The Comparative Effects of Postoperative Analgesic Therapies on Pulmonary Outcome: Cumulative Meta-Analyses of Randomized, Controlled Trials

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We performed meta-analyses of randomized, control trials to assess the effects of seven analgesic therapies on postoperative pulmonary function after a variety of procedures: epidural opioid, epidural local anesthetic, epidural opioid with local anesthetic, thoracic versus lumbar epidural opioid, intercostal nerve block, wound infiltration with local anesthetic, and intrapleural local anesthetic. Measures of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), vital capacity (VC), peak expiratory flow rate (PEFR), Pao_2, and incidence of atelectasis, pulmonary infection, and pulmonary complications overall were analyzed. Compared with systemic opioids, epidural opioids decreased the incidence of atelectasis (risk ratio [RR] 0.53, 95% confidence interval [CI] 0.33–0.85) and had a weak tendency to reduce the incidence of pulmonary infections (RR 0.53, 95% CI 0.18–1.53) and pulmonary complications overall (RR 0.51, 95% CI 0.20–1.33). Epidural local anesthetics increased Pao_2 (difference 4.56 mm Hg, 95% CI 0.058–9.075) and decreased the incidence of pulmonary infections (RR 0.36, 95% CI 0.21–0.65) and pulmonary complications overall (RR 0.58, 95% CI 0.42–0.80) compared with systemic opioids. Intercostal nerve blockade tends to improve pulmonary outcome measures (incidence of atelectasis: RR 0.65, 95% CI 0.27–1.57, incidence of pulmonary complications overall: RR 0.47, 95% CI 0.18–1.22), but these differences did not achieve statistical significance. There were no clinically or statistically significant differences in the surrogate measures of pulmonary function (FEV_1, FVC, and PEFR). These analyses support the utility of epidural analgesia for reducing postoperative pulmonary morbidity but do not support the use of surrogate measures of pulmonary outcome as predictors or determinants of pulmonary morbidity in postoperative patients. **Implications:** When individual trials are unable to produce significant results, it is often because of insufficient patient numbers. It may be impossible for a single institution to study enough patients. Meta-analysis is a useful tool for combining the data from multiple trials to increase the patient numbers. These meta-analyses confirm that postoperative epidural pain control can significantly decrease the incidence of pulmonary morbidity.

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Postoperative pulmonary dysfunction may delay recovery and, if severe, can be life-threatening. Hypoxia may impair wound healing and cognitive function, the latter especially in the elderly. Atelectasis predisposes patients to chest infection, and chest infection predisposes patients to respiratory failure. It is widely assumed that when postoperative patients are relatively pain-free, their pulmonary function is improved. They can readily expand their chests, breathe deeply, cough well, and cooperate with physical therapy (1–3). They are therefore less likely to develop atelectasis, hypoxia, or pulmonary infection, and more likely to recover quickly and uneventfully. In the process of preparing a clinical practice guideline

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on the management of postoperative pain (4), we examined the scientific evidence related to possible beneficial effects of various pain therapies on respiratory function. We present meta-analyses of data from randomized, controlled trials (RCTs) that assess the effect of specific pain treatments on respiratory function in postoperative patients.

Meta-analysis, defined as the quantitative synthesis of data from multiple trials, has become a scientific discipline with well described principles and methods (5–9). It uses an explicit, systematic approach to literature retrieval, combined with specific statistical methods to integrate and interpret the results of separate investigations to improve on the traditional subjective process of drafting a narrative review article. By combining the results of several studies, meta-analysis can increase the statistical strength of findings that may not be individually significant because of small patient numbers in the trials, and can clarify ambiguity. Meta-analysis is only valid if the studies combined are comparable in trial design, patient demographics, and therapy tested (10). Some studies are not used in the present meta-analysis because the study groups are not combinable with those in the majority of studies. Nevertheless, there was a sufficient number of combinable trials for several meta-analyses. Specifically, we examined techniques in common daily practice by evaluating trials comparing perioperative: epidural opioids versus systemic opioid, epidural local anesthetics versus systemic opioid, epidural opioid versus local anesthetic versus systemic opioid, thoracic epidural opioid versus lumbar epidural opioid, intercostal nerve blocks versus systemic opioid, wound infiltration versus no wound infiltration, and intrapleural local anesthetic versus systemic opioid.

Methods

Retrieval

RCTs examining the influence of postoperative analgesia on postoperative pulmonary function were retrieved in the process of developing scientific evidence to formulate recommendations presented in a clinical practice guideline on the management of acute pain after medical and surgical procedures and trauma (4). The search strategy was developed in conjunction with the staff of the National Library of Medicine. We initially searched 12 different databases (including nursing, sociological, psychological, and pharmacological databases) as part of a broader search for evidence related to acute pain treatment. However, for the purpose of analyses of pulmonary function, all the articles that met the inclusion criteria (RCTs evaluating the effect of pain therapy on pulmonary function) came from MEDLINE. Therefore, only MEDLINE 1966 to 1995 was searched. The following search terms were used: random, pain-postoperative, respirat, ventilat, atelectasis (MeSH heading [mh]), carbon dioxide (mh), forced expiratory volume (mh), oxygen (mh), lung (mh), peak expiratory flow rate (mh), pulmonary (mh), and vital capacity (mh). This search strategy produced 121 possibly useful trials evaluating the effects of pain treatment on pulmonary function. All 121 studies were retrieved and read by two investigators (JCB and DBC); 61 were not used in the analyses. Another 74 studies were identified from the references of the original 121 and examined; of these, 64 did not meet the criteria for inclusion in the analyses. If an author had produced several similar reports, we verified that the patients in the subsequent trials were different from those in the original trial by contacting the author (if this was not clear from the article). Of the 125 studies that were not suitable for analysis, 3 evaluated the same patients in multiple trials, 40 were found not to be RCTs, 5 did not provide satisfactory data despite being RCTs (e.g., they failed to provide any measures of variance), 53 used comparisons that were not encountered frequently enough to make meta-analysis worthwhile, and 24 did not provide specific data on pulmonary function. The remaining trials 65 trials used as a basis for the meta-analyses presented herein (from a total of 70 initially selected), which were found in sufficient number making the same treatment comparison, and assessing the same end points (see Appendix 1) (11–75). All data were extracted by one investigator (JCB) and verified by a second investigator (SdF). The 48 articles used in the meta-analyses are those containing combinable data and measures of variance (Table 1).

Quality Assessment

A cross-section of the available trials was assessed for quality using the method of Chalmers and Smith (76) and Liberati et al. (77). The articles were read and scored by two blind readers (IFA and TCC) according to a standardized checklist that considers both internal (scientific) validity and external (generalizable) validity. We performed a sensitivity analysis to determine whether the exclusion of low-quality studies changed the results, which it did not, probably because the quality ratings varied little among studies. We therefore decided to ignore the quality rating, an approach that has been justified by Emerson et al. (78).

