Impact of Epidural Analgesia on Mortality and Morbidity After Surgery

Systematic Review and Meta-analysis of Randomized Controlled Trials

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Objective: To quantify benefit and harm of epidural analgesia, compared with systemic opioid analgesia, in adults having surgery under general anesthesia.

Background: It remains controversial whether adding epidural analgesia to general anesthesia decreases postoperative morbidity and mortality.

Methods: We searched CENTRAL, EMBASE, PubMed, CINAHL, and BIOSIS till July 2012. We included randomized controlled trials comparing epidural analgesia (with local anesthetics, lasting for ≥24 hours postoperatively) with systemic analgesia in adults having surgery under general anesthesia, and reporting on mortality or any morbidity endpoint.

Results: A total of 125 trials (9044 patients, 4525 received epidural analgesia) were eligible. In 10 trials (2201 patients; 87 deaths), reporting on mortality as a primary or secondary endpoint, the risk of death was decreased with epidural analgesia (3.1% vs 4.9%; odds ratio, 0.60; 95% confidence interval, 0.39–0.93). Epidural analgesia significantly decreased the risk of atrial fibrillation, supraventricular tachycardia, deep vein thrombosis, respiratory depression, atelectasis, pneumonia, ileus, and postoperative nausea and vomiting, and also improved recovery of bowel function, but significantly increased the risk of arterial hypotension, pruritus, urinary retention, and motor blockade. Technical failures occurred in 6.1% of patients.

Conclusions: In adults having surgery under general anesthesia, concomitant epidural analgesia reduces postoperative mortality and improves a multitude of cardiovascular, respiratory, and gastrointestinal morbidity endpoints compared with patients receiving systemic analgesia. Because adverse effects and technical failures cannot be ruled out, individual risk–benefit analyses and professional care are recommended.

Keywords: epidural analgesia, mortality, morbidity, perioperative

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Epidural analgesia has gained increasing popularity since its implementation in the early fifties and is nowadays regarded as the gold standard analgesic technique in patients undergoing some types of major surgery.[1] It is well established that epidural analgesia is superior to systemic opioid analgesia for the control of postoperative pain.[2,3] However, there remain considerable uncertainties concerning further benefits that go beyond pain relief and also concerning the potential for harm with epidural analgesia. The fear of neurologic complications may have even led to a decline in its clinical use.[4] Whether epidural analgesia has a beneficial effect on postoperative mortality and morbidity, and what patients may actually benefit from it, has been one of the most contentious issues in perioperative medicine over the past decades.

Meta-analyses have tried to clarify the role of epidural analgesia in surgical patients. Most concentrated on a particular endpoint or a specific group of patients. For instance, it was shown that epidural analgesia reduced the incidence of venous thrombosis in patients undergoing orthopedic surgery.[5] One analysis has suggested that epidural analgesia may reduce the risk of cardiac events in patients undergoing vascular surgery.[6] Other analyses reported on the beneficial effect of epidural analgesia on pulmonary outcomes,[7–9] or concentrated on patients undergoing cardiac surgery.[10,11] Finally, one large analysis that was published 13 years ago concluded that neuraxial blockade (including both epidural and intrathecal techniques) reduced postoperative mortality and the incidence of major complications, including myocardial infarction, renal failure, deep vein thrombosis, transfusion requirements, and respiratory depression.[12] However, the conclusions of that analysis remained contentious since data from very diverse epidural and intrathecal analgesia regimens were included, and patients underwent minor or major surgeries, with or without a concomitant general anesthetic.[13]

The aim of this study was to systematically assess the impact of concomitant epidural analgesia, compared with systemic standard care analgesia, on mortality and morbidity in adults having surgery under general anesthesia.

METHODS

The reporting of this systematic review follows the recommendation of the PRISMA statement.[14] The protocol was submitted to the National Ministry of Education and Research, Germany, which funded the research (Grant No. 01KG1107).

Study Selection

We searched in MEDLINE, EMBASE, CENTRAL, BIOSIS, and CINAHL using a high-sensitivity and low-specificity search strategy. Key words (eg, epidural, peridural, random, general, anesthesia, and analgesia) were combined using the Boolean meanings of "OR" and "AND" (Supplementary Table A, Supplemental Digital Content Table A, available at http://links.lww.com/SLA/A465). The last electronic search was in July 2012. Bibliographies of retrieved articles

were checked for additional references. No language restriction was applied.

Abstracts were screened by 2 authors independently (DMP, MW). If there was any doubt concerning their eligibility, the full text was retrieved. All retrieved articles were then reviewed for inclusion by one author (DMP) and checked by the other (MW); queries were resolved through discussion with 2 other authors (NE, EM). Reports were screened for inclusion according to titles and abstracts. Potentially eligible reports that were published in languages other than English, German, or French were translated into English for further evaluation.

Inclusion Criteria

We included randomized controlled trials that compared epidural analgesia (experimental intervention) with systemic standard care analgesia (control intervention) in adults (≥18 years) undergoing general anesthesia for surgery.

There were 5 pre-hoc decisions for eligibility. First, epidural analgesia regimens had to start preoperatively, intraoperatively, or immediately postoperatively. Second, epidural analgesia had to be maintained postoperatively for at least 24 hours. Third, the epidural regimen had to include a local anesthetic.[15–17] Fourth, control patients had to receive systemic opioids postoperatively, either on demand or through a patient-controlled analgesia device; nonopioid adjuvants (for instance, nonsteroidal anti-inflammatory drugs or acetaminophen) could be added to the opioids. And fifth, the trials reported data on mortality, any morbidity endpoints, or epidural analgesia-related adverse effects.

