REVIEW ARTICLE

Protective Effects of Epidural Analgesia on Pulmonary Complications After Abdominal and Thoracic Surgery

A Meta-Analysis

Daniel M. Pöpping, MD; Nadia Elia, MD; Emmanuel Marret, MD; Camille Remy, MD; Martin R. Tramèr, MD, DPhil

Objective: To review the impact of epidural vs systemic analgesia on postoperative pulmonary complications.

Data Sources: Search of databases (1966 to March 2006) and bibliographies.

Study Selection: Inclusion criteria were randomized comparison of epidural vs systemic analgesia lasting 24 hours or longer postoperatively and reporting of pulmonary complications, lung function, or gas exchange. Fifty-eight trials (5904 patients) were included.

Data Extraction: Articles were reviewed and data extracted. Data were combined using fixed-effect and random-effects models.

Data Synthesis: The odds of pneumonia were decreased with epidural analgesia (odds ratio [OR], 0.54; 95% confidence interval [CI], 0.43-0.68), independent of site of surgery or catheter insertion, duration of analgesia, or regimen. The effect was weaker in trials that used patient-controlled analgesia in controls (OR, 0.64; 95% CI, 0.49-0.83) compared with trials that did not (OR, 0.30; 95% CI, 0.18-0.49) and in larger studies (OR, 0.62; 95% CI, 0.47-0.81) compared with smaller studies (OR, 0.37; 95% CI, 0.23-0.58). From 1971-2006, the incidence of pneumonia with epidural analgesia remained about 8% but decreased from 34% to 12% with systemic analgesia ($P < .001$); consequently, the relative benefit of epidural analgesia decreased also. Epidural analgesia reduced the need for prolonged ventilation or reintubation, improved lung function and blood oxygenation, and increased the risk of hypotension, urinary retention, and pruritus. Technical failures occurred in 7%.

Conclusion: Epidural analgesia protects against pneumonia following abdominal or thoracic surgery, although this beneficial effect has lessened over the last 35 years because of a decrease in the baseline risk.

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EPIDURAL LOCAL ANESTHETICS, with or without opioids, provide better postoperative pain relief than systemic opioids.[1,2] Epidural local anesthetics reduce central sympathetic stimulation, with subsequent favorable effects on coagulation and homeostasis and on gastrointestinal, metabolic, and immune function.[3,4] In patients undergoing surgery for hip replacement, epidural local anesthetics were shown to reduce the incidence of venous thrombosis.[5] It was also suggested that in patients undergoing vascular surgery, epidural analgesia may reduce the risk of cardiac events.[6]

See Invited Critique at end of article

The impact of epidural analgesia on the risk of pneumonia in a high-risk population has never been adequately investigated in a meta-analysis. Previously published meta-analyses either did not report on the risk of pneumonia[1,6]; reported on composite "pulmonary complications" outcomes, lumping very different end points, such as pulmonary infection, atelectasis, respiratory failure, or reintubation[7,8]; included populations at low risk of postoperative pneumonia (for instance, patients undergoing surgery for hip fracture)[5]; or included data from only a very limited number of small trials that tested epidural analgesia.[9] The largest meta-analysis so far included data on any neuraxial blockade (intrathecal and/or epidural analgesia with or without general anesthesia) and it remained unclear what the impact of epidural analgesia in patients at high risk of postoperative pneumonia was.[10] Moreover, none of these meta-analyses addressed the potential of harm related to the use of epidurals. This

Author Affiliations:
Department of Anesthesiology and Intensive Care, University Hospital Münster, Münster, Germany (Dr Pöpping); Department of Anesthesia and Intensive Care, Tenon University Hospital, Assistance Publique–Hôpitaux de Paris, Paris, France (Drs Marret and Remy); and Division of Anesthesiology, University Hospitals of Geneva, Geneva, Switzerland (Dr Elia and Prof Tramèr).

uncertainty may be one reason why a recently published report on the behalf of the American College of Physicians concluded that the evidence for epidural analgesia to reduce pulmonary complications after noncardiothoracic surgery was conflicting or insufficient.[11]

The benefit of epidural analgesia to reduce the risk of postoperative pulmonary complications, specifically pneumonia, remains ambiguous. Our meta-analysis was designed to address this issue.

METHODS

LITERATURE REVIEW

A wide search strategy was used to retrieve all trials that randomized surgical patients to either epidural or systemic analgesia and that reported on pulmonary complications, lung function test results, or gas exchange parameters. Since there was an intention to include only data from patients at high risk of pulmonary complications, we concentrated on abdominal or thoracic surgery.[12] The MEDLINE, Cochrane, BIOSIS, and CINAHL databases were searched from 1966 to March 2006 for reports related to epidural analgesia (epidural, peridural, extradural) and abdominal or thoracic surgery using the Boolean meanings of "or" and "and." Bibliographies of selected articles were checked for additional references. There was no language restriction.

Trials in adults (aged ≥18 years) in which epidural analgesia was started preoperatively, intraoperatively, or immediately postoperatively and lasted at least 24 hours were included. Systemic analgesia was defined as opioids given alone or in combination with nonopioid analgesics. When controls received locoregional analgesia (for instance, intercostal nerve blocks), the trial was not considered. Trials with fewer than 10 patients per group or trials on trauma patients were excluded. Each of the retrieved articles was reviewed by one of us (D.M.P.) for inclusion. Queries were resolved by discussion with 2 coauthors (E.M. and C.R.). The primary investigators of 31 reports were contacted to obtain additional information since data reporting was inadequate; 6 answered and of 3 of those,[13-15] additional data were included in our analyses.

