Improving outcomes of pancreatic surgery

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CHAPTER 13

Meta-analysis of epidural analgesia in patients undergoing pancreatoduodenectomy

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ABSTRACT

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

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

Results*:* Three randomized controlled trials and eight cohort studies (25 089 patients) were included. N-EA studied were: intravenous (iv) morphine, continuous wound infiltration (CWI), bilateral paravertebral thoracic catheters, and intrathecal morphine. EA patients had a marginally lower pain score over postoperative day 0 to 3 compared with iv morphine (mean difference (MD)=-0·50, 95 per cent confidence interval -0·80 to -0·21; *P*<0·001) and similar pain scores compared with CWI. Treatment failure occurred in 28·5 per cent of EA patients, mainly for hemodynamic instability or inadequate pain control. EA was associated with less complications (odds ratio (OR)=0·69, 0·061 to 0·79; *P*<0·001), shorter length of hospital stay (MD=-2·69 days, -2·76 to -2·62; *P*<0·001) and less mortality compared with iv morphine (OR=0·69, 0·51 to 0·93; *P*=0·01).

Conclusions*:* EA provides marginally lower pain scores in the first postoperative days compared to iv morphine and seems associated with less complications, shorter length of hospital stay, and less mortality. The authors weakly recommend the use of EA over iv morphine as first choice for reducing early postoperative pain in eligible patients undergoing pancreatoduodenectomy.

INTRODUCTION

Rationale

Patients undergoing pancreatoduodenectomy are at risk of severe postoperative pain due to the incidence of preoperative pain and opioid use, tissue damage and extent of the resection.[1] Epidural analgesia (EA) is the perioperative analgesic technique of choice for most open abdominal surgical procedures and EA has been associated with better pain control after pancreatoduodenectomy.[2-5] Moreover, patients with EA seem to have less pulmonary complications and a lower incidence of postoperative ileus.[6] On the other hand, recent studies described adverse effects of EA on postoperative complications, Intensive Care Unit (ICU) admissions, and length of hospital stay in patients undergoing pancreatoduodenectomy.[3, 5, 7, 8] Furthermore, EA has been associated with hemodynamic instability, and therefore the need for vasoactive medication and excessive fluid administration, which some believe to be associated with impaired anastomotic healing and other complications. [3, 5, 9, 10] EA also bears the risk of technique specific complications e.g. spinal hematoma, epidural abscess, and cauda equina syndrome.[11-13] The heterogeneity in use of EA (ranging 10 to 84 per cent) demonstrates that the ideal perioperative analgesic technique after pancreatoduodenectomy remains under debate.[3, 5, 8, 14]

This systematic review and meta-analysis aims to investigate if epidural analgesia (EA) has superior clinical outcomes compared to non-epidural alternatives (N-EA) in patients undergoing pancreatoduodenectomy by reviewing randomized controlled trials (RCTs) and observational cohort studies.

METHODS

Protocol and registration

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 (registration number: CRD42018085818).

Eligibility criteria

Studies were included if the following predefined inclusion criteria were met: RCTs or observational cohort studies written in English, published between 1 January 1990 and 31 August 2018, reporting >10 patients, comparative study (EA *versus* N-EA), reporting at least one outcome of interest (i.e. it was not mandatory that all outcomes of interest were reported in the study). Studies were excluded if there was no full text available. In

case authors from the same institution published two or more similar studies, the most recent or larger study was included.

Information sources

The 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. The Covidence software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at: www.covidence.org) was used to manage all literature.

Literature search

Two reviewers (J.V.G. & P.A.B.) 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 as 'pancreatoduodenectomy', 'pancreatic surgery', 'analgesia', 'epidural', and multiple synonyms. The complete literature search available at request.

Study selection

Two independent reviewers (J.V.G. & P.A.B.) screened the titles and abstracts of all obtained articles for the potential to meet the eligibility criteria. Two independent reviewers (J.V.G. & P.A.B.) checked the full texts for the eligibility criteria.

Data collection process & items

A predefined standardized data extraction form was used by two independent reviewers (J.V.G. & A.A.J.K.) to extract study characteristics (study design, nation, inclusion period), patient characteristics (sex, age, American Society of Anesthesiologists (ASA) physical status), analgesic technique protocols, primary and secondary outcomes, and risk of bias. The corresponding authors of included studies were emailed 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 a 11-point Numerical Rating Scale) during the day of surgery (postoperative day 0) up to postoperative day 3 and the percentage of patients who reported a pain score >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), length of hospital stay, and mortality.

Risk of bias

Two independent reviewers (J.V.G. & A.A.J.K.) determined the risk of bias according to the Cochrane Collaboration tool[16] for randomized controlled trials and the ROBINS-I[17] for the cohort studies. Possible publication bias was assessed visually through funnel plots.

Statistical analysis

All analyses were performed using Review Manager (RevMan version 5·3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For description of the study cohorts, continuous variables are presented as mean (standard deviation) and categorical variables are presented as numbers (percentages). When studies did not report mean (standard deviation) of continuous variables, it was estimated using the method described by Wan et al. from the available data (median and (interquartile) range).[18] EA was compared with individual N-EA strategies, by direct comparison of groups. The I^2 statistic was used to assess between study heterogeneity. An I^2 value greater than 50 per cent was considered as evidence for substantial heterogeneity. The number of included studies was limited and cohort sizes varied, therefore the Inverse Variance (continuous outcomes) and Mantel-Haenszel (dichotomous outcomes) fixed effects models were used to calculate pooled effects. Continuous variables are presented as the mean difference (MD) with 95 per cent confidence interval (c.i.) and dichotomous variables are presented as odds ratios (OR) or absolute risk difference with 95 per cent c.i. Two-tailed P <0·050 was considered as statistical significance.