Exclusion Criteria

Exclusion criteria were non- or quasirandomized trials, and trials with additional regional anesthesia techniques (for instance, intercostal nerve blocks). To overcome a random play of chance on estimation of treatment effects, studies with fewer than 10 participants per group were excluded.[18,19]

Data Extraction and Outcome Definitions

One author (DMP) extracted all relevant information from the original reports and entered the data into a tabulated electronic form that was designed by the authors for the purpose of this analysis. The other author (MW) checked the extracted data. Discrepancies were resolved by discussion with 2 other authors (NE, MRT).

The primary endpoint was mortality. Mortality was considered as any reported death irrespective of its cause. Data on mortality were extracted as the cumulative number of patients who died during the follow-up period. We made no assumptions regarding the presence or absence of deaths. We performed 3 sensitivity analyses of the impact of epidural analgesia on mortality. First, we analyzed mortality data exclusively when they were reported as a primary or a secondary endpoint of the study. Second, we analyzed all published mortality data. And finally, we analyzed any mortality data, published or unpublished. Unpublished data were sought through contact with authors.

Secondary endpoints were any dichotomous or continuous morbidity outcomes as reported in the original trials. Authors were contacted and asked for supplemental relevant information, for instance, on the exact time point of deaths, or additional information on morbidity outcomes that had potentially been studied but not reported.

Risk of Bias in Individual Studies

For each included trial, an assessment of the quality of data reporting was applied using a modified 4-item, 8-point Oxford scale, taking into account the method of randomization (0–2 points), concealment of treatment allocation (0–1), degree of blinding (0–3; 1 point each was given for the blinding of patients, caregivers, and assessors), and reporting of dropouts (0–2), as previously described.[20] The minimal score of an included randomized trial was 1. One author (DMP) performed the primary classification, which was checked by another author (MW). Discrepancies were resolved by discussion with 2 other authors (NE, MRT). Studies were classified as "low quality" if the combined Oxford score was less than the median of all scores, and as "high quality" if it was equal or higher than the median.

Statistical Analysis

As with previous similar analyses, there was an arbitrary decision that meta-analyses would be performed only when data could be combined from at least 5 trials or at least 100 patients.[21,22]

Dichotomous data were extracted as reported in the original trials, and odds ratios (ORs) with 95% confidence intervals (CIs) were computed at the study level and combined using the method by Peto and colleagues.[23] For statistically significant results, we computed numbers needed to treat (NNT) for benefit and numbers needed to harm (NNH) for adverse effects, both with 95% CI. Continuous data were extracted as means and standard deviations as reported in the original trials. Mean differences were computed at the study level and pooled into weighted (according to the inverse of the reported variance) mean differences with 95% CI. When continuous data were not reported as means with standard deviations, we contacted the authors to obtain this information. If this request was unsuccessful, we computed the data, whenever feasible, as previously proposed.[24,25]

We used a fixed-effect model if the formal test for heterogeneity did not reach statistical significance. Because heterogeneity tests have low power to detect heterogeneity, we chose a 10% cutoff for statistical significance. When the data were shown to be heterogeneous, we searched for sources of heterogeneity. When none was found, a random effects model was applied. Because the impact of epidural analgesia on mortality may be different according to settings (eg, different surgeries), we reanalyzed homogenous data using a random effects model to allow for a potential effect modification.

A cumulative meta-analysis of mortality data was performed using the Peto method according to increasing years of publication. Only those trials that reported on at least one death were included into the cumulative meta-analysis.

To account for the impact of different durations of follow-up periods on mortality, a Kaplan-Meier survival analysis was used. For this purpose we created a virtual database with individual patient data. For each of the studies, we entered for each patient the following information into the database: (1) time of entry into the study (considered 0 for all patients); (2) time of exit from the study (maximum duration of follow-up for survivors or exact times of death); and (3) status at the time of exit (dead or alive). When exact times of deaths were reported, we used them. When exact times of deaths were not reported, authors were contacted to provide these data. If this request remained unsuccessful, the time of death was modeled according to 3 scenarios: (1) deaths occurred at the beginning of the reported follow-up period of the study; (2) deaths occurred in the middle of the follow-up period; and (3) deaths occurred at the end of the follow-up period.

Additional Analyses

There was an intention to perform various sensitivity analyses to test for the robustness of the mortality results. For instance, we planned to test for the impact of the epidural regimen (level of insertion, drugs used), type of surgery, and quality of the trials. We aimed to test for the impact of the age of the trials on mortality as previous similar analyses have shown a more pronounced beneficial

effect of epidural analgesia on pulmonary outcomes in older trials.[9] For that purpose, odds of death were displayed according to year of publication for control and experimental groups to check graphically for a trend of increasing or decreasing mortality over time. We used an unweighted linear regression model to formally test the hypothesis of a linear association between odds of death and year of publication considered as a continuous variable. If the 95% CI of the coefficient for the variable "year" included 1, the association was considered nonsignificant. We intended to assess the impact of outliers (ie, trials that reported on unusually high mortality rates, on the overall result). Finally, publication bias was assessed by the means of a funnel plot displaying ORs of mortality versus sample sizes.

Analyses were performed using RevMan (Computer Program, version 5.0.25, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, Denmark), Microsoft Excel 12.3.5 for Mac, and STATA 9 (version 9, STATA Corp, College Station, TX).

