A Systematic Review of Randomized Trials Evaluating Regional Techniques for Postthoracotomy Analgesia

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BACKGROUND: Thoracotomy induces severe postoperative pain and impairment of pulmonary function, and therefore regional analgesia has been intensively studied in this procedure. Thoracic epidural analgesia is commonly considered the "gold standard" in this setting; however, evaluation of the evidence is needed to assess the comparative benefits of alternative techniques, guide clinical practice and identify areas requiring further research.

METHODS: In this systematic review of randomized trials we evaluated thoracic epidural, paravertebral, intrathecal, intercostal, and interpleural analgesic techniques, compared to each other and to systemic opioid analgesia, in adult thoracotomy. Postoperative pain, analgesic use, and complications were analyzed.

RESULTS: Continuous paravertebral block was as effective as thoracic epidural analgesia with local anesthetic (LA) but was associated with a reduced incidence of hypotension. Paravertebral block reduced the incidence of pulmonary complications compared with systemic analgesia, whereas thoracic epidural analgesia did not. Thoracic epidural analgesia was superior to intrathecal and intercostal techniques, although these were superior to systemic analgesia; interpleural analgesia was inadequate.

CONCLUSIONS: Either thoracic epidural analgesia with LA plus opioid or continuous paravertebral block with LA can be recommended. Where these techniques are not possible, or are contraindicated, intrathecal opioid or intercostal nerve block are recommended despite insufficient duration of analgesia, which requires the use of supplementary systemic analgesia. Quantitative meta-analyses were limited by heterogeneity in study design, and subject numbers were small. Further well designed studies are required to investigate the optimum components of the epidural solution and to rigorously evaluate the risks/benefits of continuous infusion paravertebral and intercostal techniques compared with thoracic epidural analgesia.

(Anesth Analg 2008;107:1026–40)

Patients undergoing thoracotomy may suffer from severe postoperative pain if analgesia is not managed appropriately. In addition, pulmonary function is impaired as a result of thoracotomy, and may be worsened by the effects of pain,[1] whereas the risk of pulmonary complications may be reduced by adequate analgesia and physical therapy.[2] Since acute postoperative pain is also a predictor of long-term pain after thoracotomy, early and aggressive treatment of pain may help to reduce the currently high frequency of chronic pain.[3–5] Although thoracic epidural analgesia is commonly considered the "gold standard" for postoperative pain treatment after thoracotomy, this technique may fail, be contraindicated

This article has supplementary material on the Web site: www.anesthesia-analgesia.org.

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Accepted for publication April 22, 2008.

Supported by Pfizer Inc., New York, NY, USA. This paper reviews regional analgesic techniques for the treatment of postthoracotomy pain and makes no specific recommendations about the use of any medical products, drugs or equipment manufactured by Pfizer Inc. or by any of its subsidiaries or any other company. Pfizer manufactures several systemic (not regional) drugs with analgesic properties (although not all are indicated for the treatment of postoperative pain); these include parecoxib, celecoxib, gabapentin, pregabalin and ketamine, but these are not reviewed in this paper. The PROSPECT recommendations are derived by consensus of the members of the PROSPECT Working Group, based on available published evidence, and are not the views of Pfizer or Choice Pharma.

Reprints will not be available from the author.

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DOI: 10.1213/ane.0b013e31817e7b40

or not be possible for a variety of reasons. Evidence has suggested that paravertebral block is also an effective technique for analgesia in thoracotomy, which is associated with fewer side effects than epidural analgesia.[6] Intercostal nerve block, intrathecal administration of opioid, and interpleural analgesia have also been developed as alternative regional techniques for postthoracotomy pain control.[5,7,8] Many of these techniques are claimed to provide good pain control and continue to undergo further study, but a systematic review of the evidence for all these regional analgesic techniques has not been performed. Such a review is needed to provide clinicians with comprehensive information to guide their choice of regional analgesic technique for the management of postthoracotomy pain, and to direct the design of future trials in this field.

The Procedure-Specific Postoperative Pain Management (PROSPECT) working group is a collaboration of anesthesiologists and surgeons working to formulate evidence-based recommendations for pain management that are specific for different surgical procedures.[9–11] Graded recommendations are based on procedure-specific evidence from a systematic review, supplementary transferable evidence from other relevant procedures, and clinical practice information. For each procedure reviewed, all this information is available at www.postoppain.org. The aim of this current systematic review, performed by the PROSPECT working group, was to evaluate the available literature comparing various regional analgesic techniques for the management of postthoracotomy pain. Postoperative pain outcomes were the primary focus of this review, but other recovery outcomes (including side effects and pulmonary complications) were also assessed where reported, and the limitations of the data were reviewed.

METHODS

Search Strategy

A systematic review of the literature concerning regional analgesia after thoracotomy was conducted according to the protocol recommended by the Cochrane Collaboration.[12] The literature search was performed in EMBASE and MEDLINE, between 1966 and May 2004. Search terms related to pain or analgesic techniques (pain, analgesia, anesthesia, anesthetic, "visual analog," VRS, McGill, epidural, neuraxial, spinal, caudal, intrathecal, "paravertebral block," narcotic, intrapleural, "intercostal block," "continuous intercostal nerve block," "combined epidural-general," "combined regional-general") were combined with procedure-specific search terms (lobectomy, "thoracic surgery," "intrathoracic surgery," "hemithoracic surgery," "chest surgery," thoracotomy, postthoracotomy, post-thoracotomy, "post thoracotomy," cardio-thoracic, pulmonectomy, pneumonectomy).

Study Inclusion Criteria

Randomized, controlled trials of regional analgesic or anesthetic interventions, in adult thoracotomy, reporting pain scores (visual analog scale or verbal/numerical rating scales [VRS/NRS]) were included. Non-English language reports were excluded. This current review focuses on those studies that compared the following regional analgesic techniques with systemic opioid analgesia and/or with each other: thoracic epidural local anesthetic (LA) plus opioid; thoracic epidural LA or opioid alone; intrathecal opioid; thoracic paravertebral block using LA with or without opioid; intercostal nerve block with LA; interpleural LA and/or opioid.

Methodological Quality of Included Studies

Eligible studies were graded using two scoring systems. First, the adequacy of allocation concealment was graded as follows: A, adequate; B, unclear; C, inadequate; D, not used. Second, each report was scored using a 5-point scale in which a score of 1 is given for each of the following: the description of the study as randomized, the description of an appropriate method of randomization, the description of the study as double-blind, the description of an appropriate method of double-blinding, and a statement of withdrawals, as described by Jadad et al.[13] As nonrandomized studies were excluded, the minimum score was 1 and the maximum 5.

Analysis of Outcomes

Summary information from each study was recorded in data tables. The primary outcome was postoperative pain scores, and secondary outcomes were supplementary analgesic requirements and adverse effects (nausea, vomiting, pruritus, urinary retention, sedation, hypotension, and pulmonary complications including atelectasis and pneumonia), where reported. Postoperative pain scores were assumed to be recorded at rest, unless otherwise specified in the study report. For qualitative and quantitative analyses, studies were stratified according to mode of delivery (peripheral, neuraxial, systemic) and type of analgesic (LA or opioid) in each comparison group. The effectiveness of each technique was evaluated qualitatively by assessing the numbers of studies showing a significant difference between treatment groups ($P < 0.05$ as reported in the study publication).