Statistical Analysis

Measures of forced expired volume in 1 s (FEV_1), forced vital capacity (FVC), peak expiratory flow rate (PEFR), Pao_2, and incidences of atelectasis, pulmonary infiltrates, and pulmonary complications in general were analyzed. These measures were chosen for the

analyses because they were used frequently in the trials. FEV_1, FVC, PEFR, and Pao_2 are presented in the articles as means, usually with some measure of variance (e.g., SD). If an article reported measurements taken at multiple time points, the value at or near 24 h after surgery was selected for the analyses, because the 24-h time point was most often reported in these studies. FEV_1, FVC, and PEFR were reported in liters or liters per minute. Pao_2 was reported either as millimeters of mercury or as kilopascals; to compare measurements, we converted kilopascals to millimeters of mercury. The incidence of atelectasis was reported as the number or proportion of patients who exhibited clinical or radiological evidence of atelectasis.

The Der Simonian and Laird random effects model was used to combine data for both continuous and dichotomous outcomes (79). The random effects model calculates a weighted average by incorporating both within-study variation (sampling error) and between-study variation (different treatment effects). Compared with the fixed effect model, which considers only the within-study variation, the random effect model generally gives a similar estimate but a wider confidence interval when heterogeneity of treatment effect is present.

Calculations for dichotomous outcome data (incidence of atelectasis, incidence of pulmonary complications, and incidence of pulmonary infections) were performed using the Meta-Analyst program (80). The overall risk ratios (the ratio of the event rate in the treatment group to the event rate in the control group) and their respective 95% confidence intervals are reported.

A random effects weighted mean difference method was used to pool continuous data of each of the relevant outcomes (FEV_1, FVC, PEFR, and Pao_2). A difference between treatment means and its correlated standard error of the difference were extracted from the original studies or calculated using the method described in Appendix 2. Some studies reported the treatment effect as the change from preoperative to postoperative values along with their respective standard errors of the difference. These results were used directly. Other studies reported only the actual mean values and the standard error of the mean for each treatment separately, before and after the operation. In this case, because the exact value of the correlation coefficient is unknown, we estimated the standard error by carrying out the analyses using three different levels of correlation coefficient (ρ = 0.25, 0.5, 0.75). This approach was taken to test the sensitivity of the results to this unknown parameter. As suggested by the data, only positive correlation coefficients were used. Because the differences did not reach statistical significance at each correlation level, we present only the more conservative level, i.e., the lowest correlation (ρ = 0.25) in Table 1. Calculations of continuous data were performed using Mathcad software (81).

Results

The results of the meta-analyses are presented in Table 1. The only significant differences found are a decrease in the incidence of atelectasis when epidural opioid was compared with systemic opioid (risk ratio [RR] 0.53, 95% confidence interval [CI] 0.33–0.85) and a decrease in the incidence of pulmonary infection (RR 0.35, 95% CI 0.21–0.65) and of pulmonary complications overall (RR 0.58, 95% CI 0.42–0.80), as well as greater a Pao_2 concentration (difference 4.56 mm Hg, 95% CI 0.058–9.075) when epidural local anesthetic was compared with systemic opioid. The cumulative meta-analyses of the first three of these positive differences are presented in Figures 1, 2, and 3. Other differences that may be clinically important but that do not attain statistical significance are as follows. Compared with systemic opioids, epidural opioids had a weak tendency to reduce the incidence of pulmonary infection (RR 0.53, 95% CI 0.18–1.53). Intercostal nerve blockade tended to reduce the incidence of atelectasis (RR 0.65, 95% CI 0.27–1.57), as well as the incidence of pulmonary complications overall (RR 0.47, 95% CI 0.18–1.22). There are no clinically or statistically significant differences in other measures of pulmonary function (FEV_1, FVC, PEFR).

Review of Contributing Studies

The following is an overview of the contributing studies (Appendix 1), how their results and the results of our meta-analyses bear on each other, and the conclusions that we can draw from the meta-analyses (Table 1).

Epidural Opioids Versus Systemic Opioids

We analyzed 24 studies that compared epidural opioid treatment with systemic opioid treatment (11–34). Pain relief was found to be significantly better with epidural opioid treatment in 9 of these studies, but in 13 other studies, there was no significant improvement in pain relief (Appendix 1). Several investigators reported a statistically significant improvement in one or more surrogate measures of pulmonary function (FEV_1, FVC, and PEFR) (14,19,24,25,30–32), but others found either no difference or a trend toward improvement that did not reach statistical significance. When the data were pooled in the meta-analyses, none of the differences in surrogate measures reached statistical significance (Table 1). On the other hand, the pooled difference in the incidence of atelectasis (measured in 11 studies) did reach statistical significance (Fig. 1),

