Meta-analysis of epidural analgesia in patients undergoing pancreatoduodenectomy


* Both authors contributed equally and share first authorship

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, 0.61 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 pancreateoduodenectomy: 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. where patients in the N-EA group had a higher ASA.

The types of EA infusion were: patient-controlled (N=1), continuous infusion (N=5), patient-controlled and continuous infusion (N=1), no information regarding infusion (N=4), bilateral thoracic paravertebral catheters (BTPC) (N=1), iv morphine and intrathecal morphine (N=1), 'not EA' (N=1), and 'conventional analgesia' (N=1). In the two studies in which the N-EA protocol was 'not EA' or 'conventional analgesia' it was considered as iv morphine in the meta-analysis, since

**Figure 1.** PRISMA flow diagram for the review
### Table 1. Study characteristics

<table>
<thead>
<tr>
<th>Centre</th>
<th>Country</th>
<th>Inclusion period</th>
<th>No. of patients</th>
<th>ASA grade I-II</th>
<th>Epidural content</th>
<th>N-EA</th>
<th>Infusion</th>
<th>Removal of EA</th>
<th>Type</th>
<th>Removal of N-EA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCTs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marandola et al.</td>
<td>Single</td>
<td>USA</td>
<td>2002–2007</td>
<td>16 (40)</td>
<td>24 (60)</td>
<td>14 (88)</td>
<td>20 (83)</td>
<td>CEI</td>
<td>n.s.</td>
<td>i.v. morphine</td>
</tr>
<tr>
<td>Mungroop et al.</td>
<td>Multi</td>
<td>NL</td>
<td>2015</td>
<td>18 (50)</td>
<td>18 (50)</td>
<td>40 (85)</td>
<td>48 (87)</td>
<td>PCEA/CEI</td>
<td>POD 3</td>
<td>POD 3</td>
</tr>
<tr>
<td>Hutchins et al.</td>
<td>Multi</td>
<td>USA</td>
<td>2012–2015</td>
<td>23 (48)</td>
<td>25 (52)</td>
<td>0</td>
<td>0</td>
<td>CEI</td>
<td>POD 4</td>
<td>BTPC</td>
</tr>
<tr>
<td><strong>Cohort studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pratt et al.</td>
<td>Single</td>
<td>USA</td>
<td>2001–2007</td>
<td>185 (79.4)</td>
<td>48 (20.6)</td>
<td>85</td>
<td>(45.9)</td>
<td>CEI</td>
<td>POD 4</td>
<td>i.v. morphine</td>
</tr>
<tr>
<td>Sakowska et al.</td>
<td>Single</td>
<td>NZ</td>
<td>2005–2008</td>
<td>18 (44)</td>
<td>23 (56)</td>
<td>33 (65)</td>
<td>77 (78)</td>
<td>n.s.</td>
<td>POD 5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Choi and Schoeniger</td>
<td>Single</td>
<td>USA</td>
<td>2004–2007</td>
<td>18 (43)</td>
<td>24 (57)</td>
<td>–</td>
<td>–</td>
<td>n.s.</td>
<td>POD 6</td>
<td>i.v. morphine</td>
</tr>
<tr>
<td>Amini et al.</td>
<td>Multi</td>
<td>USA</td>
<td>2009</td>
<td>947 (11.0)</td>
<td>7663 (89.0)</td>
<td>–</td>
<td>–</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Shah et al.</td>
<td>Multi</td>
<td>USA</td>
<td>2007–2011</td>
<td>87 (85.3)</td>
<td>15 (14.7)</td>
<td>18 (21)</td>
<td>3 (20)</td>
<td>CEI</td>
<td>POD 3–5</td>
<td>i.v. morphine</td>
</tr>
<tr>
<td>Axelrod et al.</td>
<td>Single</td>
<td>USA</td>
<td>2007–2011</td>
<td>149 (91.4)</td>
<td>14 (8.6)</td>
<td>–</td>
<td>–</td>
<td>PCEA</td>
<td>n.s.</td>
<td>i.v. morphine</td>
</tr>
<tr>
<td>Amini et al.</td>
<td>Multi</td>
<td>USA</td>
<td>2001–2012</td>
<td>1476 (9.4)</td>
<td>14212 (90.6)</td>
<td>–</td>
<td>–</td>
<td>n.s.</td>
<td>n.s.</td>
<td>Conventional analgesia</td>
</tr>
</tbody>
</table>
### Table 2. Risk of bias for RCTs according to the Cochrane Collaboration tool