Statistical Analysis

Quantitative analyses were performed using Review Manager software, which calculates the weighted mean differences for continuous data or the odds ratio for dichotomous data, between active and control groups for each study, with an overall estimate of the pooled effect. Means and standard deviations (SD) were extracted from the text, tables or graphs within the studies. The Review Manager software performs heterogeneity analyses; data that were not significantly heterogeneous ($P > 0.1$) were analyzed using a fixed effects model, and heterogeneous data ($P \leq 0.1$) were analyzed using a random effects model. For quantitative analyses, pain scores on verbal rating scale or numerical rating scale were converted to visual analog scale pain scores, 0–100 mm scale. Studies could

Table 1. Regional Analgesic Techniques Versus Systemic Analgesia: Effect on Pain Scores and Supplementary Analgesia

Regional analgesic technique versus control	Effect on pain scores				Effect on supplementary analgesic use
	Day of surgery	Day 1	Day 2	Day 3	
Thoracic epidural LA plus opioid versus systemic opioid[14–21]	▼[14,15,17,20] NS[18,19]	▼[14–16,19–21] NS[18]	▼[14–16,19–21] NS[18]	▼[14–16,19,21]	▼[16,17,19]
Thoracic epidural LA versus systemic opioid[19,22,23]	▼[22,23] NS[19]	▼[23] NS[19]	▼[23] NS[19]	NS[19,23]	▼[22] NS[19]
Thoracic epidural lipophilic opioid versus systemic opioid[24–26]	▼[24] NS[25,26]	▼[24] NS[25,26]	▼[24] NS[25]	▼[24]	▼[25,26] NS[24]
Thoracic epidural hydrophilic opioid versus systemic opioid[19,27–30]	▼[27*a*] NS[19,28–30]	NS[19,27–30]	▼[19] NS[28,30]	▼[19] NS[28]	▼[19,27*a*] NS[29]
Postoperative thoracic paravertebral block versus paravertebral saline or no paravertebral block[31–38]	▼[32–34,36*c*,37,38] NS[31,35]	▼[31–34,37,38] NS[35,36]	▼[31–33,37,38] NS[35,36]	▼[32,33,37,38] NS[31,36]	▼[31,32,34,35*b*,36*c*,37,38*bc*]
Pre-incisional thoracic paravertebral block versus no paravertebral block[39]	▼[39]	▼[39]	NS[39]	—	▼[39]
Pre-operative intrathecal lipophilic or hydrophilic opioid versus no intrathecal opioid[40]	▼[40]	NS[40]	—	—	▼[40]
Pre-operative intrathecal lipophilic + hydrophilic opioid versus no intrathecal opioid[40,41]	▼[40,41]	▼[41] NS[40]	NS[41]	NS[41]	▼[40,41]
Postoperative intrathecal lipophilic opioid versus no intrathecal opioid[42]	▼[42]	—	—	—	▼[42]
Single intraoperative dose intercostal nerve block versus saline or no intercostal nerve block[43–46]	▼[44,45]	▼[43,45] NS[44,46]	▼[43,45] NS[44,46]	▼[43,45] NS[44,46]	NS[43–46]
Repeat intercostal nerve block versus saline or no intercostal nerve block[22,46,47]	▼[22,47]	▼[47] NS[46]	NS[46]	NS[46]	▼[22,47] NS[46]
Continuous infusion intercostal nerve block versus saline[48]	▼[48]	▼[48]	▼[48]	—	▼[48]
Interpleural LA versus saline or no interpleural LA[22,49–57]	▼[49,50,52,56,57] ▲[22] NS[51,53,55]	▼[50,56] NS[51–54]	NS[50,51,54]	▼[50]	▼[49,50,52,53,57] ▲[22] NS[51,54,55]
Interpleural morphine versus intravenous morphine[58] or interpleural saline[59]	▼[58] NS[59]	▼[58] NS[59]	—	—	NS[59]

▼: Pain scores reduced at one or more time points during the specified day, or analgesic use reduced, in treatment group versus control group.

▲: Pain scores increased at one or more time points during the specified day, or analgesic use increased, in treatment group versus control group; NS: no significant difference between groups.

[a] Reduced when control group was IV PCA morphine, but NS when control group was IV infusion tramadol.

[b] Reduced when control group was no paravertebral block, but increased when control group was IM ketorolac.

[c] Reduced when control group was no paravertebral block, but NS when control group was paravertebral saline infusion.

not be included in the meta-analyses if they did not report mean and SD or standard error of the mean (SEM), or the proportion of patients.

RESULTS

Seventy-four randomized studies in thoracotomy were identified that compared regional analgesic techniques with systemic opioid analgesia or with each other. The results of these studies are summarized in Tables 1[14–59] and 2,[19,22,60–87] with additional details of the study protocols and quantitative analyses in Appendix Tables A-S (available at www.anesthesia-analgesia.org and at www.postoppain.org.).* Method-

*Further details of treatment regimens, qualitative analyses, and figures showing additional quantitative analyses for pain scores, supplementary analgesic use and adverse effects are presented at www.postoppain.org.

Table 2. Regional Analgesic Techniques Versus Other Regional Analgesic Techniques: Effect on Pain Scores and Supplementary Analgesia

Regional analgesic technique versus active control	Effect on pain scores				Effect on supplementary analgesic use
	Day of surgery	Day 1	Day 2	Day 3	
Thoracic paravertebral block with LA versus thoracic epidural LA[60–64]	▼[64] NS[60–62]	▼[64] NS[61–63]	▼[64] NS[62,63]	—	▼[64] NS[60,62,63]
Thoracic paravertebral block with LA versus thoracic epidural LA plus opioid[65,66]	▲[65] NS[66]	NS[65,66]	▼[66] NS[65]	▼[66]	▼[66] NS[65]
Thoracic paravertebral LA plus opioid versus thoracic epidural LA plus opioid[67]	▲[67]	▲[67]	NS[67]	NS[67]	NS[67]
Thoracic paravertebral block with LA versus intercostal nerve block with LA[62]	NS[62]	NS[62]	NS[62]	—	NS[62]
Intrathecal opioid versus thoracic epidural LA plus opioid[68]	—	NS[68]	NS[68]	—	—
Single intraoperative dose intercostal nerve block with LA versus thoracic epidural analgesia with LA or opioid[62,69–71]	▼[62] NS[69–71]	▲[71] NS[62,69,70]	▲[71] NS[62]	▲[71]	▲[69–71] NS[62]
Repeated dose intercostal nerve blocks with LA versus thoracic epidural analgesia with LA or opioid[22,69,70]	NS[22,69,70]	NS[69,70]	—	—	NS[22,70]
Continuous infusion intercostal nerve block with LA versus thoracic epidural LA infusion[72]	▲[72]	▲[72]	—	—	NS[72]
Interpleural LA with[63] or without[22,73] wound infiltration versus thoracic epidural LA	▲[22] NS[73]	NS[63]	▲[63]	—	▲[22,63] NS[73]
Interpleural LA with[63] or without[74,75] wound infiltration versus thoracic paravertebral LA	NS[74,75]	NS[63,74,75]	▲[63] NS[74,75]	—	▲[63] NS[74,75]
Interpleural LA versus intercostal nerve block with LA[22,76]	▲[22] NS[76]	NS[76]	NS[76]	—	▲[22] ▼[76]
Thoracic epidural LA plus lipophilic opioid versus thoracic epidural lipophilic opioid alone[77–81]	▼[78–79,81] NS[77,80]	▼[79,80] NS[77,78,81]	▼[79,80] NS[78]	—	▼[77,79,80] NS[78,81]
Thoracic epidural LA plus hydrophilic opioid versus thoracic epidural hydrophilic opioid alone[19,82,83]	▼[83] NS[19,82]	▼[83] NS[19,82]	NS[19,82]	NS[19,82]	▼[83*a*] NS[19,82]
Thoracic epidural opioid plus LA versus thoracic epidural LA alone[84] or plus systemic opioid[85,86]	▼[84*b*] NS[85]	NS[84–86]	NS[84,85]	NS[85]	▼[84] NS[85]
Thoracic epidural LA versus thoracic epidural opioid[19,70,87]	NS[19,70,87]	NS[19,70,87]	▲[19] NS[87]	▲[19] NS[87]	NS[19,70]

▼: Pain scores reduced at one or more time points during the specified day, or analgesic use reduced, in treatment group versus control group.