Table 1. Summary of Meta-Analytic Results

# Randomized Comparisons	Reference numbers	Outcome	Units	Risk Ratio	95% CI	Z	P	Difference (0.25 correlation)	95% CI	Z	P
Epidural opioid versus Systemic opioid											
6	14,14,17,21,27,30	FEV1	L					-0.1038	(-0.2493, 0.0417)	-1.398	0.162
7	11,14,14,17,21,27,30	FVC	L					-0.0511	(-0.2142, 0.1119)	-0.614	0.539
5	14,14,24,30,31	PEFR	L/min					-37.6059	(-117.3907, 42.1789)	-0.924	0.356
4	17,21,24,27	PaO2	mmHg					-1.469	(-7.9648, 5.0288)	-0.443	0.658
11	14-18,25-29,32	Atelectasis	# pts	0.53	(0.33, 0.85)	-2.6263	0.01				
5	15-18,24	Pulm. Inf.	# pts	0.53	(0.l8, l.53)	-1.1755	0.24				
4	13,22,24,25	Pulm.Comp.	# pts	0.51	(0.20, l.33)	-1.3759	0.17				
Epidural local anestheic versus Systemic opioid											
1	40	FEV1	L								
3	39-41	FVC	L					-0.2425	(-0.6601, 0.1752)	-1.138	0.255
1	39	PEFR	L/min								
6	36,37,38,38,39,41	PaO2	mmHg					-4.5666	(-9.0747, -0.0585)	-1.985	0.047
4	36,37,39,41	Atelectasis	# pts	0.74	(0.50, 1.11)	-1.45	0.15				
5	35-37,39,41	Pulm. Inf.	# pts	0.36	(0.21, 0.65)	-3.4432	<0.001				
6	13,22,35-37,39	Pulm.Comp.	# pts	0.58	(0.42,0.80)	-3.3297	<0.001				
Epidural opioid plus local anesthetic versus Systemic opioid											
0		FEV1	L								
1	43	FVC	L								
0		PEFR	L/min								
1	45	PaO2	mmHg								
2	45,46	Atelectasis	# pts	0.84	(0.58, l.24)	-0.8892	0.37				
2	44,45	Pulm. Inf.	# pts	0.83	(0.55, l.25)	-0.8951	0.37				
2	13,22	Pulm.Comp.	# pts	0.84	(0.l2, 5.80)	-0.1822	0.86				
Thoracic epidural opioid versus Lumbar epidural opioid											
5	14,47,48,50,51	FEV1	L					0.0478	(-0.1451, 0.2407)	0.4857	0.627
5	14,47,48,50,51	FVC	L					-0.0294	(0.245,0.1862)	-0.267	0.789
4	14,47,48,50	PEFR	L/min					-19.7792	(-83.2101, 43.6518)	-0.611	0.541
1	51	Pa02	mmHg								
1	14	Atelectasis	# pts								
0		Pulm Inf.	# pts								
0		Pulm. Comp.	# pts								
Intercostal nerve blockade versus Control											
2	54,55	FEV1	L					0.0326	(-0.4025,0.4678)	0.1468	0.883
2	54,55	FVC	L					-0.0514	(-0.5346, 0.4319)	-0.209	0.835
2	24,54	PEFR	L/min					-20.1986	(-225.5594, 185.1623)	-0.193	0.847
4	24,57-59	PaO2	mmHg					-0.399	(-5.9744, 5.1763)	-0.14	0.888
5	26,55,59-61	Atelectasis	# pts	0.65	0.27,1.57	-0.9556	0.34				
3	55,60,61	Pulm. Inf.	# pts	0.71	0.27,1.84	-0.706	0.48				
6	24,55-58,60	Pulm.Comp.	# pts	0.47	0.18,1.22	-1.5517	0.12				
Wound Infiltration versus Control											
2	64,66	FEV1	L					-0.2043	(-0.6414,0.2327)	-0.916	0.36
2	64,66	FVC	L					-0.5217	(-1.6234, 0.5799)	-0.928	0.353
0		PEFR	L/min								
5	66,67,67,67,68	PaO2	mmHg					-4.7428	(-11.5158, 2.0302)	-1.373	0.17
3	64,66,68	Atelectasis	# pts	0.83	0.47,1.45	-0.668	0.5				
2	64,67	Pulm. Inf.	# pts	1.04	0.69,1.58	0.1874	0.85				
1	66	Pulm. Comp.	# pts								
Intrapleural local anesthetic versus Control											
5	23,70-73	FEV1	L					-0.0262	(-0.3517, 0.2992)	-0.158	0.875
5	23,70-73	FVC	L					0.0488	(-0.2015, 0.2407)	0.4326	0.665
0		PEFR	L/min								
0		PaO2	mmHg								
0		Atelectasis	# pts								
0		Pulm. Inf.	# pts								
0		Pulm.Comp.	# pts								

In all cases, the first treatment is the experimental treatment and the second is the control treatment; for example, epidural opioid (experimental) versus systemic opioid (control). A negative sign denotes a difference in favor of the experimental treatment, whereas a positive sign denotes a difference in favor of the control treatment.

RCT = randomized controlled trial, CI = confidence interval, FEV1 = forced expired volume in one second, FVC = forced vital capacity, PEFR = peak expiratory flow rate, PaO2 = arterial partial pressure of oxygen, Pulm. Inf. = pulmonary infection rate, Pulm. Comp. = pulmonary complication rate.

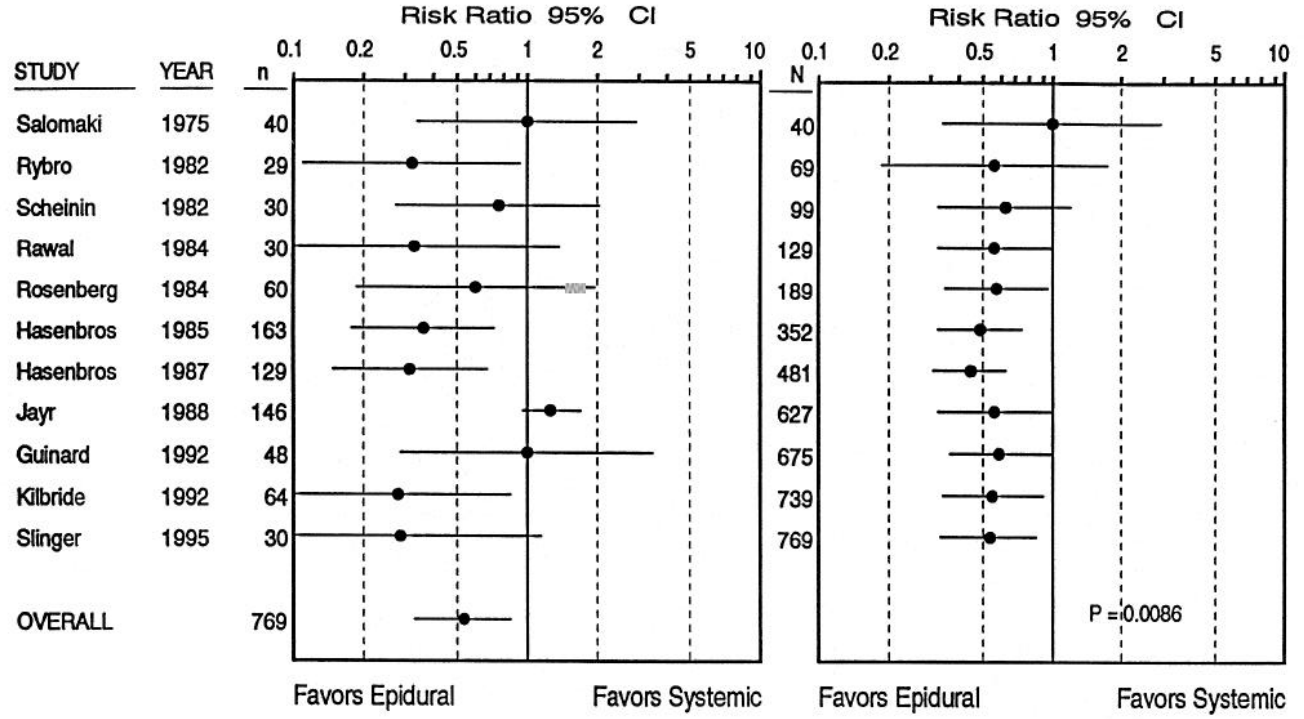

Figure 1. Epidural opioids versus systemic opioids: incidence of atelectasis based on the random effects model of Der Simonian and Laird. The cumulative meta-analysis is shown on the right. CI = confidence interval.

