Pain Control after Thoracic Surgery

A Review of Current Techniques

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A preliminary step in the assessment of a health care treatment modality is to conduct a randomized controlled trial. In many fields, randomized controlled trials have been conducted and the results disseminated, but they have not had the appropriate impact on clinical practice.[1] It is now apparent that not only should the original studies be conducted and reported systematically and scientifically, but so too should medical review articles.[1,2] For clinical research to find its way into clinical practice, the results of trials must be incorporated into timely and accessible review articles.[1-3]

Analgesia after thoracic surgery is of particular significance for several reasons. First, thoracotomy has been reported to be among the most intense clinical postoperative pain experiences known,[4-7] and successful therapy is one of the hallmarks of optimal postoperative surgical and anesthetic management. Second, the sources of the perceived pain are multiple and include the site of the surgical incision, disruption of ribs and intercostal nerves, inflammation of chest wall structures adjacent to the incision, incision or crushing of pulmonary parenchyma or pleura, and the almost universal placement of single or multiple thoracostomy drainage tubes. In addition, the nociceptive pathways

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subserving postthoracotomy pain are poorly understood.[8] Third, systemic opioids have traditionally formed the basis for the treatment of postthoracotomy pain, but the condition is amenable to a variety of alternative systemic and regional techniques. Some of these techniques are potentially hazardous or of controversial utility, and despite a lack of clear-cut data, the benefits are hotly debated among anesthesiologists and thoracic surgeons. Fourth, it is likely that the severe postoperative pain experienced by these patients contributes to postoperative pulmonary dysfunction.[9,10] Finally, specific associated pain syndromes may develop in these patients during the acute[11,12] and long-term[12,13] postoperative courses as a result of the surgical[12,13] or the analgesic[14] techniques.

Few centers appear to practice a wide variety of different modalities,[15] and therefore although many options exist for the postthoracotomy patient, few individual practitioners or centers can offer the full range of available techniques. A clear idea as to which modalities are—or are not—associated with demonstrable benefit has hampered the refinement and expansion of clinical practice, and results in a lack of progressive clinical research in the field.

Over the past 30 yr, more than 100 original articles, involving more than 4,000 patients, focusing on pain control after thoracic surgery have appeared in a variety of journals. The result is a large body of literature that is difficult for clinicians to integrate into functionally useful information. Moreover, because the literature consists of studies that differ widely in design, methods, and technique, it is difficult for clinical researchers to extend and develop the field in a rational and scientific manner. Although the randomized controlled trial may not be representative of "real-life" postoperative patient management, it offers the only rational basis available for adequate assessment and evaluation of comparative methods of postoperative analgesia.

The purposes of this review are (1) to present a 15-item rating system developed specifically for assessing the quality of research concerned with postthoracotomy pain and analgesia; (2) to describe briefly and rate the available English-language publications on this topic; (3) to describe briefly the techniques and to examine in detail the results of studies that were randomized, prospective, double-blind, and controlled and that assessed pain with patient-rated instruments; and (4) to make recommendations for clinical practice and future research.

Methods

Data Identification

The titles of the original scientific papers referenced in this review were obtained from a MEDLINE computer search up to and including June 1993. The key words used were: Pain; postoperative, postthoracotomy. Analgesia; postoperative. Surgical procedure; thoracotomy. Anesthesia; general, regional. The reference sections of eligible studies were examined for relevant publications that may have been missed by the computer search as were the reference sections of these secondary studies.

Data Selection

All non–English-language articles, abstracts, letters and non–peer-reviewed publications were excluded from consideration. Studies that included patients undergoing sternotomy or thoracoabdominal incisions also were excluded. Only studies that mentioned or reported assessments of postoperative pain or analgesic consumption or that purported to measure or report pain or analgesic consumption were assessed. All papers were initially assessed by two of the authors (B.P.K. and J.K.) independently, and subsequently in conference. This process was repeated to ensure accuracy.

Data Synthesis and Integration

Rationale. The requirement that clinical trials be designed in a prospective, randomized, double-blind, and controlled fashion is now well established.[16-18] It is difficult to abstract clinically useful information from a large series of heterogeneous studies. Conventional means of reviewing the results of a large number of studies of various designs and methods make it difficult for the reader to synthesize the information. Metaanalysis has been used to consolidate analysis of the results of a large number of studies into a unified body of clinically applicable data.[19] Although this technique appears to be an attractive option for searching through an apparently narrowly focused topic such as analgesia after thoracic surgery, metaanalysis requires the ability to standardize study design, ability to combine or homogeneity, control of bias, statistical analysis, sensitivity analysis and application of results.[20] The literature on postthoracotomy pain encompasses a wide range of study designs and therapeutic regimens, rendering direct comparisons between studies or meaningful grouping of the data impossible.

There may be limitations to the "external validity" (applicability) of controlled clinical studies, particu-

larly when the studies are conducted under closely controlled conditions, which seldom reflect real-life clinical situations. For some therapies, the benefits and shortcomings are obvious, and in other cases, the trials are not possible. Nevertheless, there is ample opinion to suggest that the prospective randomized controlled trial, involving sufficient numbers of participants, is a basic requirement for the correct interpretation of experimental data, and that data obtained under other conditions is not appropriate for objective assessment of medical interventions.[1,21]

To evaluate the outcome of a clinical trial accurately, a clear description of the study methods is necessary.[22] Ideally, there should be detailed information on areas such as eligibility criteria, sample size calculation, statistical analysis and methods, randomization, method of allocation to study group, assessment of outcome, complications of therapy, and power analysis for negative effects.[22]

Rating Criteria. In an effort to address some of these difficulties guidelines have been proposed for the uniform planning, statistical appraisal and reporting of clinical studies.[23-26] Some of these guidelines have been set out in the form of check lists for reviewers of scientific manuscripts, and in general, are concerned with the semiquantitative description of areas such as study design, conduct of trials, statistical analysis, and presentation. In addition, to facilitate interpretation of results from a large number of studies, novel approaches have been used to describe the collective data in quantitative and qualitative fashions.[22,27]

Based on these models and guidelines, we developed a set of 15 rating criteria (table 1) to systematically appraise the published literature on techniques used to treat postthoracotomy pain. The criteria were developed specifically to enable objective and pertinent analysis of clinical studies of postoperative pain. Each study was evaluated according to these criteria, and the results of the evaluation are presented in tables 2 and 3. Table 2 lists studies (n = 32) that fulfilled the following criteria: randomized, prospective, concurrent controls; double-blinding; and patient-rated pain scores. These studies were identified as those that could be reliably interpreted and were chosen for clinical comment. Table 3 lists the remainder of the studies (n = 76), which did not fulfill all of the above criteria and therefore are presented in tabular form and without additional comment. A full description of the 15 criteria and the procedures used to rate each study is contained in the appendix.

Table 1. Rating Criteria Used to Evaluate Studies of Pain and Analgesic Consumption after Thoracic Surgery

Criteria	Ratings
Description of aim	Clear
	Not clear
Entry criteria	Clear
	Not clear
Study design	Prospective
	Retrospective
	Not clear
Controls	Concurrent
	Historic
	Absent
Treatment regimens	Clear
	Not clear
Randomization	Yes
	No
Blinding of study	Double-blind
	Single-blind
	Not blinded
	Not clear
Evaluation of pain	Patient-rated
	Observer-rated
	None
	Not clear
Analgesic use	Patient-controlled
	Not patient-controlled
	No data
Power analysis	Present
	Not required
	Absent
Prestudy comparability of groups	Comparable
	Not comparable
	No analysis
	Not clear
Report of adverse effects	Yes
	No
Patient withdrawals	No withdrawals
	Reasons given
	No reasons given
	No comment
Data presentation	Complete
	Incomplete
	None
Statistical procedures	Clear
	None
	Not clear

Techniques Used To Treat Pain after Thoracotomy

In this section, we briefly describe the techniques used for the treatment of postthoracotomy pain. We then focus on the results of studies that fulfill the following criteria: use of randomized, prospective, concurrent controls; double-blinding; and use of patient-

Table 2. Randomized, Double-blind, Prospective, Controlled Trials That Used a Patient-rated Pain Evaluation

