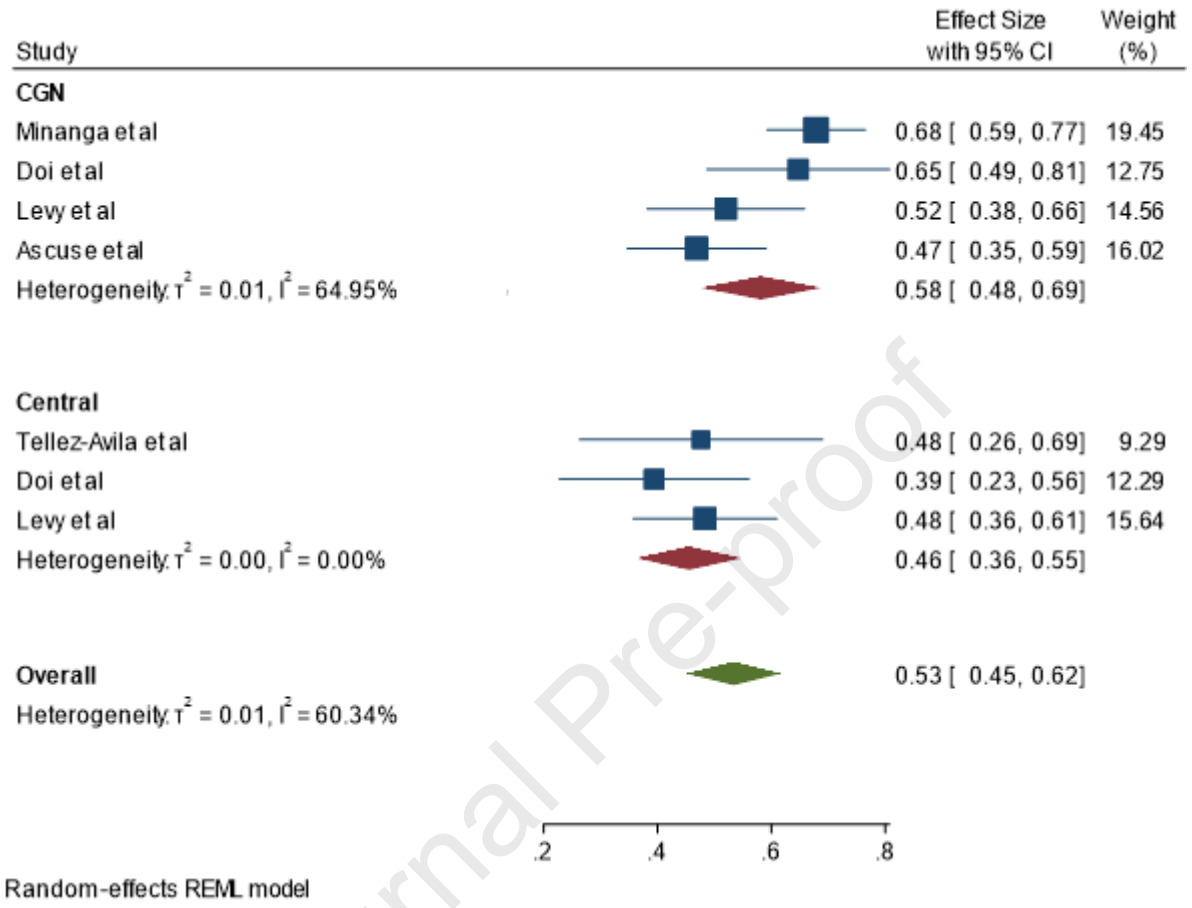


Table 2. Exploration of within the studies heterogeneity with meta-regression analysis: none of the examined co-variates moderates the treatment response.

Week 2	**Difference in proportion of treatment responders**	**95% CI**	**p-value**
Central l injection	Reference	Reference	-
Bilatera Injection	6%	[-13% to 26%]	0.34
Celiac Ganglia Injection	15%	[- 4% to 35%]	0.51
Every year of age	-0.9%	[-3% to 1%]	0.45
Gender (male)	<0.01%	*	0.38
Head of Pancreas Tumour	<0.01%	*	0.68
Every unit of VAS at baseline	0.3%	[-6 % to 11 %]	0.51
Tumour stage IV	<0.01%	*	0.88
Week 4	**Difference in proportion of treatment responders**	**95% CI**	**p-value**
Central Injection	Reference	Reference	-
Celiac Ganglia Injection	15%	[-37 % to 68 %]	0.17
Every year of age	0.6%	[-4 % to 9 %]	0.73
Male gender	<0.01%	*	0.80
Head of Pancreas Tumour	<0.01%	*	0.88
Every unit of VAS at baseline	0.3%	[-3 % to 9 %]	0.43
Tumour stage IV	<0.01%	*	0.67

*values < 0.001% were omitted from the table.

