Systematic review

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Meta-analysis of epidural analgesia in patients undergoing pancreatoduodenectomy

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Background: **The optimal analgesic technique after pancreatoduodenectomy remains under debate. This study aimed to see whether epidural analgesia (EA) has superior clinical outcomes compared with non-epidural alternatives (N-EA) in patients undergoing pancreatoduodenectomy.**

Methods: **A systematic review with meta-analysis was performed according to PRISMA guidelines. On 28 August 2018, relevant literature databases were searched. Primary outcomes were pain scores. Secondary outcomes were treatment failure of initial analgesia, complications, duration of hospital stay and mortality.**

Results: **Three RCTs and eight cohort studies (25 089 patients) were included. N-EA treatments studied were: intravenous morphine, continuous wound infiltration, bilateral paravertebral thoracic catheters and intrathecal morphine. Patients receiving EA had a marginally lower pain score on days 0–3 after surgery than those receiving intravenous morphine (mean difference (MD) −0·50, 95 per cent c.i. −0·80 to −0·21; $P < 0·001$) and similar pain scores to patients who had continuous wound infiltration. Treatment failure occurred in 28·5 per cent of patients receiving EA, mainly for haemodynamic instability or inadequate pain control. EA was associated with fewer complications (odds ratio (OR) 0·69, 95 per cent c.i. 0·06 to 0·79; $P < 0·001$), shorter duration of hospital stay (MD −2·69 (95 per cent c.i. −2·76 to −2·62) days; $P < 0·001$) and lower mortality (OR 0·69, 0·51 to 0 93; $P = 0·02$) compared with intravenous morphine.**

Conclusion: **EA provides marginally lower pain scores in the first postoperative days than intravenous morphine, and appears to be associated with fewer complications, shorter duration of hospital stay and less mortality.**

J.V.G. and A.A.J.K. contributed equally to this publication and share first authorship.

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Introduction

Patients undergoing pancreatoduodenectomy can experience severe postoperative pain due to the incidence of preoperative pain and opioid use, tissue damage and the extent of the resection[1]. Epidural analgesia (EA) is the perioperative analgesic technique of choice for most open abdominal surgical procedures and has been associated with better pain control after pancreatoduodenectomy[2–5]. Patients receiving EA appear to have fewer pulmonary complications and a lower incidence of postoperative ileus[6]. However, some studies[3,5,7,8] have noted adverse effects related to EA, including increased postoperative complication rates, ICU admissions and duration of hospital stay in these patients. EA has been associated with haemodynamic instability, sometimes requiring vasoactive medication or excessive fluid administration, thought to be associated with impaired anastomotic healing and other complications[3,5,9,10]. EA also carries risks of technique-specific complications including spinal haematoma, epidural abscess and cauda equina syndrome, as well as technical failure[11–13]. Heterogeneity in the use of EA (ranging from 10 to 84 per cent) implies that the ideal perioperative analgesic technique after pancreatoduodenectomy remains under debate[3,5,8,14].

This systematic review and meta-analysis aimed to see whether EA has superior clinical outcomes compared with non-epidural alternatives (N-EA) in patients undergoing pancreatoduodenectomy by reviewing RCTs and observational cohort studies.

Methods

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[15] and was registered with PROSPERO (CRD42018085818).

Eligibility criteria

Studies were included if the following predefined inclusion criteria were met: RCT or observational cohort study written in English, published between 1 January 1990 and 28 August 2018, reporting on more than ten patients, comparative study (EA *versus* N-EA), reporting at least one outcome of interest (it was not mandatory that all outcomes of interest were reported in the study). Studies were excluded if no full text was available. Where authors from the same institution published two or more similar studies, the most recent or larger study was included.

Information sources

PubMed, Embase, Web of Science and Cochrane Library databases were searched for relevant literature. The reference lists of all relevant articles were screened manually and cross-referenced to identify any additional studies. Covidence systematic review software (Veritas Health Innovation, Melbourne, Victoria, Australia; available at www.covidence.org) was used to manage all literature.

Literature search

Two reviewers performed preliminary literature searches for relevant studies. Thereafter, the definite literature search was composed and performed on 28 August 2018 by a librarian using terms 'pancreatoduodenectomy', 'pancreatic surgery', 'analgesia', 'epidural' and multiple synonyms, as indicated in the complete literature search provided in *Appendix S1* (supporting information).

Study selection

Two independent reviewers screened the titles and abstracts of all obtained articles for the potential to meet the eligibility criteria. Two independent reviewers checked the full texts for eligibility criteria.

Data collection process and items

A predefined standardized data extraction form was used by two independent reviewers to extract study characteristics (study design, nation, inclusion period), patient characteristics (sex, age, ASA physical status), analgesic technique protocols, primary and secondary outcomes, and risk of bias. The corresponding authors of included studies were e-mailed to request additional data on outcomes of interest if outcomes were unclear or not reported.

Outcomes and prioritization

The primary clinical outcomes were pain scores (measured on an 11-point numerical rating scale) during the day of surgery (postoperative day (POD) 0) up to POD 3, and the percentage of patients who reported a pain score above 4. Secondary clinical outcomes were incidence and reason of treatment failure of initial analgesia, overall complications (reported as any complication, overall morbidity, all morbidity, any morbidity), specific complications (pneumonia, postoperative pancreatic fistula, ileus), duration of hospital stay and mortality.