Reference No.	Year	No. of Patients	Analgesic Technique	Aim of Study	Entry Criteria	Study Design	Type of Controls	Treatment Regimen	Randomization	Binding of Study	Evaluation of Pain	Analgesic Use	Power Analysis	Prestudy Comparability	Report of Adverse Effects	Patient Withdrawals	Data Presentation	Statistical Procedures
Baxter[39]	1991	52	LO + SO (PC)	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	+PCA	Not required	Comparable	Yes	No comment	Complete	Clear
Benzon[41]	1993	36	TO; SO (PC)	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	+PCA	Not required	No analysis	Yes	Reasons given	Complete	Not clear
Bigler[74]	1992	28	TL + TO + NA; TL + TO	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Present	Not comparable	Yes	Reasons given	Complete	Clear
Chan[42]	1991	20	IC + SO; SO	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Not required	Comparable	Yes	No comment	Complete	Not clear
Coe[127]	1991	58	TO; LO	Clear	Not clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Absent	Not comparable	Yes	Reasons given	Complete	Not clear
Dich-Nielsen[43]	1992	30	SK; SO	Clear	Not clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Not required	Not clear	Yes	No comment	Complete	Clear
Dryden[44]	1993	20	IC + SO (PC); SO (PC)	Clear	Not clear	Prospective	Concurrent	Clear	Yes	Double	Patient	+PCA	Not required	No analysis	Yes	Reasons given	Complete	Clear
El-Baz[121]	1984	90	TL; TO; TO + SO	Clear	Not clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Not required	Not clear	Yes	Reasons given	Complete	Not clear
Etches[141]	1991	15	LO	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Not required	Comparable	Yes	Reasons given	Complete	Clear
Galway[45]	1975	138	IB + SO; SO	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Not required	Data absent	Yes	No comment	Complete	Clear
George[129]	1991	25	TO; TO + TL	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Not required	Not clear	Yes	Reasons given	Complete	Not clear
Gordh[47]	1988	20	TC + SO (PC); SO (PC)	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	+PCA	Absent	Comparable	Yes	No comment	Complete	Not clear
Gowan[143]	1988	29	LO + SO	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Absent	Not clear	Yes	Reasons given	Incomplete	Clear
Grant[48]	1992	34	LO (PC); SO (PC)	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	+PCA	Not required	Comparable	Yes	Reasons given	Complete	Clear
Harbers[131]	1991	28	TL + TO; TL + SO	Clear	Not clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Absent	Comparable	Yes	Reasons given	Incomplete	Not clear
Jones[46]	1985	22	NS + SO (PC); SO (PC)	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	+PCA	Absent	Comparable	Yes	Reasons given	Incomplete	Clear
Katz[144]	1992	30	LO + SO (PC)	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	+PCA	Not required	Not comparable	Yes	No comment	Complete	Clear
Keenan[49]	1983	60	SO; CY + SO; NA + SO; CY + NA + SO	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Not required	Comparable	Yes	No comment	Incomplete	Clear
Mann[51]	1992	40	IP + SO; SO	Clear	Clear	Prospective	Concurrent	Not clear	Yes	Double	Patient	-PCA	Not required	Not comparable	Yes	No comment	Complete	Clear
Merry[65]	1992	20	NA + SO (PC); SO (PC)	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	+PCA	Not required	Not clear	Yes	Reasons given	Complete	Clear
Moller[79]	1989	63	CY + SO + NA; SO + NA	Clear	Not clear	Prospective	Concurrent	Not clear	Yes	Double	Patient	-PCA	Absent	Not clear	Yes	No comment	Incomplete	Clear
Pavy[50]	1990	60	NA + SO; SO	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Not required	No analysis	Yes	Reasons given	Complete	Clear
Perttunen[75]	1992	30	NA + SO (PC) + IB; SO (PC) + IB	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	+PCA	Not required	Comparable	Yes	No comment	Complete	Clear
Sabanathan[81]	1990	56	IC + SO + NA; SO + NA	Clear	Clear	Prospective	Concurrent	Not clear	Yes	Double	Patient	-PCA	Not required	No analysis	Yes	No comment	Complete	Not clear
Salomaki[52]	1991	40	TO; SO	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Not required	Comparable	Yes	No comment	Complete	Clear
Sandler[53]	1986	13	LO; SO	Clear	Not clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Not required	Not clear	Yes	No comment	Complete	Not clear
Sandler[54]	1992	29	LO; SO	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Present	Comparable	Yes	None	Complete	Clear
Schneider[55]	1993	20	IP + SO; SO	Clear	Clear	Prospective	Concurrent	Not clear	Yes	Double	Patient	-PCA	Absent	Comparable	Yes	Reasons given	Complete	Not clear
Shulman[10]	1984	30	LO; SO	Clear	Clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Not required	Comparable	Yes	No comment	Complete	Clear
Swann[62]	1991	20	IB + NA + SO	Clear	Not clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Absent	Not comparable	Yes	No comment	Complete	Clear
Symreng[56]	1989	21	IP + SO; SO	Clear	Not clear	Prospective	Concurrent	Clear	Yes	Double	Patient	No data	Absent	No analysis	No	No comment	Complete	Clear
Whiting[151]	1988	22	LO	Clear	Not clear	Prospective	Concurrent	Clear	Yes	Double	Patient	-PCA	Absent	Comparable	Yes	Reasons given	Complete	Not clear

Each study was rated on the 15 criteria presented in table 1. Cy = cryoanalgesia; EP = extrapleural catheter; IB = intercostal block with local anesthetic; IC = intercostal catheter with local anesthetic; ICP = intercostal phenol; IO = intrathecal opioid; IP = intrapleural catheter; LL = lumbar epidural with locall anesthetic; LO = lumbar epidural with opioid; NA = nonsteroidal anti-inflammatory; PC = patient-controlled analgesia; PL = paravertebral block; SK = systemic ketamine; SO = systemic opioid; SU = systemic analgesia, undefined; TC = thoracic epidural with clonidine; TL = thoracic epidural with local anesthetic; TNS = transcutaneous electrical nerve stimulation; TO = thoracic epidural with opioid.

rated pain scores. Despite fulfilling these criteria, some studies have inherent problems that must be taken into account when considering the findings. The ratings for these studies on the 15 criteria outlined in table 1 are listed in table 2.

Medications for postthoracotomy analgesia can be either systemically or regionally administered.

Systemic Analgesia

Systemic analgesia may be considered under three headings: systemic opioids, systemic nonsteroidal antiinflammatory drugs (NSAIDs), and systemic ketamine.

Systemic Opioids. Traditional therapy for postthoracotomy analgesia consists of intramuscular or intravenous administration of opioid analgesics.[28] The mechanism of action of the opioid agents are well described.[29] The major clinical problem is the narrow therapeutic window. Moderate dose ranges result in adverse effects including nausea and vomiting, somnolence and respiratory depression.[30] The latter problem is especially pertinent after general anesthesia, in view of the residual effects of volatile anesthetic agents on respiratory drive,[31] and the high incidence of pulmonary dysfunction.[32] Recently reported respiratory depression associated with the use of opioids by patient-controlled analgesia (PCA) systems is cause for considerable concern.[33,34] Full descriptions of the role of postoperative systemic opioid analgesics are available.[8,28,35] Studies have been reported on the use of intramuscular opioids alone,[36] subcutaneous opioids,[37] nurse-controlled intravenous opioids[38] and on the assessment of intravenous PCA.[39,40] Systemic opioids are generally considered to be the usual control against which all other treatment modalities are compared, and many well-conducted studies reflect this.[10,41-56] Comparisons of systemic opioids alone with alternative modes of therapy are summarized in table 4. Because most studies have evaluated systemic opioids in the context of comparisons with other modes of treatment,[10,36,37,41-72] few studies have documented the usefulness of systemic opioids alone. Likewise, examination of comparative modalities for delivery of systemic opioids, such as PCA opioids of various classes and non-PCA analgesics through the intravenous, intramuscular, or subcutaneous routes, has been inadequate.