RESULTS

Study Selection

We retrieved 294 articles for detailed evaluation (Fig. 1). Of those, 169 were subsequently excluded. Nine articles were published at least twice; for each cluster, we considered the report original if that provided the most relevant and complete information for the purpose of this analysis,[26–33] and excluded the duplicate.[34–43] One article was not available through interlibrary loan.[44]

We eventually included 125 trials involving 9044 patients, of whom 4525 received epidural analgesia (Supplementary Table B, Supplemental Digital Content Table B, available at http://links.lww.com/SLA/A466).[16,26–33,36,45–159] Affiliations of the authors of 106 trials were available. They were contacted for additional information; 42 responded to our inquiry (response rate, 39.6%) and provided useful information on various endpoints from 2495 patients that could be included into our analyses.

Description of Studies

The trials were published between 1971 and 2011. The median quality score was 3 (range, 1–7). Patients underwent a variety of surgeries: thoracic (47 trials), abdominal (48), vascular (10), gynecologic or urologic (9), and orthopedic (7). Four trials included different surgical interventions.

In 124 trials, median duration of postoperative follow-up was 8 days (range, 1–730); in one trial, it was 12 to 15 years.[88] The long-term follow-up of 1 large trial was not considered because it concentrated on a subgroup of cancer patients.[160]

In experimental groups, the epidural regimen was administered continuously (117 trials) or intermittently (8 trials). Local anesthetics were bupivacaine (94 trials), ropivacaine (28 trials), lidocaine (2 trials), or not specified (1 trial). In 91 trials, an opioid was added to the epidural local anesthetic: fentanyl (43 trials), sufentanil (22 trials), morphine (22 trials), meperidine (2 trials), hydromorphone (1 trial), or diamorphine (1 trial). Insertion of the epidural catheter was thoracic in 103 trials [median, Th7 (range, 1–12)], lumbar in 19 trials [median, L3 (range, 1–3)], and cervical in 2 trials (both C7). The median duration of epidural analgesia was 2 days (range, 1–6).

In control groups, patients received 1 of 13 different systemic opioids: morphine (76 trials), piritramide (17 trials), fentanyl (6 trials), oxycodone (4 trials), meperidine or tramadol (3 trials each), diamorphine, pentazocine, ketobemidone or nicomorphine (2 trials each), and buprenorphine, hydromorphone, or sufentanil (1 trial each). Five trials did not provide details on the opioids

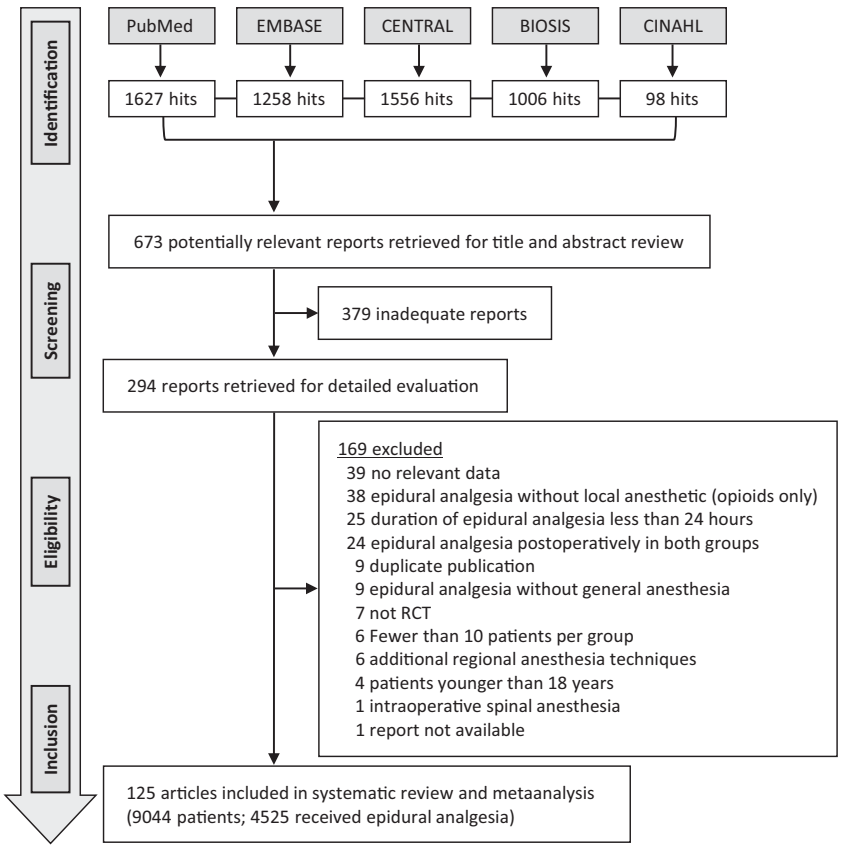

FIGURE 1. Process of study selection. "Inadequate reports" indicate study subject other than epidural analgesia in surgical patients; RCT, randomized controlled trial.

used. In 63 of the 125 (50.4%) trials, opioids were administered intravenously using a patient-controlled analgesia device.

In the experimental groups, patients received minimal to no systemic opioids postoperatively. In 47 trials (37.6%), no information was provided on additional opioids in the experimental group. In a further 47 trials (37.6%), it was stated that any need for opioids because of insufficient epidural analgesia was regarded as an exclusion criterion, or it was specified that none of the patients who were randomized to epidural analgesia received additional opioids for rescue. Finally, in 31 trials (24.8%), patients in the experimental group had access to rescue opioid treatment.

In 51 trials, patients of both experimental and control groups received nonopioid adjuvants concomitantly, and in a controlled manner, for instance, nonsteroidal anti-inflammatory drugs (23 trials), paracetamol (20 trials), or both (8 trials).