▲: Pain scores increased at one or more time points during the specified day, or analgesic use increased, in treatment group versus control group; NS: no significant difference between groups.

[a] Reduced proportion of patients requiring treatment for breakthrough pain, but no significant difference in total hydromorphone requirement.

[b] Reduced with epidural ropivacaine plus fentanyl, but not epidural bupivacaine plus fentanyl, versus epidural ropivacaine.

ological quality of these studies varied (Table 3[14–87]): the majority of studies had a numerical quality score of at least 3 of 5, and 9 studies described appropriate allocation concealment, whereas 64 reports did not make this clear. Qualitative outcomes were reported for all studies, but only limited quantitative analyses could be performed because many studies did not report mean and SD or SEM data (41 studies reported the mean and SD or SEM for pain scores, 3 reported the mean and 95% confidence intervals, 11 reported the mean but no SD or SEM, whereas 15 reported median values, and other studies reported the number of patients with a particular score). Quantitative analyses were not always possible for analgesic use and side effect outcomes, as these were not reported consistently, and the time of measurement of different outcomes varied considerably.

Table 3. Quality Assessment of Included Randomized Trials of Regional Analgesic Techniques for Postthoracotomy Analgesia

Quality score (Allocation concealment: A–D; randomization, blinding and withdrawals score: 1–5)	Included studies
A1	—
A2	—
A3	—
A4	19,31,36,50,54,81
A5	27,29,77
B1	14,33,53,69,70
B2	16–18,20–23,28,35,39,51,61–63,66,68,71
B3	15,25,26,30,34,41,43,45,46,58,60,64,65, 67,74,76
B4	32,38,42,44, 47,49,52,55–57,59,72,73,78, 79,80,82,83,85,86
B5	24,37,40,48,75,84,87

Regional Analgesia Versus Systemic Analgesia

Thoracic Epidural Analgesia Versus Systemic Opioid Analgesia (Administration Started or Continued Postoperatively)

Overall, thoracic epidural analgesia using LA plus opioid (fentanyl, sufentanil or morphine), LA alone or lipophilic opioid alone (fentanyl) was associated with significant reductions in pain scores and/or supplementary analgesic requirements compared to systemic opioid analgesia (respectively, seven[14–17,19–21] of eight[18] studies, two[22,23] of three[19] studies, and three[24–26] of three studies, showed benefits) (Table 1). However, when epidural hydrophilic opioids (morphine or nicomorphine) were compared with systemic opioids (morphine, nicomorphine or tramadol; five studies[19,27–30]), mixed results for pain intensity and analgesic use were documented (Table 1). In most studies, thoracic epidural analgesia was administered pre-/intraoperatively and continued as an infusion for 2 or 3 days. Quantitative analyses showed significant reductions in pain scores for 3 days in patients receiving thoracic epidural combining LA plus opioid (fentanyl, sufentanil or morphine) compared with systemic opioid analgesia (Fig. 1). Thoracic epidural combining LA plus opioid (fentanyl, sufentanil or morphine) was associated with an increase in the incidence of hypotension compared with systemic opioid analgesia (Fig. 2). There was no significant difference in the incidence of pulmonary complications between thoracic epidural analgesia and systemic opioid analgesia (with LA and/or opioid, Table 4).

Thoracic Paravertebral Block with LA Versus Paravertebral Saline or no Paravertebral Block (Systemic Analgesia Available to all Patients)

Paravertebral block (with bupivacaine or lidocaine) was superior to control (paravertebral saline or no paravertebral block) for significantly reducing pain scores and/or opioid use in nine[31–39] of nine studies (Table 1). In most studies, paravertebral block was administered as an infusion for three or more days. Quantitative analyses found that paravertebral block with bupivacaine significantly reduced pain scores on day one (Fig. 3). Paravertebral block with bupivacaine significantly reduced the incidence of pulmonary complications compared with control (quantitative analysis of data from seven studies) (Fig. 4). For thoracic paravertebral block, the number of patients needed to be treated to prevent one pulmonary complication was calculated to be 4.2 ± 0.08 (derived from 346 patients).

Intrathecal Opioid Versus no Intrathecal Opioid (Systemic Analgesia Available to all Patients)

Three[40–42] of three studies showed that a single bolus of intrathecal sufentanil and/or morphine significantly reduced pain scores in the early postoperative period, but not beyond 24 h (Table 1). Three[40–42] of three studies showed a significant reduction in morphine or meperidine use, compared with no intrathecal opioid (Table 1). A pooled analysis of data from all patients receiving intrathecal opioid (sufentanil and/or morphine) in three treatment arms of one study,[40] showed a significantly higher frequency of urinary retention in the intrathecal opioid groups compared with the control group.

Intercostal Block Versus Intercostal Saline or no Intercostal Block (Systemic Analgesia Available to all Patients)

Intercostal nerve blocks with bupivacaine significantly reduced postoperative pain scores compared with intercostal saline or no intercostal LA, when administered as single blocks (three[43–45] of four[46] studies), or repeat blocks (two[22,47] of three[46] studies) or as a continuous infusion (one study[48]) (Table 1). Intercostal nerve blocks were also associated with significantly reduced supplementary analgesic requirements when administered as repeat blocks (two[22,47] of three[46] studies) and continuous infusion (one study[48]), but not as a single intraoperative block (four[43–46] of four studies) (Table 1).

Interpleural Analgesia Versus Systemic Opioid Analgesia

Ten studies compared interpleural LA (bupivacaine or lidocaine) with systemic opioid analgesia,[22,49–57] and two studies compared interpleural morphine with IV morphine,[58,59] and these showed inconsistent results for postoperative pain scores and analgesic use (Table 1).

Comparisons of Alternative Regional Analgesic Techniques

Thoracic Paravertebral Block Versus Epidural Analgesia

Four[60–63] of five[64] studies showed that paravertebral bupivacaine was comparable with thoracic epidural bupivacaine for pain scores and supplementary analgesic requirements (Table 2). Two studies compared paravertebral LA (bupivacaine[66] or ropivacaine[65]) versus thoracic epidural combining LA plus opioid (bupivacaine plus fentanyl[66] or ropivacaine plus sufentanil[65]), with