Risk of bias

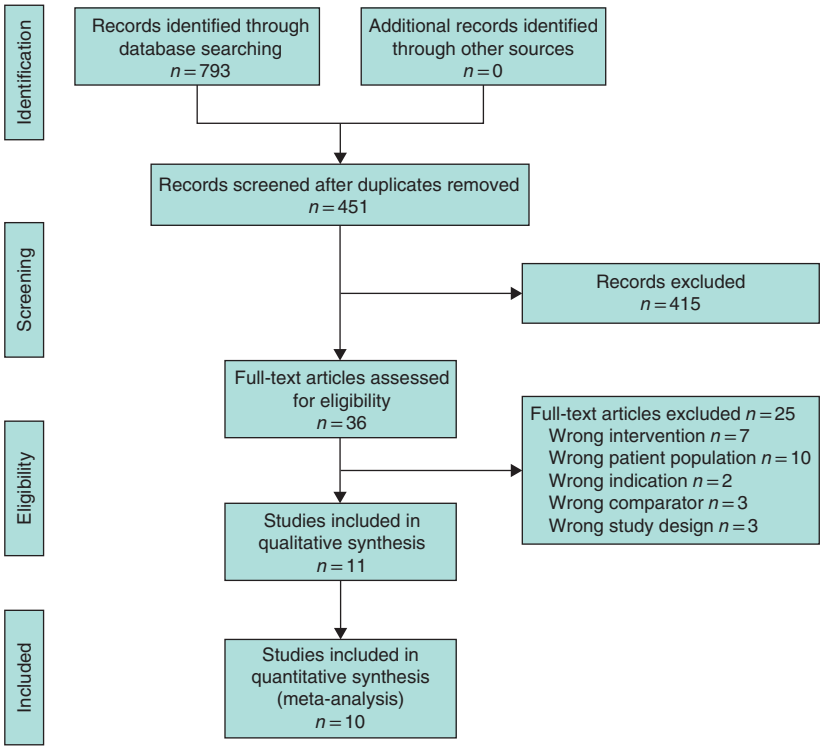
Two independent reviewers determined the risk of bias according to the Cochrane Collaboration tool[16] for RCTs and the ROBINS-I tool[17] for cohort studies. Possible publication bias was assessed visually through means of funnel plots.

Statistical analysis

All analyses were performed using Review Manager (RevMan version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014). For description of the study cohorts, continuous variables are presented as mean(s.d.) values and categorical variables as numbers with percentages. When studies did not report the mean(s.d.) of continuous variables, these were estimated using the method described by Wan *et al.*[18] from the available data (median (i.q.r.)). EA was compared with individual N-EA strategies by direct comparison of groups.

The I^2 statistic was used to assess heterogeneity between studies. An I^2 value greater than 50 per cent was considered to represent substantial heterogeneity. The number

Fig. 1 PRISMA flow diagram for the review



of included studies was limited and cohort sizes varied; therefore inverse variance (continuous outcomes) and Mantel–Haenszel (dichotomous outcomes) fixed-effect models were used to calculate pooled effects. Continuous variables are presented as mean differences (MDs) with 95 per cent c.i., and dichotomous variables as odds ratios (ORs) or absolute risk differences with 95 per cent confidence intervals. Two-tailed $P < 0{\cdot}050$ was considered statistically significant.

Confidence in evidence

The strength of the evidence and recommendations provided by this systematic review and meta-analysis was assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system[19].

Results

The literature search identified 451 studies. After screening of titles and abstracts, 36 were identified for full-text review (*Fig. 1*). Of these, three RCTs[4,20,21] and eight cohort studies[3,5,7,14,22–25] were included. Reasons for exclusion of full texts are provided in *Table S1* (supporting information). The included studies described 25 089 patients undergoing pancreatoduodenectomy: 3010 (12·0 per cent) received EA and 22 079 (88·0 per cent) had N-EA treatment. The inclusion period of all studies ranged from 2001 to 2015. Eight studies[3–5,14,20,22,23,25] were from the USA, two[7,21] from Europe, and one study[24] was conducted in New Zealand (*Table 1*). The study cohorts were largely comparable regarding sex, age and ASA grade, except one study[7] in which patients in the N-EA group had a higher ASA grade.

The types of EA infusion were: patient-controlled (1)[23], continuous infusion (5)[4,5,7,20,25], patient-controlled and continuous infusion (1)[21], and no information regarding infusion (4)[3,14,22,24]. The EA protocols warranted termination between POD 3 and 6 (4 studies did not provide information on duration of EA).

The N-EA protocols consisted of intravenous morphine (6 studies)[3–5,7,23,25], continuous wound infiltration (1)[21], bilateral thoracic paravertebral catheters (1)[20], intravenous morphine and intrathecal morphine (1)[24], 'not EA' (1)[22] and 'conventional analgesia' (1)[14]. In the two studies in

Table 1 Study characteristics

	Centre	Country	Inclusion period	No. of patients		ASA grade I–II		Epidural content		N-EA	
				EA	N-EA	EA	N-EA	Infusion	Removal of EA	Type	Removal of N-EA
RCTs											
Marandola *et al.*[4]	Single	USA	2002–2007	16 (40)	24 (60)	14 (88)	20 (83)	CEI	n.s.	i.v. morphine	n.s.
Mungroop *et al.*[21]	Multi	NL	2015	18 (50)	18 (50)	40 (85)*	48 (87)*	PCEA/CEI	POD 3	CWI	POD 3
Hutchins *et al.*[20]	Multi	USA	2012–2015	23 (48)	25 (52)	0†	0†	CEI	POD 4	BTPC	POD 4
Cohort studies											
Pratt *et al.*[5]	Single	USA	2001–2007	185 (79·4)	48 (20·6)	85 (45·9)	13 (27)	CEI	POD 4	i.v. morphine	‡
Sakowska *et al.*[24]	Single	NZ	2005–2008	18 (44)	23 (56)	33 (65)*	77 (78)*	n.s.	POD 5	ITM/i.v. morphine	n.s.
Choi and Schoeniger[3]	Single	USA	2004–2007	18 (43)	24 (57)	–	–	n.s.	POD 6	i.v. morphine	POD 6
Amini *et al.*[22]	Multi	USA	2009	947 (11·0)	7663 (89·0)	–	–	n.s.	n.s.	Not EA§	n.s.
Shah *et al.*[25]	Multi	USA	2007–2011	87 (85·3)	15 (14·7)	18 (21)	3 (20)	CEI	POD 3–5	i.v. morphine	POD 3–5
Patel *et al.*[7]	Single	UK	2006–2009	73 (85)	13 (15)	–	–	CEI	POD 3–4	i.v. morphine	n.s.
Axelrod *et al.*[23]	Single	USA	2007–2011	149 (91·4)	14 (8·6)	–	–	PCEA	n.s.	i.v. morphine	n.s.
Amini *et al.*[14]	Multi	USA	2001–2012	1476 (9·4)	14 212 (90·6)	–	–	n.s.	n.s.	Conventional analgesia§	n.s.