DATA EXTRACTION AND ANALYSIS

One of us (D.M.P.) extracted information on type of epidural analgesia (level of insertion, duration, regimen), systemic analgesia (regimen, route of administration), number of patients, length of observation period, and surgery. Data on pulmonary complications, lung function, gas exchange, and adverse events were extracted from tables or text; definitions were taken as reported in the original articles. For each included trial, the method of randomization, concealment of treatment allocation, degree of blinding, and reporting of dropouts was assessed. Two of us (C.R. and E.M.) checked all extracted information. Discrepancies were resolved by discussion with a coauthor (M.R.T.).

For continuous data, weighted mean differences with 95% confidence intervals (CIs) were calculated. For dichotomous data, Peto odds ratios (ORs) with 95% CIs were computed since there were many zero cells. Trials that had 2 zero cells for an end point (ie, no event occurred in either group) were excluded from the summary OR. An OR less than 1 indicated a beneficial effect with epidural. When the 95% CI around the OR did not include 1, the result was considered statistically significant.

We performed formal heterogeneity testing ($P < .10$ was considered heterogeneous). When the data were homogenous, we used a fixed-effect model to combine data. When the data were heterogeneous, there was an intention to use a random-effects model. However, sensitivity analyses were performed to identify sources of heterogeneity.

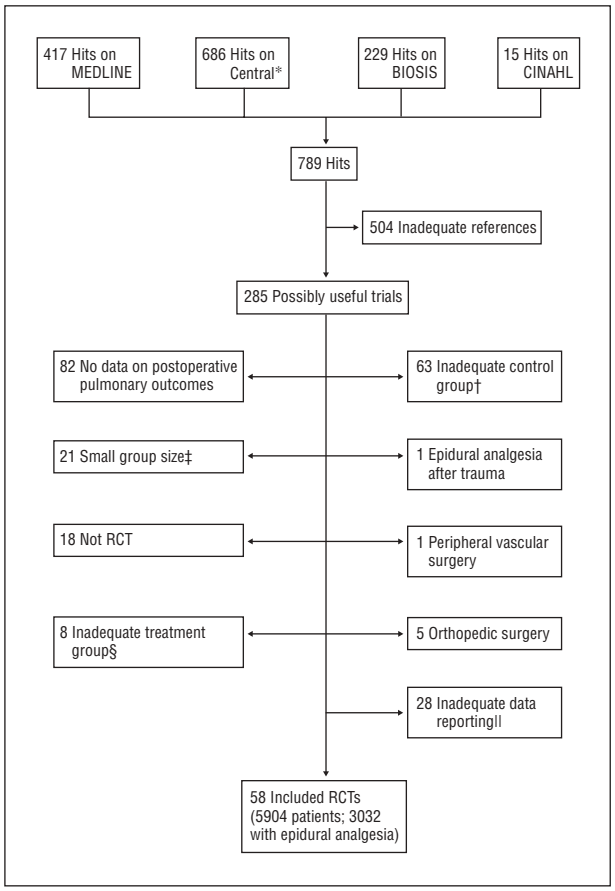

Figure 1. Flowchart of retrieved, excluded, and analyzed trials. *Cochrane Central Register of Controlled Trials. †Regional anesthesia (for instance, intercostal nerve block or wound infiltration with local anesthetics). ‡Fewer than 10 patients per treatment group. §Duration of epidural analgesia only intraoperatively or less than 24 hours postoperatively. ‖Continuous data presented as means but without standard deviation, no dichotomous data. RCT indicates randomized controlled trial.

Since ORs cannot be easily extrapolated into daily clinical practice, we computed the number needed to treat (NNT) for beneficial effects and the number needed to harm (NNH) for harmful effects using the control event rate and the OR. We calculated 95% CIs around the NNT/NNH only when the 95% CI around the OR indicated that the result was statistically significant.[16]

Statistical analyses were performed using STATA (version 9; StataCorp, College Station, Texas) and ReviewManager software (version 4.2; Cochrane Collaboration, Oxfordshire, England).

RESULTS

RETRIEVED AND INCLUDED STUDIES

We retrieved 789 reports but rejected 731 for a variety of reasons, including 3 duplicate publications[17-22] (**Figure 1**). A total of 58 studies met all inclusion criteria.[13-15,23-77] They were published between 1971 and 2006 and reported on data from 5904 patients. Of the 41 epi-