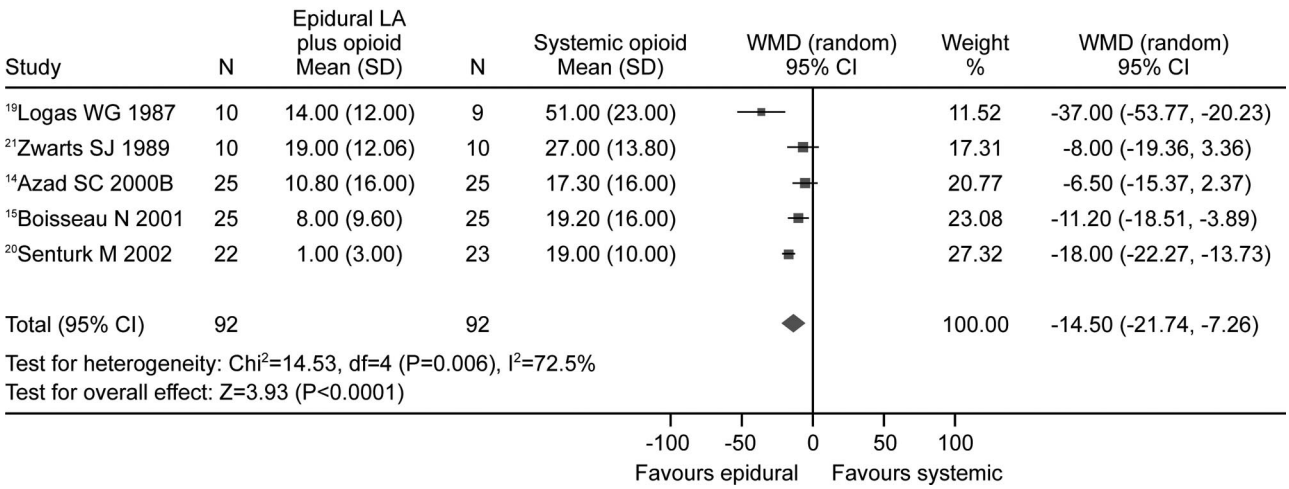

Figure 1. Weighted mean difference for visual analog scale pain scores recorded at rest on day 1: thoracic epidural combining local anesthetic plus opioid versus systemic opioid.

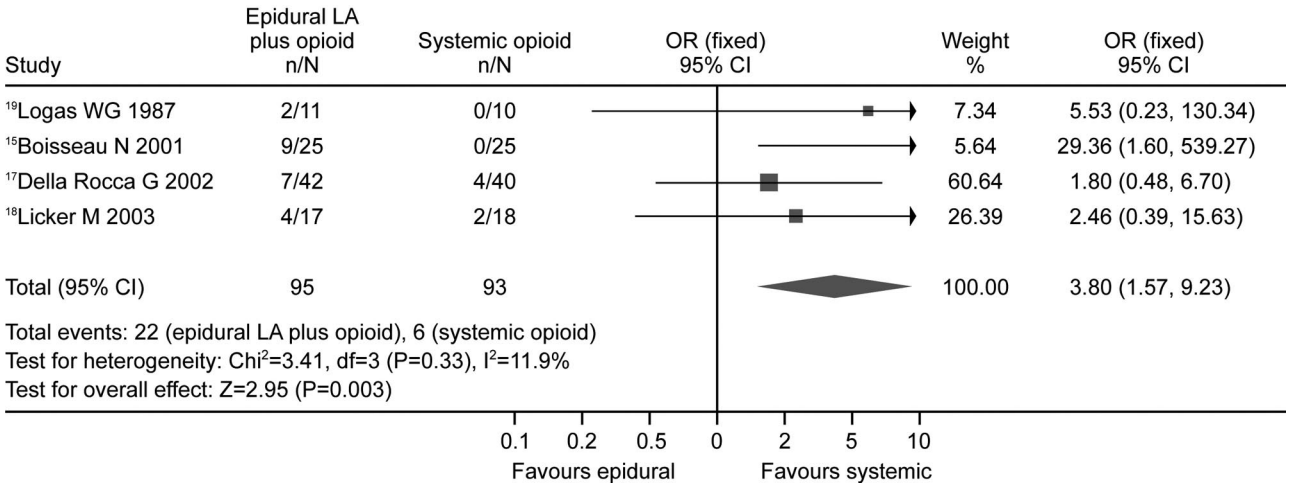

Figure 2. Odds ratio for the incidence of hypotension: thoracic epidural combining local anesthetic plus opioid versus systemic opioid.

mixed results for pain scores and supplementary analgesic requirements (Table 2). One study reported that pain scores were higher in patients who received paravertebral bupivacaine plus fentanyl compared with patients who received thoracic epidural bupivacaine plus fentanyl, whereas there were no significant differences in supplementary analgesic requirements[67] (Table 2). In the majority of these studies, paravertebral block or epidural analgesia was administered as an intraoperative bolus and infusion continuing for at least 2 days. No meta-analyses of pain scores could be performed because of heterogeneity in the reporting of data (i.e., different times of measurement of pain scores; reporting of median and range, rather than mean and SD). However, scatter plots to illustrate the spread of average pain scores among studies show that overall, postoperative analgesia is comparable between paravertebral LA (with or without opioid) and thoracic epidural LA (with or without opioid) at day 1 or 24 h (Fig. 5A), whereas, when opioid was added to LA in either or both groups, paravertebral block tended to be associated with higher pain scores during the early postoperative period (Fig. 5B).

Quantitative analyses demonstrated that paravertebral bupivacaine reduced the incidence of hypotension compared with thoracic epidural bupivacaine (Fig. 6).

Thoracic Paravertebral Block Versus Intercostal Nerve Block

The only study that compared thoracic paravertebral block with bupivacaine versus intercostal nerve block with bupivacaine showed no significant difference between groups for pain scores or supplementary morphine use[62] (Table 2).

Intrathecal Opioid Versus Thoracic Epidural LA Plus Opioid

There were no significant differences in pain scores or rescue morphine use in the only study that compared patients receiving repeated boluses of intrathecal morphine and those receiving thoracic epidural bupivacaine plus fentanyl, as a bolus and then infusion[68] (Table 2).

Table 4. Effect on the Incidence of Pulmonary Complications of Thoracic Epidural Analgesia Compared with Systemic Opioid Analgesia

Thoracic epidural LA plus opioid versus systemic opioid analgesia

Study	Study design: Epidural LA + opioid (number of patients) versus systemic analgesia (number of patients)	Incidence of pulmonary complications: OR (epidural LA + opioid versus systemic analgesia)
Administration started or continued postoperatively		
Azad et al. 2000[14]	Epidural infusion bupivacaine/ropivacaine + fentanyl (25) versus IV PCA piritramide (25)	Data from four studies: Azad et al. 2000;[14] Boisseau et al. 2001;[15] Della Rocca et al. 2002;[17] Logas et al. 1987[19]
Boisseau et al. 2001[15]	Epidural infusion ropivacaine + sufentanil (25) versus IV PCA morphine (25)	
Brichon et al. 1994[16]	Epidural infusion bupivacaine + fentanyl (46) versus IV buprenorphine injection (33)	OR = 0.92 [0.48, 1.75], $p = 0.79$
Della Rocca et al. 2002[17]	Epidural infusion bupivacaine/lidocaine + morphine (286) versus IV PCA morphine (277)	
Licker et al. 2003[18]	Epidural infusion bupivacaine + fentanyl (17) versus IV PCA morphine (18)	
Logas et al. 1987[19]	Epidural infusion bupivacaine + morphine (11) versus IM morphine injection (10)	
Senturk et al. 2002[20] (comparison arm 1)	Epidural bupivacaine + morphine, pre, intra- and PCEA postoperatively (22) versus IV PCA morphine (23)	
Senturk et al. 2002[20] (comparison arm 2)	Epidural bupivacaine + morphine, PCEA postoperatively (24) versus IV PCA morphine (23)	
Zwarts et al. 1989[21]	Epidural infusion bupivacaine + sufentanil (10) versus IM nicomorphine injection (10)	