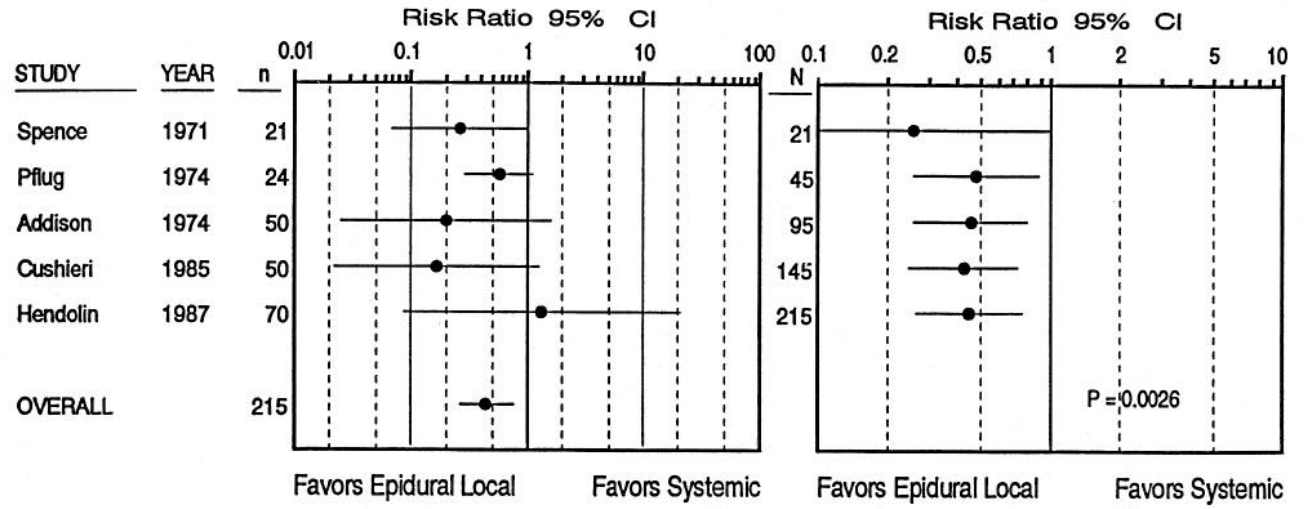

Figure 2. Epidural local anesthetics versus systemic opioids: incidence of pulmonary infection based on the random effects model of Der Simonian and Laird. The cumulative meta-analysis is shown on the right. CI = confidence interval.

even though it was only found to be significant in 3 of the individual studies (15,16,18). The difference in the incidence of pulmonary complications seems to tend toward statistical significance (4 studies) (Fig. 4) (see above).

Epidural Local Anesthetics Versus Systemic Opioids

Eleven papers contributed to these analyses (12,13,22,35–41). Most of the differences found by these investigators were positive, favoring the experimental treatment (epidural), although few of the differences in measures of pulmonary function actually attained statistical significance, except in the case of pulmonary complications. In the meta-analyses, there were no statistically significant differences in surrogate measures of pulmonary function (FEV_1, FVC, and PEFR), but both the incidence of pulmonary infection (Fig. 2) and the incidence of pulmonary complications (Fig. 3) were significantly lower in the epidural group.

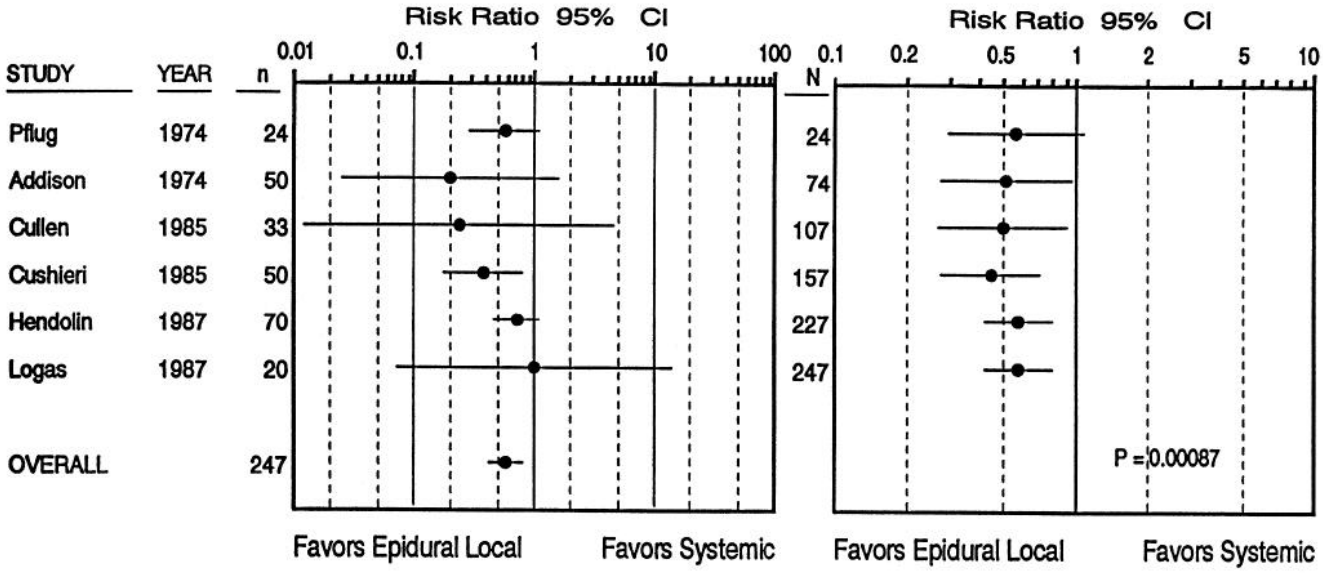

Figure 3. Epidural local anesthetics versus systemic opioids: incidence of pulmonary complications based on the random effects model of Der Simonian and Laird. The cumulative meta-analysis is shown on the right. CI = confidence interval.