Table 1. Pneumonia, Prolonged Ventilation, and Reintubation

	No. of Trials	No. of Events/No. (%) of Patients: Epidural Analgesia	No. of Events/No. (%) of Patients: Systemic Analgesia	OR (95% CI)	*P* Hetero	NNT (95% CI)[a]
Pneumonia						
All available data	19	121/1606 (7.5)	208/1619 (12.8)	0.54 (0.43 to 0.68)	.04	18 (14-27)
Sensitivity Analyses, Pneumonia						
Analgesia in controls						
PCA	8	102/1300 (7.8)	151/1312 (11.5)	0.64 (0.49 to 0.83)	.21	26 (18-57)
No PCA	11	19/306 (6.2)	57/307 (18.6)	0.30 (0.18 to 0.49)	.22	8 (7-12)
Site of surgery						
Thoracic	4[b]	33/309 (10.7)	66/307 (21.5)	0.42 (0.27 to 0.66)	.28	9 (7-16)
Abdominal	14	87/1269 (6.9)	133/1287 (10.3)	0.63 (0.48 to 0.84)	.12	29 (18-76)
Insertion site						
Thoracic	12[b]	80/918 (8.7)	141/918 (15.4)	0.51 (0.38 to 0.68)	.09	14 (11-23)
Lumbar	5	13/159 (8.2)	23/166 (13.9)	0.56 (0.27 to 1.14)	.07	18
Duration of epidural analgesia, d						
2	6	8/158 (5.1)	18/172 (10.5)	0.40 (0.17 to 0.92)	.10	17 (12-138)
3	6	69/1049 (6.6)	101/1045 (9.7)	0.66 (0.48 to 0.90)	.10	33 (21-116)
4	2	9/97 (9.3)	17/105 (16.2)	0.53 (0.22 to 1.26)	.20	15
5	5	35/302 (11.6)	72/297 (24.2)	0.41 (0.27 to 0.62)	.20	8 (6-13)
Epidural regimen						
Local anesthetics alone	7	46/346 (13.3)	93/343 (27.1)	0.42 (0.29 to 0.61)	.24	7 (6-12)
Local anesthetics + opioids	11	74/1230 (6.0)	114/1236 (9.2)	0.63 (0.46 to 0.84)	.045	31 (21-76)
Opioids alone	1	1/30 (3.3)	1/40 (2.5)	1.34 (0.08 to 22.6)	NA	–120
Size of trial						
<100 patients/group	16	25/464 (5.4)	63/481 (13.1)	0.37 (0.23 to 0.58)	.09	13 (10-20)
>100 patients/group	3	96/1142 (8.4)	145/1138 (12.7)	0.62 (0.47 to 0.81)	.20	22 (16-47)
Prolonged Ventilation						
All available data	7	37/649 (5.7)	57/631 (9.0)	0.61 (0.40 to 0.93)	.38	30 (19-167)
Reintubation						
All available data	7	158/1135 (13.9)	209/1125 (18.6)	0.70 (0.55 to 0.88)	.84	21 (14-62)

Abbreviations: CI, confidence interval; Hetero, heterogeneity; NA, not available; NNT, number needed to treat; OR, odds ratio; PCA, patient-controlled analgesia.
[a] 95% CIs are shown for statistically significant results only.
[b] Number of trials does not add up since some trials did not fit into one of the two categories.

dural studies that were included in a previous similar meta-analysis,[9] we excluded 21 because the surgery was not abdominal or thoracic, data on postoperative pulmonary complications or lung function could not be extracted, they were not randomized, or controls did not receive systemic opioids.

The included trials tested thoracic, lumbar, or both thoracic and lumbar epidurals. Epidural analgesia was commenced before or at the end of surgery; median duration was 3 days (range, 2 to 5 days). Epidural regimens were with local anesthetics, opioids, or both. Controls received subcutaneous, intravenous, or intramuscular opioids with or without nonopioid analgesics. Opioids were given on demand, regularly, or via patient-controlled analgesia (PCA).

PNEUMONIA

Nineteen trials (3504 patients) reported the number of patients who had pneumonia. With epidural analgesia, the odds of pneumonia were significantly decreased (OR, 0.54; 95% CI, 0.43-0.68; NNT, 18 [range, 14-27]) (**Table 1**). The symmetrical funnel suggested that publication bias was unlikely (**Figure 2**); however, the data were heterogeneous (Table 1).

Sensitivity analyses were performed to identify potential sources of heterogeneity (Table 1). We looked at the impact of type of analgesia in controls (PCA vs none), site of surgery (thoracic vs abdominal), insertion site of epidurals (thoracic vs lumbar), duration of analgesia (2-5 days), epidural drug regimens (local anesthetics vs opioids vs both), and trial size (<100 vs >100 patients per group). Epidural analgesia was significantly more efficacious compared with systemic analgesia in preventing pneumonia in trials where controls did not receive PCA (OR, 0.30) compared with trials where controls did receive such a device (OR, 0.64) ($P<.01$). Similarly, epidural analgesia was more efficacious in preventing pneumonia in trials with fewer than 100 patients per group (OR, 0.37) compared with larger trials (OR, 0.62) ($P=.08$). Site of surgery, insertion site of epidurals, and duration of postoperative analgesia had no significant impact on the efficacy of epidurals. Epidural local anesthetics were as efficacious as combinations of local anesthetics and opioids. The efficacy of epidural opioids alone was tested in one small trial only.

Since the trials were published over a period of 35 years, we tested whether older trials reported on different estimates of efficacy compared with younger trials. First, cumulative meta-analysis was performed using pneumonia

as the end point (**Figure 3**). Over the years, the cumulative OR moved toward unity, suggesting that the efficacy of epidurals, compared with systemic analgesia, had decreased between 1971 and 2006. Second, trials were divided into subgroups representing 4 decades since publication of the first trial in 1971; meta-analyses were performed within each stratum (**Figure 4**A). In the 1970s, 2 trials were published; the OR for the prevention of pneumonia with epidural compared with systemic analgesia was 0.17 (NNT, 4). In the 1980s, the OR was 0.36 (NNT, 9); in the 1990s, it was 0.46 (NNT, 23); and between 2000 and 2006, it was 0.62 (NNT, 25). Although the OR moved toward unity, the evidence that the effect of epidurals on pneumonia was modified by periods was weak (χ^2_3=5.04; P=.17).