SYNTHESIS OF RESULTS

Mortality

Ten trials (2201 patients) provided information on mortality as the primary or secondary endpoint of the study.[36,52,54,75,84,95,112,122,142,154] There were 87 deaths; 35 in 1138 patients receiving epidural analgesia (average mortality rate, 3.1%) and 52 (4.9%) in 1063 controls (OR, 0.60; 95% CI, 0.39–0.93; NNT, 56; 95% CI, 29–565) (Fig. 2). Data were homogeneous ($P = 0.44$; $I^2 = 0\%$).

Seventy-three trials reported on 66 additional deaths, although in these trials, postoperative mortality was not a primary or secondary endpoint.

In all 83 trials that reported on perioperative mortality, there were 153 deaths; 68 in 3911 patients receiving epidural analgesia (average mortality rate, 1.7%) and 85 (2.2%) in 3855 controls (OR, 0.75; 95% CI, 0.54–1.04) (Fig. 2). The data were homogenous ($P = 0.66$; $I^2 = 0\%$).

Through contact with authors, we gathered additional information on 49 unpublished deaths from 7 trials.[65,76,88,116,117,145,146] Thirty-three deaths alone were from 1 trial with a follow-up of 12 to 15 years.[88] Thus, when all mortality data were considered, both published and unpublished, there were 202 deaths; 80 in 3911 patients receiving epidural analgesia (average mortality rate, 2.0%) and 122 (3.2%) in 3855 controls (OR, 0.69; 95% CI, 0.51–0.92; NNT, 90; 95% CI, 55–244) (Supplementary Fig. A, Supplemental Digital Content Fig. A, available at http://links.lww.com/SLA/A467). The data were homogenous ($P = 0.76$; $I^2 = 0\%$). The funnel plot using data of all published and unpublished 202 deaths was symmetrical (Supplementary Fig. B, Supplemental Digital Content Fig. B, available at http://links.lww.com/SLA/A468).

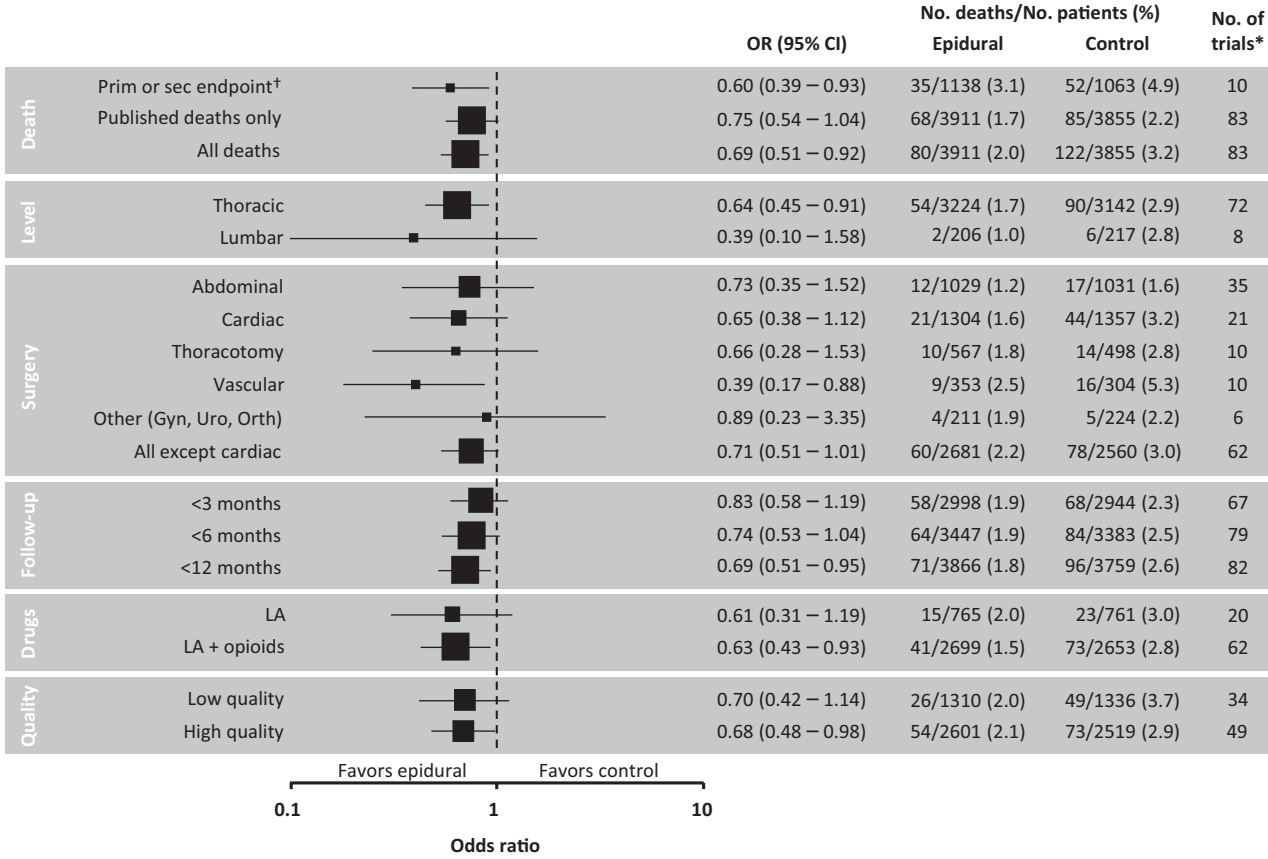

FIGURE 2. Mortality sensitivity analysis. *Cumulative numbers of trials may not add up because some trials that reported on mortality did not provide the necessary information for sensitivity analyses. †Death was the primary or secondary endpoint of the study. Gyn indicates gynecologic surgery; high quality, Oxford scale 3 to 7 (ie, equal or higher than the median of all trials); LA, local anesthetic; low quality, Oxford scale 1 to 2 (ie, less than the median of all trials); Orth, orthopedic surgery; Uro, urologic surgery.