Systemic Nonsteroidal Antiinflammatory Drugs. NSAIDs including indomethacin,[49,50,73] piroxicam,[74] tenoxicam,[66] lysine acetyl salicylate,[48] and diclofenac[75] have been assessed for their ability to reduce pain after thoracic surgery. The mechanisms of action of these agents have been extensively reviewed,[76] and from a clinical perspective, potential problems include gastrointestinal bleeding, acute reversible renal dysfunction, and systemic bleeding associated with platelet dysfunction. These effects are unlikely to cause significant clinical problems with short-term use.[76,77] Several studies have included NSAIDs in various regimens, without specifically examining the contribution of these agents to the analgesic outcome.[78-83]

Postoperative rectal indomethacin (200 mg postoperatively and 100 mg twice daily for 48 h; n = 24) resulted in a reduction in pain scores on a visual analogue scale (VAS) by as much as 60% and a reduction in opioid consumption by approximately 30%, compared with placebo (n = 28).[50] Two potential difficulties with interpretation of this study are: the supplemental analgesia was not administered by PCA, and the group comparisons of demographic data lack statistical analysis.

In a study examining the effects of rectal indomethacin (100 mg rectally three times daily for 72 h) and cryoanalgesia, indomethacin resulted in a reduction in opioid analgesic requirements, and lower VAS pain scores both at rest and on movement.[49] Although the indomethacin was given for 3 days, the pain ratings and analgesic consumption data are reported only for the first 48 h after surgery. This study is discussed below.

Intravenous lysine-acetyl salicylic acid (1.8-g bolus, 7.2 g·24 h^{-1}; n = 10) was compared with intravenous morphine (10 mg bolus, 40 mg·24 h^{-1}; n = 10).[48] The VAS pain scores and PCA paparveretum use were similar in the two groups, indicating that the NSAID was as effective as the morphine infusion.

A single intravenous dose of long acting NSAID (tenoxicam 20 mg; n = 10) was compared with a placebo (n = 9).[66] Between 0 and 12 h, the amount of PCA opioids were reduced in the tenoxicam group, but the differences were not maintained after 12 h. There was no difference in the VAS pain ratings between the groups.

Bigler et al.[74] reported that perioperative rectal administration of piroxicam (40 mg at 12 and 1 h preoperatively and 20 mg at 24 h postoperatively) did not enhance an already highly effective regimen consisting of thoracic epidural bupivacaine and morphine.

Perttunen and co-workers demonstrated that a continuous intravenous infusion of diclofenac (2 mg·kg^{-1}·24 h^{-1}) for 2 days after thoracic surgery re-

Table 3. Studies Not Fulfilling Criteria: Randomized, Double-blind, Prospective, Controlled Trials That Used a Patient-rated Pain Evaluation

Reference No.	Year	No. of Patients	Analgesic Technique	Aim of Study	Entry Criteria	Study Design	Type of Controls	Treatment Regimen	Randomization	Binding of Study	Evaluation of Pain	Analgesic Use	Power Analysis	Prestudy Comparability	Report of Adverse Effects	Patient Withdrawals	Data Presentation	Statistical Procedures
Asantila[57]	1986	51	SO; IB + SO; TL + SO; TO + SO	Clear	Not clear	Prospective	Concurrent	Clear	No	None	Patient	–PCA	Not required	No analysis	Yes	Reasons given	Complete	Not clear
Badner[138]	1990	10	LO	Clear	Clear	Prospective	Absent	Clear	No	None	Patient	–PCA	Not required	No analysis	Yes	No comment	Complete	Clear
Bergh[88]	1966	51	IB + SU; SU	Clear	Clear	Prospective	Concurrent	Not clear	No	None	Not clear	–PCA	Not required	No analysis	Yes	No comment	Complete	None
Boulanger[29]	1993	40	SO (PC); SO	Clear	Not clear	Prospective	Concurrent	Not clear	Yes	None	Patient	+PCA	Present	Not comparable	Yes	No comment	Complete	Clear
Brodsky[140]	1990	44	LO	Clear	Not clear	Prospective	Absent	Clear	No	None	Patient	–PCA	Absent	Not clear	Yes	Reasons given	Complete	None
Bryant[89]	1971	40	IC + SO	Clear	Not clear	Not clear	Absent	Not clear	No	None	Not clear	–PCA	Absent	Data absent	Yes	Reasons given	Incomplete	None
Byrnitz[164]	1986	27	CY + SU; SU	Not clear	Not clear	Prospective	Concurrent	Not clear	Yes	Not clear	Not clear	–PCA	Not required	Not clear	Yes	Reasons given	Incomplete	Clear
Conacher[120]	1983	58	TL + SO	Clear	Not clear	Retrospective	Absent	Not clear	No	None	Not clear	–PCA	Absent	not clear	Yes	Reasons given	Complete	None
de la Rocha[90]	1984	20	IB + SU; IC + SU; TNS + SU	Clear	Not clear	Prospective	Concurrent	Not clear	Yes	None	None	No data	Absent	Not comparable	No	No comment	None	None
Deaton[91]	1953	84	IB + SO	Not clear	Not clear	Not clear	Absent	Not clear	No	Not clear	Not clear	–PCA	Absent	Data absent	Yes	No comment	Incomplete	None
Dellikan[92]	1973	40	IB + SO	Clear	Clear	Prospective	Concurrent	Not clear	No	Double	Not clear	–PCA	Not required	No analysis	Yes	No comment	Incomplete	Not clear
Deneuville[56]	1993	86	IC + SO; SO	Clear	Clear	Prospective	Concurrent	Clear	Yes	None	Patient	–PCA	Not required	No analysis	Yes	Reasons given	Complete	Clear
Elman[93]	1993	18	IP ± NA ± SO	Clear	Clear	Prospective	Concurrent	Not clear	Yes	None	Patient	–PCA	Absent	Not comparable	Yes	No comment	Incomplete	Not clear
Ferrante[106]	1991	20	IP + SO	Clear	Not clear	Prospective	Concurrent	Clear	Yes	None	Patient	–PCA	Not required	Data absent	No	No comment	Complete	Not clear
Fromme[128]	1985	122	LO; TO	Clear	Not clear	Retrospective	Historic	Not clear	No	None	None	–PCA	Absent	Data absent	Yes	No comment	Complete	Clear
Gallon[142]	1982	30	LO	Not clear	Not clear	Not clear	Absent	Not clear	No	None	Patient	No data	Absent	Data absent	Yes	No comment	Incomplete	None
Glynn[59]	1980	29	CY + SO; SO	Clear	Not clear	Not clear	Not clear	Not clear	No	Not clear	None	–PCA	Not required	Data absent	Yes	No comment	Incomplete	Not clear
Gough[100]	1988	86	CY + SO; TO	Clear	Clear	Prospective	Concurrent	Clear	Yes	None	Patient	–PCA	Not required	Data absent	Yes	Reasons given	Complete	Not clear
Gray[158]	1986	50	IO + SU	Clear	Clear	Prospective	Not clear	Clear	No	None	None	–PCA	Not required	Not comparable	Yes	No comment	Complete	Clear
Griffiths[122]	1975	20	TL	Clear	Clear	Not clear	Not clear	Clear	No	None	Patient	–PCA	Absent	Not clear	Yes	Reasons given	Complete	None
Guinard[60]	1992	50	LO; TO; SO	Clear	Clear	Prospective	Concurrent	Clear	Yes	None	Patient	–PCA	Not required	Not comparable	Yes	Reasons given	Complete	Clear
Hasenbos (1)[61]	1985	163	TO; SO	Clear	Not clear	Prospective	Concurrent	Clear	Yes	None	Patient	–PCA	Absent	Not comparable	Yes	Reasons given	Complete	Clear
Hasenbos (2)[62]	1985	163	TO; SO	Clear	Not clear	Prospective	Concurrent	Clear	Yes	None	Patient	–PCA	Not required	Not comparable	Yes	Reasons given	Complete	Clear
Hasenbos (3)[63]	1987	129	TO; SO	Clear	Not clear	Prospective	Not clear	Clear	Yes	None	Patient	–PCA	Not required	Not comparable	Yes	Reasons given	Complete	Clear
Hasenbos[132]	1988	23	TO	Clear	Not clear	Prospective	Concurrent	Clear	No	Double	Patient	–PCA	Not required	Not clear	Yes	No comment	Complete	Not clear
Hasenbos[154]	1989	40	TL + TO	Clear	Not clear	Prospective	Concurrent	Clear	No	None	Patient	–PCA	Not required	No analysis	Yes	No comment	Incomplete	Not clear