To better understand the change in efficacy of epidural analgesia over time, we analyzed the incidences of pneumonia with epidural and systemic analgesia separately (Figure 4B and C). In patients receiving epidural analgesia, the average incidences of pneumonia during the 4 decades were between 3.9% and 8.6%; the score test for linear trend of odds with year was not significant (χ^2_1=0.00; P=.99) (Figure 4B). In controls receiving systemic analgesia, the average incidence of pneumonia during the 4 decades decreased from 34.3% to 8.3% and then increased to 12%; the score test for linear trend of odds with year was highly significant (χ^2_1=21.02; $P<.001$) (Figure 4C). The definition of pneumonia, the use of concomitant physiotherapy, and the technique of epidural analgesia have not changed over time. However, there was a change in systemic analgesia techniques toward PCA and multimodal analgesia methods (**Table 2**).

Since the method of analgesia in controls (PCA) and trial size had an impact on the incidence of pneumonia in controls and the efficacy of epidurals, 2 further sensitivity analyses were performed. In control groups, the score test for linear trend of odds with year remained statistically significant when only trials that did not use PCA in controls were considered (χ^2_1=19.58; $P<.001$) or when only trials with fewer than 100 patients per group were considered (χ^2_1=33.83; $P<.001$).

FURTHER OUTCOMES

Epidural analgesia significantly decreased the odds of prolonged (>24 hours) ventilation and reintubation (Table 1). Definitions and diagnosis of atelectasis and respiratory depression varied considerably between trials; meta-analysis was deemed inappropriate. Epidural analgesia significantly increased forced vital capacity at 24 hours, forced expiratory volume in 1 second at 24 hours, and peak expiratory flow rate at 24 hours (**Table 3**). Epidural analgesia significantly increased arterial oxygen pressure at 24 and 72 hours (Table 3).

Fourteen trials reported on the incidence of postoperative myocardial infarction. Definitions of infarction included an increase in serum concentration of myocardial-specific isoenzyme fractions of creatine kinase or lactic dehydrogenase and typical electrocardiogram changes (elevation/depression of the ST segment and/or new Q waves). The odds of myocardial infarction were significantly decreased with epidural analgesia (OR, 0.55; NNT, 48) (**Table 4**).

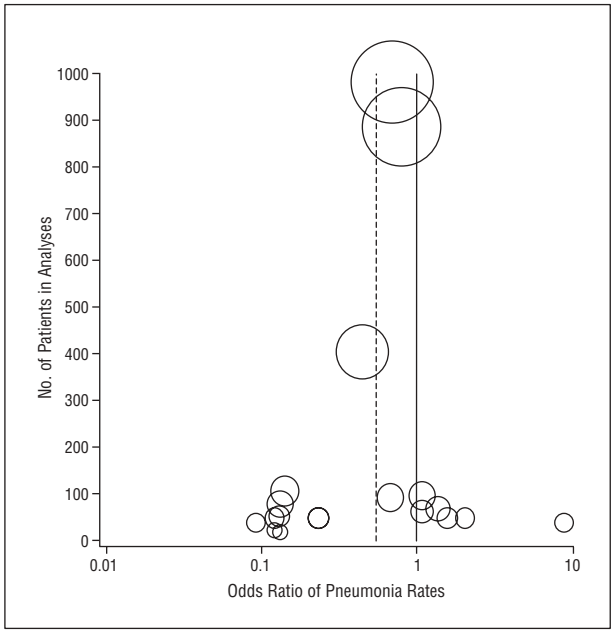

Figure 2. Funnel plot of natural logarithm of odds ratio vs sample size among all studies reporting on pneumonia. Data are odds ratios plotted against weight (sample size) for each trial included in the meta-analysis on pneumonia. An odds ratio of less than 1 signifies less pneumonia with epidural analgesia. The sizes of the bubbles correspond to the sizes of the trials. The dotted vertical line represents the combined odds ratio (0.54).

Epidural analgesia significantly increased the odds of intraoperative arterial hypotension (OR, 2.03; NNH, 41) and of postoperative urinary retention (OR, 2.15; NNH, 16) (Table 4). The risk of pruritus depended on the injected opioid (Table 4); with epidural morphine, there was the maximum risk and with sufentanil citrate, the least risk. Ten trials (501 patients) reported on epidural-related technical problems; in 1 trial, the insertion level was lumbar, and in all others, it was thoracic. In 36 patients (7.2%), epidural analgesia had to be abandoned. In 2 trials, the incidence of failures was high, 12% and 15.8%; in the others, it varied between 3.9% and 7.4%. There was no relationship between the publication date of the trials and the rate of technical failures. There was no evidence of any effect of epidural analgesia on renal insufficiency, nausea or vomiting, or in-hospital mortality (Table 4).

COMMENT

In patients undergoing abdominal or thoracic surgery, epidural analgesia decreases the risk of postoperative pneumonia compared with systemic analgesia. Epidural analgesia also decreases the risk of prolonged ventilation or reintubation and improves some lung function parameters and blood oxygenation. The biological basis underlying these associations remains unclear; the improved outcome may be because of a better pain control with epidural analgesia, with subsequently enhanced respiratory function.