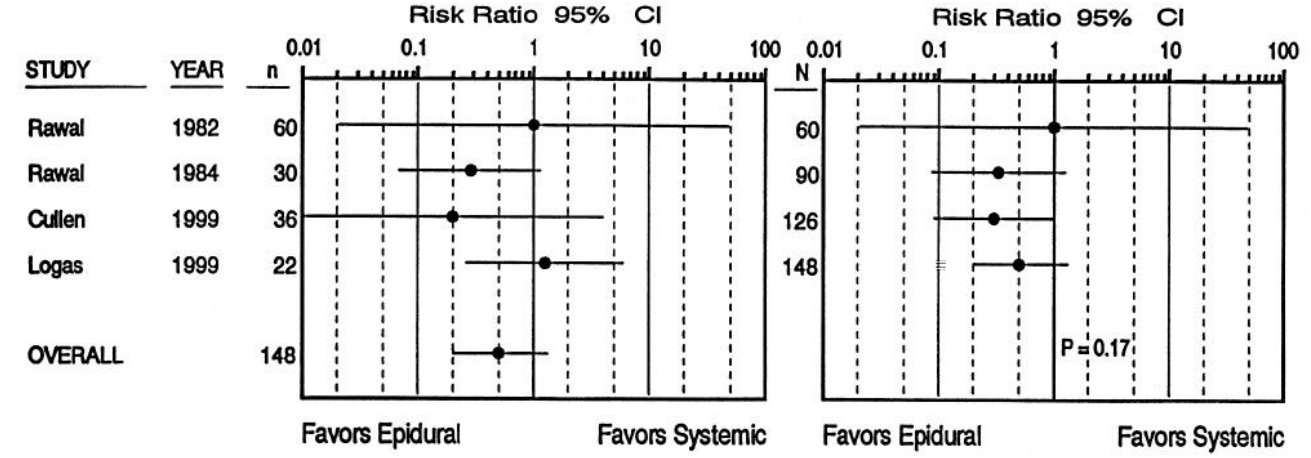

Figure 4. Epidural opioids versus systemic opioids: incidence of pulmonary complications based on the random effects model of Der Simonian and Laird. The cumulative meta-analysis is shown on the right. CI = confidence interval.

Oxygenation was also significantly better overall in patients receiving the epidural treatment (Table 1), but without data on whether supplementary oxygen was given, it is difficult to interpret this finding.

Epidural Local Anesthetics with Opioids Versus Systemic Opioids

Only seven RCTs contained data on pulmonary function (13,22,42–46). The epidural treatment was associated with superior analgesia in all trials. Although Brichon et al. (42), George et al. (43), and Jayr et al. (45) found statistically significant improvements in surrogate measures of pulmonary function (FEV1 and FVC), none of their data could be used in the meta-analyses; therefore, we cannot report an overall result. Only two of the studies contributed to the analyses of pulmonary complications—Jayr et al. (45) and Logas et al. (22)—and although the epidural treatment was associated with a lower incidence of complications overall, the differences did not reach statistical significance. In fact, Logas et al. (22) reported fewer pulmonary complications (not statistically significant), whereas Jayr et al. (45) reported no difference. With such a small number of trials, small number of patients, and inconclusive findings, it is not surprising that the meta-analyses did not produce significant results for this comparison.

Thoracic Versus Lumbar Epidural Opioids

There are eight papers that make this comparison (14,47–53). There are few positive findings and no significant differences in the analgesic effects of the

two treatments. Only Guinard et al. (14) found a statistically significant improvement in pulmonary function when catheters were placed in the thoracic region. In the meta-analyses, there were no clinically or statistically significant differences in analgesia or pulmonary function between thoracic and lumbar epidural opioids.

Intercostal Block Versus Systemic Opioid

Eleven papers contributed to these analyses (24,26, 54–62). Three potentially useful papers were excluded (82–84) because patients in these studies were also included in the updated study by Eng and Sabanathan (56). This was a difficult group to analyze because of differences in the treatments evaluated. Most examined the effect of a single (one time only) series of intercostal injections, but others used catheters and repeated the injections, or gave continuous infusions of a local anesthetic (54–56). In most of the studies, a systemic opioid was given on an as-needed basis to all patients (experimental and control), but in two of the studies (26,59), systemic medications were not given to patients receiving intercostal nerve blocks. However, because the measurements of pulmonary function we chose to analyze were taken within the likely duration of effectiveness of single-shot injections, before breakthrough medication was requested, we ignored these differences. Many investigators found statistically significant differences in surrogate measures of pulmonary function favoring the intercostal treatment (54,56–60,62), but overall, although differences do exist, none attained statistical significance. With regard to the analyses of pulmonary complications, most studies claimed no statistically significant differences (26,55,57,60,61), the only exception being a decrease in pulmonary complications associated with the intercostal treatment found by Eng and Sabanathan (56). However, RRs calculated in the meta-analyses (0.47, $P = 0.12$ for pulmonary complications overall; 0.65, $P = 0.34$ for atelectasis) suggest a clinically significant benefit to intercostal nerve blockade in terms of pulmonary outcome. In view of the preponderance of positive studies, intercostal nerve blockade might be effective in improving certain measures of pulmonary function, but additional trials are required to produce statistically significant differences. The question arises as to whether intercostal nerve blockade should be chosen instead of epidural treatments. We discovered only three studies (24,26,85) that address this issue in relation to pulmonary function, and the comparison was not made in the meta-analyses. To summarize the findings of the three studies, two [Rawal et al. (24) and Rosenberg et al. (26)] reported superior analgesia associated with the epidural treatment, but no significant differences in pulmonary function. Richardson et al. (85) reported that the intercostal treatment is as effective as the epidural treatment in all respects, including the effect on pulmonary function. Practical issues of the difficulty and risks of actually performing and maintaining intercostal nerve blockade also affect the utility of intercostal nerve blockade. On balance, evidence from the literature does not support the use of intercostal nerve blockade as a first-line treatment to improve either postoperative analgesia or pulmonary function, but does indicate that the treatment may be beneficial and, therefore, a useful option when epidural treatment is contraindicated or fails.

Wound Infiltration Versus No Wound Infiltration

Seven papers contributed to these analyses (63–69). Few differences in pulmonary function or analgesia were found. Improved analgesia was only demonstrated in one study, that of Levack et al. (65). In the meta-analyses, no statistically significant or clinically worthwhile differences emerged.

Intrapleural Infusion of Local Anesthetics Versus Systemic Opioids

Seven papers contributed to these analyses (23,70–75). A statistically significant increase in FEV_1 and FVC was the finding of three of the studies (70,74,75), but one (72) actually found a significant decrease in FEV_1 and FVC. In the meta-analyses, there was no demonstrable improvement in pulmonary function attributable to the intrapleural therapy (Table 1). However, analgesia was improved by the intrapleural treatment in studies except that of Oxorn and Whatley (72). In aggregate, the evidence indicates that the intrapleural infusion of local anesthetics may be a useful alternative to epidural analgesia in providing analgesia, despite a lack of convincing evidence of an improvement in pulmonary function.

Discussion

We conducted a systematic review of the effects of various analgesic therapies on pulmonary function. Although a conventional narrative review article can tease out different aspects of the individual trials for scrutiny and comment, it has the disadvantage of relying on the subjective approach to literature retrieval and to interpretation of the available data. Hence, one does not come away with concrete, rigorous data in support of the overview (86). The principal weakness of our systematic, quantitative approach is that we were forced, to pool sufficient data for meaningful analyses, to combine studies that are heterogeneous

(i.e., varying design, differing patient populations, different therapeutic regimens, and different surgical groups) (Appendix 1). On the other hand, our primary goal was not to argue for the advantage of one therapy over another in one patient group, or one therapeutic group, or one surgical group over another, but rather to derive concrete measures of the effects of selected postoperative analgesic therapies on pulmonary function.