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

Study selection and characteristics

The literature search identified 451 unique studies. After screening of titles and abstracts, 36 studies were identified for full-text review (Figure 1). Of these studies, 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 supporting information. The included studies (N=11) described 25 089 patients undergoing pancreatoduodenectomy: 3 010 (12·0 per cent) EA patients and 22 079 (88·0 per cent) N-EA patients. The inclusion period of all studies ranged from 2001 to 2015. Eight studies were conducted in the United Stated of America[3–5, 14, 20, 22, 23, 25], two studies were conducted in Europe[7, 21], and one study was conducted in New Zealand[24] (Table 1). The study cohorts were largely comparable regarding sex, age, (data not shown)

and ASA. Except in the study by Pratt et al.[7] where patients in the N-EA group had a higher ASA.

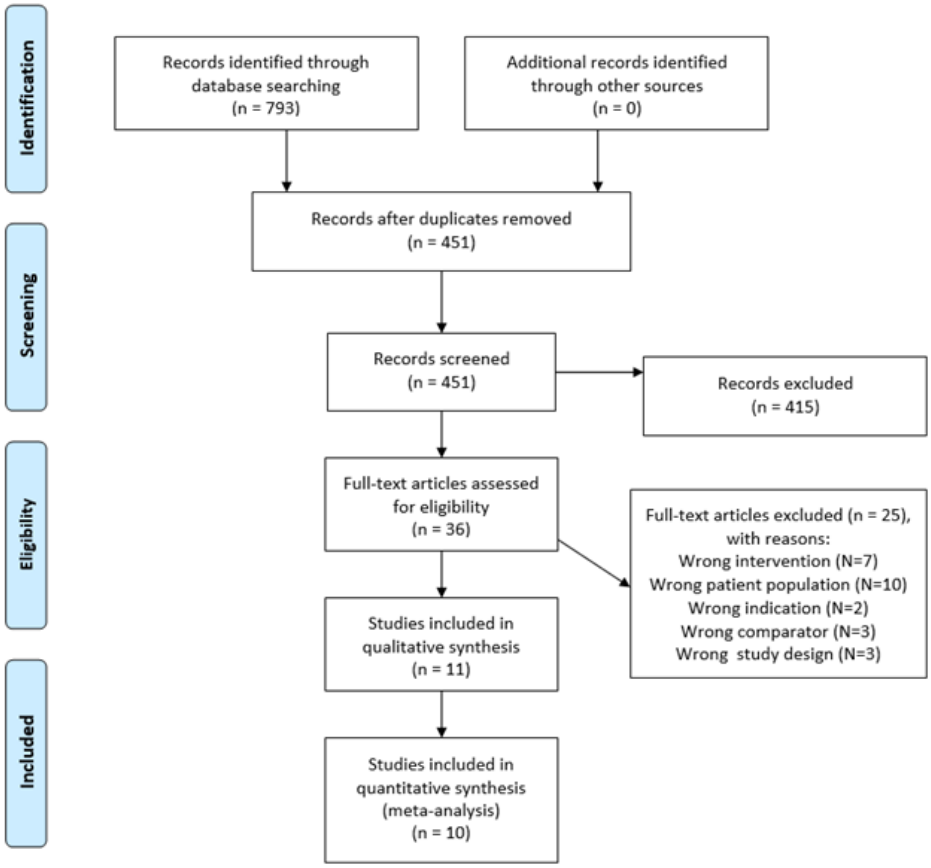

Figure 1. PRISMA flow diagram for the review

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

The N-EA protocols consisted of intravenous (iv) morphine (N=6)[3-5, 7, 23, 25], continuous wound infiltration (CWI) (N=1)[21], bilateral thoracic paravertebral catheters (BTPC) (N=1)[20], iv morphine and intrathecal morphine (N=1)[24], 'not EA' (N=1)[22], and 'conventional analgesia' (N=1)[14]. In the two studies[14, 22] in which the N-EA protocol was 'not EA'[22] or 'conventional analgesia'[14] it was considered as iv morphine in the meta-analysis, since

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)	14212 (90.6)	–	–	n.s.	n.s.	Conventional analgesia#	n.s.

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

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

this is the most used alternative in contemporary literature. A detailed description of analgesic technique protocols is provided in supporting information.

The corresponding author of three studies (Mungroop et al.[21], Shah et al.[25], and Hutchins et al.[20]) provided additional unpublished data at request of the authors.

Risk of bias within studies

The RCT from Marandola et al.[4] was judged as Poor quality, mostly due to unclear quality statements. In the RCTs from Mungroop et al.[21] and Hutchins et al.[20], the domain 'blinding of participants and personnel' was interpreted as high risk of bias and therefore the RCTs were both judged as Fair quality (Table 2). In the cohort studies, mostly the domains 'confounding', 'measurement of outcomes', and 'selection of reported results' were judged as moderate or serious risk of bias, therefore three studies were judged as having a serious[3, 5, 25] and five as a moderate[7, 14, 22-24] overall risk of bias (Table 3).