Table 3. Adverse events following EUS-CPN; Spinal stroke observed twice in a total of 817 patients. The two cases were associated with EUS-CGN and EUS-BPN, respectively.

Study	Total number of participants	Diarrhoea	Hypotension	Pain	GI Bleed	inebriation	Spinal Stroke
Central Injection							
LeBlanc et al [25]	21	not reported	not reported	not reported	not reported	not reported	0
Tellez-Avila et al [33]	21	0	0	0	0	0	0
Doi et al [6]	33	3	2	7	0	1	0
Iwata et al [36]	47	11	8	0	0	4	0
Seican et al [42]	32	not reported	not reported	not reported	not reported	not reported	0
Sahai et al [28]	30	0	0	0	0	0	0
Wyse et al [4]	49	not reported	not reported	not reported	0	not reported	0
Kanno et al [32]	23	not reported	not reported	not reported	not reported	not reported	0
Levy et al [7]	60	6	10	5	0	0	0
Facciorusso et al [55]	58	14	not reported	20	0	0	0
% of affected participants in the CI group		14%	4%	11%	0	0	0
Bilateral Injection							
LeBlanc et al [25]	29	not reported	not reported	not reported	not reported	not reported	0
Tellez-Avila et al [33]	32	0	0	1	0	0	0
Wiechovwska et al [40]	29	3	1	2	0	0	0
Wieserma et al [38]	29	3	0	0	0	0	0
Sahai et al [28]	42	0	0	0	0	0	0
Gunaratnam et al [39]	58	9	11	0	0	0	0
% of affected participants in the BI group		10%	8%	2%	0	0	0
Celiac Ganglia Injection							
Levy et al [7]	50	6	7	22	0	0	1

Minanga et al [41]	112	4	5	4	0	9	1
Doi et al [6]	34	2	1	10	1	1	0
Si-Jie et al [37]	42	0	2	0	0	0	0
Ascuse et al [35]	40	15	1	1	0	0	0
% of affected participants in the BI group		11%	7%	15%	0.40%	4%	0.40%
Total number of events	871	76	48	72	1	15	2
Percentage of affected participants		9%	6%	8%	0.10%	2%	0.10%

* Patient received EUS-BPN

Table 4. Characteristics of patients who experienced spinal stroke. Two of them received EUS-CPN in the context of a clinical trial. Another three were published as case reports.

Author	Year	Country	Age	Technique	Anaesthetic support	Volume of alcohol	Needle diameter	Survival
Minanga et al [43]	2016	Japan	73	BI	deep sedation	20 ml	25G	>90 days
Minanga et al [41]	2016	Japan	Not reported	BPN	not reported	40 ml	25G	not reported
Koker et al [56]	2017	Turkey	74	BI	deep sedation	20 ml	22G	60 days
Fuji et al [45]	2012	USA (Mayo)	76	Combined CGN	GA	24 ml	22G	24 days
Mittal et al [44]*	2012	USA (Mayo)	76	Combined CGN	not reported	24 ml	22G	not reported
Levy et al[7]	2019	USA (Mayo)	66±10	Combined CGN	not reported	21±4.5 ml	22G	not reported

*Epinephrine was used in the injectate mixture.

Table 5 Methodological characteristics which could account for heterogeneity in the effect sizes of the pooled studies.