There was graphical evidence that death rates in patients receiving epidural analgesia and in controls receiving standard care analgesia have remained stable between 1980 and 2011 (Supplementary Fig. C, Supplemental Digital Content Fig. C, available at http://links.lww.com/SLA/A469).

The beneficial effect on mortality became statistically significant in 2001 with a cumulative number of 2278 randomized patients, and has remained consistently significant since 2003 and a cumulative number of 4135 randomized patients (Fig. 3).

One hundred forty-seven deaths (72.8% of all deaths, published and unpublished) occurred during the first 2 months postoperatively. Kaplan-Meier survival estimates were significantly different in patients with epidural analgesia compared with patients receiving systemic analgesia (log-rank test $P = 0.029$) (Supplementary Fig. D, Supplemental Digital Content Fig. D, available at http://links.lww.com/SLA/A470). This result was independent of the scenario that was chosen to define the time points of deaths.

Mortality Sensitivity Analyses

The beneficial effect of epidural analgesia on mortality was robust across various sensitivity analyses (Fig. 2). The level of catheter insertion (lumbar vs thoracic), type of surgery, epidural regimens, or quality of data reporting had no impact on the association between epidural analgesia and mortality. Similarly, the duration of follow-up of trials, or the inclusion of unpublished deaths, did not change the result significantly.

Mortality results of some trials were based on mainly coronary surgery patients. We therefore performed an additional sensitivity analysis for mortality benefits in all noncardiac patients. The OR for mortality in noncardiac patients was 0.71 (95% CI, 0.51–1.01).

For the majority of trials, death rates were below 10% (Supplementary Fig. E, Supplemental Digital Content Fig. E, available at http://links.lww.com/SLA/A471). There were 3 obvious outliers.[88,145,154] The first was from the United States and was one of the oldest trials; it reported on a 0% death rate with epidural analgesia but a 16% death rate in controls.[154] That trial provided information on mortality as a primary endpoint. Excluding that trial from the main mortality analysis (that included all 10 trials with mortality as a primary endpoint) resulted in an OR of 0.66 (95% CI, 0.42–1.02). The second outlier was from Sweden and reported on cumulative death rates of 17.8% with epidural analgesia and 26.0% with systemic analgesia after a 12 to 15 years of follow-up period.[88] The third was from Lithuania; the death rate was 22.7% with epidural analgesia and was 27.8% with systemic analgesia.[145] Because these 3 outliers may have had undue weight on the overall result of mortality, we excluded them in a further sensitivity analysis. There remained 68 deaths in 3820 patients receiving epidural analgesia (average, 1.8%) and 88 deaths in 3716 controls (average, 2.4%); the OR moved toward unity and the upper limit of the 95% CI was 1 (OR, 0.73; 95% CI, 0.53–1.00).

Morbidity

Epidural analgesia significantly decreased the odds of various cardiovascular morbidity endpoints (Fig. 4): atrial fibrillation (OR, 0.63; 95% CI, 0.49–0.82; NNT, 12; 95% CI, 7.7–26), supraventricular tachycardia (OR, 0.69; 95% CI, 0.55–0.87; NNT, 19; 95% CI, 11–57). Similarly, the risk of pulmonary morbidity endpoints was reduced with epidural analgesia: respiratory depression (OR, 0.61; 95% CI, 0.39–0.93; NNT, 68; 95% CI, 40–225), atelectasis (OR, 0.67; 95% CI, 0.48–0.93; NNT, 22; 95% CI, 12–103), pneumonia (OR, 0.56; 95% CI, 0.45–0.70; NNT, 25; 95% CI, 18–39). Finally, epidural analgesia had beneficial effects on gastrointestinal symptoms: decreased incidence of ileus (OR, 0.43; 95% CI, 0.21–0.88; NNT, 21; 95% CI, 11–107) and of postoperative nausea and vomiting (OR, 0.76; 95% CI, 0.58–0.99; NNT, 15; 95% CI, 8.6–53). Also, epidural analgesia accelerated return to normal bowel function (Supplementary Fig. F, Supplemental Digital Content Fig. F, available at http://links.lww.com/SLA/A472).

Reporting of intraoperative blood loss was inconsistent as there was no common definition of this endpoint. When these data were combined, there was no significant difference in intraoperative blood loss between patients receiving epidural analgesia compared with controls; mean difference was −66.7 mL (95% CI, −184.1–50.7 mL). There was no significant difference either in the need for intra- or postoperative transfusion between epidural analgesia and control (Fig. 4).

Adverse Effects

Epidural analgesia increased the odds of pruritus (when epidural opioids were used) (OR, 1.47; 95% CI, 1.15–1.88; NNH, 21; 95% CI, 13–53), urinary retention (OR, 1.60; 95% CI, 1.02–2.51; NNH, 25; 95% CI, 13–444), and motor blockade (OR, 12.7; 95% CI, 5.26–30.5; NNH, 14, 95% CI, 11–19) (Fig. 4).

The odds of arterial hypotension was also increased with epidural analgesia (Fig. 4). As we may assume that this adverse effect is mainly due to the local anesthetic, we performed a sensitivity analysis comparing hypotension with regimens that contained a local anesthetic alone with regimens that contained a combination of a local anesthetic with an opioid. In 5 trials, only local anesthetics were administered; the incidence of hypotension with epidural analgesia was 20.7% (23 of 111) and in controls was 1.7% (2 of 119) (OR, 9.94; 95% CI, 3.17–31.19; NNH, 6; 95% CI, 4–9). In 20 trials, opioids were administered concomitantly with the local anesthetic; the incidence of hypotension with epidural analgesia was 8.9% (73 of 820) and in controls was 2.3% (18 of 785) (OR, 4.19; 95% CI, 2.53–6.94; NNH, 16; 95% CI, 11–23).