Primary clinical outcomes

Pain scores on postoperative days 0 to 3

Five studies reported mean pain scores on postoperative day 0 to 3 (435 patients; Figure 2).[4, 5, 7, 21, 25] The mean pain score on postoperative days 0 to 3 was significantly lower in EA compared with iv morphine patients (MD=-0·50, -0·80 to -0·21; P<0·001; Figure 2 (upper)).[4, 5, 25] The analysis of separate postoperative days showed that there was no difference on postoperative day 0 (MD=-0·61, -1·28 to 0·06; P=0·07)[4, 5, 25], but a statistically significant difference on postoperative day 1 (MD=-1·08, -1·66 to -0·50; P<0·001)[4, 5, 25] and postoperative day 2 (MD=-0·66, -1·25 to -0·07; P=0·03) with substantial heterogeneity (I^2=55 per cent; P=0·05)[5, 25], whereas on postoperative days 3 there was no difference (MD=0·16, -0·36 to 0·69; P=0·54)[5, 25]. In addition, Choi et al.[3] reported (42 patients) median pain scores (without interquartile range) and P-values in EA *versus* iv morphine patients and observed no differences: on postoperative day 1 (1·2 *versus* 1·8; P=0·3), postoperative day 2 (1·3 *versus* 2·3; P=0·03), and postoperative day 3 (0·4 *versus* 0·0; P=0·4).

The mean pain score on postoperative days 1 to 3 was similar in EA compared with CWI patients (36 patients; Figure 2 (lower)).[21] Also the analysis of separate postoperative day showed similar mean pain scores.

Hutchins et al.[20] showed (48 patients) no difference in median (range) sum of total maximum pain scores on postoperative days 0 to 4 in EA patients compared with BTPC patients (34·6 (18 to 43) *versus* 30·0 (17 to 51); P=0·364).

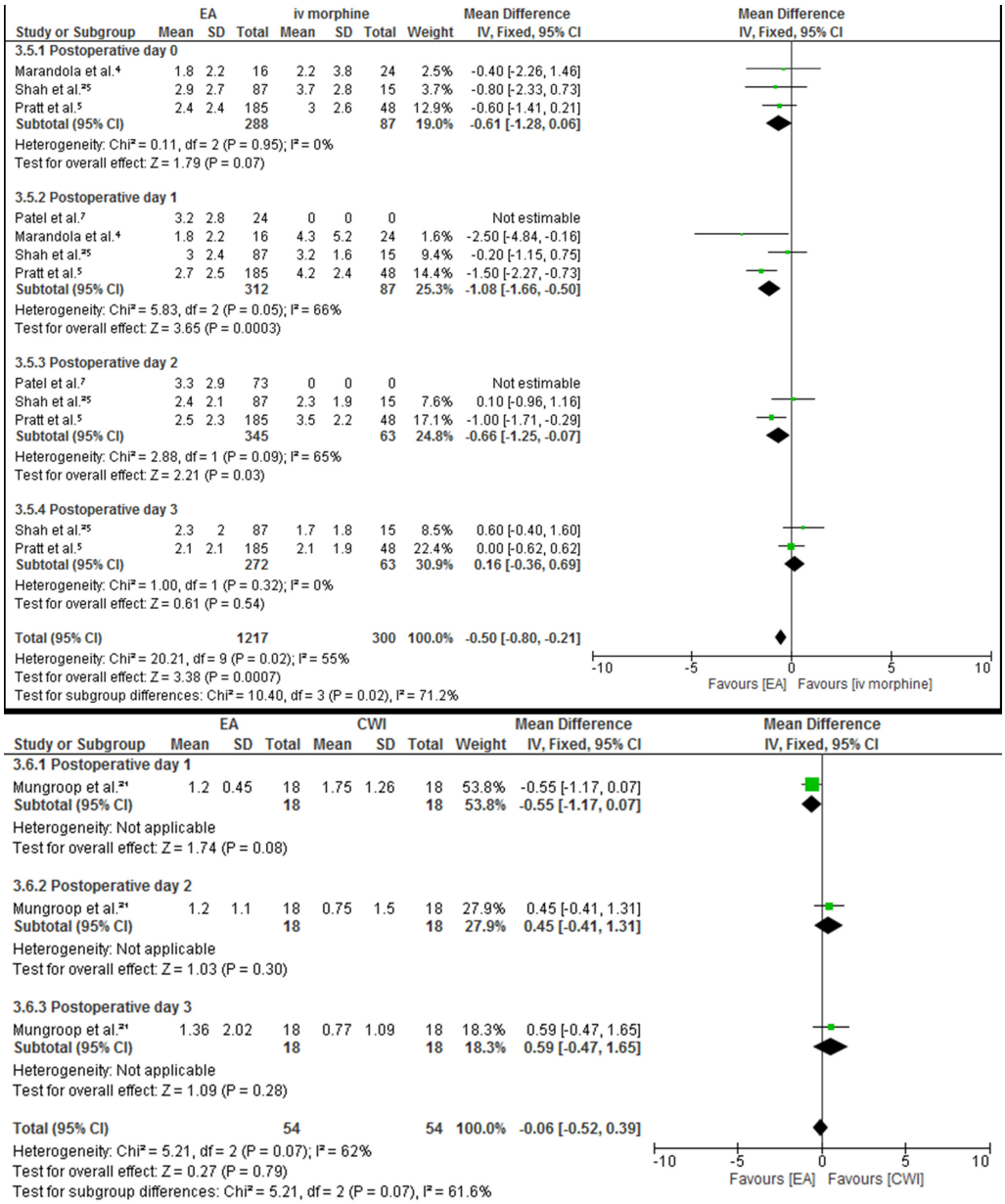

Figure 2. Forest plot of pain scores following treatment with epidural anaesthesia versus non-epidural anaesthesia

Pain scores >4

No studies reported data on this outcome.