Although the beneficial effects of epidurals are numerous and well documented,[1,3,5-7,78,79] the evidence of the usefulness of epidural analgesia for the prevention of post-

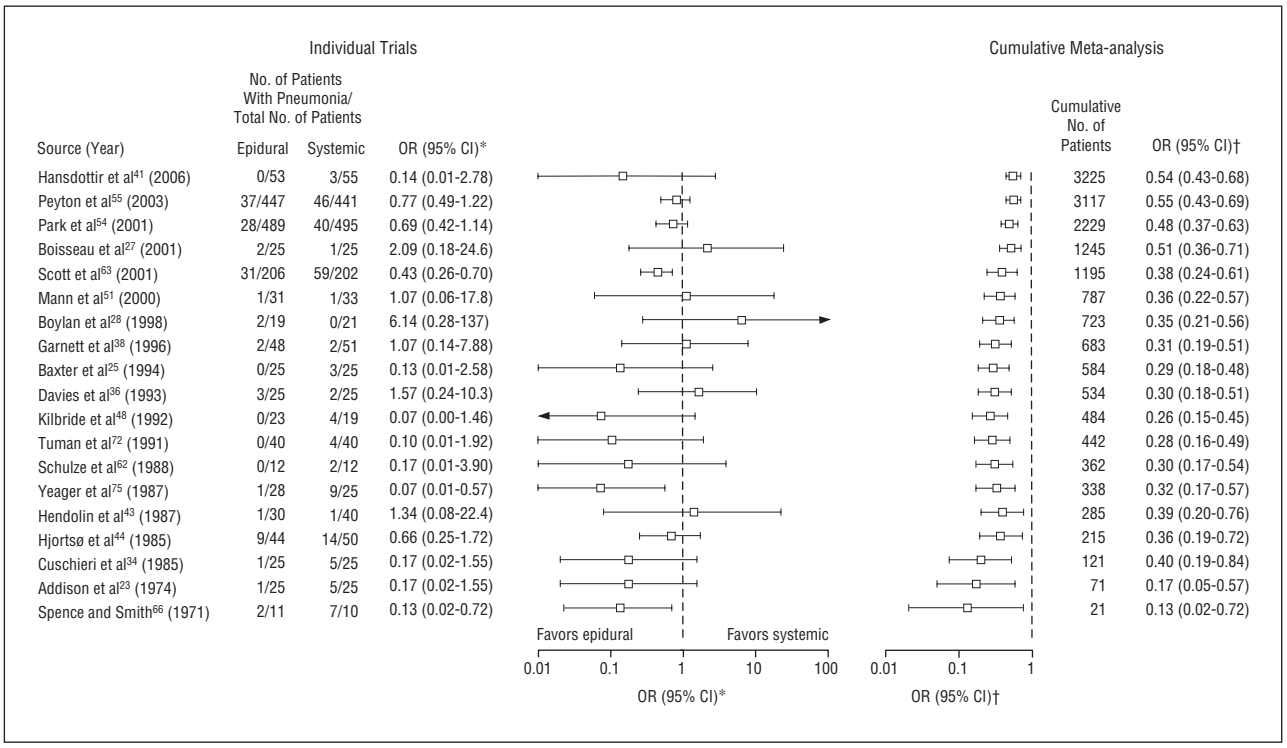

Figure 3. Postoperative pneumonia with epidural analgesia compared with systemic analgesia: individual trials and cumulative meta-analysis. *Odds ratio (OR) and 95% confidence interval (CI) in individual trials. †Cumulative OR and 95% CIs. Trials are arranged according to date of publication. Trials with zero events are not shown.

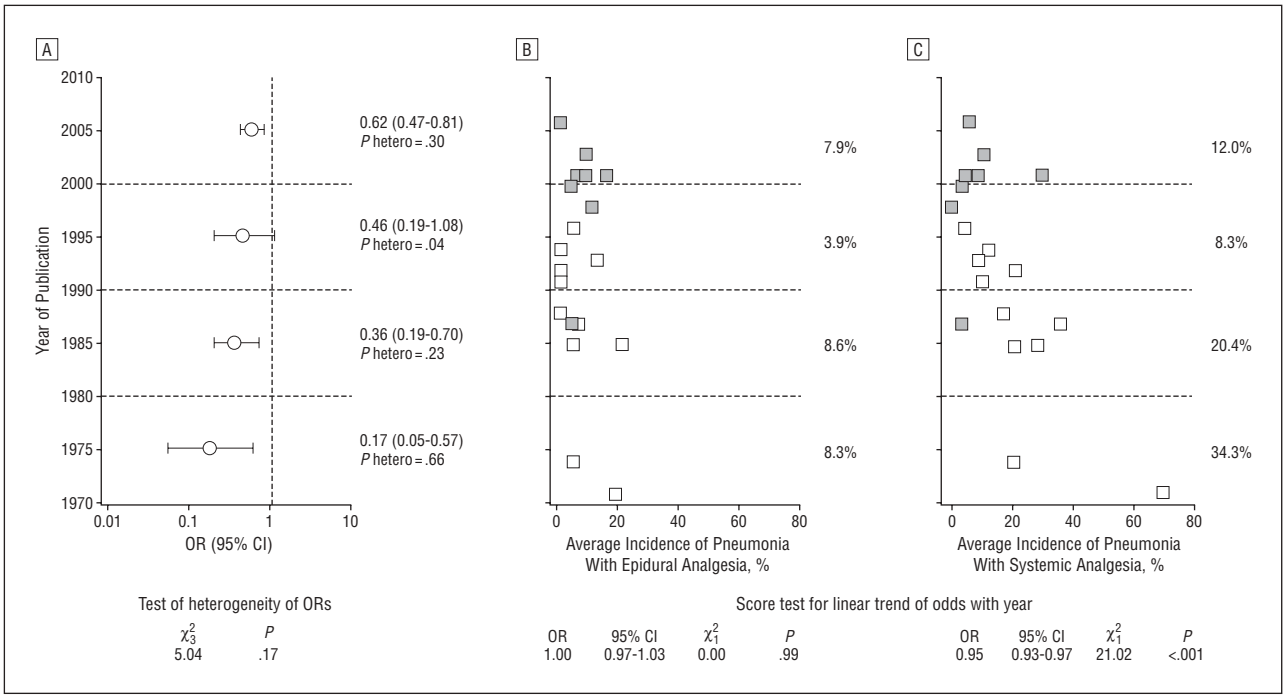

Figure 4. Relationship between the year of publication, the incidence of pneumonia with epidural and systemic analgesia, and the efficacy of epidural analgesia in preventing pneumonia compared with systemic analgesia. Gray symbols indicate trials that used patient-controlled analgesia in controls; white symbols, trials that did not use patient-controlled analgesia in controls. Periods for subgroup analyses were chosen by convenience. Score test for linear trend of odds with year: the odds ratio (OR) estimate is an approximation to the OR for a 1-unit increase per year. Hetero indicates heterogeneity; CI, confidence interval. Trials with zero events are not shown.