Technical failures with epidural analgesia occurred in 6.1% of patients. No technical failures (for instance, of patient-controlled analgesia devices) were reported in control patients. None of the trials reported on cases of severe neurologic complications because of epidural hematoma or abscess, meningitis, or direct traumatic spinal cord injury.

DISCUSSION

This systematic review aimed to test whether epidural analgesia—added to a general anesthetic in patients undergoing surgery, and compared with systemic, opioid-based standard care analgesia—provided any beneficial effect that goes beyond pain relief alone. There were 4 main findings. First, epidural analgesia was associated with a reduced risk of postoperative mortality. The strength of the association was clinically relevant and ranged from a statistically significant decrease in the odds of death of 40% to a borderline significant decrease in the odds of 25%, depending on the trials that were included. The NNT suggested that about 60 patients undergoing major surgery with a general anesthetic needed to receive a concomitant epidural analgesia for 1 additional death to be prevented, which would have occurred had they all received systemic opioid-based analgesia. Second, epidural analgesia had a beneficial effect on various major cardiovascular and pulmonary complications, and also on gastrointestinal symptoms. Third, typical adverse effects were arterial hypotension, pruritus, urinary retention, and motor blockade. And finally, there were no reports of severe neurologic complications because of hematoma, infection, or trauma.

Our study has several strengths. Contrary to previously published similar meta-analyses,[12,56] we concentrated on one, clearly defined locoregional anesthetic technique, and we aimed to provide an exhaustive quantitative overview of all beneficial and harmful effects that can be expected when epidural analgesia is added to a general anesthetic. Only trials testing an epidural regimen that

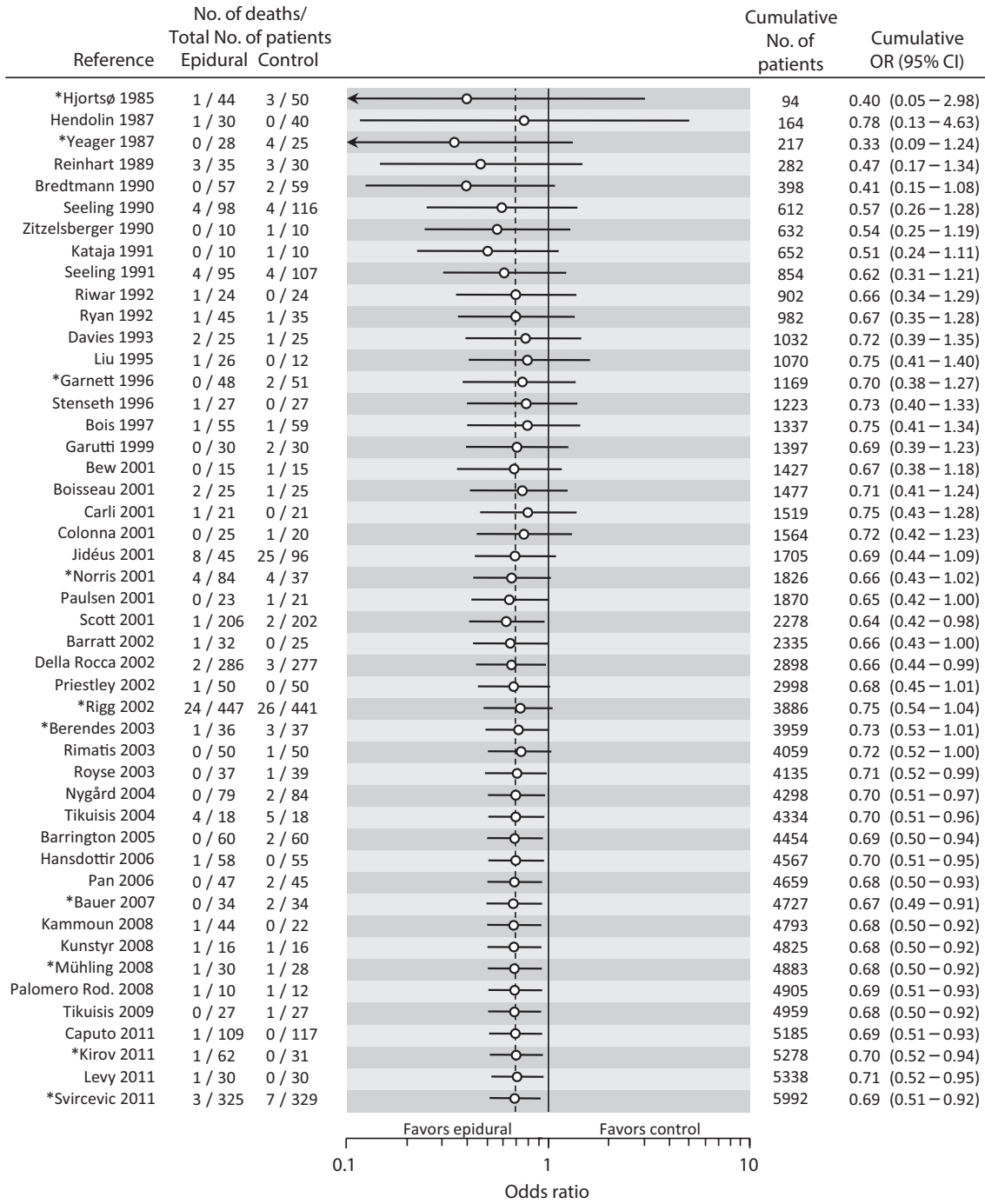

FIGURE 3. Cumulative meta-analysis of all published and unpublished mortality data. Trials are arranged according to the date of publication. There was consistent evidence of a statistically significant benefit from 2003 and 4135 randomized patients. *Mortality was a primary or secondary endpoint of the study. The cumulative number of patients (n = 5992) does not add up to the total number of randomized patients of all trials (n = 7766) because trials with zero events in both groups were not considered for the cumulative meta-analysis.