Secondary clinical outcomes

Treatment failure of initial analgesia

Four studies reported on treatment failure of EA (425 patients).[3, 5, 7, 23] Overall, treatment failure occurred in 121 (28·5 per cent) EA patients (range between studies: 14·8 to 55·6 per cent). The reason for treatment failure of EA was specified in 111 patients in three studies[5, 7, 23] with the following results: 49 (44·1 per cent) patients due to hemodynamic compromise, 47 (42·3 per cent) patients due to inadequate pain control, and 15 (13·5 per cent) patients due to catheter migration or malfunction.[5, 7, 23] In addition, Hutchins et al.[20] reported that two (8·7 per cent) EA and none BTPC patients required an intervention due to hypotension (unclear if this led to treatment failure).

One study reported on treatment failure of N-EA and this occurred in two (9 per cent) N-EA patients.[3]

Complications

Six studies reported on overall complications (9 150 patients; Figure 3).[3, 5, 21-23, 25] There was a significant difference in overall complications between the EA and iv morphine patients (OR=0·69, 0·061 to 0·79; *P*<0·001)[3, 5, 22, 23, 25] Mungroop et al.[21] showed no difference in overall complications between EA and CWI patients.

There was a significant difference in pneumonia between the EA and iv morphine patients (OR=0·46, 0·33 to 0·63; *P*<0·001; Figure 3)[3, 5, 22, 23] The absolute risk difference in pneumonia between EA (53/1 299=4·1 per cent) and iv morphine (609/7 749=7·9 per cent) patients was -4·2 per cent (-5·5 to -2·9; *P*<0·001).[3, 5, 22, 23]

No significant differences were observed in postoperative pancreatic fistula and ileus between EA and iv morphine patients (Figure 3).[3, 5, 23]

Length of hospital stay

Four studies reported on length of hospital stay (8 928 patients; Figure 4).[5, 20, 22, 24] There was a significant difference in the length of hospital stay between the EA and iv morphine patients (MD=-2·69, -2·76 to -2·62; *P*<0·001) with substantial heterogeneity (I^2=99 per cent; *P*<0·001).[5, 22] Between EA and intrathecal morphine[24] or BTPC patients[20] there was no significant difference.