James[123]	1981	53	TL + SO	Clear	Not clear	Retrospective	Absent	Not clear	No	None	None	-PCA	Absent	Not clear	Yes	Reasons given	Complete	None
Jenkins[36]	1966	15	SO	Clear	Not clear	Not clear	Absent	Clear	No	None	None	-PCA	Absent	No analysis	Yes	No comment	Complete	None
Kambam[107]	1989	24	IP	Clear	Not clear	Prospective	Not clear	Not clear	No	None	Patient	-PCA	Absent	Data absent	Yes	No comment	Incomplete	Clear
Kaplan[64]	1975	18	IB + SO	Clear	Not clear	Prospective	Concurrent	Clear	No	Double	Not clear	-PCA	Not required	Not clear	Yes	No comment	Complete	Not clear
Katz[53]	1980	24	CY + SO; SO ± IB	Clear	Not clear	Prospective	Concurrent	Not clear	No	None	Patient	-PCA	Not required	Not clear	Yes	No comment	Complete	Clear
Lange[42]	1988	16	SO; SO (PC)	Clear	Not clear	Prospective	Concurrent	Not clear	Yes	None	None	+PCA	Not required	Not clear	Yes	No comment	Complete	Clear
Larsen[27]	1986	20	TO + SO; SO	Clear	Not clear	Prospective	Concurrent	Clear	No	None	Patient	-PCA	Absent	Comparable	Yes	No comment	Complete	Not clear
Laveaux[155]	1993	30	TO + TL	Clear	Not clear	Prospective	Concurrent	Clear	Yes	Single	Patient	-PCA	Absent	Comparable	Yes	No comment	Complete	Not clear
Loder[105]	1962	30	IB + SO	Not clear	Not clear	Retrospective	Historic	Clear	No	None	None	-PCA	Absent	Data absent	Yes	No comment	Incomplete	None
Logas[65]	1987	53	TO + SO; TL + SO; TO + TL + SO; SO	Clear	Not clear	Prospective	Concurrent	Not clear	Yes	Not clear	Patient	-PCA	Not required	Not clear	Yes	No comment	Complete	Clear
Maiwand[165]	1981	100	CY + SU	Not clear	Not clear	Not clear	Absent	Not clear	No	None	None	-PCA	Absent	Data absent	Yes	No comment	Incomplete	None
Maiwand[87]	1982	300	CY + SU; IB + SU; SO	Not clear	Not clear	Not clear	Not clear	Not clear	No	None	Patient	-PCA	Absent	Not clear	Yes	No comment	Incomplete	None
Maiwand[78]	1986	600	CY + SO + NA	Not clear	Not clear	Not clear	Historic	Not clear	No	Not clear	Patient	-PCA	Absent	Not clear	Yes	No comment	Incomplete	None
Majid[104]	1992	12	EP + SO	Clear	Not clear	Prospective	Absent	Clear	No	None	Patient	-PCA	Absent	Not clear	Yes	No comment	Incomplete	None
Matthews[124]	1989	20	PL; TL	Clear	Not clear	Prospective	Concurrent	Clear	Yes	None	Not clear	-PCA	Absent	Not clear	Yes	Reasons given	Incomplete	Not clear
McIlvaine[106]	1988	14	IP	Not clear	Not clear	Prospective	Absent	Not clear	No	None	Observer	+PCA	Not required	No analysis	Yes	No comment	Complete	None
Melendez[145]	1989	17	LO	Clear	Not clear	Prospective	Absent	Clear	No	None	Patient	-PCA	Not required	Not clear	Yes	No comment	Complete	Not clear
Mourisse[125]	1992	50	TL; TO; TL + TO	Clear	Not clear	Prospective	Concurrent	Clear	No	None	Patient	-PCA	Not required	Comparable	Yes	Reasons given	Incomplete	Not clear
Murphy[38]	1991	60	SO	Clear	Clear	Prospective	Absent	Clear	No	None	Patient	-PCA	Absent	Data absent	Yes	Reasons given	Complete	None
Murphy[73]	1993	50	NA + SO	Clear	Clear	Prospective	Concurrent	Clear	Yes	None	Patient	-PCA	Absent	No analysis	Yes	No withdrawals	Complete	Clear
Nelson[87]	1974	38	CY + SO; SO	Not clear	Not clear	Not clear	Not clear	Not clear	No	None	None	-PCA	Not required	Data absent	Yes	No comment	Incomplete	Clear
Neustein[72]	1993	30	IO + SO; SO	Clear	Not clear	Prospective	Concurrent	Clear	Yes	Single	Observer	-PCA	Not required	Not clear	Yes	No comment	Complete	Clear
Nordberg[146]	1986	14	LO + SO	Clear	Not clear	Prospective	Concurrent	Clear	Yes	Double	None	-PCA	Absent	No analysis	Yes	None given	Complete	Not clear
Olive[57]	1980	21	IC + SO	Clear	Not clear	Not clear	Absent	Not clear	No	None	Patient	No data	Absent	Data absent	Yes	No comment	None	None
Orr[55]	1981	45	CY + SO; IB + SO	Clear	Not clear	Prospective	Concurrent	Clear	Yes	None	Patient	-PCA	Not required	Not comparable	No	No comment	Complete	Clear
Orr[56]	1983	84	CY + SO; IB + SO	Clear	Not clear	Not clear	Not clear	Clear	Yes	None	Patient	-PCA	Not required	No analysis	Yes	No comment	Incomplete	Clear
Patrick[147]	1991	22	LO	Clear	Not clear	Prospective	Concurrent	Clear	Yes	None	Patient	-PCA	Absent	No analysis	Yes	Reasons given	Complete	Not clear

(Table continues)

Table 3. Studies Not Fulfilling Criteria: Randomized, Double-blind, Prospective, Controlled Trials That Used a Patient-rated Pain Evaluation (continued)

Reference No.	Year	No. of Patients	Analgesic Technique	Aim of Study	Entry Criteria	Study Design	Type of Controls	Treatment Regimen	Randomization	Blinding of Study	Evaluation of Pain	Analgesic Use	Power Analysis	Prestudy Comparability	Report of Adverse Effects	Patient Withdrawals	Data Presentation	Statistical Procedures
Phillips[133]	1984	27	TO + SO (PC)	Clear	Clear	Prospective	Concurrent	Clear	No	None	Observer	+PCA	Absent	Comparable	Yes	No comment	Incomplete	None
Richardson[80]	1993	20	LO + SO + NA; IC + SO + NA	Clear	Clear	Prospective	Concurrent	Clear	Yes	Single	Patient	-PCA	Not required	No analysis	Yes	No comment	None	Not clear
Roberts[103]	1988	144	CY + SO; IB + SO	Not clear	Not clear	Prospective	Concurrent	Not clear	Yes	Not clear	Patient	-PCA	Not Required	Data absent	Yes	No comment	Incomplete	Not clear
Rooney[68]	1983	44	TNS + SO; SO	Clear	Clear	Prospective	Concurrent	Not clear	Yes	Double	None	-PCA	Not required	Data absent	No	No comment	Complete	Clear
Rooney[166]	1986	75	TNS + SU; CY + SU; SU	Clear	Not clear	Prospective	Concurrent	Not clear	Yes	Not clear	None	No Data	Absent	Data Absent	NY	No comment	None	None
Rosenberg[111]	1987	14	IP + SO	Clear	Not clear	Prospective	Absent	Clear	No	None	Patient	-PCA	Absent	No analysis	Yes	No comment	Complete	None
Rosseel[154]	1988	22	LO; TO	Clear	Not clear	Prospective	Concurrent	Clear	Yes	None	Patient	-PCA	Not Required	Data absent	Yes	No comment	Complete	Not clear
Roviaro[98]	1986	73	ICP + SU; SU	Clear	Not clear	Prospective	Concurrent	Not clear	Yes	None	Patient	No data	Absent	Data absent	Yes	No comment	None	None
Roxburgh[148]	1987	53	CY + LO + SU; LO + SU	Clear	Not clear	Prospective	Concurrent	Not clear	Yes	Not clear	Patient	-PCA	Absent	No analysis	Yes	Reasons given	Complete	Clear
Sabanathan[99]	1988	81	IC + SO	Not clear	Not clear	Not clear	Absent	Not clear	No	None	None	-PCA	Absent	No analysis	Yes	No comment	Complete	None
Safran[100]	1990	20	IC	Clear	Not clear	Prospective	Absent	Clear	No	None	Patient	No data	Absent	No analysis	Yes	None	Incomplete	Not clear
Sawchuk[135]	1993	30	LO; TO	Clear	Not clear	Prospective	Concurrent	Clear	Yes	None	Patient	-PCA	Not required	Not clear	Yes	Reasons given	Complete	Clear
Scheinin[109]	1989	20	IP + SO; SO	Clear	Clear	Prospective	Concurrent	Clear	Yes	Not clear	Patient	-PCA	Not required	No analysis	Yes	No comment	Complete	None
Shulman[149]	1987	21	LO	Not clear	Not clear	Retrospective	Absent	Clear	Yes	Double	Patient	-PCA	Not required	No analysis	Yes	Reasons given	Complete	None
Shuman[126]	1976	8	TL	Not clear	Not clear	Not clear	Absent	Not clear	No	None	None	-PCA	Absent	Data absent	Yes	No comment	Complete	Not clear
Stanton-Hicks[136]	1988	20	TO	Clear	Not clear	Prospective	Absent	Clear	No	None	Not clear	-PCA	Absent	Data absent	Yes	No comment	Complete	None
Stenseth[137]	1985	56	TO	Clear	Not clear	Prospective	Absent	Not clear	No	None	Patient	-PCA	Absent	Data absent	Yes	Reasons given	Complete	Not clear
Stubbing[69]	1988	40	TNS + SO; SO	Clear	Not clear	Prospective	Concurrent	Clear	No	None	Not clear	-PCA	Absent	Data absent	Yes	No comment	Complete	Not clear
Toledo-Pereya[101]	1979	20	IB + SU; SU	Clear	Not clear	Prospective	Concurrent	Not clear	Yes	None	Not clear	No Data	Not required	Comparable	Yes	No comment	None	Not clear
Warfield[70]	1985	24	TNS + SO; SO	Clear	Not clear	Prospective	Concurrent	Not clear	Yes	Not clear	Patient	-PCA	Not required	Data absent	Yes	No comment	Complete	Clear
Welch[150]	1981	30	LO + SO	Clear	Not clear	Prospective	Absent	Not clear	No	None	Patient	-PCA	Absent	No analysis	Yes	Reasons given	Complete	Not clear
Willdeck-Lund[102]	1975	39	IB	Clear	Not clear	Prospective	Concurrent	Not clear	No	Double	None	-PCA	Absent	Data absent	Yes	No comment	Incomplete	None
Zwarts[71]	1989	20	TO + TL; SO	Clear	Clear	Prospective	Concurrent	Clear	Yes	None	Patient	-PCA	Not required	Not comparable	Yes	No comment	Complete	Not clear