Values in parentheses are percentages. *Data for entire cohort, not solely patients having pancreatoduodenectomy; †all included patients had ASA grade III disease; ‡until oral pain medication tolerated; §considered as intravenous (i.v.) morphine for analysis. EA, epidural anaesthesia; N-EA, non-epidural anaesthesia; CEI, continuous epidural infusion; n.s., not specified; NL, the Netherlands; PCEA, patient-controlled epidural analgesia; POD, postoperative day; CWI, continuous wound infiltration; BTPC, bilateral thoracic paravertebral catheter; NZ, New Zealand; ITM, intrathecal morphine.

Table 2 Risk of bias for RCTs according to the Cochrane Collaboration tool[16]

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessments	Incomplete outcomes data	Selective reporting	Other bias	AHRQ standard*
Marandola *et al.*[4]	Unclear	Unclear	Unclear	Low	Unclear	Low	Unclear	Poor
Mungroop *et al.*[21]	Low	Low	High	Low	Low	Low	Low	Fair
Hutchins *et al.*[20]	Low	Low	High	Low	Low	Low	Unclear	Fair

*Agency for Healthcare Research and Quality (AHRQ) standard: good quality, low for each domain; fair quality, high risk of bias for one domain or two criteria unclear, and the assessment that this was unlikely to have biased the outcome, and there is no known important limitation that could invalidate the results; poor quality, high risk of bias for one domain or two criteria unclear, and the assessment that this was likely to have biased the outcome and there are important limitations that could invalidate the results; two or more criteria listed as high risk of bias; more than two criteria listed as unclear risk of bias.

which the N-EA protocol was 'not EA'[22] or 'conventional analgesia'[14], the protocol was considered as intravenous morphine in the meta-analysis, as this is the most widely used alternative in contemporary literature. A detailed description of analgesic technique protocols is provided in *Table S2* (supporting information).

The corresponding authors of three studies[20,21,25] provided additional unpublished data at request of the authors.

Risk of bias within studies

One RCT[4] was judged as of poor quality, mostly due to unclear quality statements. In the other two RCTs[20,21] the domain 'blinding of participants and personnel' was interpreted as at high risk of bias and thus they were both judged as fair quality (*Table 2*). In the cohort studies, the domains confounding, measurement of outcomes and selection of reported results were frequently judged as at moderate or serious risk of bias, so that three studies[3,5,25] were considered to have serious and five[7,14,22–24] to have moderate overall risks of bias (*Table 3*).