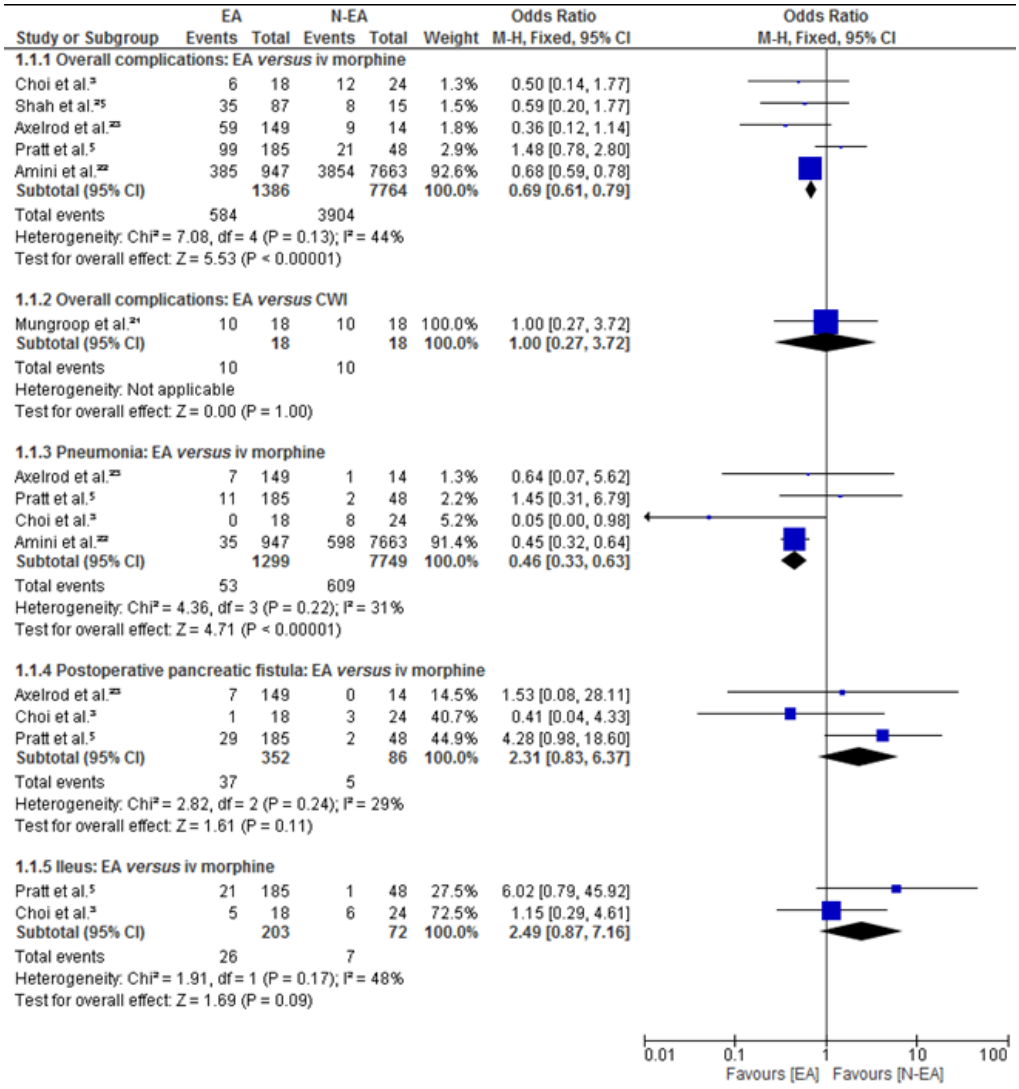

Figure 3. Forest plot of overall complications, pneumonia, postoperative pancreatic fistula and ileus following treatment with epidural anaesthesia versus non-epidural anaesthesia

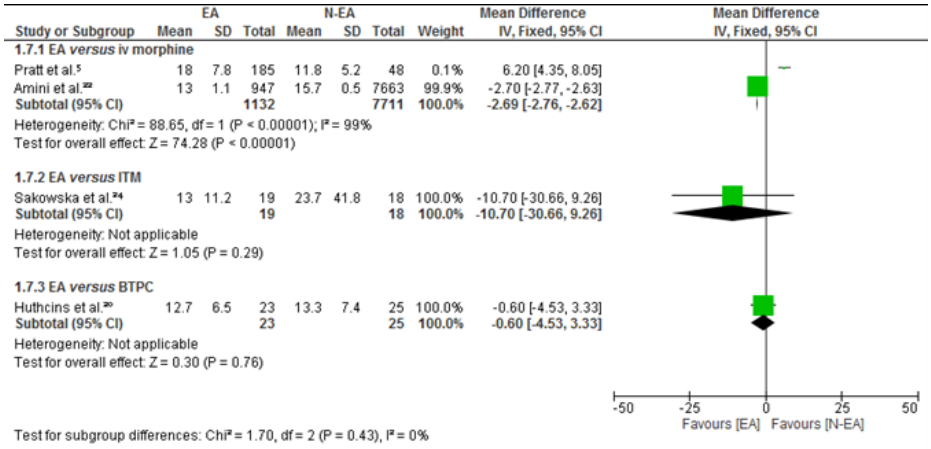

Figure 4. Forest plot of duration of hospital stay following treatment with epidural anaesthesia versus non-epidural anaesthesia

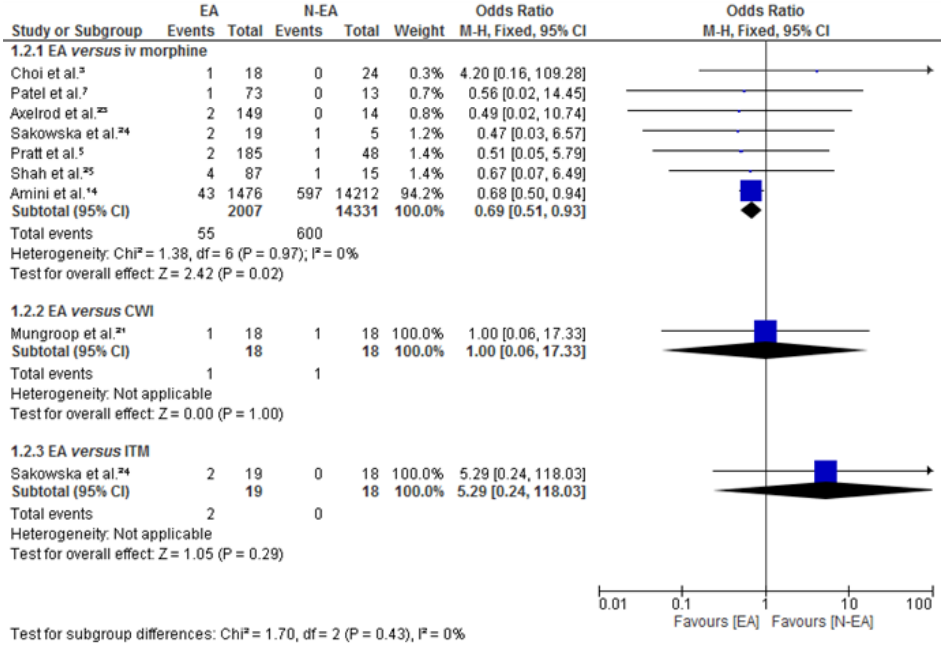

Figure 5. Forest plot of mortality following treatment with epidural anaesthesia versus non-epidural anaesthesia

Mortality

Eight studies reported on mortality (16 392 patients; Figure 5).[3, 5, 7, 14, 21, 23-25] The study from Amini et al.[22] was excluded from this meta-analysis since it was overlapping with the larger study from Amini et al.[14]. There was a significant difference in mortality between EA and iv morphine patients (OR=0·69, 0·51 to 0·93; *P*=0·02). The absolute risk difference in mortality between EA (55/2 007=2·7 per cent) and iv morphine (600/14 331=4·2 per cent) patients was -1·5 per cent (-2 to 0; *P*=0·01).[3, 5, 7, 14, 23-25] Mungroop et al.[21] (EA *versus* CWI) and Sakowska et al.[24] (EA *versus* intrathecal morphine) showed no differences in mortality.