operative pulmonary complications has been ambiguous. Previous meta-analyses have included limited relevant data[9,11] or have tested the effect of epidural analgesia in patients at low risk of pulmonary complications.[5] For instance, the recently published systematic review on behalf of the American College of Physicians included only

Table 2. Randomized Trials Reporting on Postoperative Pneumonia

Source (Year)	Surgery	Quality of Reporting: Randomization[a]	Concealment[b]	Blinding[c]	Follow-up[d]	No. of Patients: Epidural Analgesia	Systemic Analgesia	Epidural Analgesia: Level of Insertion	Start of Analgesia[e]	Local Anesthetic	Opioid	Duration, d
2000-2006												
Hansdottir et al[41] (2006)	Th	2	1	0	2	53	55	Th	B	B	F	4
Peyton et al[55] (2003)	Ab	1	0	1	1	447	441	Th	B	R	F	3
Boisseau et al[27] (2001)	Th	2	0	0	2	25	25	Th	B	R	S	5
Park et al[54] (2001)	Ab	1	0	0	2	489	495	Lu/Th	B	B	M	3
Scott et al[63] (2001)	Th	2	1	0	1	206	202	Th	B	B	5	
Mann et al[51] (2000)	Ab	2	0	0	1	31	33	Th	B	B	S	5
1990-1999												
Boylan et al[28] (1998)	Aortic	1	0	0	2	19	21	Lu	B	B	M	2
Garnett et al[38] (1996)	Aortic	1	0	0	1	48	51	Lu	B	B	M	2
Baxter et al[25] (1994)	Th	2	1	2	0	25	25	Lu	B	B	M	2
Davies et al[36] (1993)	Aortic	1	0	0	2	25	25	Th	B	L/B		3
Kilbride et al[48] (1992)	Ab	2	0	0	1	23	19	Lu	B	B		3
Tuman et al[72] (1991)	Aortic	1	0	0	0	40	40	Lu/Th	B	B	M	3
1980-1989												
Schulze et al[62] (1988)	Chol	1	0	0	1	12	12	Th	B	B		5
Hendolin et al[43] (1987)	Chol	1	0	0	0	30	40	Th	B		F	2
Yeager et al[75] (1987)	Ab/Th	1	1	0	2	28	25	Th	B	B	M	5
Cuschieri et al[34] (1985)	Chol	1	0	0	2	25	25	Th	E	B	F	3
Hjortsø et al[44] (1985)	Ab	1	0	0	1	44	50	Lu	B	B		4
To 1979												
Addison et al[23] (1974)	Chol	1	0	0	0	25	25	Th	E	B		2
Spence and Smith[66] (1971)	Ab	1	0	0	0	11	10	Th	E	B		2

Source (Year)	Surgery	Systemic Analgesia: Opioid	PCA	Continuous IV Opioids	On-Demand IV Opioids	Regular IM/SC Opioids	On-Demand IM/SC Opioids	Nonopioid Analgesics	Physiotherapy	Definition of Pneumonia: Clinical Signs	Radiological Signs	Elevated WBC Count	Microbiologically
2000-2006													
Hansdottir et al[41] (2006)	Th	M	+					+		+	+	+	+
Peyton et al[55] (2003)	Ab	NS	+	+	+			+		+	+	+	+
Boisseau et al[27] (2001)	Th	M	+					+	+	+	+		
Park et al[54] (2001)	Ab	M	+	+	+	+	+			+	+	+	+
Scott et al[63] (2001)	Th	M	+					+		+	+	+	+
Mann et al[51] (2000)	Ab	M	+					+	+	+	+		
1990-1999													
Boylan et al[28] (1998)	Aortic	M	+							ND	ND	ND	ND
Garnett et al[38] (1996)	Aortic	M		+						+	+		+
Baxter et al[25] (1994)	Th	M					+	+		ND	ND	ND	ND
Davies et al[36] (1993)	Aortic	NS			+		+			+	+	+	+
Kilbride et al[48] (1992)	Ab	M		+						+	+	+	+
Tuman et al[72] (1991)	Aortic	M				+				+	+		
1980-1989													
Schulze et al[62] (1988)	Chol	O		+		+		+	+	+	+	+	
Hendolin et al[43] (1987)	Chol	M	+							ND	ND	ND	ND
Yeager et al[75] (1987)	Ab/Th	M			+	+				+	+		
Cuschieri et al[34] (1985)	Chol	NS			+		+			+	+	+	+
Hjortsø et al[44] (1985)	Ab	M		+					+	+	+	+	+
To 1979													
Addison et al[23] (1974)	Chol	Pe					+			+	+		
Spence and Smith[66] (1971)	Ab	M					+		+	+	+		

Abbreviations: A, alfentanil hydrochloride; Ab, abdominal; B, bupivacaine hydrochloride; Chol, cholecystectomy; F, fentanyl citrate; IM, intramuscular; IV, intravenous; L, lidocaine hydrochloride, Lu, lumbar; M, morphine; ND, no data; NS, not specified; O, oxycodone hydrochloride; Pe, pethidine hydrochloride (meperidine hydrochloride); Pi, piritramide; PCA, patient-controlled analgesia; R, ropivacaine hydrochloride, S, sufentanil citrate; SC, subcutaneous; Th, thoracic; WBC, white blood cell; +, present.