Thoracic epidural LA versus systemic opioid analgesia

Study	Study design: Epidural LA (number of patients) versus systemic analgesia (number of patients)	Incidence of pulmonary complications: OR (epidural LA versus systemic analgesia)
Administration started or continued postoperatively		
Bachmann-Mennenga 1993[22]	Epidural infusion bupivacaine (10) versus IV buprenorphine injection (10)	Data from two studies: Von Dossow et al. 2001;[23] Logas et al. 1987[19]
Logas 1987[19]	Epidural infusion bupivacaine (10) versus IM morphine injection (10)	OR = 0.43 [0.12, 1.60], $P = 0.21$
Von-Dossow 2001[23]	Epidural bupivacaine at intervals (25) versus IV PCA piritramide (25)	

Thoracic epidural opioid versus systemic opioid

Study	Study design: Epidural opioid (number of patients) versus systemic analgesia (number of patients)	Incidence of pulmonary complications: OR (epidural opioid versus systemic analgesia)
Lipophilic opioid		
Administration started or continued postoperatively		
Benzon et al. 1993[24]	Epidural infusion fentanyl (18) versus IV PCA morphine (18)	Data from two studies: Guinard et al. 1992;[25] Salomaki et al. 1991[26]
Guinard et al. 1992[25]	Epidural infusion fentanyl (16) versus IV infusion fentanyl (16)	
Salomaki et al. 1991[26]	Epidural infusion fentanyl (20) versus IV infusion fentanyl (20)	OR = 0.84 [0.27, 2.65], $P = 0.77$
Hydrophilic opioid		
Administration started or continued postoperatively		
Bloch et al. 2002[27]	Epidural infusion morphine (30) versus IV PCA morphine (30)	No meta-analyses possible
Hasenbos et al. 1986[28]	Epidural bolus nicomorphine (14) versus IM injection nicomorphine (10)	
Larsen et al. 1986[30]	Epidural morphine at intervals (10) versus SC nicomorphine injections (10)	
Logas et al. 1987[19]	Epidural infusion morphine (12) versus IM injection morphine (10)	
Bloch et al. 2002[27]	Epidural infusion morphine (30) versus IV infusion tramadol (29)	
James et al. 1996[29]	Epidural infusion morphine (19) versus IV injection tramadol (20)	

IV = intravenous; IM = intramuscular; OR = odds ratio; PCA = patient controlled analgesia; SC = subcutaneous; PCEA = patient controlled epidural analgesia.

Intercostal Nerve Block Versus Thoracic Epidural Analgesia

Comparisons of single intercostal nerve block with bupivacaine versus thoracic epidural analgesia with bupivacaine or morphine in four studies showed mixed results for pain scores, and three[69–71] of the four[62] studies showed an increase in opioid requirements with intercostal nerve block (Table 2). Three studies[22,69,70] comparing repeat intercostal nerve blocks using bupivacaine versus thoracic epidural analgesia using bupivacaine or morphine found no difference between groups in pain scores for 24 h after surgery, or in supplementary analgesic use (Table 2). However, one study found that pain scores were higher with a continuous infusion intercostal nerve block with bupivacaine compared with thoracic epidural bupivacaine[72] (Table 2).

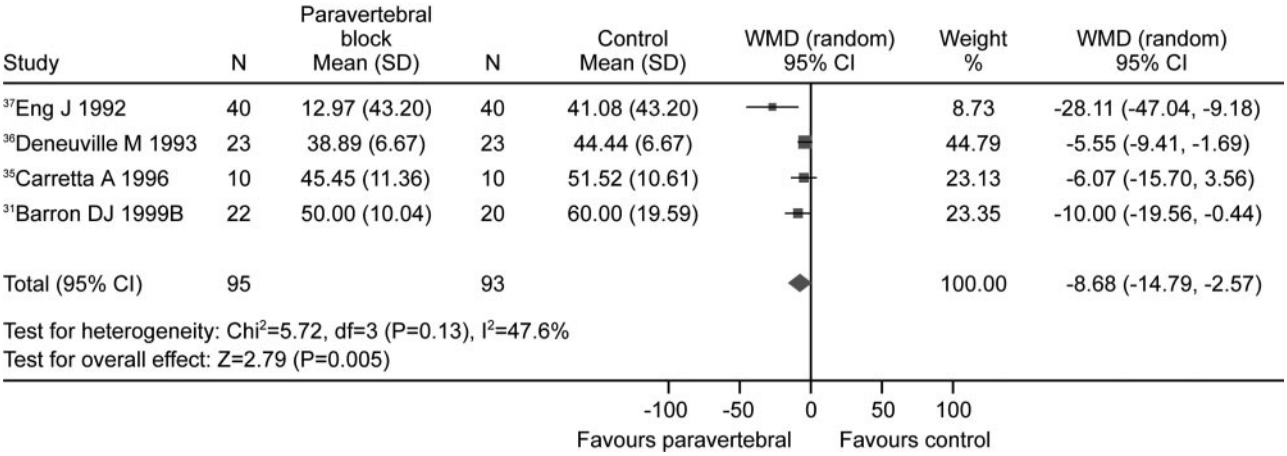

Figure 3. Weighted mean difference for visual analog scale pain scores recorded at rest on day 1: thoracic paravertebral block with local anesthetic versus paravertebral saline or no paravertebral block (systemic analgesia was available to all patients).

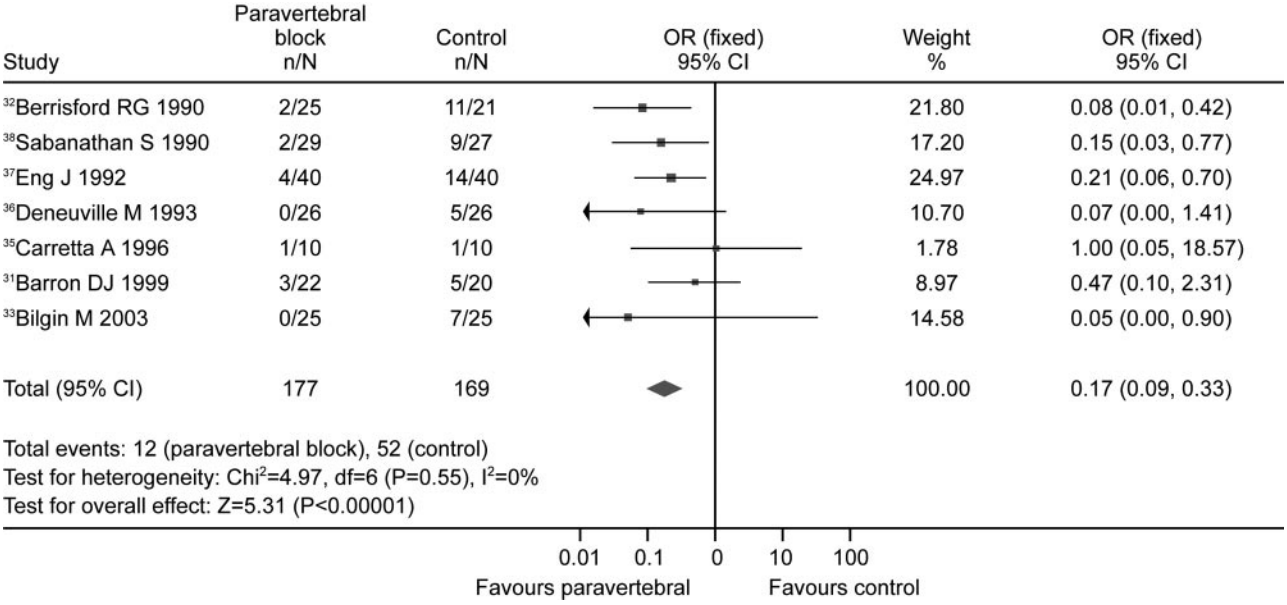

Figure 4. Odds ratio for the incidence of pulmonary complications: thoracic paravertebral block with local anesthetic versus paravertebral saline or no paravertebral block (systemic analgesia was available to all patients).