Few statistically significant differences were found in any of these meta-analyses (Table 1). However, the differences that were found are important, being measures of outcome and concerning epidural treatments—the most widely used of the therapies under study. Other differences may reach statistical significance when more studies are available. We demonstrated a statistically significant decrease in the incidence of atelectasis in association with epidural opioid therapy (11 studies) (Fig. 1), and in the incidence of pulmonary infections (5 studies) and pulmonary complications overall (6 studies) in association with epidural local anesthetics (Figs. 2 and 3). If we also examine the graphical depiction of the cumulative meta-analysis of the incidence of pulmonary complications in relation to epidural opioid treatment (Fig. 4), a trend toward statistical significance seems to develop. If the evolution of the literature on pulmonary infections were to parallel that on atelectasis, the CI interval would decrease, and the effect would achieve significance as the number of available studies increased. Indeed, all of the variables analyzed herein show at least a trend in favor of the experimental treatments in terms of their effect on pulmonary function. With an increase in the number of well designed published trials, many of the measures could attain statistical significance in meta-analyses (87).

A key issue that arises from the failure of these meta-analyses to demonstrate a beneficial effect of the various pain therapies on physiological (surrogate) measures of pulmonary function (FEV_1, FVC, and PEFR), despite positive effects on pulmonary outcomes, is whether one should consider physiological measures as secondary findings without primary clinical importance. Not all studies that demonstrate superior analgesia in association with experimental treatments also demonstrate improvements in pulmonary function (Appendix 1). This suggests that factors other than pain are important in the etiology of postoperative pulmonary impairment. In fact, several investigators have elucidated an effect of surgery and general anesthesia on diaphragmatic function that is independent of pain or analgesia; namely, a reflex inhibition of phrenic nerve or diaphragmatic activation (88–94). In addition, changes in chest wall compliance independent of pain may result in postoperative pulmonary dysfunction (91,95). Analgesia *per se* may have little effect on these factors, but epidural anesthesia (using local anesthetics as opposed to opioids) may block the inhibitory reflex and result in an improvement in diaphragmatic and, hence, pulmonary function (92–94). Furthermore, the traditional measures of pulmonary function (all measures of expiratory flow) reported in the trials available may not be the best predictors of poor pulmonary outcome (96). Measures of inspiratory flow, airway pressure, diaphragmatic dynamics, or respiratory muscle contractile state might be better indicators of risk and more relevant measures of dysfunction. Hence, although the physiological (surrogate) measures that we used may not reveal significance, other measures could, and could account for the favorable effects on outcome that have been demonstrated by these studies. At the same time, the analgesic measures used in the trials we analyzed (i.e., measures of pain at rest) may be poor predictors of changes in pulmonary mechanics, whereas measures of pain with activity (i.e., during deep breathing or cough) might correlate better with pulmonary function (97). The effects of improved analgesia at rest, in themselves, do not seem to sufficiently account for improved pulmonary mechanics (Appendix 1), but perhaps the picture would be different if other measures of pain and pulmonary function were used.

We should also note the improved Pao_2 during epidural local anesthetic treatment (difference 4.56 mm Hg, $P = 0.047$). Maintenance of adequate oxygenation is obviously important, particularly in the early postoperative period, when hypoxemia resulting from the effects of surgery and anesthesia is common and can provoke or exacerbate myocardial ischemia (98,99). Hypoxemia can be a devastating consequence of postoperative pulmonary dysfunction. Postoperative epidural analgesia using local anesthetics may be particularly beneficial because it avoids the use of respiratory depressant opioids. However, in the trials that we studied, there was little, if any, control of the use of supplementary oxygen. The results of an individual study that does control the use of supplementary oxygen (38) may be important (Appendix 1), but whether our result can be taken as a true indication that the epidural local anesthetic treatment is superior in terms of oxygenation is debatable. Hence, because of the general inattention to the use of supplementary oxygen in the trials, the result of this meta-analysis must be viewed with caution.

We conclude that postoperative respiratory dysfunction is universally observed after abdominal and thoracic surgery (100–102). Abnormalities that contribute to reduced lung volumes and hypoxemia in the postoperative period include impaired central ventilatory control; abnormal pulmonary mechanics due to limited abdominal, intercostal, and diaphragmatic muscle contraction; and changes in the pulmonary

circulation and pulmonary gas exchange. Observed abnormalities are due not only to sequelae of the operation itself, such as tissue injury or pain, but also to residual effects of anesthetics and analgesics (4,90–92,94,95). Such effects have been widely studied and well described (103). Our goal was to assess differences in clinical outcomes with respect to respiratory status as explored in RCTs of commonly applied postoperative analgesic techniques.

Our meta-analyses show that clinical measures of pulmonary outcome (incidence of atelectasis, infection, and other complications) are significantly improved by epidural opioid and epidural local anesthetic treatments. Differences in physiological (surrogate) measures of pulmonary function did not reach statistical significance, but this could be due to either the small number of patients analyzed or the failure of the chosen measures to reflect pulmonary outcome. Perhaps for the same reasons, no significant differences were found for treatments other than epidural opioid and epidural local anesthetics.

Further analysis might help to outline possible correlations between pulmonary function and factors such as doses, volumes, and mixtures of drugs used; segmental level of anesthetic blockade; type of nerve block used; and area of peripheral neural blockade. However, such analyses are beyond the scope of this paper and would be unwarranted given the paucity of published RCTs. Despite these methodological difficulties, these meta-analyses provide convincing evidence that postoperative epidural analgesia can significantly decrease pulmonary morbidity.