[a] Randomization: 1=mentioned but not specified; 2=mentioned and adequate.

[b] Concealment: 0=none; 1=yes.

[c] Blinding: 0=none, 1=mentioned but not specified; 2=mentioned and adequate.

[d] Follow-up: 0=none, 1=reported but not complete; 2=complete (intention-to-treat analysis possible).

[e] Start of epidural analgesia: B=at the beginning of surgery; E=at the end of surgery.

6 trials compared with 58 in our analyses.[11] This may reflect the fact that our literature search was more comprehensive and that our review focused on a specific intervention. Also, in the Urwin et al meta-analysis,[5] data from 1200 patients undergoing hip fracture repair were included, and the incidence of pulmonary complications was about 5%. If we assume that epidural analgesia has the power of reducing the odds of pneumonia by 46% (OR, 0.54) (Table 1), then 3400 orthopedic patients are needed to be 95% confident to detect a significant difference in favor of epidural analgesia. We included more trials and more data than previous analyses, and we concentrated on patients at high risk for postoperative pulmonary complications.

Most other pulmonary outcome data may be regarded as surrogate. Atelectasis and respiratory depression were reported, but, as in similar analyses,[80,81] definitions varied widely and made it impossible to pool the

Table 3. Pulmonary Function and Gas Exchange

	No. of Trials	Epidural Analgesia: No. of Patients	Epidural Analgesia: Median of Means (Range)	Systemic Analgesia: No. of Patients	Systemic Analgesia: Median of Means (Range)	WMD[a] (95% CI)	*P* Hetero
Pulmonary Function							
Forced vital capacity at 24 h, L	14	361	1.38 (1.03 to 2.62)	345	1.45 (0.80 to 2.07)	0.17 (0.05 to 0.29)	.001
Forced expiratory volume in 1 s at 24 h, L	9	293	1.30 (1.00 to 2.07)	284	1.20 (0.80 to 1.48)	0.18 (0.02 to 0.34)	<.001
Peak expiratory flow rate at 24 h, L min–1	6	154	232 (141 to 290)	139	178 (99 to 247)	43.0 (27.2 to 58.8)	.84
Gas Exchange							
Arterial oxygen pressure at 24 h, kPa	15	341	10.7 (9.44 to 22.0)	349	10.2 (8.40 to 20.0)	0.89 (0.42 to 1.35)	.01
Arterial oxygen pressure at 48 h, kPa	6	129	10.4 (9.50 to 13.2)	138	9.8 (9.07 to 13.0)	0.80 (–0.10 to 1.70)	.02
Arterial oxygen pressure at 72 h, kPa	7	195	10.2 (9.60 to 13.0)	203	9.8 (8.60 to 13.0)	0.50 (0.10 to 0.80)	.80

Abbreviations: CI, confidence interval; Hetero, heterogeneity; WMD, weighted mean difference.
[a]The WMDs were computed using a fixed-effect model when trials were homogeneous ($P > .10$) and a random-effects model otherwise.

Table 4. Further Beneficial and Harmful Effects of Epidural Analgesia

	No. of Trials	No. of Events/No. (%) of Patients: Epidural Analgesia	No. of Events/No. (%) of Patients: Systemic Analgesia	OR (95% CI)	*P* Hetero	NNT/NNH[a] (95% CI)[b]
Further Beneficial Effects of Epidurals						
Myocardial infarction	14	35/1335 (2.6)	61/1322 (4.6)	0.55 (0.37 to 0.84)	.66	48 (29 to 153)
Harmful Effects of Epidurals						
Arterial hypotension	7	47/944 (5.0)	22/892 (2.5)	2.03 (1.24 to 3.34)	.03	–41 (–19 to –175)
Urinary retention	8	27/238 (11.3)	15/237 (6.3)	2.15 (1.07 to 4.33)	.32	–16 (–6 to –1465)
Pruritus	18	148/647 (22.9)	70/583 (12.0)	2.41 (1.76 to 3.30)	.001	–7.8 (–5 to –15)
Pruritus with morphine	10	70/211 (33.2)	16/171 (9.4)	6.46 (3.72 to 11.2)	.79	–3.2 (–2 to –5)
Pruritus with fentanyl citrate	6	31/125 (24.8)	13/110 (11.8)	3.05 (1.50 to 6.19)	.045	–5.8 (–3 to –30)
Pruritus with sufentanil citrate	2	47/311 (15.1)	41/302 (13.6)	1.13 (0.72 to 1.78)	.93	–65
Failure of epidural	10	36/501 (7.2)	NA			
Lack of Evidence of Effect of Epidurals						
Renal insufficiency	7	51/1279 (4.0)	66/1263 (5.2)	0.75 (0.51 to 1.08)	.28	81
Nausea or vomiting	11	65/256 (25.4)	69/224 (30.8)	0.80 (0.53 to 1.22)	.38	19
Hospital mortality	21	58/1958 (3.0)	57/1915 (3.0)	1.01 (0.70 to 1.44)	.85	∞

Abbreviations: CI, confidence interval; Hetero, heterogeneity; NA, not applicable; NNH, number needed to harm; NNT, number needed to treat; OR, odds ratio; ∞, infinity (ie, absolute risk difference=0%).
[a]A positive number corresponds to a beneficial effect with epidurals; a negative number, to a harmful effect.
[b]95% CIs are shown for statistically significant results only.