No meta-analyses of pain scores could be performed for the comparison of intercostal nerve blocks with thoracic epidural analgesia because of heterogeneity in the reporting of data (i.e., different times of measurement of pain scores; reporting of median and range, rather than mean and SD). However, a scatter plot shows that pain scores tended to be marginally higher at day 1 or 24 h after intercostal nerve blocks (Fig. 7).

Interpleural LA Versus Other Regional Techniques

Two[22,63] out of three[73] studies showed that interpleural bupivacaine was less effective for reducing pain scores than thoracic epidural bupivacaine, and two[22,63] of three[73] studies showed significantly greater opioid use in the interpleural group (Table 2). However, interpleural bupivacaine and thoracic paravertebral block with bupivacaine were comparable for pain scores or supplementary morphine use in two[74,75] of three[63] studies (Table 2). The third study found that pain scores and opioid use were significantly higher with interpleural bupivacaine plus wound infiltration compared with thoracic paravertebral block with bupivacaine.[63] Two studies[22,76] compared interpleural bupivacaine versus intercostal nerve block using bupivacaine, and showed mixed results for pain scores and supplementary opioid use (Table 2).

Epidural Solution: LA and/or Opioid Versus LA or Opioid Alone

Thoracic Epidural LA Plus Opioid Versus Opioid Alone

Four[78–81] of five[77] studies showed that thoracic epidural bupivacaine plus lipophilic opioid (fentanyl or sufentanil) was associated with significantly reduced pain scores compared with thoracic epidural lipophilic opioid alone (fentanyl or sufentanil) (Table

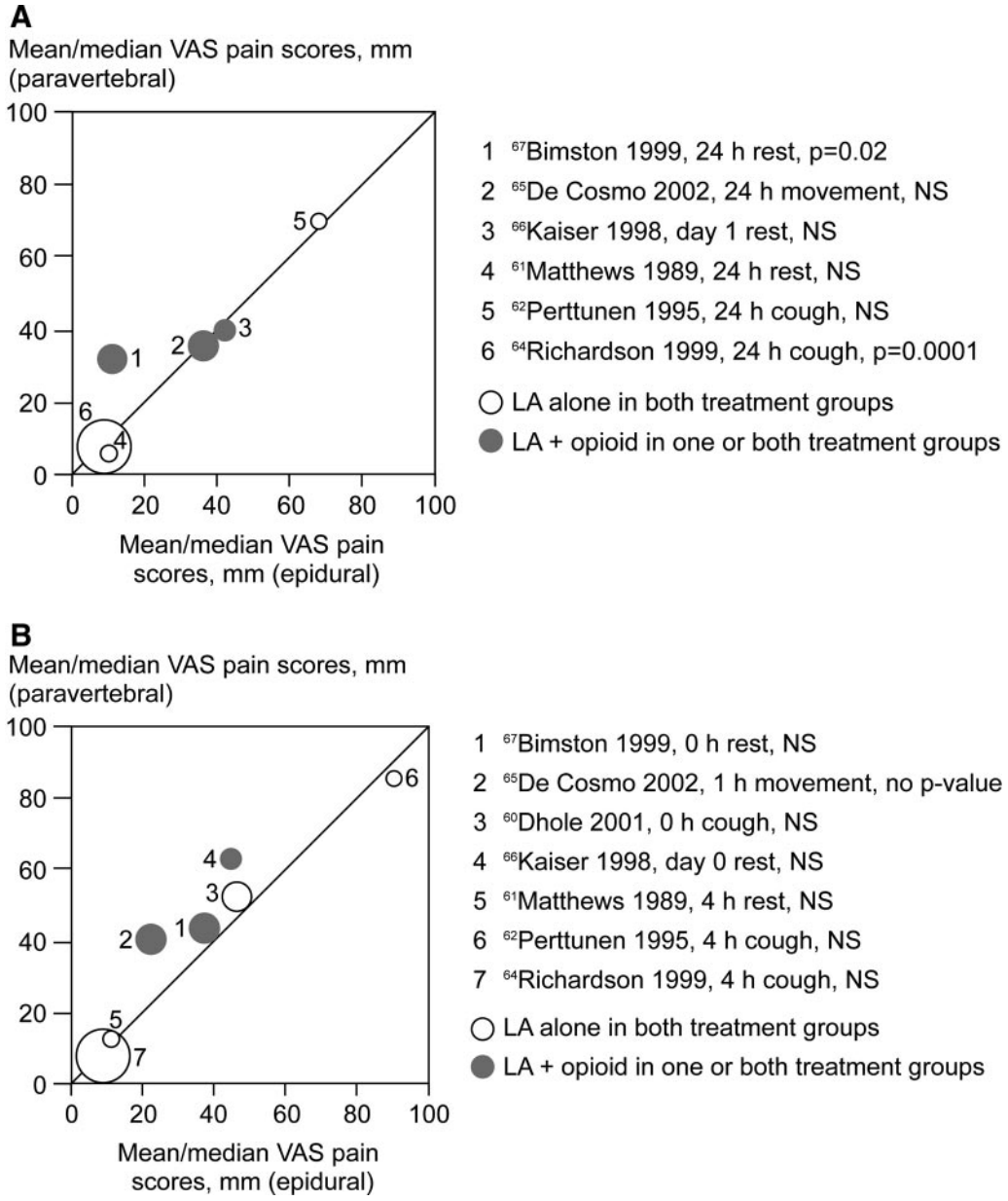

Figure 5. Effect of thoracic paravertebral block versus thoracic epidural analgesia on visual analog scale (VAS) pain scores (at rest, cough or movement as indicated) postoperatively in thoracotomy patients at (A) day 1; (B) the earliest pain score measurement on the day of surgery (0–4 h). Mean or median data are plotted from individual studies as indicated. Larger circles indicate studies with greater numbers of patients. Statistical significance of individual study results is indicated; NS = no significant difference.

2), and three[77,79,80] of five[78,81] studies showed a significant reduction in supplementary analgesic use. However, when bupivacaine was added to thoracic epidural hydrophilic opioid (morphine, hydromorphone or meperidine), two[19,82] of three[83] studies found no significant differences in pain scores or opioid use compared with epidural hydrophilic opioid alone (Table 2).

Thoracic Epidural Opioid Plus LA Versus Thoracic Epidural LA with or Without Systemic Opioid

In one study,[84] thoracic epidural ropivacaine plus fentanyl, but not bupivacaine plus fentanyl, was superior to thoracic epidural ropivacaine alone for pain scores (Table 2). Thoracic epidural fentanyl plus bupivacaine or ropivacaine was associated with significantly reduced supplementary analgesic requirements compared with thoracic epidural ropivacaine alone[84] (Table 2). Two studies compared thoracic epidural opioid (sufentanil[85] or diamorphine[86]) plus bupivacaine versus thoracic epidural bupivacaine plus the same opioids given systemically, with no significant difference in pain scores or opioid use (Table 2).