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessments</th>
<th>Incomplete outcomes data</th>
<th>Selective reporting</th>
<th>Other bias</th>
<th>AHRQ standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marandola et al. 4</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Poor</td>
</tr>
<tr>
<td>Mungroop et al. 21</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Fair</td>
</tr>
<tr>
<td>Hutchins et al. 20</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Fair</td>
</tr>
</tbody>
</table>

### Table 3. Risk of bias for cohort studies according to the ROBINS-I tool

<table>
<thead>
<tr>
<th>Study</th>
<th>Confounding</th>
<th>Selection of participants</th>
<th>Classification of intervention</th>
<th>Deviations of intended interventions</th>
<th>Missing data</th>
<th>Measurement of outcomes</th>
<th>Selection of reported results</th>
<th>Overall risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pratt et al. 5</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Serious</td>
<td>Moderate</td>
<td>Serious</td>
</tr>
<tr>
<td>Sakowska et al. 24</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Choi and Schoeniger 3</td>
<td>Serious</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Serious</td>
<td>Moderate</td>
<td>Serious</td>
</tr>
<tr>
<td>Amini et al. 14</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Shah et al. 25</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Serious</td>
<td>Moderate</td>
<td>Serious</td>
</tr>
<tr>
<td>Patel et al. 7</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Axelrod et al. 23</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Amini et al. 14</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
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.\textsuperscript{21}, Shah et al.\textsuperscript{25}, and Hutchins et al.\textsuperscript{20}) provided additional unpublished data at request of the authors.

**Risk of bias within studies**

The RCT from Marandola et al.\textsuperscript{4} was judged as Poor quality, mostly due to unclear quality statements. In the RCTs from Mungroop et al.\textsuperscript{21} and Hutchins et al.\textsuperscript{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\textsuperscript{3, 5, 25} and five as a moderate\textsuperscript{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).\textsuperscript{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)).\textsuperscript{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; \(P=0.07\))\textsuperscript{4, 5, 25}, but a statistically significant difference on postoperative day 1 (MD=-1.08, -1.66 to -0.50; \(P<0.001\))\textsuperscript{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; \(P=0.05\))\textsuperscript{5, 25}, whereas on postoperative days 3 there was no difference (MD=0.16, -0.36 to 0.69; \(P=0.54\))\textsuperscript{5, 25}. In addition, Choi et al.\textsuperscript{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)).\textsuperscript{21} Also the analysis of separate postoperative day showed similar mean pain scores.

Hutchins et al.\textsuperscript{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). 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 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. In addition, Hutchins et al. 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.

Complications
Six studies reported on overall complications (9 150 patients; Figure 3). 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) Mungroop et al. 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). 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).

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

Length of hospital stay
Four studies reported on length of hospital stay (8 928 patients; Figure 4). 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 (I²=99 per cent; P<0·001). Between EA and intrathecal morphine or BTPC patients 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). The study from Amini et al. was excluded from this meta-analysis since it was overlapping with the larger study from Amini et al. 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 (55/2007=2.7 per cent) and iv morphine (600/14331=4.2 per cent) patients was -1.5 per cent (-2 to 0; P=0.01). Mungroop et al. (EA versus CWI) and Sakowska et al. (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 result 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. 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 of limited clinical relevance. 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. Unfortunately, also the important pain scores during mobilization were not widely reported in the included studies. 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.
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.\textsuperscript{20} (EA \textit{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.\textsuperscript{33, 34, 36, 37} In this study, solely Amini et al.\textsuperscript{22} (EA \textit{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.\textsuperscript{5, 8, 23} Especially hemodynamic instability as reason for treatment failure is feared, since aggressive fluid therapy may cause pulmonary and anastomotic complications.\textsuperscript{5, 13, 38} The authors believe careful patient selection and a dedicated and specialized team (including an Acute Pain Service team)\textsuperscript{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.\textsuperscript{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.\textsuperscript{37} This will become more relevant since there is increasing interest in ERAS pathways in pancreatoduodenectomy.\textsuperscript{40} Solely the included study from Mungroop et al.\textsuperscript{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)\textsuperscript{41} and a national cohort study (259 037 patients)\textsuperscript{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.\textsuperscript{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.\textsuperscript{43} comparing EA \textit{versus} iv morphine will show whether analgesic technique influences the incidence of complications and mortality after pancreatoduodenectomy and 2) Pak et al.\textsuperscript{44} will give insight in the postoperative opioid consumption of EA \textit{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.\textsuperscript{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.\textsuperscript{46-48} Therefore, the authors are conducting a RCT to compare EA \textit{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.\textsuperscript{22} (8 610 patients) and Amini et al.\textsuperscript{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.\textsuperscript{4}) and two cohort studies (Pratt et al.\textsuperscript{5} and Shah et al.\textsuperscript{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).\textsuperscript{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.
REFERENCES