Each study was rated on the 15 criteria presented in table 1.

CY = cryoanalgesia; EP = extrapleural catheter; IB = intercostal block with local anesthetic; IC = intercostal catheter with local anesthetic; ICP = intercostal phenol; IO = intrathecal opioid; IP = intrapleural catheter; LL = lumbar epidural with local anesthetic; LO = lumbar epidural with opioid; NA = nonsteroidal anti-inflammatory; PC = patient-controlled analgesia; PL = paravertebral local anesthetic; SK = systemic ketamine; SO = systemic opioid; SU = systemic analgesia, undefined; TC = thoracic epidural with clonidine; TL = thoracic epidural with local anesthetic; TNS = transcutaneous electrical nerve stimulation; TO = thoracic epidural with opioid.

Table 4. Techniques That Were Compared Against Systemic Opioids Alone

Reference	Technique	Beneficial
Epidural opioids		
Benzon[41]	Thoracic Epi fentanyl	Yes
Salomäki[52]	Thoracic Epi fentanyl	Possible
Sandler[54]	Lumbar Epi fentanyl	No
Grant[46]	Lumbar Epi fentanyl(PC)	Yes
Sandler[53]	Lumbar Epi morphine	Possible
Shulman[10]	Lumbar Epi morphine	Yes
Intrapleural analgesia		
Symreng[56]	Intrapleural + SO	Yes
Mann[51]	Intrapleural + SO	Yes
Schneider[55]	Intrapleural + SO	No
Epidural clonidine		
Gordh[47]	Thoracic Epi clonidine + SO(PC)	No
Systemic ketamine		
Dich-Nielsen[43]	Systemic ketamine	Yes
Intercostal analgesia		
Chan[42]	Intercostal catheter + SO	Yes
Dryden[44]	Intercostal catheter + SO	Yes
Galway[45]	Intercostal block + SO	No
NSAIDs		
Jones[48]	NSAI + SO(PC)	Yes
Keenan[49]	SO ± NSAI ± cryoanalgesia	Yes
Pavy[50]	NSAI + SO	Yes
Merry[66]	NSAI + SO (PC)	

The studies included in this table are prospective, randomized, double-blind, controlled trials that used a patient-rated pain evaluation.

SO = systemic opioids; PC = patient-controlled; Epi = epidural; NSAIDs = nonsteroidal anti-inflamatory drugs.

duced intravenous PCA morphine consumption by over 60%, with significant reductions in VAS pain ratings as well.[75] Both the PCA morphine and the intravenous diclofenac (or intravenous placebo) infusions were commenced upon arrival in the postanesthesia care unit, and both groups were given direct intrathoracic local anesthetic intercostal nerve blocks before wound closure. Diclofenac had no effects on intraoperative blood loss, platelet adhesion, bleeding time, or total platelet count. Although there was no significant difference between the groups in serum creatinine levels, the diclofenac group exhibited a significantly lower urinary output on the 1st postoperative day. In addition to the beneficial effects on analgesia and morphine consumption, this study also documented improved oxygenation, as indicated by an increase in the ratio of arterial oxygen tension to inspired oxygen fraction and a reduction in respiratory depression, as indicated by decreased arterial carbon dioxide tension, in the patients treated with intravenous diclofenac.[75]

NSAIDs are potent and safe adjuncts to systemic opioid analgesia after thoracic surgery, resulting in clear benefits in terms of pain and analgesic consumption. They have not been shown to improve the excellent analgesia afforded by a combined regimen of thoracic epidural bupivacaine and morphine.

Systemic Ketamine. Low-dose intramuscular ketamine has been used for short-term treatment of pain after thoracic surgery with no reported adverse effects.[43] Dich-Nielsen and colleagues compared the analgesic efficacy of intramuscular ketamine (1.0 $mg \cdot kg^{-1}$; n = 15) with intramuscular meperidine (1.0 $mg \cdot kg^{-1}$; n = 15) shortly after thoracic surgery.[43] The two regimens were equally efficacious, with less respiratory depression observed in the ketamine group. Although not specifically addressed in this study, the data suggest that ketamine may be a useful adjunct to systemic opioids for postthoracotomy analgesia.

These observations, together with recent laboratory data concerning the role of N-methyl-D-aspartate (NMDA) receptor activation in postinjury central sensitization and hyperalgesia,[84,85] suggests that systemic ketamine, a noncompetitive NMDA antagonist, may have an important role to play in the treatment of postthoracotomy pain.

Regional Analgesia

Several regional approaches are available for the administration of analgesic medication after thoracic surgery.[8,28,35,86] These techniques include intercostal, intrapleural, intraspinal and paravertebral blockade; cryoanalgesia; and transcutaneous electrical nerve stimulation (TENS).

Intercostal Analgesia. Intercostal neuronal blockade has been used extensively for analgesia after thoracic surgery.[42,44,45,57,58,64,81,82,87-104] Agents may be administered as a single treatment under direct vision, before chest closure,[45,64,87,90,92,95,96,98,101,102,105] as a single preoperative percutaneous treatment,[82] as multiple percutaneous serial injections[57,88] or via an indwelling intercostal catheter.[42,44,58,80,81,89-91,97,99,100,104] The main concern with the technique is a high level of systemic absorption although clinical studies of patients after thoracic surgery have documented safe plasma levels of local anesthetics.[42,45,100]

Chan et al.[42] reported a study in which patients received bolus doses of either 0.5% bupivacaine (n = 10) or normal saline (n = 10) via indwelling inter-

costal catheters every 6 h, for 24 h after surgery. The bupivacaine group had significantly, but transiently lower VAS pain scores after each injection, and consumed fewer opioid analgesics than the control group over the 24-h study period.

Sabanathan et al.[81] also examined the effectiveness of indwelling intercostal catheters, in which the patients received a continuous infusion of either 0.5% bupivacaine (n = 29) or normal saline (n = 27). The authors report lower VAS pain scores and less opioid consumption in the bupivacaine group.