Primary clinical outcomes

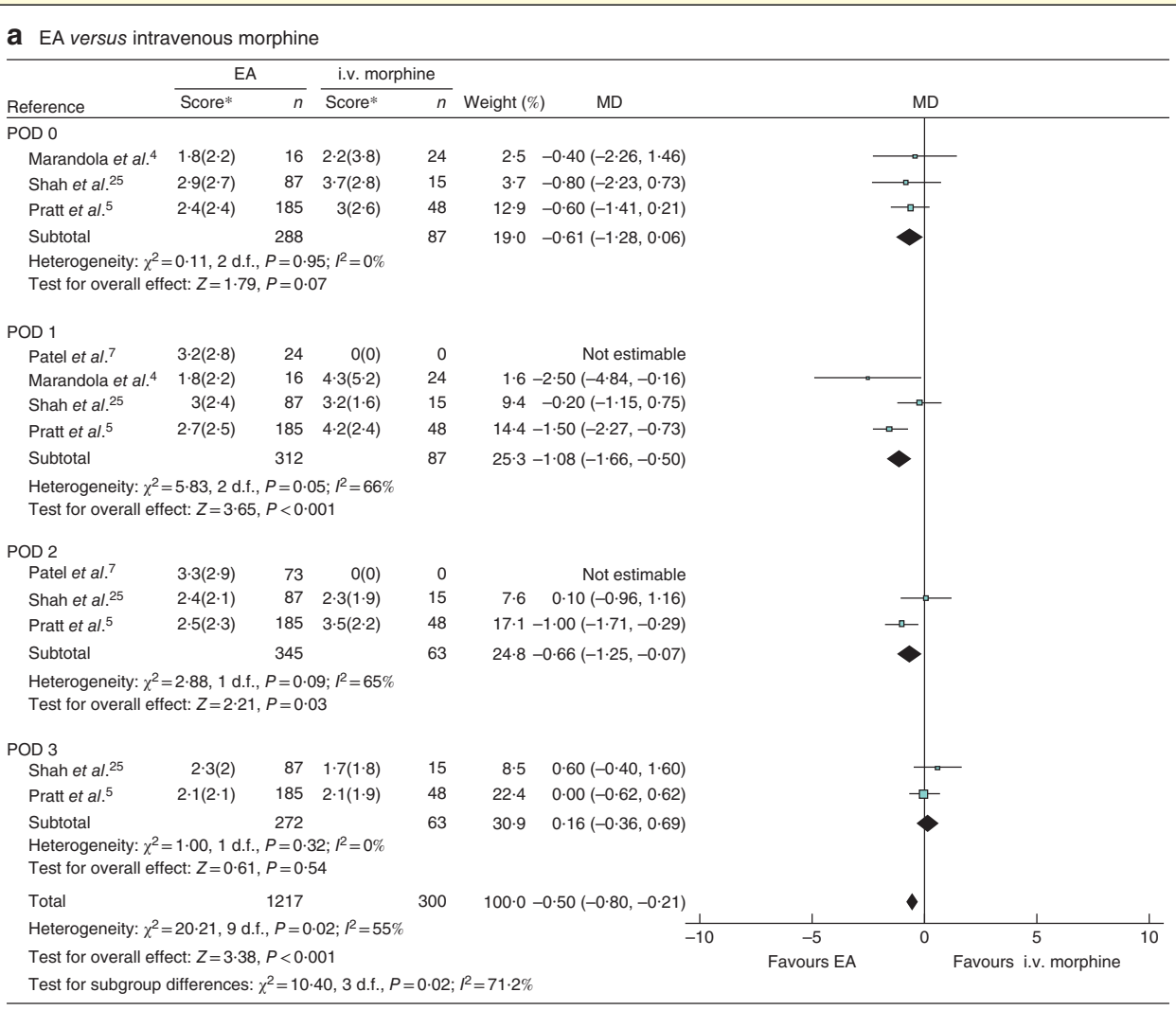
Pain scores on postoperative days 0–3

Five studies[4,5,7,21,25] reported mean pain scores on POD 0–3 (435 patients) (*Fig. 2*). The mean pain score on POD 0–3 was significantly lower for EA compared with intravenous morphine (MD −0·50, 95 per cent c.i. −0·80 to −0·21; $P < 0·001$) (*Fig. 2a*)[4,5,25]. The analysis of separate postoperative days showed that there was no difference on

Table 3 Risk of bias for cohort studies according to the ROBINS-I tool[17]

	Confounding	Selection of participants	Classification of intervention	Deviations of intended interventions	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias
Pratt *et al.*[5]	Moderate	Low	Low	Low	Low	Serious	Moderate	Serious
Sakowska *et al.*[24]	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Choi and Schoeniger[3]	Serious	Low	Low	Low	Low	Serious	Moderate	Serious
Amini *et al.*[22]	Moderate	Low	Moderate	Low	Low	Low	Moderate	Moderate
Shah *et al.*[25]	Moderate	Low	Low	Low	Low	Serious	Moderate	Serious
Patel *et al.*[7]	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
Axelrod *et al.*[23]	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Amini *et al.*[14]	Moderate	Low	Moderate	Low	Low	Low	Moderate	Moderate

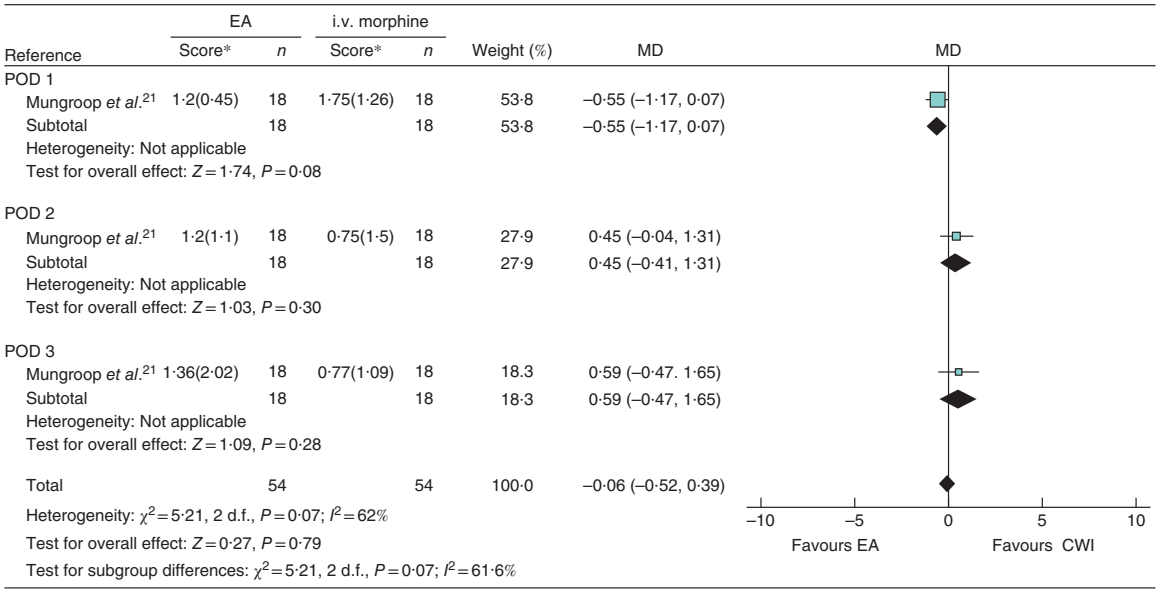
Fig. 2 Forest plot of pain scores following treatment with epidural anaesthesia *versus* non-epidural anaesthesia.



a Epidural anaesthesia (EA) *versus* intravenous (i.v.) morphine; **b** EA *versus* continuous wound infiltration (CWI). POD, postoperative day. *Values are mean(s.d.). An inverse-variance fixed-effect model was used for meta-analysis. Mean differences (MDs) are shown with 95 per cent confidence intervals

Fig. 2 Continued

b EA *versus* CWI



POD 0 (MD −0·61, −1·28 to 0·06; $P = 0·07$)[4,5,25], but a statistically significant difference on POD 1 (MD −1·08, −1·66 to −0·50; $P < 0·001$)[4,5,25] and POD 2 (MD −0·66, −1·25 to −0·07; $P = 0·03$) with substantial heterogeneity ($I^2 = 66$ per cent, $P = 0·05$, and $I^2 = 65$ per cent, $P = 0·09$, respectively)[5,25], whereas on POD 3 there was no difference (MD 0·16, −0·36 to 0·69; $P = 0·54$)[5,25]. One study[3] reported the median pain score in 42 patients and *P* values for EA *versus* intravenous morphine and observed no differences: POD 1 (1·2 *versus* 1·8; $P = 0·30$), POD 2 (1·3 *versus* 2·3; $P = 0·03$) and POD 3 (0·4 *versus* 0·0; $P = 0·40$).

The mean pain score on POD 1–3 was similar for EA and continuous wound infiltration (36 patients) (*Fig. 2b*)[21], with similar mean pain scores on the individual days.

There was no difference in a study of 48 patients in the sum of total maximum pain scores on POD 0–4 for EA compared with bilateral thoracic paravertebral catheter treatment (median 34·6 (range 18–43) *versus* 30·0 (17–51); $P = 0·364$)[20].