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Appendix 1. Study Details

EPIDURAL OPIOID VERSUS SYSTEMIC OPIOID

	STUDY CHARACTERISTICS					AUTHORS' FINDINGS					
AUTHOR	PROCEDURE	CONTROL GROUP	NUMBER OF PATIENTS (EXP/CONTR)	EPIDURAL LEVEL	EPIDURAL DRUG	FEV1	FVC	PEFR	PaO2	Pulmonary Complications	Analgesia
Benzon et al 1993 (11)	thoracotomy	PCA	18/18	T	fentanyl		0				+
Brownridge and Frewin 1985 (12)	C-section & lower abdominal	CONV	19/19	L	meperidine	0					+
Cullen et al 1985 (13)	abdominal	IV or IM DEMAND	18/18	T&L	morphine					0	+
Guinard et al 1992 (14)	thoractomy	CONV	16/16	T&L	fentanyl	+	+	+		0	0
Hasenbos et al 1985 (15)	thoracotomy	CONV	83/80	T	nicomorphine					+	
Hasenbos et al 1987 (16)	thoracotomy	CONV	58/71	T	nicomorphine					+	+
Jayr et al 1988 (17)	abdominal	SQ DEMAND	64/67	T	morphine	0	0		0	0	+
Kilbride et al 1992 (18)	abdominal	CONV & PCA	23/19/22*	L	morphine					+	+
Kirsch et al 1991 (19)	thoracotomy	IV DEMAND	9/10	L	morphine		+		0		0
Klinck and Lindop 1982 (20)	upper abdominal	CONV	10/10	T	morphine	0				0	0
Larsen et al 1986 (21)	thoracotomy	SQ DEMAND	10/10	T	morphine	0	0	0	0		0
Logas et al 1987 (22)	thoracotomy	CONV	12/10	T	morphine					0	0
Miguel and Hubbell 1993 (23)	thoracotomy	IV DEMAND	10/11	L	morphine	0	0				0
Rawal et al 1982 (24)	upper abdominal	CONV	30/30	T	morphine			+		0	0
Rawal et al 1984 (25)	upper abdominal	CONV	15/15	T	morphine		0	+	0	0	0
Rosenberg et al 1984 (26)	upper abdominal	CONV & PCA	20/20/20*	T	morphine			0		0	0
Rybro et al 1982 (27)	upper abdominal	CONV	14/15	T	morphine	0	0		+	0	
Salomaki et al 1991 (28)	thoracotomy	CONT IV	20/20	T	fentanyl					0	0
Scheinin and Rosenberg 1982 (29)	upper abdominal	CONV	10/10/10*	T	morphine	0				0	+
Sshulman et al 1984 (30)	thoracotomy	IV DEMAND	14/14	L	morphine	+	+	+	0		+
Simpson et al 1993 (31)	abdominal	CONV	6/7	unknown	morphine	+	+				0
Slinger et al 1995 (32)	thoracotomy	PCA	15/15	L	meperidine	+				0	+
Tsui et al 1991 (33)	thoracotomy & upper abdominal	CONV	17/16/14*	L	morphine & fentanyl	0	0	0			0
Welchew and Thorton 1982 (34)	upper abdominal	CONV	10/10	T	fentanyl	+	+	+			0

EPIDURAL LOCAL ANESTHETIC VERSUS SYSTEMIC OPIOID

	STUDY CHARACTERISTICS					AUTHORS' FINDINGS					
AUTHOR	PROCEDURE	CONTROL GROUP	NUMBER OF PATIENTS (EXP/CONTR)	EPIDURAL LEVEL	EPIDURAL DRUG	FEV1	FVC	PEFR	PaO2	Pulmonary Complications	Analgesia
Addison et al 1974 (35)	cholecystectomy	CONV	25/25	T	bupivacaine					+	+
Brownridge and Frewin 1985 (12)	C-section & lower abdominal	CONV	19/19	L	bupivacaine	0					0
Cullen et al 1985 (13)	abdominal	IV or IM DEMAND	15/18	T & L	bupivacaine					0	+
Cuschieri et al 1985 (36)	cholecystectomy	CONV	25/25	T	bupivacaine				+	+	+
Hendolin et al 1987 (37)	cholecystectomy	CONV	30/40	T	bupivacaine	0	0	+	0	+	
Logas et al 1987 (22)	thoracotomy	CONV	10/10	T	bupivacaine					0	0
Muneyuki et al 1968 (38)	upper abdominal	IV DEMAND	17/19	T	mepivacaine				+		
Pflug et al 1974 (39)	upper abdominal & hip	CONV	13/11	T	bupivacaine		0	0	0	+	
Rademaker et al 1992 (40)	laparoscopic cholecystectomy	CONV	10/10	T	bupivacaine	0	+	0			0
Scheinin and Rosenberg 1982 (29)	upper abdominal	CONV	10/10	T	bupivacaine	0				0	0
Spence and Smith 1971 (41)	upper abdominal	CONV	11/10	T	bupivacaine		0		+	+	

Appendix 1.—*Continued*

EPIDURAL OPIOID PLUS LOCAL ANESTHETIC VERSUS SYSTEMIC OPIOID

	STUDY CHARACTERISTICS					AUTHORS' FINDINGS					
AUTHOR	PROCEDURE	CONTROL GROUP	NUMBER OF PATIENTS (EXP/CONTR)	EPIDURAL LEVEL	EPIDURAL DRUG	FEV1	FVC	PEFR	PaO2	Pulmonary Complications	Analgesia
Brichon et al 1994 (42)	thoracotomy	IV DEMAND	46/33	T	fentanyl & bupivacaine	+	+				+
Cullen et al 1985 (13)	adbominal	IV or IM DEMAND	15/18	T & L	morphine & bupivacine					0	+
George et al 1994 (43)	upper abdominal	PCA	10/11	T	fentanyl & bupivacaine	0	+	+			+
Hjortso et al 1985 (44)	abdominal	CONV	44/50	unknown	morphine & bupivacine					0	+
Jayr et al 1993 (45)	abdominal	IV DEMAND	78/75	T	morphine & bupivacine	+	+		+	0	+
Liem et al 1992 (46)	CABG	IV DEMAND	25/25	T	sufentanyl & bupivacaine				0	+	+
Logas et al 1987 (22)	thoracotomy	CONV	11/10	T	morphine & bupivacine					0	+

THORACIC EPIDURAL OPIOID VERSUS LUMBAR EPIDURAL OPOIOD

	STUDY CHARACTERISTICS				AUTHORS' FINDINGS					
AUTHOR	PROCEDURE		NUMBER OF PATIENTS (EXP/CONTR)	EPIDURAL DRUG	FEV1	FVC	PEFR	PaO2	Pulmonary Complications	Analgesia
Grant et al 1993 (47)	thoracotomy		10/10	morphine	0	0	0			0
Guinard et al 1993 (14)	thoracotomy		16/16	fentanyl	+	+	+	0	0	0
Hakanson et al 1989 (48)	cholecystectomy		20/17	morphine	0	0	0			0
Hurford et al 1993 (49)	thoracotomy		28/17	fentanyl & bupivacaine						0
Larsen et al 1985 (50)	upper abdominal		15/15	morphine	0	0	0	0		0
Sawchuk et al 1993 (51)	thoracotomy		15/15	fentanyl	0	0		0		
Swenson et al 1994 (52)	thoracotomy		10/12	sufentanyl		0				0
Verborgh et al 1994 (53)	cholecystectomy		20/20	sufentanyl	0	0	0			0