Author	Year	Country	Study Design	Alcohol dose	Baseline VAS	Definition of treatment response	Opioid users (%)	Mean opioid dose (mg)	Chemo- or radiotherapy (%)	Risk of Bias
Central Injection										
LeBlanc et al [25]	2011	USA	randomised	20	-	≥40%	-	-	-	Moderate
Tellez-Avila et al [33]	2013	Mexico	non-randomised	10	9.5 (6-10)	≥50%	-	-	-	High
Doi et al [6]	2013	Japan	randomised	20	6.1 (1.7)	≥30%	32%	-	11%	Moderate
Levy et al [7]	2019	USA	randomised	10	3.6 (2.5)	≥30%	81%	45	87%	Low
Iwata et al [36]	2011	Japan	single arm	20	6 (5-9)	≥30%	38%	60		High
Facciorusso et al [55]	2016	Italy	single arm	20		≥30%	86%	-	100%	High
Seican et al [42]	2012	Romania	single arm	10-15	-	≥30%	100%	-	0%	High
Bilateral Injection										
LeBlanc et al [25]	2011	USA	randomised	20	-	≥40%	-	-	-	Moderate
Tellez-Avila et al [23]	2013	Mexico	non-randomised	20	9.0 (5-10)	≥50%	-	-	-	High
Wiechovwska et al [40]	2012	Polland	single arm	20	7.9 (6-10)	≥30%	100%	-	38%	High
Wieserma et al [38]	2001	USA	single arm	20	6.6 (2.2)	≥30%	100%	95	52%	Moderate
Gunaratnam et al [39]	1996	USA	single arm	20	5.8 (2.7)	≥30%	100%	24	30%	Moderate
Celiac Ganglia Injecton										
Minanga et al [41]	2016	Japan	single arm	20-40	7.3 (3-10)	≥30%	-	12	-	High
Doi et al [6]	2013	Japan	randomised	10-20	6.1 (1.9)	≥30%	29%	-	9%	Moderate
Levy et al [7]	2019	USA	randomised	21±4.5	3.7 (2.1)	≥30%	82%	41	76%	Low
Si-Jie et al [37]	2014	China	single arm	20	7.4 (5-10)	≥30%	-	-	-	High
Ascuse et al [35]	2011	USA	single arm	20	6.4 (2.0)	≥20%	-	-	-	High

The (-) symbol signifies that the relevant variable was not reported in the original study.

Figure 5. Funnel Plot of effect sizes at week 2, demonstrating low likelihood of publication bias. Empty dots represent the effect sizes of the "filled-in" studies by the "Trim and Fill Method".

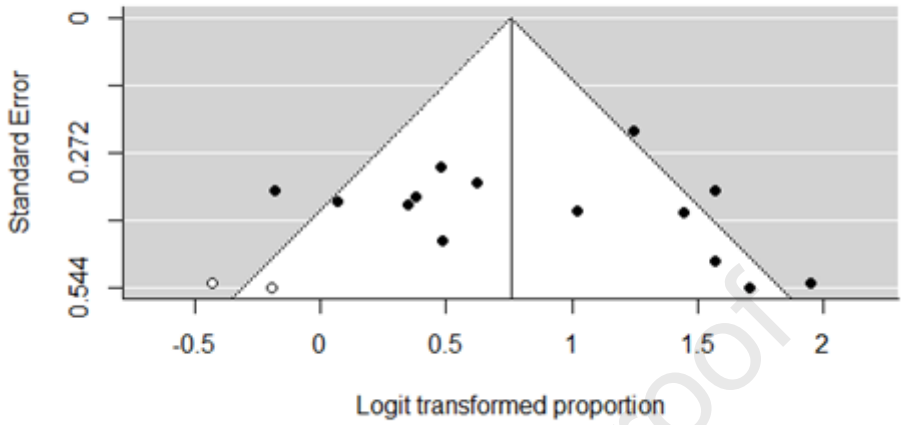
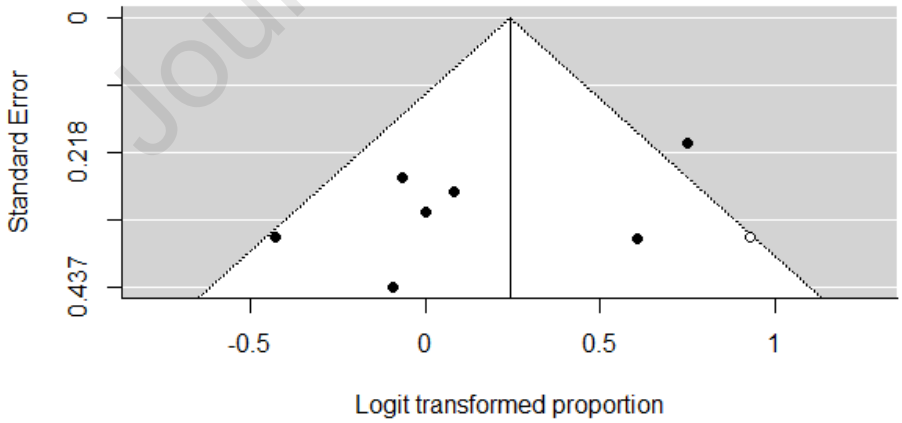


Figure 6. Funnel Plot of effect sizes at week four, demonstrating low likelihood of publication bias. Empty dots represent the effect sizes of the "filled-in" studies by the "Trim and Fill" Method..