Pain scores above 4

No studies reported data on this outcome.

Secondary clinical outcomes

Treatment failure of initial analgesia

Four studies[3,5,7,23] reported on treatment failure of EA, which occurred in 121 (28·5 per cent) of 425 patients (range between studies 14·8–55·6 per cent). The reason for EA treatment failure was specified in 111 patients in three studies[5,7,23]: 49 (44·1 per cent) due to haemodynamic compromise, 47 (42·3 per cent) to inadequate pain control and 15 (13·5 per cent) to catheter migration or malfunction. In the study[20] that looked at EA and paravertebral catheters, two patients (8·7 per cent) receiving EA but none who had paravertebral catheter treatment required intervention for hypotension, although it was unclear whether this led to treatment failure.

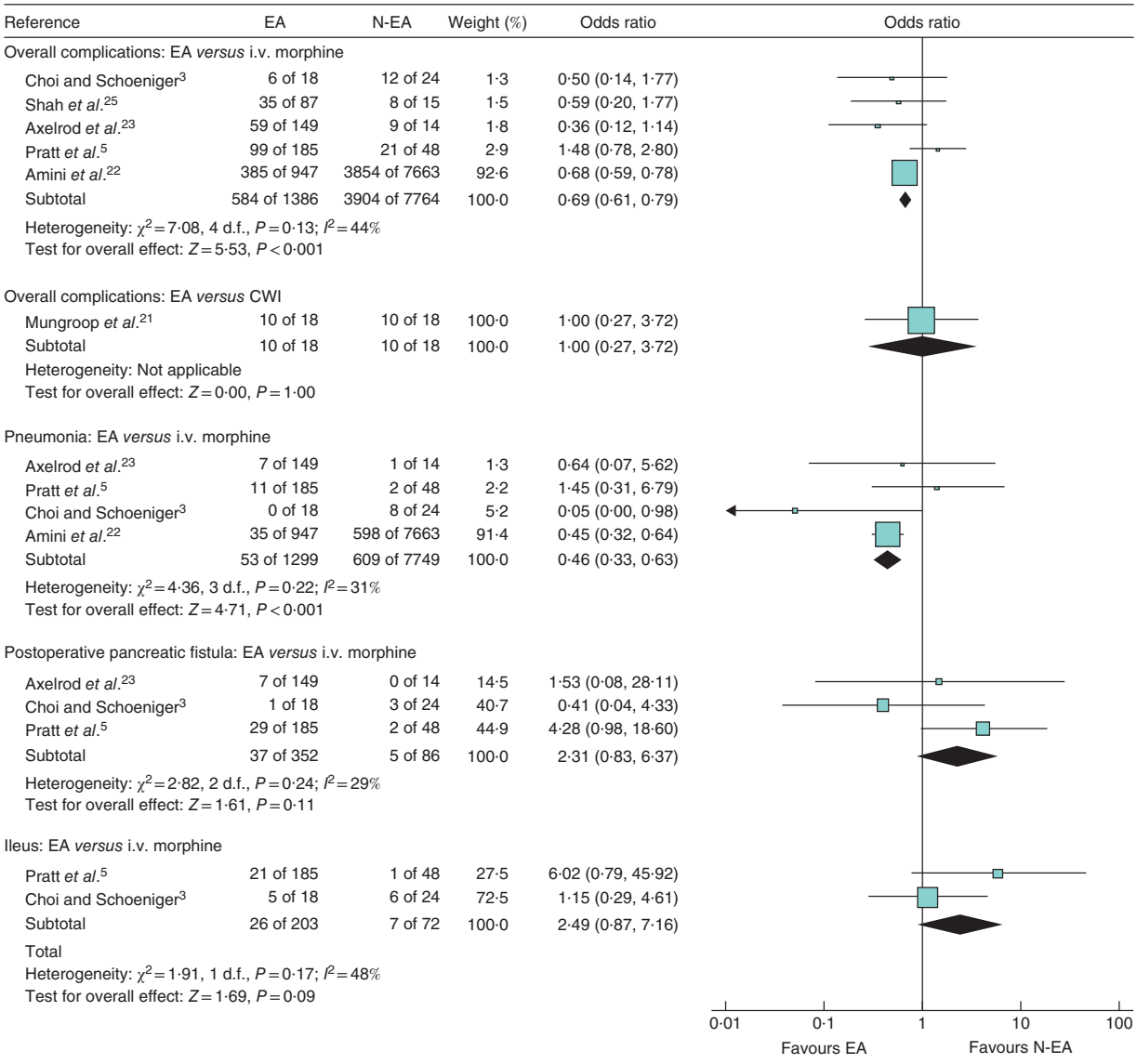
One study[3] reported on treatment failure of N-EA, which occurred in 9 per cent of their patients.

Complications

Six studies[3,5,21–23,25] reported on overall complications (9186 patients) (*Fig. 3*). There was a significant difference in overall complications between EA and intravenous morphine treatment (OR 0·69, 95 per cent c.i. 0·06 to 0·79; $P < 0·001$)[3,5,22,23,25]. The study[21] comparing EA with continuous wound infiltration found no difference in overall complications.

There was a significant difference in pneumonia between EA and intravenous morphine (OR 0·46, 0·33 to 0·63; $P < 0·001$) (*Fig. 3*)[3,5,22,23]. The absolute risk difference in pneumonia between EA (53 of 1299, 4·1 per cent) and intravenous morphine (609 of 7749, 7·9 per cent) was −4 (95 per cent c.i. −5 to −3) per cent ($P < 0·001$)[3,5,22,23].

Fig. 3 Forest plot of overall complications, pneumonia, postoperative pancreatic fistula and ileus following treatment with epidural anaesthesia *versus* non-epidural anaesthesia.



EA, epidural anaesthesia; N-EA, non-epidural anaesthesia; i.v., intravenous; CWI, continuous wound infiltration. A Mantel–Haenszel fixed-effect model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals

No significant differences were observed in postoperative pancreatic fistula or ileus between EA and intravenous morphine treatments (*Fig. 3*)[3,5,23].