### SUPPLEMENTARY MATERIAL

**Table S1.** Reason for exclusion of full texts

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


<table>
<thead>
<tr>
<th>Reference</th>
<th>Content</th>
<th>Protocol</th>
<th>Infusion Content</th>
<th>Removal Type</th>
<th>Infusion of N-EA</th>
<th>N-EA Type</th>
<th>Content</th>
<th>Protocol</th>
<th>Infusion Content</th>
<th>Removal of N-EA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized controlled trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marandola et al.¹</td>
<td>Mepi, ropi, mor</td>
<td>3-mL mepi 20 mg/mL (test), 10-12 mL ropi 7.5 mg/mL + ropi (2 mg/mL) &amp; mor (0.05 mg/mL) at an infusion rate of 5 mL/h.</td>
<td>CEI</td>
<td>NS</td>
<td>iv morphine</td>
<td>Mor</td>
<td>20 mg IV mor in 48 mL saline at 2 mL/h</td>
<td>CI</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mungroop et al.²</td>
<td>Bupi, sul</td>
<td>PCEA bupi 0.25% &amp; 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% &amp; sul 0.5 µg/mL at 0.1 mL/kg/h</td>
<td>PCEA/CEI</td>
<td>POD 3</td>
<td>CWI</td>
<td>Bupi</td>
<td>30 mL bupi 0.25% (at start) + 30 mL bupi 0.25% at 12 mL/h</td>
<td>CWI</td>
<td>POD 3</td>
<td></td>
</tr>
<tr>
<td>Hutchins et al.³</td>
<td>Bupi, HM</td>
<td>Epidural infusion consisted of bupivacaine 0.125% with hydromorphone 6 mcg/mL and was administered via a pump</td>
<td>CEI</td>
<td>POD 4</td>
<td>Paravertebral block</td>
<td>Lido, Epi</td>
<td>1–3 mL of 1.5% lidocaine with epinephrine</td>
<td>CI</td>
<td>POD 4</td>
<td></td>
</tr>
<tr>
<td><strong>Cohort studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pratt et al.⁴</td>
<td>Lido, epi, HM, bupi</td>
<td>1.5% lido + epi (test), 8 ml/h HM 20 µg/ml + bupi 0.1% 1 mg/ml (n=105) or HM 20 µg/ml + bupi 0.1% 1 mg/ml or local bupi 0.1% 1 mg/ml (n=11)</td>
<td>CEI</td>
<td>POD 4</td>
<td>iv morphine</td>
<td>Fen</td>
<td>Fen IV, PCA IV postop</td>
<td>PCA</td>
<td>&gt;</td>
<td></td>
</tr>
<tr>
<td>Sakowskaet al.⁵</td>
<td>Ropi en Fen</td>
<td>Ropi 0.2% + Fen 2 µg/mL</td>
<td>NS</td>
<td>POD 5</td>
<td>ITM/iv morphine</td>
<td>Mor, Fen, Bupi</td>
<td>NS</td>
<td>ITM/PCA</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Choi et al.⁶</td>
<td>Bupi and HM or Bupi and Fen</td>
<td>(No standard regimen)</td>
<td>NS</td>
<td>POD 6</td>
<td>iv morphine</td>
<td>Mor or HM</td>
<td>(No standard regimen)</td>
<td>PCA</td>
<td>POD 6</td>
<td></td>
</tr>
<tr>
<td>Amini et al.⁷</td>
<td>Not specified</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>Not EA#</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Shah et al.⁸</td>
<td>Bupi, mor, HM</td>
<td>0.25% bupi &amp; HM or mor</td>
<td>CEI</td>
<td>POD 3–5</td>
<td>iv morphine</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>PCA</td>
<td>POD 3–5</td>
</tr>
<tr>
<td>Study</td>
<td>Anesthesia Type</td>
<td>Solution Details</td>
<td>Pain Management</td>
<td>Device</td>
<td>Delivery</td>
<td>Notes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>-----------------------</td>
<td>--------</td>
<td>----------</td>
<td>-----------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patel et al.</td>
<td>CEI</td>
<td>0.1% Bupi and 2 µg/mL Fen, with 10 mL 0.25% Bupi + IV PCM 1 g every 6h</td>
<td>POD 3-4 iv morphine</td>
<td>PCA</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axelrod et al.</td>
<td>PCEA</td>
<td>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</td>
<td>NS iv morphine</td>
<td>PCA</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amini et al.</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>Conventional analgesia#</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


#considered as iv morphine for analyses

>Until oral pain medication tolerated
REFERENCES


Chapter 13 - Meta-analysis of epidural analgesia in patients undergoing pancreaticoduodenectomy