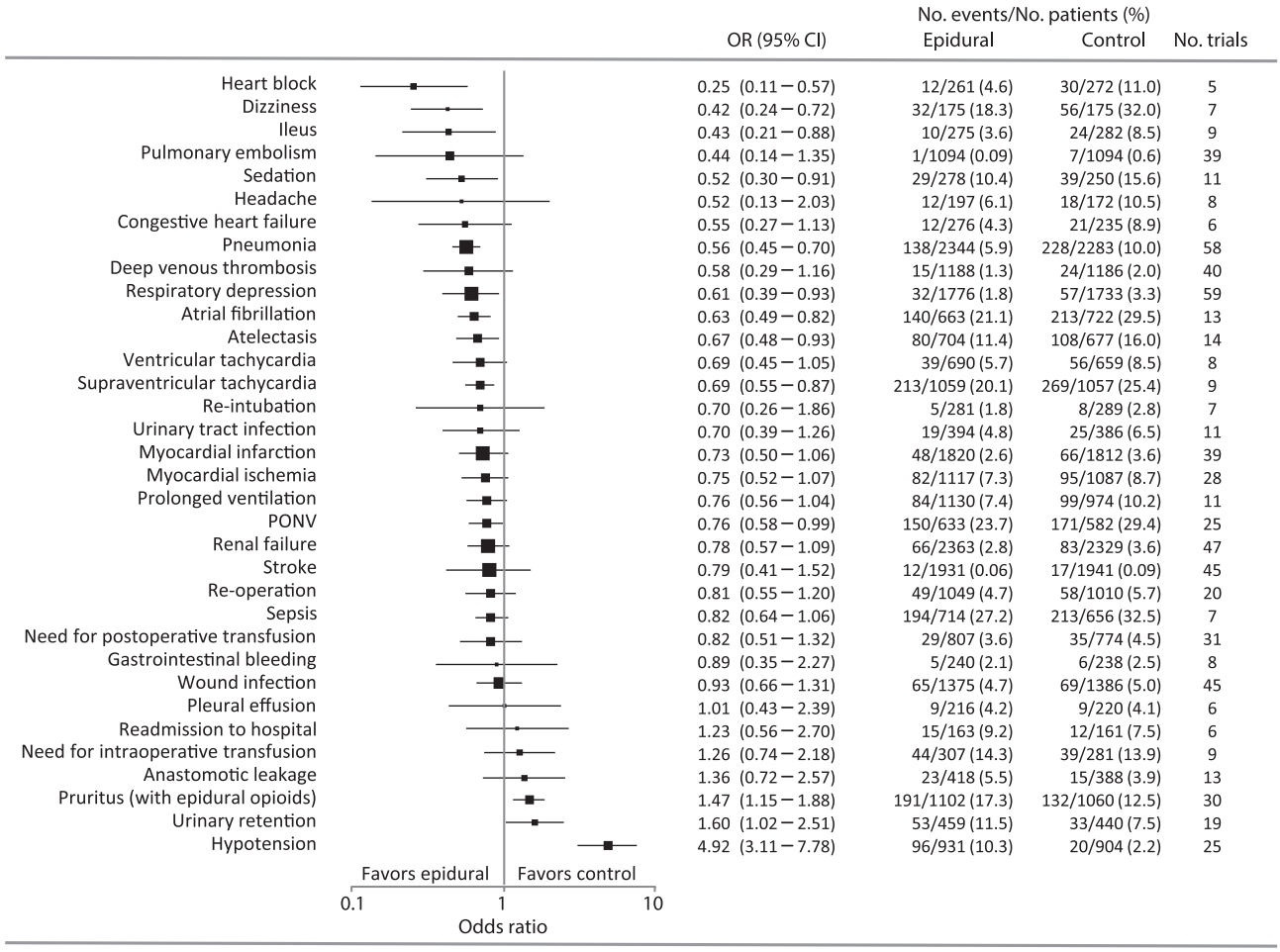

FIGURE 4. Perioperative morbidity: dichotomous outcomes. Control indicates systemic, opioid-based analgesia; PONV, postoperative nausea and vomiting.

included a local anesthetic, with or without a concomitant opioid, for at least 24 hours postoperatively in patients having surgery under general anesthetic were included. Also, all controls received systemic, opioid-based analgesia. This uniform setting facilitates clinical decision making. The final database included 125 randomized trials with data from more than 9000 patients. We were able to include additional unpublished data of 2495 patients from 42 trials through contact with the original authors. This illustrates the central role of systematic reviews to unearth relevant outcomes that are not reported in the published literature.

The beneficial result on mortality has to be interpreted cautiously because only a minority of these trials had been designed to investigate primarily the impact of epidural analgesia on perioperative mortality. A conservative approach would rely exclusively on these trials. Also, we performed numerous sensitivity analyses that suggested that the association between epidural analgesia and death was robust and was largely independent of the inclusion of unpublished data, level of catheter insertion, type of surgery, epidural regimen, quality of the trials, duration of follow-up, or exclusion of outliers.