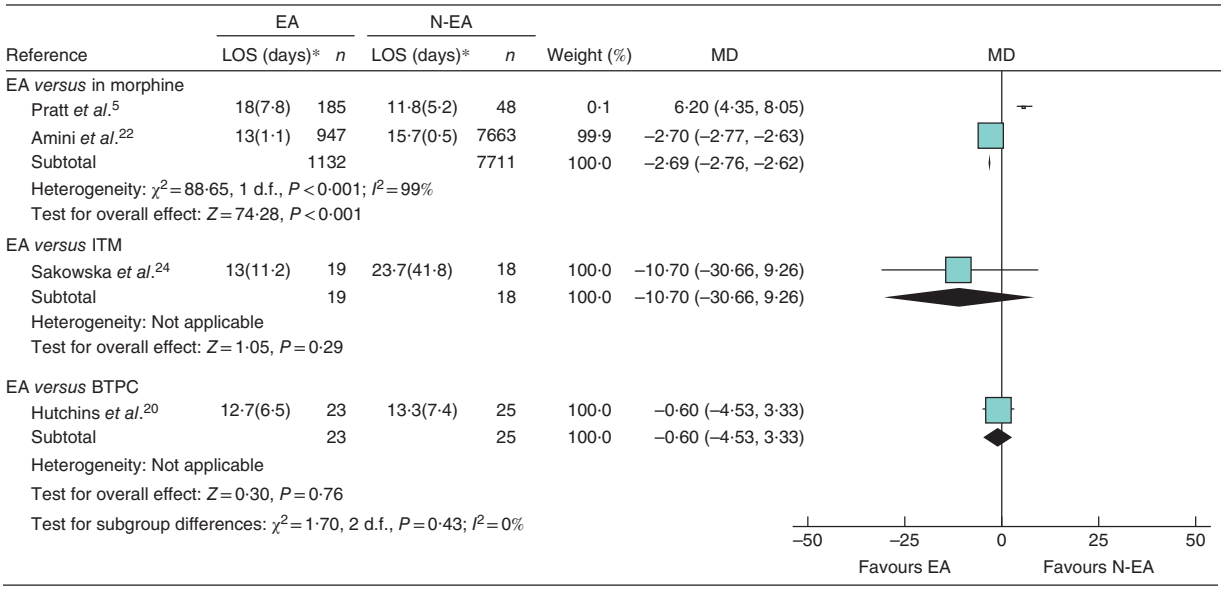
Duration of hospital stay

Four studies[5,20,22,24] reported on duration of hospital stay (8928 patients) (*Fig. 4*). There was a significant difference between EA and intravenous morphine treatments (MD −2·69 (95 per cent c.i. −2·76 to −2·62) days; $P < 0·001$) with substantial heterogeneity ($I^2 = 99$ per cent; $P < 0·001$)[5,22]. There was no significant difference between EA and intrathecal morphine[24] or bilateral thoracic paravertebral catheter[20].

Mortality

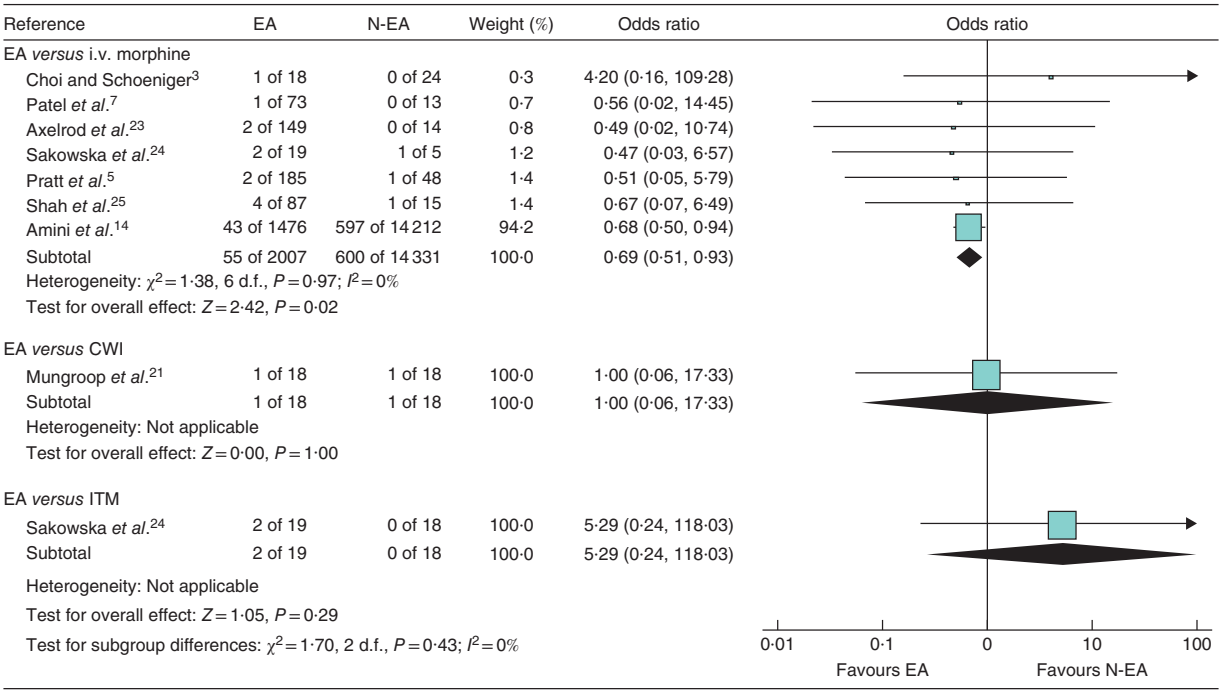
Eight studies[3,5,7,14,21,23–25] reported on mortality (16 392 patients) (*Fig. 5*). One study[22] was excluded from this meta-analysis as it overlapped with a larger study[14]. There

Fig. 4 Forest plot of duration of hospital stay following treatment with epidural anaesthesia *versus* non-epidural anaesthesia.