Risk of bias across studies

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

DISCUSSION

This systematic review and meta-analysis of analgesic techniques in patients undergoing pancreatoduodenectomy has several important outcomes. EA provided marginally lower pain scores on postoperative day 0 to 3 compared with iv morphine patients. Results of separate postoperative days showed lower pain scores in EA patients on postoperative days 1 and 2 compared with iv morphine. Treatment failure of EA occurred in 28·5 per cent of patients, mainly as a results of hemodynamic instability or inadequate pain control. Furthermore, there could be a benefit of EA over iv morphine regarding complications, pneumonia, length of hospital stay and mortality. The authors weakly recommend the use of EA over iv morphine as first choice for reducing early postoperative pain in eligible patients undergoing pancreatoduodenectomy. Also this review highlights the lack of evidence there is on analgesic techniques in patients undergoing pancreatoduodenectomy and emphasizes the need for further studies.

Adequate postoperative pain control is of paramount importance because it has been related to less complications and shorter length of hospital stay.[26, 27] The marginal difference in mean pain score (-0·50 on a 11-point Numerical Rating Scale) on postoperative day 0 to 3 between EA and iv morphine patients might be on itself of limited clinical relevance.[28] The largest difference in mean pain score (-1·08) was on postoperative day 1 in favor of EA and might be of more clinical relevance. There was no data available on patients reporting a pain score >4 (transition from mild to moderate pain) which could have been of more clinical relevance.[29] Unfortunately, also the important pain scores during mobilization were not widely reported in the included studies.[30] Furthermore, it is notable that only two studies used patient controlled EA, since patient controlled EA is associated with improved pain scores, patient satisfaction and safety parameters.[31, 32]

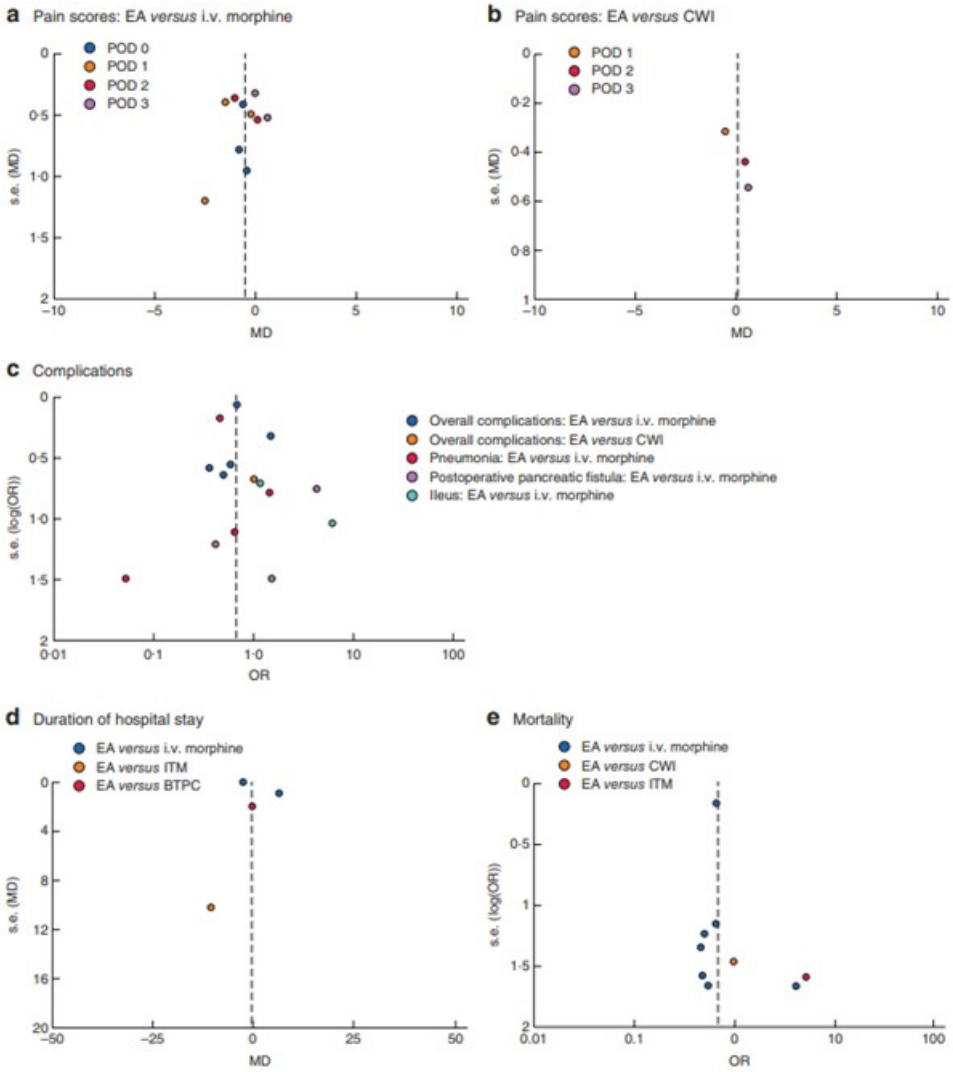

Figure 6. Funnel plots for all outcomes

Nevertheless, in concordance with recent RCTs in major abdominal surgery, the observed differences show that EA has a albeit marginal beneficial effect on pain scores during the first postoperative days compared to iv morphine.[33, 34] The included RCT from Mungroop et al.[21] (EA *versus* CWI) showed non-inferiority regarding pain scores and patient reported outcomes (i.e. Overall Benefit of Analgesia Score) in the subgroup analysis of patients undergoing pancreatoduodenectomy. Furthermore, a recent systematic review and meta-analysis showed improved recovery parameters and patient satisfaction in EA *versus* CWI in abdominal surgery patients and similar pain scores.[35] The included RCT

from Hutchins et al.[20] (EA *versus* BTPC) observed similar maximum pain scores, though this trial was designed to prove a 2-point difference in favor of BTPC.