A large study of two different regimens (2% lidocaine plus epinephrine [n = 46] and 0.5% bupivacaine plus epinephrine [n = 46]) administered as intercostal injections before chest closure, compared with no therapy (n = 46), reported that there was no difference between the three groups in time to first analgesic request.[45] However, initial assessment suggested that patients in the treatment groups had less pain than those in the untreated control group. Problems with interpretation of this study include a very prolonged mean time to first analgesic request 203 ± 39 min (mean ± SEM) for the control group, suggesting an atypical clinical course after thoracic surgery. This finding is even more surprising since patients did not receive opioids during the surgical procedure. The authors suggest that the untreated patients were more easily nursed, and do not recommend the use of intercostal injections as used in the study.

A recent study using a cross-over design[44] (n = 20) reported a significant reduction in VAS pain scores and in PCA morphine consumption during infusion of 0.25% bupivacaine through paired indwelling intercostal catheters. These authors confirmed the correct anatomic placement of the catheters, in the interspaces above and below the intercostal incision, by injection of radio-opaque contrast. Although confirming the efficacy in terms of analgesia and reduction in PCA morphine consumption, this study may have significantly underestimated the true benefit of the technique because of insufficient washout time in the group that received the saline infusion after the bupivacaine infusion and because of the pooling of all of the VAS pain ratings into two sections.

The hypothesis that alkalinization of a bupivacaine-epinephrine mixture would extend the duration of action of postoperative intercostal nerve blocks was recently addressed in a study of 20 patients.[82] The results showed that there was no evidence to support the hypothesis.

Based on the results of these studies, we conclude that intercostal nerve blockade by intermittent or con-tinuous infusion of 0.5% bupivacaine with epinephrine is an effective method, as is continuous infusion of 0.25% bupivacaine through indwelling intercostal catheters, for supplementing systemic opioid analgesia for postthoracotomy pain. The value of single preclosure injections is doubtful, and there does not appear to be any benefit associated with alkalinization of the injectate.

Intrapleural Analgesia. Intrapleural administration of local anesthetics has found increasing use after thoracic surgery[51,55,56,83,106–110] since publication the work of Rosenberg et al.[111] The mechanisms of action of intrapleural analgesia are incompletely understood.[112,113] Local anesthetic agents may be administered via an indwelling intrapleural catheter by intermittent[51,55,56,83,106,107,109,110] or continuous-infusion regimens.[108,111] Concerns about systemic absorption and toxicity from local anesthetics have not been substantiated in clinical studies that assayed plasma levels.[56,106–109,111]

Intrapleural bupivacaine (0.25%) administered in 20-ml bolus doses every 4 h for 48–72 h after surgery resulted in reduced postoperative pain at 4, 24 and 72 h, compared with interpleural normal saline (n = 40).[51] There were no differences in opioid consumption between the groups and the difference in pain scores was not significant at 48 h.

Intrapleural bupivacaine 0.5% (1.5 mg · kg^{-1}; n = 7) at 8 and 16 h after surgery was compared with saline (n = 8).[56] The patients receiving bupivacaine reported a significant, but transient, reduction in pain scores and opioid use lasting 2–5 h after injection. There were no significant intergroup differences in total opioid consumption.

Schneider et al. compared intrapleural bupivacaine (0.5%; n = 9) with intrapleural saline (n = 9) administered in 30-ml bolus doses every 4 h for a total of 12 doses after surgery.[55] They reported no differences in VAS pain scores or analgesic requirements between the two groups. However, VAS pain scores were reported on only two occasions in the 48-h postoperative period. Furthermore, analgesia was supplied on a non-PCA basis, and there are inadequate details concerning the intraoperative use of analgesics. In addition, VAS pain scores were not reported immediately after intrapleural administration of bupivacaine, raising the possibility that transient benefits may have been missed.

These data suggest that intrapleural bupivacaine (0.25–0.5%) may improve analgesia in patients after thoracic surgery. The benefits are of short duration and

there does not appear to be a significant overall opioid-sparing effect. The optimum concentration and dosing regimen remain to be defined.

Intraspinal Analgesia. Intraspinal techniques that have been described for postthoracotomy analgesia include thoracic local anesthetics, epidural opioids (including opioid agonist-antagonists), thoracic epidural opioids combined with local anesthetics, thoracic epidural adrenergic agonists, and intrathecal opioids.

The techniques, mechanisms of action and adverse effects of these modalities have been extensively reviewed.[114-116] The serious but infrequent adverse effects include: high spinal blockade or significant systemic toxicity after intraspinal local anesthetics; respiratory depression after intraspinal opioids[117]; and rare cases of spinal cord or nerve trauma, hematoma, infection or inflammatory reaction associated with introduction of the catheter or needle.[118,119] Less serious, but troublesome problems include nausea, pruritus, and urinary retention after intraspinal opioids[114,118]; hypotension, temporary paralysis, urinary retention, and paresthesia after intraspinal local anesthetics; and a low incidence of post–dural puncture headache after instrumentation for either mode of treatment.[114,118,119]

Thoracic Epidural Local Anesthetics. Thoracic epidural local anesthetics have been used in several studies,[57,65,120-126] and are administered with the aim of creating a circumscribed band of dense analgesia in the dermatomal region of the thoracotomy incision.

El-Baz and colleagues evaluated intermittent administration of bupivacaine (0.5%, 5-ml bolus doses; n = 30) through a thoracic epidural catheter, and found that analgesia was comparable to continuous infusions (n = 30) or intermittent bolus doses (n = 30) of thoracic epidural morphine.[121] There was however, a prohibitive incidence of urinary retention, hypotension, and upper limb weakness and paresthesia related to the bupivacaine administration. The results section documenting the statistical comparisons between the groups is difficult to decipher.

Studies of epidural local anesthetics alone have been limited to intermittent—and occasionally toxic—bolus administration, or have examined continuous infusions with either concomitant administration of systemic opioids, epidural opioids, or systemic NSAID analgesics. However, the true efficacy of epidural local anesthesia for postthoracotomy analgesia has not been determined in appropriately conducted clinical studies. Combinations of epidural local anesthetic and opiate are discussed later in the text.

Thoracic or Lumbar Epidural Opioids. Epidural opioids have been administered by the thoracic[37,41,52,57,60-63,65,121,125,127-137] or lumbar[10,46,53,54,60,80,127,128,134,135,138-151] routes. In addition to epidural opioid agonists, epidural agonist–antagonists[139,141] and concomitant intravenous opioid antagonists[143] have been administered to reduce postoperative respiratory depression selectively while maintaining adequate postoperative analgesia. The choices of method and route have depended on individual preference, familiarity with techniques, and the perceived safety of the procedure.[127,152,153]

Lumbar epidural morphine administered as a 5.0 mg bolus dose (n = 15) was compared with non-PCA intravenous morphine bolus administration (n = 15) by our research group.[10] Epidural morphine was associated with reduced pain scores and improved postoperative pulmonary function. Although the mean respiratory rate was lower in the epidural group, significant respiratory depression did not occur in either group.

These results were not reproduced in a smaller study (n = 13) by our research group,[53] in which we compared epidural and intravenous administration of morphine and produced equivalent postoperative analgesia. Although this study was designed primarily to define the occurrence and time course of respiratory depression after epidural morphine, the small sample size may in part explain the absence of a significant intergroup difference in postoperative pain and analgesic effect.

A further study conducted by our research group[141] compared the efficacy of repeated bolus doses of lumbar epidural morphine (5.0 mg) with two groups receiving different bolus doses of lumbar epidural nalbuphine (n = 15 total) (see below). Although the epidural morphine was associated with better analgesia, respiratory depression was unpredictable. A different study design[139] comparing single postoperative doses of lumbar epidural morphine with a range of nalbuphine doses (see below), confirmed that lumbar epidural morphine (0.1 mg·kg^{-1}; n = 12) provided superior analgesia compared with epidural nalbuphine, and was associated with reduced supplemental PCA intravenous fentanyl consumption.[139]

El Baz *et al.*[121] reported that a continuous infusion of thoracic epidural morphine (1.0 mg·h^{-1}) with intravenous supplementation resulted in comparable analgesia to that provided by intermittent thoracic epidural boluses of either bupivacaine or morphine (5.0

mg boluses) (see above). In addition, the continuous infusion was associated with fewer adverse effects than the other two regimens. As mentioned above, the presentation of the results is confusing.