INTERCOSTAL NERVE BLOCKADE VERSUS CONTROL

	STUDY CHARACTERISTICS				AUTHORS' FINDINGS					
AUTHOR	PROCEDURE	CONTROL GROUP	NUMBER OF PATIENTS (EXP/CONTR)	CONTINUOUS OR ONCE ONLY	FEV1	FVC	PEFR	PaO2	Pulmonary Complications	Analgesia
Chan et al 1991 (54)	thoracotomy	IV DEMAND	10/10	continuous	+	+	+			+
Deneuville et al 1993 (55)	thoracotomy	IM RTC	26/26/34*	continuous	0	0			0	0
Eng and Sabanathan 1992 (56)	thoracotomy	CONV	40/40	continuous	+	+	+		+	+
Engberg 1975 (57)	upper abdominal	CONV	37/37	once only	+	+	+	0	0	
Engberg 1985 (58)	upper abdominal	CONV	21/22	once only	+	+	+	+		
Faust and Nauss 1976 (59)	thoracotomy	CONV	17/17	once only		+		0	0	
Kaplan et al 1975 (60)	thoracotomy	CONV	6/6	once only	+	+		+	0	+
Rowal et al 1982 (24)	cholecystectomy	CONV	30/30	once only			0	0	0	0
Rosenberg et al 1984 (26)	cholecystectomy	CONV & PCA	20/20/20*	once only			0		0	0
Ross et al 1989 (61)	cholecystectomy	CONV	31/35	once only	0	0	0	0	0	0
Toledo-Pereyra and DeMeester 1979 (62)	thoracotomy	CONV	10/10	once only	+	+				

Appendix 1.—*Continued*

WOUND INFILTRATION VERSUS CONTROL													
	STUDY CHARACTERISTICS					AUTHORS' FINDINGS					
AUTHOR	PROCEDURE	CONTROL GROUP	NUMBER OF PATIENTS (EXP/CONTR)			FEV1	FVC	PEFR	PaO2	Pulmonary Complications	Analgesia
Aull et al 1990 (63)	abdominal	PCA	29/29						0		0
Egan et al 1988 (64)	abdominal	CONV	202/213			0	0			0	
Levack et al 1986 (65)	abdominal	CONV	25/25				+				+
Patel et al 1983 (66)	cholecystectomy	CONV	17/23			0	0		0	+	
Pfeiffer et al 1991 (67)	aortic surgery	CONV	37/33			0	0	0	0	0	0
Russell et al 1993 (68)	cholecystectomy	CONV	14/16/16*			0	0	0	0	0	0
van Raay et al 1992 (69)	cholecystectomy	SQ DEMAND	25/25			0	0				

INTRAPLEURAL LOCAL ANESTHETIC VERSUS CONTROL													
	STUDY CHARACTERISTICS					AUTHORS' FINDINGS					
AUTHOR	PROCEDURE	CONTROL GROUP	NUMBER OF PATIENTS (EXP/CONTR)			Conv FEV1	FVC	PEFR	PaO2	Pulmonary Complications	Analgesia
Frenette et al 1991 (70)	cholecystectomy	CONV	22/20			+	+				+
Lee et al 1990 (71)	cholecystectomy	PCA	10/10			0	0				+
Miguel and Hubbell 1993 (23)	thoractomy	IV DEMAND	10/11			0	0				+
Oxorn and Whatley 1989 (72)	cholecystectomy	CONV	12/12			-	-			0	0
Raffin et al 1994 (73)	thoractomy	PCA	8/8			0	0	0	0		+
Symreng et al 1989 (74)	thoracotomy	IV DEMAND	7/8			+	+	+			+
VadeBoncouer et al 1989 (75)	cholecystectomy	PCA	10/10			+	0				

EXP = experimental, CONTR = control, C-section = cesarean section, CABG = coronary artery bypass grafting, PCA = patient-controlled analgesia, CONV = conventional analgesia (intramuscular opioid given on an as-needed basis), DEMAND = as needed, SQ = subcutaneous, RTC = round the clock, T = thoracic, L = lumbar, FEV1 = forced expired volume in 1 s, FVC = forced vital capacity, PEFR = peak expiratory flow rate, PaO2 = arterial partial pressure of oxygen.

0 = the variable was studied but no statistical significance was found, + = a statistically significant result in favor of the experimental treatment, − = a statistically significant result in favor of the control treatment.

In all cases, the first treatment is the experimental, and the second is the control treatment; for example, epidural opioid (experimental) versus systemic opioid (control). In the comparison "intercostal nerve block versus control," when treatment is continuous, the control group received saline through the indwelling catheter. When treatment was by single injection, there were no placebo injections.

*For cases in which comparisons are more complex than EXP versus CONTR, the following apply: Kilbride et al., 92, EXP/CONV/PCA; Rosenberg et al., 84, EXP/CONV/PCA; Scheinin and Rosenberg, 82, EXP (large dose)/EXP (small dose)/CONV; Tsui et al., 91, EXP (morphine)/EXP (fentanyl)/CONV; Deneuville et al., 93, EXP/saline through catheter/no catheter; Russell et al., 93, EXP (plain)/EXP (with dextran)/CONV.

The right side of the table summarizes the *authors' findings* and is presented to aid the reader's interpretation of the results of the meta-analyses. As far as possible, we have reported what the authors actually concluded about significance, rather than drawing our own conclusions from their data. Occasionally, the significance or nonsignificance of results is open to conjecture.

Appendix 2

When the standard error of the difference of the pre- and posttreatment means of a treatment group was not reported, we estimated the standard error using the method described herein.

For each treatment group, the relationship between the correlation coefficient ρ, the pre- and posttreatment covariance [*Cov(pre, post)*], the standard error of the pretreatment mean (σ_{pre}), and the standard error of the posttreatment mean (σ_{post}), was defined as:

$$\rho = \frac{\text{Cov(pre, post)}}{(\sigma_{pre} \cdot \sigma_{post})}.$$

Using the definition of the variance of the difference of pre- and posttreatment means, we have:

$$\text{Var(pre} - \text{post)} = \text{Var(pre)} + \text{Var(post)} - 2 \cdot \text{Cov(pre, post)}.$$

It follows that, for each treatment group, the standard error of difference of pre- and posttreatment means is:

$$\sigma_{pre - post} = \sqrt{\sigma^2 pre + \sigma^2 post - 2 \cdot \rho \cdot \sigma pre \cdot \sigma post}.$$

Because the exact value of the correlation coefficient ρ was unknown, we estimated the standard error by performing analyses using three different levels of the correlation coefficient (ρ = 0.25, 0.5, 0.75). As suggested by the data, only positive correlation coefficients were used. Because the differences failed to reach statistical significance at each correlation level, we presented only the more conservative level, i.e., the lowest correlation (ρ = 0.25), in Table 1.

Because the comparison treatment groups (x, y) are independent (e.g., epidural versus conventional), the variance is simply:

$$\text{Var}(x_{[pre - post]} - y_{[pre - post]}) = \text{Var}(x_{[pre - post]}) + \text{Var}(y_{[pre - post]}).$$

The standard error could now be estimated as:

$$\sigma x_{[pre - post]} - y_{[pre - post]} = \sqrt{\sigma^2 x_{[pre - post]} + \sigma^2 y_{[pre - post]}}.$$

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