Less complications occurred in EA compared to iv morphine patients in this study, which is in contrast with previous studies.[33, 34, 36, 37] In this study, solely Amini et al.[22] (EA *versus* iv morphine) reported significantly less complications in EA patients, which remained significant after adjustment for several factors. It remains unclear why results of different studies are contradicting. Treatment failure of EA has been associated with increased postoperative complications and occurred in 28·5 per cent of EA patients in this study.[5, 8, 23] Especially hemodynamic instability as reason for treatment failure is feared, since aggressive fluid therapy may cause pulmonary and anastomotic complications.[5, 23, 38] The authors believe careful patient selection and a dedicated and specialized team (including an Acute Pain Service team[39]) are pivotal for the success of all analgesic techniques.

The observation of a shorter length of hospital stay in EA compared to iv morphine patients was mainly based on the study of Amini et al.[22] conducted in the United States of America. National and hospital health care practices (i.e. discharge criteria) are of major influence on length of hospital stay, one can argue that this beneficial effect of EA on length of hospital stay is not easily generalizable to other clinical settings. A systematic review and meta-analysis of analgesia after abdominal surgery in an Enhanced Recovery After Surgery (ERAS) setting could not prove that EA is associated with a shorter length of hospital stay.[37] This will become more relevant since there is increasing interest in ERAS pathways in pancreatoduodenectomy.[40] Solely the included study from Mungroop et al.[21] specified whether an ERAS setting was used (no data on length of hospital stay). Hence, it cannot be concluded that EA after pancreatoduodenectomy is associated with a shorter length of hospital stay compared to other analgesic techniques.

This meta-analysis showed an absolute risk difference of -1·5 per cent (-2 to 0; P=0·01) on mortality of EA compared to iv morphine. A meta-analysis of RCTs (2 201 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 abdominal surgery patients in both studies. The only included study, Amini et al.[14], that showed lower mortality in EA patients did also perform adjusted analysis for potential confounders in their total cohort (pancreatic and liver resections) in which the beneficial effects of EA remained. As with the outcome overall complications in this study, the influence of residual confounding remains debatable. On the other hand, the analysis of overall complications and mortality showed no significant heterogeneity or publication bias.

This systematic review showed there are only few studies on analgesic techniques after pancreatoduodenectomy. Currently there are two ongoing RCTs: 1) Klotz et al.[43] comparing EA *versus* iv morphine will show whether analgesic technique influences the incidence of complications and mortality after pancreatoduodenectomy and 2) Pak et al.[44] will give insight in the postoperative opioid consumption of EA *versus* iv hydromophone patients after pancreatoduodenectomy. It will be interesting to see how the increasing use of minimally invasive surgery will influence indications for analgesic techniques.[45] Recent studies and experience within the authors region have shown encouraging results and benefits of sublingual sufentanil (non-invasive, rapid absorption and pain relief, and less side effects) over EA and iv morphine.[46-48] Therefore, the authors are conducting a RCT to compare EA *versus* 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) since this was the main source of risk of bias due to non-blinding. The studies from Amini et al.[22] (8 610 patients) and Amini et al.[14] (15 688 patients) were large and showed results in favor of EA which mainly determined the secondary outcomes of this meta-analysis. Third, inter-study differences in definitions of the outcomes (treatment failure of initial analgesia, postoperative pancreatic fistula and ileus) might have affected the results. However, the primary outcome (pain scores: all measured on a 11-point Numerical Rating Scale) and other secondary outcomes (overall complications, mortality) are fairly universal in definition. This study pooled data from an RCT (Marandola et al.[4]) and two cohort studies (Pratt et al.[5] and Shah et al.[25]) for estimation of the mean pain scores on postoperative day 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. And lastly, it is uncertain to what extent the inter-study differences regarding the pain score measurement (e.g. during rest/movement) and analgesic technique (e.g. type and composition of infusion) have influenced the results. To minimize the effect of analgesic technique differences, analysis were performed separately for each type of N-EA.

As a consequence of the risk of bias assessment and mentioned limitations, the evidence should be considered as 'low quality': future studies will have an important impact on the confidence in the evidence and will likely change the evidence. Also, the recommendations should be considered as 'weak': the 'low quality' evidence suggests that desirable and undesirable effects of individual analgesic techniques are in balance (GRADE criteria).[19] Therefore, caution has to be taken when drawing conclusions from this systematic review and meta-analysis.

Strengths of this systematic review and meta-analysis include registration of a predefined protocol, compliance to the PRISMA guidelines, two independent authors who performed the study selection, data extraction and assessment of risk of bias, attempts to contact corresponding authors to provide additional data, and grading of evidence according to the GRADE criteria. This systematic review and meta-analysis summarizes all currently available evidence on EA in patients undergoing pancreatoduodenectomy and analgesic and surgical outcomes.

Clinicians and patients should weigh the possible (marginal) desirable effects of EA (pain scores, complications, length of hospital stay and mortality) with the possible undesirable effects (treatment failure) in every patient, in which patient characteristics such as preoperative pain and opioid use, anticoagulant use and risk of venous thrombosis, cardiopulmonary conditions, inflammatory bowel diseases etc. should all be taken into account.