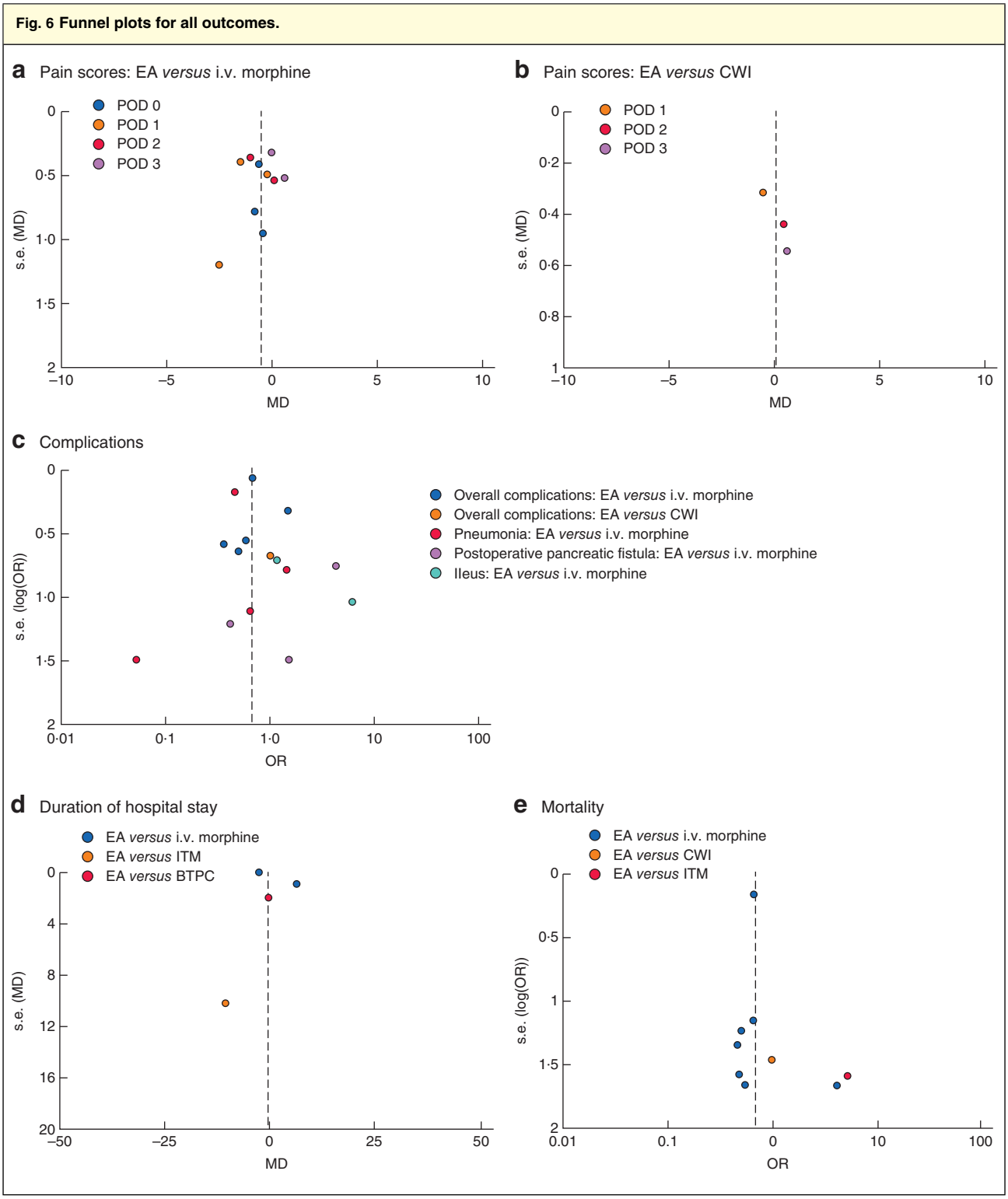
EA, epidural anaesthesia; N-EA, non-epidural anaesthesia; LOS, length of stay; i.v., intravenous; ITM, intrathecal morphine; BTPC, bilateral thoracic paravertebral catheter. *Values are mean(s.d.). An inverse-variance fixed-effect model was used for meta-analysis. Mean differences (MDs) are shown with 95 per cent confidence intervals

Fig. 5 Forest plot of mortality following treatment with epidural anaesthesia *versus* non-epidural anaesthesia.



EA, epidural anaesthesia; N-EA, non-epidural anaesthesia; i.v., intravenous; CWI, continuous wound infiltration; ITM, intrathecal morphine. A Mantel–Haenszel fixed-effect model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals

Fig. 6 Funnel plots for all outcomes.



a Pain scores for epidural anaesthesia (EA) *versus* intravenous (i.v.) morphine; **b** pain scores for EA *versus* continuous wound infiltration (CWI); **c** complications; **d** duration of hospital stay; **e** mortality. POD, postoperative day; MD, mean difference; OR, odds ratio; ITM, intrathecal morphine; BTPC, bilateral thoracic paravertebral catheter

was a significant difference in mortality between EA and intravenous morphine treatment (OR 0·69, 95 per cent c.i. 0·51 to 0·93; $P = 0·02$). The absolute risk difference in mortality between EA (55 of 2007, 2·7 per cent) and intravenous morphine (600 of 14 331, 4·2 per cent) was −1 (95 per cent c.i. −2 to 0) per cent ($P = 0·01$)[3,5,7,14,23–25]. Neither the study[21] comparing EA with continuous wound infiltration nor the study[24] comparing EA and intrathecal morphine found any difference in mortality.

Risk of bias across studies

The funnel plots showed a nearly symmetrical scatter around the mean for all outcomes (*Fig. 6*).