data. Pneumonia is perhaps the most important pulmonary outcome in this context since it may prolong duration of hospitalization and may lead to death.[81-83]

Although cardiac morbidity was not our primary end point, there was evidence that with epidurals, the incidence of myocardial infarction was decreased. The OR was similar to the Beattie et al analysis[6] but we analyzed more data, and this may explain why our result was statistically significant. About 50 patients would need to receive an epidural to prevent an infarction in 1 of them. We do not know whether that protective effect is due to the epidural analgesia itself, to improved pain relief or arterial oxygenation, a combination of these factors, or yet another mechanism. We were unable to compare lumbar with thoracic epidurals, since most trials that reported on myocardial infarction tested thoracic epidurals.

Epidural analgesia is not without risk, although severe complications appear to be rare.[84-87] One transient neurological injury in 1700 patients undergoing cardiothoracic surgery with epidural analgesia was estimated.[87] In the trials included in our analysis, no severe complications were reported. However, no reporting of adverse events does not mean that none have occurred. Pruritus, although minor harm, was related to specific opioids. Some trials reported on technical failures; the combined estimate was very similar to previous analyses.[2] The incidence of technical failures, implying that the attempt to provide postoperative pain relief with an epidural catheter has to be abandoned, has not changed during the last 35 years. This is not surprising since the technique has remained much the same.

The relative benefit of epidural analgesia has decreased over the last 3 decades. In the early 1970s, of 4 patients who received an epidural, 1 had no pneumonia postoperatively, which would have been the case had they all received conventional systemic analgesia. Thirty-five years later, this ratio has decreased to 1 in 25. The decrease in the protective effect of epidural analgesia compared with systematic analgesia does not seem to be related to a decrease in the efficacy of the epidurals per se but rather to a

decrease in the baseline risk of pneumonia in patients who received systemic analgesia. The reason for this phenomenon is not obvious. The definition of pneumonia, although variable, has not changed over the years (Table 2). Other features of patient care, for instance, respiratory physiotherapy, the routine use of nasogastric tubes and prophylactic antibiotics, or early mobilization, may all have favorably influenced the baseline risk of pneumonia, although the impact of routine prophylactic respiratory physiotherapy on pulmonary complications after thoracic and abdominal surgery remains unproven.[80,81] Also, any change in standard care would be expected to have an impact on the incidence of pneumonia with both epidural and systemic analgesia. A remarkable observation was the change in analgesia provided to controls. In trials published in the early 1970s, analgesia in controls was exclusively with subcutaneous on-demand opioids. In the 1980s, clinical practice changed to morphine infusions and the first PCA devices appeared. Since the 1990s, PCA and multimodal approaches with concomitant nonopioid analgesics became standard care. Patient-controlled analgesia with strong opioids may decrease the risk of pulmonary complications compared with conventional on-demand opioid administration.[88] Indeed, in controls receiving PCA, the baseline risk of pneumonia was decreased, and this may explain why the relative impact of epidural analgesia in reducing the risk of pneumonia was lower (Table 1). However, even in trials that did not use PCA, a significant decrease in the baseline risk of pneumonia over time could be observed. Whether changes in standard-care analgesia had a direct impact on the incidence of postoperative pneumonia, or whether the decrease in the baseline risk reflects yet other changes in patient care, remains to be elucidated. Modification of standard care leading to changes in the baseline risk has been described in other settings.[89,90] A change in the baseline risk may explain why, sometimes, meta-analyses and subsequently published large trials reach different conclusions.[91] Those performing meta-analyses should be aware of this phenomenon when combining data from trials of different epochs that do not necessarily represent contemporary clinical practice. This does not mean that older trials should be excluded from meta-analysis, but the impact of changes in standard care on the efficacy of an experimental intervention should be explored in appropriate sensitivity analyses.

Our analysis has limitations. Some are related to problems that are inherent to meta-analyses. First, we cannot exclude that we missed trials, and some trials could not be included since data reporting was incomplete. Second, we did not analyze pain data since most trials did not report on such data. It has been shown before that epidural analgesia provided better pain relief than systemic analgesia.[1] Third, the periods for sensitivity analyses were chosen arbitrarily and by convenience, although it is unlikely that different subgroups would have changed our findings. Fourth, we have taken definitions of outcomes as provided in the original trials. Finally, we chose the time of publication of a trial as an indicator of the age of that trial, although time of publication does not mean time of performance of a trial.

CONCLUSIONS

In patients undergoing abdominal or thoracic surgery, epidural analgesia is associated with a statistically significant and clinically relevant decrease in the risk of postoperative pneumonia, although the degree of efficacy has lessened over the last decades. That phenomenon is probably due to a decrease in the baseline risk of pneumonia. There is also evidence that pulmonary function and arterial oxygenation are improved with epidural analgesia and that the risk of myocardial infarction is reduced. Postoperative pain control with epidural analgesia is time-consuming, specific technical and pharmacological skills are needed, and professional surveillance of the patients must be guaranteed. Clearly, epidural analgesia is not without risk, and failures may occur. Our analyses provide an evidence base for rational decision making to ensure the most beneficial use of epidurals in surgical patients.

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Correspondence: Daniel M. Pöpping, MD, Klinik für Anästhesiologie und Intensivmedizin, Universitätsklinikum, Albert-Schweitzer-Strasse 33, D-48149 Münster, Germany (poppind@uni-muenster.de).
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