Thoracic epidural LA Versus Thoracic Epidural Opioid

In two[70,87] of three[19] studies, no significant differences were reported between thoracic epidural

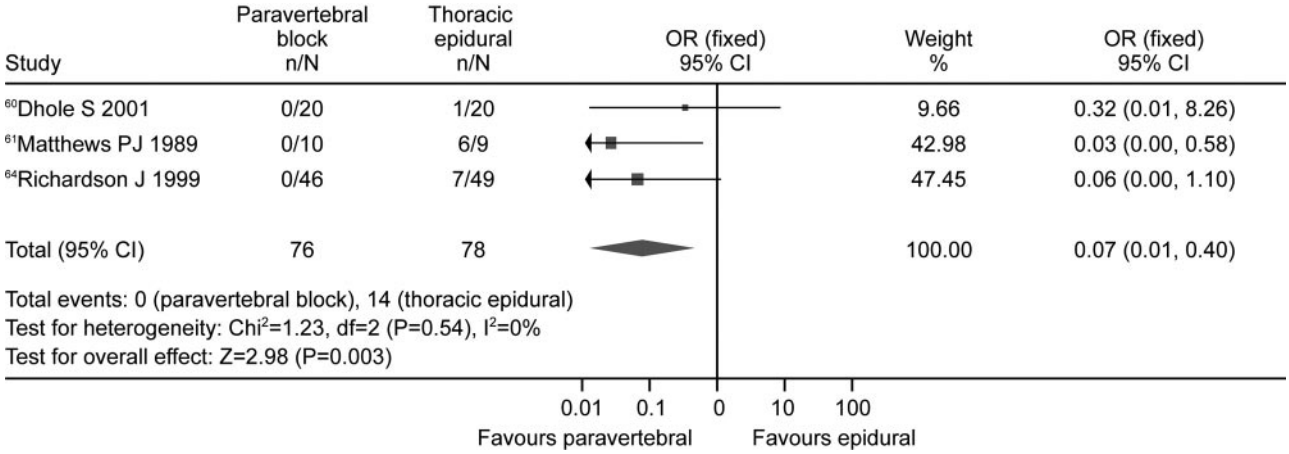

Figure 6. Odds ratio for the incidence of hypotension: thoracic paravertebral block with local anesthetic versus thoracic epidural local anesthetic.

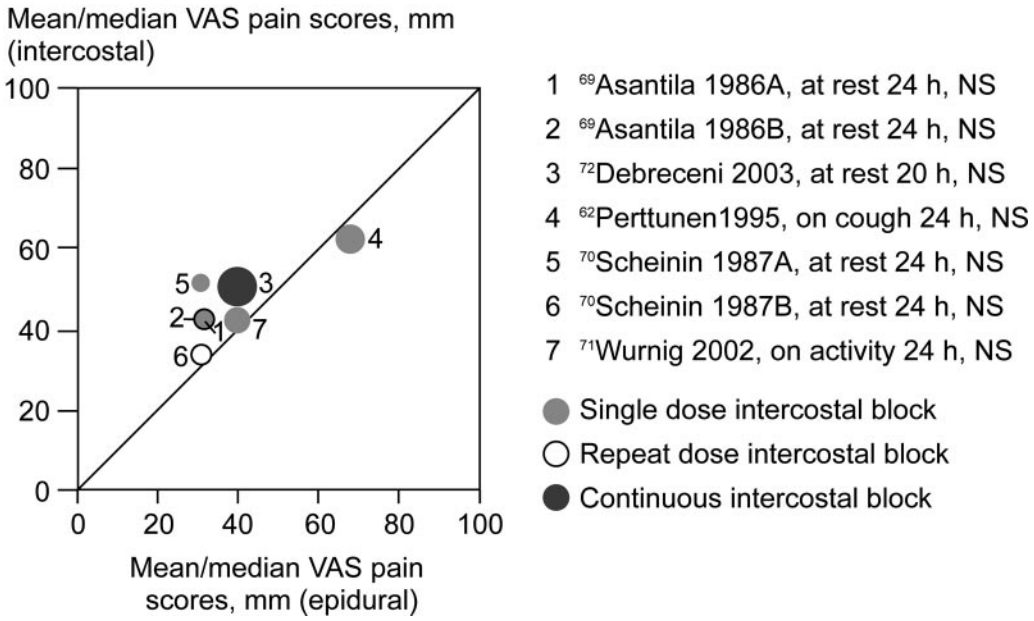

Figure 7. Effect of intercostal nerve block versus thoracic epidural analgesia on visual analog scale pain scores (at rest or cough as indicated) postoperatively in thoracotomy patients at 24 h. Mean or median data are plotted from individual studies as indicated. Larger circles indicate studies with greater numbers of patients. Statistical significance of individual study results is indicated; NS = no significant difference.

bupivacaine and thoracic epidural morphine for pain scores or supplementary analgesic requirements (Table 2). The third study found that pain scores were lower in patients receiving thoracic epidural morphine compared with those receiving thoracic epidural bupivacaine, although no statistical analyses were reported.[19]

DISCUSSION

Although thoracic epidural analgesia is commonly cited as the gold standard for postthoracotomy pain treatment,[5,88,89] a review of other available regional techniques was warranted because epidural techniques may not always be possible and are associated with complications, including hypotension, and a risk of epidural hematoma and nerve injury.[90] In a recent meta-analysis, paravertebral block provided comparable pain relief to epidural analgesia, with a superior side effect profile.[6] Alternative regional techniques also require evaluation, since systemic analgesia has often proven to be insufficient for pain relief when used alone.[88]

Many alternative protocols have been studied in regional analgesic techniques, and therefore it is sometimes difficult to draw definite conclusions. Epidural analgesia, for example, can be performed with LA, opioid or both. Intercostal blocks can be performed as single, repeated or continuous injections with short- or long-acting LA. This limits the studies with homogeneous design from which data can be pooled. Nevertheless, the analyses performed allow us to put forward recommendations for pain treatment after thoracotomy that consider both analgesic efficacy and side effects (Fig. 8).