Lumbar epidural sufentanil bolus doses of (30 µg; n = 9), (50 µg; n = 6), and (75 µg; n = 7) have been studied on a dose–response basis by our research group.[151] The results showed that sufentanil provided rapid and effective analgesia, but with a brief duration of action. Furthermore, increasing the dose resulted in an increased incidence of respiratory depression without any additional analgesic benefits.

Studies of epidural fentanyl have focused on the optimum route of administration.[46,52,54,127] This is of importance from the clinical therapeutics point of view, in addition to providing clinical evidence of the mechanisms and sites of action of epidurally administered lipid soluble opioids. A comparison of thoracic and lumbar epidural fentanyl administration suggested that pain and fentanyl requirements were reduced when the thoracic route was used.[127] These trends did not reach statistical significance. Since a power analysis was not reported, the negative findings are difficult to interpret.

Two studies compared administration of lumbar epidural fentanyl with intravenous fentanyl.[46,54] Grant et al.[46] compared lumbar epidural PCA fentanyl (n = 14) with intravenous PCA fentanyl (n = 15) and used continuous (variable) background infusions for both regimens. VAS pain scores were similar in the two groups, but the epidural PCA group consumed significantly less fentanyl than the intravenous PCA group. However pharmacokinetic data are not presented. Our research group[54] reported that lumbar epidural fentanyl results in similar analgesic and respiratory effects compared with intravenous administration. Fentanyl was administered as observer-controlled bolus doses, with a continuous (variable) background infusion. Detailed pharmacokinetic data showed that the epidural administration is associated with higher infusion rates than intravenous administration, but with similar clearance values.[54] It is possible that the different mode of delivery—PCA versus observer-controlled analgesia—could account for the differences observed.

A comparison by Salomäki et al. of thoracic epidural fentanyl with intravenous fentanyl found that when fentanyl infusions were titrated to patient VAS pain ratings, the epidural administration produced similar analgesia to the intravenous route but with fewer adverse effects and lower infusion rates.[52] This study supports the suggestion that the administration of a highly lipid soluble opioid should be in the dermatomal region of the surgical incision. The pharmacokinetic data confirmed that the thoracic epidural fentanyl administration results in significantly lower plasma fentanyl levels than intravenous administration.[52] The results of this study have been corroborated by a comparison of thoracic epidural fentanyl and intravenous PCA morphine,[41] in which thoracic epidural fentanyl resulted in lower pain, less sedation, but more pruritus than the intravenous PCA morphine. Despite impressive differences in pain ratings, there were no differences in postoperative pulmonary mechanics or arterial carbon dioxide.

Two studies have examined the role of lumbar epidural nalbuphine.[139,141] Baxter et al. compared four groups of ten patients each that received a single different dose of nalbuphine (range 0.075–0.30 mg·kg^{-1}) with a group (n = 12) that received a single dose of lumbar epidural morphine (0.01 mg·kg^{-1}) after surgery.[139] In all cases, the pain scores and use of supplementary intravenous fentanyl by PCA were greater in the nalbuphine groups. Our research group[141] found that despite repeated doses of lumbar epidural nalbuphine 10 mg (n = 4) or 20 mg (n = 5), most patients were withdrawn from the study because of inadequate analgesia, in contrast to those who received lumbar epidural morphine. Patients in the morphine group, however, demonstrated unpredictable respiratory depression.

Gowan and colleagues attempted to define the effects of intravenous naloxone infusions in combination with lumbar epidural morphine.[143] They studied four groups of patients who received intravenous bolus doses of naloxone (0.0–4.0 µg·kg^{-1}) followed by intravenous naloxone infusions (0.0–4.0 µg·kg^{-1}·h^{-1}) to reduce the adverse effects associated with epidural morphine while retaining the analgesic effects. The authors discontinued testing in the high-dose naloxone group because of the suggestion of intense antianalgesic effects. The results were equivocal because sample size was small (n = 24) and because the patients received systemic morphine after the epidural morphine. The authors concluded that the concomitant use of intravenous naloxone with epidural morphine is not useful in this setting.

Therefore, the optimal methods for administering epidural morphine include lumbar epidural bolus doses and low-dose continuous thoracic infusion with intravenous supplementation as required. Both modes

appear safe and effective. The addition of piroxicam does not improve the efficacy of thoracic epidural morphine when the morphine is co-administered with thoracic epidural bupivacaine. The role, level of administration and optimal dose of epidural sufentanil remain to be defined. There is little justification for the lumbar epidural administration of fentanyl, but thoracic epidural administration may have advantages. Intravenous fentanyl is probably as effective as lumbar epidural fentanyl, and may have less associated risk. Further comparison of thoracic *versus* lumbar epidural fentanyl may be warranted. There do not appear to be beneficial effects associated with the concomitant administration of epidural or intravenous opioid agonist-antagonists with epidural opioids in the treatment of postthoracotomy pain.

Combined Thoracic Epidural Local Anesthetics and Opioids. Epidural opioids have been combined with epidural local anesthetics with the aim of synergistically blocking spinal nociceptive pathways while reducing the dose-related adverse effects of either class of agent alone. Several studies have examined the effectiveness of this technique after thoracotomy.[65,71,74,125,129,131,154,155]

George et al.[129] assessed the effect of adding bupivacaine (0.2%; n = 10) or normal saline (n = 10) to a continuous thoracic epidural infusion of fentanyl (50 $\mu g \cdot h^{-1}$). The addition of bupivacaine resulted in reduced pain scores on the 1st day. However, the regimens were not titrated or controlled by PCA, so there was no opportunity to detect differences in analgesic use. Furthermore, the pain scores were so low in both groups, that differences after the 1st day would have been difficult to detect. Finally, the comparability of the groups in terms of demographics is unclear.

Harbers et al. compared intravenous with thoracic epidural sufentanil administration in patients with indwelling thoracic epidural catheters who were receiving continuous infusions of 0.125% bupivacaine.[131] Patients received infusions of sufentanil by either the thoracic epidural (n = 13) or intravenous route (n = 14). The two groups showed comparable analgesia, which was excellent at all times, and the infusion rates of sufentanil were similar. Although no pharmacokinetic data were presented, the results suggest that when used as an adjunct to a continuous thoracic epidural infusion of bupivacaine, intravenous sufentanil is equivalent to thoracic epidural sufentanil.[131]

Bigler et al.[74] compared the effects of thoracic epidural bupivacaine plus morphine in combination with

rectal administration of either piroxicam (n = 14) or placebo (n = 14). Both groups reported excellent analgesia with similar need for supplemental intravenous opioid analgesics. This study was designed to assess the additional benefits of NSAID to the comprehensive epidural regimen. It is therefore not possible to assess the specific contributions of the epidural local anesthetic or opioid components. However, the addition of a systemic NSAID did not enhance the analgesic effect of a combination regimen consisting of thoracic epidural morphine and bupivacaine.

The coadministration of local anesthetics and opioids by the thoracic epidural route has been partially explored. Clearly, excellent analgesia can be achieved with combinations of these agents. NSAIDs do not appear to enhance analgesia when already effective in this context. However, the optimum agents, combinations, dose regimens and comparative benefits remain to be determined.

Thoracic Epidural Adrenergic Agonists. Epidural adrenergic agonists have the potential for effective antinociceptive activity after systemic or intraspinal administration.[116,156] The mechanism of action appears to be modulation of the endogenous postsynaptic adrenergic receptors in the dorsal horn cells.[157]

The efficacy of a single dose of thoracic epidural clonidine (3 $\mu g \cdot kg^{-1}$; n = 10) was compared with a saline placebo (n = 10).[47] No analgesic benefits were observed. Dose–response data are required to define the efficacy and complications associated with intraspinal clonidine and other α_2 agonists in postthoracotomy analgesia.

Lumbar Intrathecal Opioids. Lumbar intrathecal opioids have been used as an adjunct to postthoracotomy analgesia in published studies.[72,158] The advantages of the technique include simplicity, reliability, and because of the small doses used, potentially fewer adverse effects from systemic opioid absorption.[72,159] Unfortunately, it is not possible to comment on the clinical utility of this technique for postthoracotomy analgesia on the basis of the available literature.