Discussion

This systematic review and meta-analysis of analgesic techniques in patients undergoing pancreatoduodenectomy found that EA provided marginally lower pain scores on POD 0–3 compared with intravenous morphine. Treatment failure with EA, however, was common, occurring in 28·5 per cent of patients, mainly as a result of haemodynamic instability or inadequate pain control. There also appeared to be a benefit of EA over intravenous morphine regarding complications, pneumonia, duration of hospital stay and mortality. This suggests a weak recommendation for the use of EA over intravenous morphine in reducing early postoperative pain in eligible patients undergoing pancreatoduodenectomy. This review has also highlighted the lack of evidence related to analgesic techniques in patients undergoing pancreatoduodenectomy, emphasizing the need for further and better quality studies.

Adequate postoperative pain control is of paramount importance because it is related to fewer complications and shorter duration of hospital stay[26,27]. The marginal difference in mean pain score (−0·50 on an 11-point numerical rating scale) on POD 0–3 between EA and intravenous morphine might be of limited clinical relevance[28]. The largest difference in mean pain score (−1·08) was on POD 1, in favour of EA, and might be more relevant. There were no data available on patients reporting a pain score above 4 (transition from mild to moderate pain), which also seems important[29]. Similarly, pain scores during mobilization were not reported specifically in the included studies[30]. It is notable that only two studies[21,23] used patient-controlled EA, despite evidence that this technique is associated with improved pain scores, patient satisfaction and safety parameters[31,32]. Nevertheless, in concordance with recent RCTs in major abdominal surgery, EA has marginal beneficial effects on pain scores during the early postoperative period compared with intravenous morphine[33,34]. Although the RCT[21] that compared EA with continuous wound infiltration showed non-inferiority regarding pain scores and patient-reported outcomes (the overall benefit of analgesia score) in the subgroup analysis of patients undergoing pancreatoduodenectomy, a recent systematic review and meta-analysis[35] did show improved recovery parameters and patient satisfaction in favour of continuous wound infiltration over EA in patients undergoing abdominal surgery with similar pain scores. The RCT[20] comparing EA with bilateral thoracic paravertebral catheter use observed similar maximum pain scores, although this trial was designed to prove a 2-point difference in favour of the latter technique.

Fewer complications occurred following EA treatment than with intravenous morphine in the present analysis, in contrast to findings in previous studies[33,34,36,37]. Here, only one study[22] (EA *versus* intravenous morphine) reported significantly fewer complications with EA, the difference remaining significant after adjustment for several factors. It remains unclear why the results of different studies are contradictory. EA treatment failure has been associated with increased postoperative complications[5,8,23], especially haemodynamic instability, as aggressive fluid therapy may cause pulmonary and anastomotic complications[5,23,38]. Careful patient selection and a dedicated and specialized team, including an acute pain service team[39], may be a solution to this problem.

The observation of a shorter duration of hospital stay for EA compared with intravenous morphine was based mainly on a single study[22] conducted in the USA. National and hospital healthcare practices, such as discharge criteria, influence duration of hospital stay, and this beneficial effect of EA may not be generalizable to other healthcare systems. A systematic review and meta-analysis[37] of analgesia after abdominal surgery in an enhanced recovery after surgery (ERAS) setting could not prove that EA is associated with a shorter duration of hospital stay. This will become more relevant with the increasing interest in ERAS pathways related to pancreatoduodenectomy[40].

This meta-analysis showed an absolute risk difference of −1 (−2 to 0) per cent ($P = 0·01$) on mortality following treatment with EA compared with intravenous morphine. A meta-analysis of RCTs (2201 patients)[41] and a national cohort study (259 037 patients)[42] in patients undergoing surgery also showed a beneficial effect of EA on mortality, although this benefit disappeared in the subgroup analysis of patients undergoing abdominal surgery in both studies. As with the outcome 'overall complications' in the present study, the influence of residual confounding remains debatable, although the analysis of overall complications

and mortality showed no significant heterogeneity or publication bias.

There are two ongoing RCTs comparing EA with intravenous morphine[43] and with intravenous hydromorphone[44], designed to determine how analgesic technique influences the incidence of complications and mortality after pancreatoduodenectomy. It will be interesting to see how the increasing use of minimally invasive surgery will influence indications for analgesic techniques[45]. Recent experience[46–48] with sublingual sufentanil (non-invasive, rapid absorption, rapid pain relief, few side-effects) seems promising, leading to a proposed RCT comparing EA with sublingual sufentanil in patients undergoing pancreatoduodenectomy (www.trialregister.nl; TC 7318).

This systematic review and meta-analysis has limitations. The quality of included studies varied. *Post hoc* sensitivity analysis without studies of 'poor quality' and 'serious risk of bias' showed similar results for the secondary outcomes. This could not be performed for the primary outcome (pain scores) as this was the main source of risk of bias due to non-blinding. The two studies by Amini and colleagues, involving 8610[22] and 15 688[14] patients, were large and showed results in favour of EA that mainly determined the secondary outcomes of the meta-analysis. Interstudy differences in definitions of the outcomes (treatment failure of initial analgesia, postoperative pancreatic fistula and ileus) may also have affected the results. However, the primary outcome (pain scores all measured on an 11-point numerical rating scale) and some secondary outcomes (overall complications, mortality) were fairly universal in definition. In pooling data from an RCT[4] and two cohort studies[5,25] for estimation of the mean pain scores on POD 0 and 1, this mix of study designs might have introduced heterogeneity. *Post hoc* sensitivity analysis showed similar results when analyses were performed separately per study design. It is uncertain to what extent the interstudy differences regarding the pain score measurement (for example during rest or movement) and analgesic technique (such as type and composition of infusion) may have influenced the results. To minimize the effect of analgesic technique differences, analyses were performed separately for each type of N-EA.

As a consequence of the risk-of-bias assessment and these limitations, the evidence should be considered as low quality. As a result, recommendations can only be described as weak.

Clinicians and patients should weigh the potential desirable effects of EA on pain scores, complications, duration of hospital stay and mortality against its possible undesirable effects (treatment failure). Patient characteristics such as preoperative pain and opioid use, anticoagulant use and risk of venous thrombosis, cardiopulmonary and other systemic conditions, should all be taken into account in making a decision about the perceived optimal approach to achieving good pain relief.

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Supporting information

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