GRADE Quality of Evidence Assessment

Figure 7. GRADE (Grades of Recommendation, Assessment, Evaluation, Development and Evaluation) Quality of Evidence Assessment		
	Result of GRADE ASSESSMENT	**COMMENT**
Risk of bias	High	Recruitment of non-consecutive cases, confounders not considered, selective reporting (see risk of bias assessment section).
Inconsistency	Moderate	Inconsistency is likely to be attributed to the clinical and methodological heterogeneity (see heterogeneity section).
Indirectness	Moderate	Studies use different comparators, such as morphine, central injection, bilateral injection, CGN or BPN.
Imprecision	Moderate	The majority of the studies reporting proportion of pain responders do not report standard error and confidence intervals, hence precision is questionable
Publication Bias	Low	Symmetrical funnel plots and negative statistic tests (see publication bias section).

Appendix 1. Search Strategies on MEDLINE.

Search for clinical trials

1. pancrea$.mp.
2. (cancer or carcinoma or adenocarcinoma or tumour).mp. or Neoplasms/
3. (EUS or endoscopic ultrasound).mp.
4. (celiac plexus neurolysis or celiac plexus neurolysis or CPN or celiac ganglia neurolysis or celiac ganglia neurolysis or broad plexus neurolysis or radiofrequency ablation or RFA).mp.
5. (randomi$ed controlled or RCT or trial).mp. or Randomized Controlled Trials as Topic/
6. 1 and 2 and 3 and 4
7. 6 not (case report or review).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
8. remove duplicates from 7

Search for adverse events

1. pancreatic cancer.mp.
2. (complication* or side effect* or adverse event*).mp.
3. (celiac plexus neurolysis or celiac plexus neurolysis or CPN or celiac ganglia neurolysis or celiac ganglia neurolysis or broad plexus neurolysis).mp.
4. 1 and 2 and 3
5. 5 limit 4 to original articles
6. 5 not review*.mp.
7. 6 not abstract.mp.
8. 7 not chronic pancreatitis.mp.
9. (endoscopic ultrasound or EUS).mp.
10. 8 and 9
11. remove duplicates from 10
12. 11 not editorial*.mp.
13. 12 not conference abstract.mp.

14. 13 not conference proceeding*.mp.

APPENDIX 4. Risk of Bias Assessment

Risk of Bias in non-Randomised Studies using ROBINS-I								
Author	**Bias Due to Confounding Factors**	**Bias in Selection of Participants**	**Bias In Measurement of Exposure**	**Bias in Blinding of Outcome Assessment**	**Bias Due to Missing Data**	**Bias in Measurement of Outcomes**	**Bias due to Selective Reporting**	**Overall Judgement**
Si-Jie et al[37],2014.	HIGH	SOME CONCERN	LOW	LOW	SOME CONCERN	LOW	HIGH	HIGH
Ascuse et al[35], 2011.	HIGH	SOME CONCERN	LOW	LOW	HIGH	LOW	HIGH	HIGH
Tellez-Avila et al[33], 2013.	HIGH	SOME CONCERN	LOW	LOW	SOME CONCERN	LOW	HIGH	HIGH
Seican et al[42]	HIGH	SOME CONCERN	LOW	LOW	SOME CONCERN	LOW	HIGH	HIGH
Minanga et al, 2016	HIGH	SOME CONCERN	LOW	LOW	HIGH	LOW	HIGH	HIGH
Wiechovwska et al[40], 2012.	HIGH	HIGH	LOW	LOW	LOW	LOW	SOME CONCERN	HIGH

Gunaratnam et al[39], 2001.	LOW	SOME CONCERN	LOW	LOW	SOME CONCERN	LOW	LOW	SOME CONCERN
Wiesema et al[38], 1996.	LOW	SOME CONCERN	LOW	LOW	SOME CONCERN	LOW	LOW	SOME CONCERN
Iwata et al[36], 2011.	HIGH	HIGH	LOW	LOW	SOME CONCERN	LOW	HIGH	HIGH
Facciorusson et al [55], 2017	HIGH	HIGH	LOW	LOW	SOME CONCERN	LOW	HIGH	HIGH