Our findings on mortality are consistent with findings from studies with alternative designs. For instance, large retrospective investigations of Medicare databases including up to 250,000 patients have suggested a beneficial impact of epidural analgesia on postoperative mortality.[161,162] Interestingly, the mortality baseline reported in studies included in our systematic review was lower than in those reported elsewhere; death rates up to 4.3% after urologic surgery,[163] 6.0% after abdominal surgery,[164] 7.6% after vascular surgery,[165] 10% after thoracic surgery,[166] and 10.5% after orthopedic surgery[167] have been described. Only three trials reported on death rates above 10% in controls.[88,145,154]

Our analysis has also some limitations. Although our search strategy was exhaustive, we may have missed some trials. Some trials could not be included because data reporting was incomplete and authors failed to respond to our inquiry. Major morbidity endpoints or even deaths may have been underreported in the original trials, and we cannot exclude that authors who were contacted by us provided unpublished information selectively only and eventually shared exclusively "favorable" findings. However, the risk of reporting bias because of the inclusion of unpublished outcomes seemed to be low because sensitivity analyses suggested that the impact of epidural analgesia on mortality was not significantly modified when unpublished data were included in the analysis. There was no intention to specifically ask authors to provide details of unreported epidural-related adverse effects, and this may explain why no cases of severe neurologic complications were identified. Finally, we did not analyze data on pain intensity or opioid consumption. Efficacy of epidural

analgesia has been well demonstrated,[2,168] and we may assume that in all these trials, pain relief with epidural analgesia was adequate.

The question remains why epidural analgesia reduces the risk of major perioperative complications including death. It may be speculated that in surgical patients receiving epidural analgesia, the reduction of some of the cardiac complications, such as atrial fibrillation, supraventricular tachycardia, and heart block, is due to improved pain relief and reduced perioperative stress response. Also, the reduction of major pulmonary complications, including pneumonia, may be related to improved analgesia that enables patients to mobilize faster and to perform, for instance, respiratory physiotherapy after surgery.[9] Furthermore, major perioperative complications such as thromboembolic events or renal failure happened also less often in patients receiving epidural analgesia. The impact of epidural analgesia on death may thus be explained through its impact on major morbidity endpoints. The association between major morbidity and perioperative mortality has been previously described.[169,170]

It is possible that some of the beneficial results with epidural analgesia were related to avoidance of specific harmful effects of the systemic, mainly opioid-based, analgesia techniques in controls. The reduced risk of dizziness, respiratory depression, or postoperative nausea and vomiting, and the faster return to normal bowel function are most likely due to an opioid-sparing rather than a specific epidural analgesia effect. Most of these outcomes may be perceived as minor or surrogate. However, their prevention facilitates faster mobilization and reduces the risk of more serious postoperative complications.

Typical epidural analgesia-related adverse effects were arterial hypotension, urinary retention, and pruritus. These are well known and may easily be explicable through the presence of the local anesthetic (arterial hypotension), the opioid (pruritus), or both (urinary retention) in the epidural regimen. Usually, these adverse effects are minor and none of them restricts the use of epidural analgesia in most surgical patients. Arterial hypotension may interfere with early mobilization[171]; as with intrathecal regimens, it may be useful to add an opioid to a reduced dose of the local anesthetic to minimize the risk of hypotension.[172] Epidural-related hypotension may be treated with intravenous fluids or vasopressors. We found no difference in the incidence of anastomotic leakages in patients with epidural analgesia compared with controls.

As expected, technical failures occurred. According to these trials, in about 1 in 15 patients receiving an epidural catheter, an alternative analgesic method has to be chosen because the catheter has dislodged or another technical problem has been encountered. Amazingly, no cases of epidural hematoma, abscess, meningitis, or direct traumatic spinal cord injury were mentioned in these trials. This may indicate that these complications did not occur, or that patients presenting such a complication were excluded from the trials, or that the authors did not consider these complications important enough to be reported. Evidence exists that epidural-related complications occur more often than previously assumed, although permanent neurologic injuries are rare.[1,3,173–175] For example, the risk for epidural hematoma ranges from 1 in 2700 to 1 in 200,000.[174,176–178] Consequently, close perioperative observation of these patients is mandatory to enable early detection of associated symptoms (sensory or motor deficit, incontinence, cauda-equina syndrome, back pain, or fever).

CONCLUSIONS

In conclusion, in adult patients undergoing surgery under general anesthesia, concomitant epidural analgesia using local anesthetics with or without an opioid, and maintained for at least 24 hours postoperatively, reduces postoperative mortality possibly through a beneficial effect on a multitude of cardiovascular, respiratory, and gastrointestinal morbidity endpoints compared with patients receiving systemic, standard care analgesia. The strength of most associations was statistically significant and clinically relevant. It is also interesting to note that the OR point estimate for mortality has remained unchanged over the past 10 years and seemed to be robust to various sensitivity analyses. The beneficial effect was largely independent of epidural regimen, trial quality, or the inclusion of unpublished data. A prospective randomized trial aiming to demonstrate a similar impact of epidural analgesia on mortality (ie, a decrease from about 3% to 2%), with a power of 80% and a 2-sided test with alpha fixed at 0.05, would need more than 8000 patients to be included. This begs the question whether any further trials testing the impact of epidural analgesia on postoperative mortality are necessary, or even ethical. However, epidural analgesia is associated with an increased risk of arterial hypotension, pruritus, urinary retention, and motor blockade. Also, technical failures may occur and neurologic complications cannot be ruled out, although we were unable to quantify them. This comprehensive analysis adds to the evidence base for rational decision making to ensure the most beneficial use of epidural analgesia in surgical patients.

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