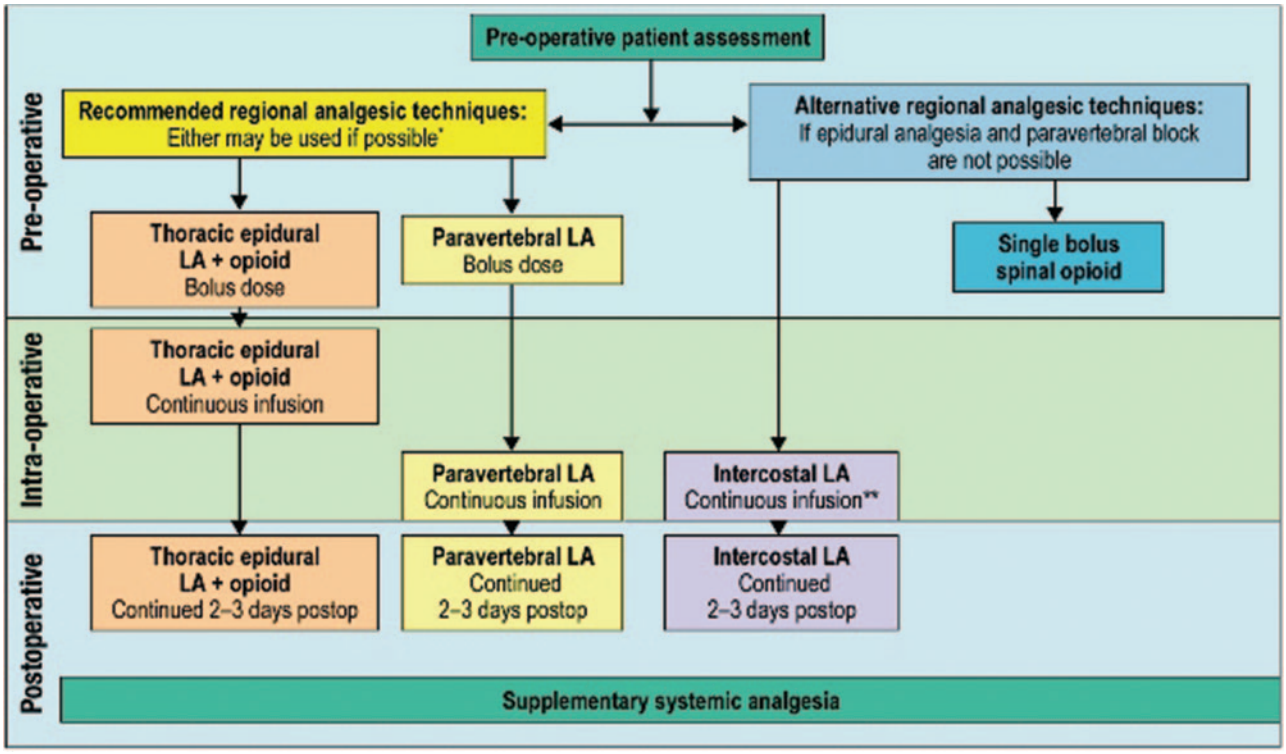

Figure 8. Overall PROSPECT recommendations: regional techniques for post-thoracotomy analgesia. *Either thoracic epidural local anesthetic (LA) + opioid or paravertebral block with LA is recommended as the primary analgesic approach; further studies on efficacy and safety are necessary to determine which technique is superior. **If intercostal LA is used, administration by continuous infusion is recommended, despite limited data, because of the requirement for continuous analgesia for the long duration of post-thoracotomy pain.

Evidence from this review supported the efficacy of thoracic epidural combining LA plus opioid, as well as thoracic epidural LA alone and thoracic epidural lipophilic opioid (e.g., fentanyl) alone for thoracotomy. In agreement with another systematic review comparing epidural with systemic analgesia in various procedures,[91] thoracic epidural hydrophilic opioid (e.g., morphine or nicomorphine) did not show overall benefit over systemic opioids. Further well designed studies are needed to determine the most effective components of epidural solution. Overall, however, the most consistently effective analgesia was provided by continuous infusion of thoracic epidural combining LA plus opioid (Table 1).[14–21] This combination is believed to provide synergistic analgesia, requiring smaller doses and thus fewer side effects.[92] Thoracic epidural infusion of LA plus opioid is recommended, and may be started in the pre-/intraoperative period and continued for 2–3 days after surgery, since this was the duration of epidural analgesia in the majority of positive studies. Addition of epinephrine to low-dose thoracic epidural LA improved analgesia in several studies,[93–95] but further investigation is necessary to confirm this point, particularly in thoracic surgery. Lumbar epidural analgesia has also been studied in thoracotomy, but thoracic epidural LA plus opioid is recommended due to the consistency of evidence supporting its use; a comparison of the efficacy of epidural analgesia via the different sites of administration is beyond the scope of this review.

Thoracic paravertebral block with LA, as a bolus and continuous infusion for 2–3 days, is also recommended, based on evidence that the technique provides comparable analgesia to thoracic epidural with LA alone, and may be associated with fewer adverse effects, including hypotension, nausea and urinary retention.[60–64] Quantitative analyses found that thoracic paravertebral block reduced the incidence of pulmonary complications compared with systemic analgesia, whereas thoracic epidural analgesia did not. These findings support the results of the meta-analysis of Davies et al., which showed reduced pulmonary morbidity with thoracic paravertebral block compared with epidural analgesia.[6] In another systematic review, epidural analgesia did reduce pulmonary morbidity in high-risk patients compared with systemic analgesia, but this analysis was not procedure-specific.[96] Due to the limited thoracotomy-specific data on pulmonary morbidity from studies using different regimens of epidural analgesia, and since transferable evidence shows advantageous effects of epidural analgesia, the choice between epidural and paravertebral techniques should not depend on the currently limited evidence for a reduction of pulmonary morbidity. Three studies directly compared thoracic paravertebral block with the thoracic epidural combination of LA plus opioid (rather than LA alone),

and showed mixed results for analgesia.[65–67] Further evaluation of the risks and benefits of these techniques is warranted.

If thoracic epidural analgesia or paravertebral block are not feasible for any reason, including failure of the technique (although this is unusual), other regional techniques may be used. In this situation, intercostal nerve block with LA is recommended based on reduced pain and analgesic use compared with systemic analgesia in most procedure-specific studies. Comparisons with other regional analgesic techniques are limited, with especially few data concerning continuous intercostal nerve blocks,[72] whereas this approach would appear logical considering the duration of postoperative pain after thoracotomy. Studies show a tendency towards greater pain and opioid consumption for intercostal nerve blocks compared with thoracic epidural analgesia.

Alternatively, if epidural analgesia or paravertebral block techniques cannot be used, a single, preoperative bolus of intrathecal opioid is recommended as part of a multi-analgesic regimen, in preference to IV patient-controlled analgesia opioids, based on a greater reduction in pain for up to 24 h. However, it is important to note that intrathecal administration of opioid as a single shot does not provide analgesia for more than 24 h, which is insufficient for most thoracotomy patients.

Interpleural LA is not recommended due to lack of efficacy compared with other regional techniques, and potential toxicity associated with high absorption of LA. Interpleural opioid is also not recommended because the only two studies show inconsistent results.

Limitations of the Systematic Review

Methodological quality of the randomized trials in this systematic review varied. Allocation concealment, an important source of bias,[97–99] was commonly unclear, while many studies were not double-blind. Quantitative analyses were limited as a result of heterogeneity in study design and outcome measures, and the number of subjects in the analyses was small. Although postoperative pain was the primary outcome of interest and a criterion for inclusion in the systematic review, it was not always the primary outcome of included studies, and measurements were often reported at limited time points, using different scales, and without statistical analyses. Not every study reported all outcomes of interest, such as pulmonary complications or pain on coughing/movement. Therefore, certain questions about the relative benefits of the different regional techniques remain unanswered until further large, well conducted trials are performed.

CONCLUSION

In conclusion, evidence supported the use of thoracic paravertebral block as an effective alternative to thoracic epidural LA alone, and showed that paravertebral block reduced the incidence of postoperative pulmonary complications compared with systemic analgesia. However, further studies are required to determine whether thoracic paravertebral block is equivalent to thoracic epidural combining LA plus opioid in terms of pain relief and morbidity. Apart from thoracic paravertebral block, all other regional analgesic techniques were inferior to thoracic epidural analgesia; in particular, interpleural techniques do not provide adequate analgesia. However, where thoracic epidural or paravertebral techniques are not possible or are contraindicated, then intercostal nerve block or preoperative intrathecal opioid are recommended.

ACKNOWLEDGMENTS

The authors would like to thank Iradj Reza (PhD, Biomedical Information Scientist, Pfizer, Sandwich, UK) for his help and expertise in performing literature searches in Embase and Medline; and Caroline Sharp (MSc, Medical Projects Coordinator, Choice Pharma, Hitchin, UK), Christine Drewienkiewicz (BSc, Scientific Services Director, Choice Pharma) and James Pickford (BSc, Editorial Director, Choice Pharma) for editorial assistance.

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NOTICE OF RETRACTION

The manuscript cited below is now retracted. After its publication, the editorial office of *Anesthesia & Analgesia* was notified by the corresponding author that their study was based on mutations developed by Dr. Shetuan Zhang in the Department of Physiology at the University of Manitoba, Winnipeg, Manitoba, Canada. These mutations were used without the consent of Dr. Zhang.

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DOI: 10.1213/01.ane.0000333274.63501.ff