Risk of Bias in Randomised Trials using RoB 2.0 Tool						
	Potential Sources of Bias					
Author	**Randomisation Process**	**Deviation from Intended Intervention**	**Missing Outcome Data**	**Measurement of the Outcome**	**Selection of Reported Result**	**Overall Judgement**
Kanno et al[32], 2020.	SOME CONCERN	LOW	HIGH	LOW	HIGH	HIGH
Wyse et al[4], 2011.	LOW	LOW	LOW	LOW	LOW	LOW
Doi et al[6], 2013.	SOME CONCERN	LOW	LOW	LOW	SOME CONCERN	SOME CONCERN
Levy et al[7], 2019.	LOW	LOW	LOW	LOW	LOW	LOW
LeBlanc et al[25], 2011.	LOW	LOW	LOW	SOME CONCERN	SOME CONCERN	SOME CONCERN

Appendix 3. Grey Literature: List of studies registered in ClinicalTrials.gov, which remain unpublished upon completion.

Study 1:

Title:	EUS-guided CGN for Inoperable Cancer
Status:	Terminated
Study Results:	No Results Available
Locations:	Chinese University of Hong Kong, Hong Kong, Hong Kong, China
URL:	https://ClinicalTrials.gov/show/NCT02356640

Study 2:

Title:	Randomized, Controlled Trial of Endoscopic Ultrasound-Guided Bilateral Celiac Plexus Neurolysis vs Celiac Ganglia Neurolysis to Control Pain in Inoperable Pancreatic Cancer Patients with Inadequate Pain Control by Pain Killer
Status:	unknown status
Study Results:	No Results Available
Locations:	Unknown
URL:	https://ClinicalTrials.gov/show/NCT02220062

Study 3:

Title:	Evaluation of Injection Techniques in Celiac Plexus Neurolysis
Status:	Completed
Study Results:	No Results Available
Locations:	Florida Hospital, Orlando, Florida, United States
URL:	https://ClinicalTrials.gov/show/NCT02068677

Study 4:

Title:	Trial Comparing Two Techniques of Celiac Plexus Neurolysis for Treatment of Pain in Carcinoma Pancreas
Status:	Unknown status
Study Results:	No Results Available
Locations:	Asian Institute of Gastroenterology, Hyderabad, Andhra pradesh, India
URL:	https://ClinicalTrials.gov/show/NCT01182831

Study 5:

Title:	Endoscopic Ultrasound (EUS) Guided-Celiac Plexus Neurolysis (CPN) in Unresectable Pancreatic Cancer
Status:	Completed
Study Results:	No Results Available
Locations:	University of Alabama at Birmingham, United States
URL:	https://ClinicalTrials.gov/show/NCT00968175

Study 6:

Title:	Randomized Trial of EUS Neurolysis in Pancreas Cancer
Status:	Completed
Study Results:	No Results Available
Locations:	Mayo Clinic Scottsdale, Scottsdale, Arizona, United States
URL:	https://ClinicalTrials.gov/show/NCT00279292

Appendix 4. List of Studies which have been published only as Conference Proceedings.

1. Pike S., Roberts K. Endoscopic ultrasound-guided celiac plexus neurolysis for pain management in chronic pancreatitis and pancreatic cancer. Anaesthesia [Internet]. July 2019 74(Supplement 3):22. In: Embase Available from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexa&NEWS=N&AN=628858998

2. Doi S., Yasuda I., Sekine K., Tsujikawa T., Mabuchi M. Long-term results of endoscopic ultrasound-guided celiac plexus neurolysis. Dig. Endosc. [Internet]. February 2017 29(Supplement 1):203. In: Embase Available from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexa&NEWS=N&AN=614371516

3. Thosani N., Sharma N.R., Raijman I., Thosani A.J., Kannadath B.S., Guider J.C., Raza A., Guha S. Safety and efficacy of endoscopic ultrasound guided radiofrequency ablation (EUS-RFA) in the treatment of pancreatic lesions: A multicenter experience. Gastrointest. Endosc. [Internet]. June 2018 87(6 Supplement 1):AB84. In: Embase Available from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed19&NEWS=N&AN=622899315

4. Goyal D., Cen P., Wray C.J., Rowe J., Guha S., Singhal S., Rahimi E.F., Ertan A., Thosani N. Feasibility, safety, and efficacy of endoscopic ultrasound (EUS) guided radiofrequency ablation (RFA)

of the pancreatic lesions: Single center us experience. Gastrointest. Endosc. [Internet]. May 2017 85(5 Supplement 1):AB144. In: Embase Available from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed18&NEWS=N&AN=619108184

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