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SUPPLEMENTARY MATERIAL

Table S1. Reason for exclusion of full texts

Study	Reason for exclusion of full-text
Ahn et al.[1]	Wrong patient population
Aloia et al.[2]	Wrong patient population
Bjersa et al.[3]	Wrong indication
Brandsborg et al.[4]	Wrong intervention
Cyr et al.[5]	Wrong study design
Deng et al.[6]	Wrong intervention
Gastinger et al.[7]	Wrong intervention
Iliescu et al.[8]	Wrong patient population
Klotz et al.[9]	Wrong study design
Lee et al.[10]	Wrong comparator
Min et al.[11]	Wrong comparator
Nakashima et al.[12]	Wrong indication
Niraj et al.[13]	Wrong patient population
Robertson et al.[14]	Wrong patient population
Richardson et al.[15]	Wrong patient population
Rockemann et al.[16]	Wrong intervention
Sanford et al.[17]	Wrong patient population
Seeling et al.[18]	Wrong patient population
Seeling et al.[19]	Wrong patient population
Smith et al.[20]	Wrong study design
Soriano et al.[21]	Wrong intervention
Sugimoto et al.[22]	Wrong comparator
Thompson et al.[23]	Wrong intervention
Wichmann et al.[24]	Wrong intervention
Wu et al.[25]	Wrong patient population

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Table S2. Analgesic treatment protocols

	Epidural content				N-EA				
Reference	**Content**	**Protocol**	**Infusion**	**Removal of EA**	**Type**	**Content**	**Protocol**	**Infusion**	**Removal of N-EA**
Randomized controlled trials									
Marandola et al.[1]	Mepi, ropi, mor	3-mL mepi 20 mg/mL (test), 10-12 mL ropi 7.5 mg/mL + ropi (2 mg/mL) & mor (0.05 mg/mL) at an infusion rate of 5 mL/h.	CEI	NS	iv morphine	Mor	20 mg IV mor in 48 ml saline at 2ml/h	CI	NS
Mungroop et al.[2]	Bupi, sul	PCEA bupi 0·25% & sul 1 µg/mL before incision. Post-op PCEA bupi 0.125% and sul 1 µg/mL at 6 mL/h. CEI bupi 0.125% & sul 0.5 µg/mL at 0.1 mL/kg/h	PCEA/ CEI	POD 3	CWI	Bupi	30 mL bupi 0·25% (at start) + 30 mL bupi 0.25% at 12 mL/h	CWI	POD 3
Hutchins et al.[3]	Bupi, HM	epidural infusion consisted of bupivacaine 0.125% with hydromorphone 6 mcg/mL and was administered via a pump	CEI	POD 4	Paravertebral block	Lido, Epi	1–3 mL of 1.5% lidocaine with epinephrine	CI	POD 4
Cohort studies									
Pratt et al.[4]	Lido, epi, HM, bupi	1.5% lido + epi (test), 8 ml/h HM 20 µg/ml + bupi 0.1% 1mg/ml (n=105) or HM 20 µg/ml + bupi 0.1% 1mg/ml or local bupi 0.1% 1 mg/ml (n=11)	CEI	POD 4	iv morphine	Fen	Fen IV, PCA IV postop	PCA	>
Sakowskaet al.[5]	Ropi en Fen	Ropi 0.2% + Fen 2 µg/ml	NS	POD 5	ITM/iv morphine	Mor, Fen, Bupi	NS	ITM/PCA	NS
Choi et al.[6]	Bupi and HM or Bupi and Fen	(No standard regimen)	NS	POD 6	iv morphine	Mor or HM	(No standard regimen)	PCA	POD 6
Amini et al.[7]	Not specified	NS	NS	NS	Not EA#	NS	NS	NS	NS
Shah et al.[8]	Bupi, mor, HM	0.25% bupi & HM or mor	CEI	POD 3-5	iv morphine	NS	NS	PCA	POD 3–5

Table S2. Continued

Patel et al.[9]	Bupi, Fen, Bupi, PCM	0.1% Bupi and 2 µg/mL Fen, with 10 mL 0.25% Bupi + IV PCM 1 g every 6h	CEI	POD 3-4	iv morphine	Mor, Fen, PCM	0.25 mg/kg IV Mor and 2 µg/kg IV Fen, post-op IV Fen (initially 10-20 µg every 5 minutes IV + IV PCM 1g every 6h	PCA	NS
Axelrod et al.[10]	Bupi, Ropi, Lido, Mor, HM, Fen	0.125% Bupi, 0.2% Ropi or 1% Lido and 0.1 mg/ml Mor, 0.05 mg/ml HM and 10 µg/ml Fen	PCEA	NS	iv morphine	Mor, HM, Fen	0.1 mg/ml Mor, 0.05 mg/ml HM and 10 µg/ml Fen.	PCA	NS
Amini et al.[11]	NS	NS	NS	NS	Conventional analgesia#	NS	NS	NS	NS

Mepi: Mepivacaine, Ropi: Ropivacaine, Mor: morphine, Bupi: bupivacaine, Sul: sulfentanyl, Lido: lidocaine, epi: epinephrine, HM: hydromorphone, Fen: fentanyl, PCM: paracetamol, NS: not specified
#considered as iv morphine for analyses
>Until oral pain medication tolerate

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