Paravertebral Blockade. Unilateral paravertebral neuronal blockade has been used for postthoracotomy analgesia because the pain after lateral thoracotomy is almost always unilateral.[124] The anatomical basis for paravertebral blockade has been reviewed.[160–162] The benefits of unilateral paravertebral blockade are twofold. First, because the concomitant sympathetic blockade is unilateral, the incidence of adverse effects such as hypotension and urinary retention is lower.[8,124]

Second, a smaller quantity of local anesthetic agent is required, and so the risk of systemic local anesthetic toxicity may be less.

It is not possible to determine, from the available literature, whether the technique of paravertebral blockade is useful in the postoperative analgesic management of patients after thoracotomy.

Cryoanalgesia. Cryoanalgesia, introduced by Lloyd et al.,[163] consists of freezing the intercostal nerves by the intraoperative application of a cryoprobe to its posterior aspect, and then allowing the nerve to thaw.[49,59,67,78,79,87,93,95,96,103,130,148,164-166] The cycle may then be repeated and may be performed on several nerves subserving the dermatomal region of the incision.[167] Because the neurolytic lesion produced is partial, and the endoneurium is preserved, axonal regeneration is possible and normal sensation should return after surgery.[67] Concerns have been raised about possible long-term neuralgia.[14,148]

Keenan et al.[49] compared cryoanalgesia alone (n = 15), cryoanalgesia and indomethacin (n = 15), indomethacin alone (n = 15), and a control (n = 15). Cryoanalgesia reduced VAS pain scores at rest but had no effect on VAS pain scores after movement. The amount of opioids used was reduced only when cryoanalgesia was used in conjunction with rectal indomethacin. The perioperative anesthetic management of these patients is not clear from the paper, the supplementary analgesia was not administered by PCA, and a measure of dispersion for the pain scores is not provided. Finally, there is no comment on the development of late intercostal neuralgia.

A simpler two-group study that compared cryoanalgesia (n = 30) with a control group (n = 33) that did not receive cryoanalgesia suggested that there were no advantages associated with the treatment.[79] The potential problems with interpretation of this study include lack of clear inclusion and exclusion criteria, insufficient detail concerning the treatment regimens, and absence of power analysis in the face of a negative result. Approximately 20% of the treated patients developed intercostal neuralgias by 6 weeks after surgery.

There appears to little beneficial role for the routine use of cryoanalgesia in the prevention of pain after thoracic surgery, and its use may be accompanied with a significant incidence of adverse effects.

Transcutaneous Electrical Nerve Stimulation. TENS was introduced into clinical practice by Wall and Sweet.[168] TENS may result in spinal gating of small diameter unmyelinated C-fiber input by larger myelinated Aβ-fibers,[169] and it may also activate descending inhibitory pathways.[170] Endogenous opioid and nonopioid (e.g., γ-aminobutyric acid) mechanisms may be involved in mediating TENS-induced analgesia.[171] TENS has been used to relieve pain after thoracic surgery.[68-70,90,166] The only significant adverse effects are local skin hypersensitivity[172] and the possibility that the electrical current could interfere with the function of cardiac pacemakers. On the basis of the available published data, it is not possible to determine the role of TENS in the treatment of postthoracotomy analgesia.

Preemptive Analgesic Regimens

The suggestion that central nervous system sensitization may increase postoperative pain has recently been reviewed in detail.[173,174] The basic science findings and clinical evidence for this phenomenon has prompted investigation into the role of preemptive analgesic regimens in the management of postthoracotomy analgesia.[73,144]

Our research group have produced evidence that the timing of lumbar epidural fentanyl administration may be important in the prevention of postoperative pain.[144] Pain scores and PCA morphine use in patients who received lumbar epidural fentanyl 15 min before incision (n = 15) were lower than in those who received the identical dose of epidural fentanyl 15 min after incision (n = 15); the difference was small but significant. The results suggest that pain after thoracic surgery may be lessened by preincisional, rather than postincisional, administration of epidural fentanyl, and supported the hypothesis that noxious afferent signals during incision and surgery contribute to central sensitization and to increased postoperative pain. However, a significant age difference between the groups may complicate interpretation.

Further research is required to evaluate the potential benefits of preemptive analgesia for postthoracotomy pain. Issues that require clarification include determining the most useful classes of agents (or combination of agents), doses, timing and routes of administration. Whether preemptive analgesia will prove useful in reducing the problem of long-term postthoracotomy chest wall pain remains to be determined.

Conclusions and Recommendations

There has been a remarkable improvement in the standard of clinical studies of postthoracotomy anal-

gesia in recent years. Nevertheless, the majority of studies are difficult, if not impossible to interpret because of fundamental problems with design, methods, or statistical treatment of data. A minority of studies are clearly interpretable because they are randomized, prospective, double-blind, have concurrent controls, and include a measure of patient-rated pain. The following recommendations are based on these well-designed and controlled studies.

Systemic opioids form the cornerstone of postthoracotomy analgesia therapy, and have constituted the control group in the majority of clinical studies. Pain or analgesic consumption are reduced significantly with the following techniques: indwelling intercostal catheters with bupivacaine, interpleural catheters with bupivacaine, epidural morphine (with an infusion in the thoracic route or bolus administration in the lumbar route), combined infusions of thoracic epidural bupivacaine with either thoracic epidural or intravenous sufentanil, thoracic epidural fentanyl, and systemic NSAIDs as adjuncts to systemic opioids. The short-term use of low-dose intramuscular ketamine is a promising alternative, and potential adjunct to systemic opioids.

The combination of thoracic epidural local anesthetics and opioids can essentially abolish postoperative pain, but considerable experience is required for safe insertion and monitoring. NSAID on the other hand would not be expected to be sufficient when used as sole agents, but are an economical and extremely effective adjunct to systemic opioid analgesics.

There is little evidence that the following techniques provide effective pain relief for patients after thoracic surgery: cryoanalgesia; lumbar epidural nalbuphine; lumbar epidural, as opposed to intravenous or thoracic epidural fentanyl administration.

When choosing a method of postthoracotomy pain control, the physician must consider the following factors: (1) the physician's experience, familiarity, and complication rate with specific techniques; (2) the specific clinical circumstances, including the presence of contraindications to various analgesic techniques and medications; (3) availability of an appropriate atmosphere for the safe and effective commencement and maintenance of the technique; (4) availability of appropriate facilities for patient assessment and monitoring; and (5) the acceptance by all parties that treatment may be undertaken, that the technique falls within reasonable risk–benefit and cost–benefit constraints, and that it contributes to patient satisfaction in addition to providing analgesia. These factors are a function of the physician's training, maintenance of competence, and ongoing education of hospital anesthetic and perioperative surgical support staff. The issues of complications and contraindications associated with specific techniques were briefly discussed in the appropriate sections (see above), and these issues and monitoring recommendations are discussed extensively elsewhere.[8,14,28,76,78,86,112,114,117–119,152,161,172,175–185]

Cost–benefit issues are assuming progressively greater importance in the perioperative management of patients.[186,187] Although methods for the accurate assessment of analgesic cost have been reported,[188] comprehensive data have not been published regarding cost–benefit analysis for analgesia after thoracic surgery. A description of detailed financial cost comparisons of two methods of thoracic surgery has been reported.[189] This report details how considerations such as the cost of equipment, differences in operating room time, duration of hospital stay or care in a special care setting, and the cost involved in treating adverse complications could be included in a comparative assessment of analgesic interventions. Thought must also be given to the additional burdens inherent in learning new techniques and in in-servicing support staff involved in patient care. Novel developments in surgical technique may lessen the burden of postthoracotomy pain,[189,190] and thus further improve patients' prospects for improved postoperative analgesia.

Further work is required in the following areas: (1) the optimal concentration, volume and dosing regimen, site of administration and concomitant opioid use with thoracic epidural local anesthetics; (2) efficacy and optimal site (lumbar vs. thoracic) of administration of epidural lipid-soluble opioids; (3) delineation of the roles epidural and systemic α_2-adrenergic agonists, ketamine, TENS, and preemptive analgesia; and (4) development of postthoracotomy analgesic techniques to reduce the incidence of long-term pain syndromes.

Future studies should be designed after careful consideration of the issues detailed in the 15 rating criteria presented in table 1 and discussed in the appendix. Whenever possible, studies should carried out in a prospective, randomized, double-blind, placebo-controlled manner. Pain should be measured with a valid and reliable patient-rated measurement instrument. Postoperative systemic opioid use should be administered in a standardized manner, preferably by PCA. Outcomes other than pain and analgesic use, including cost–benefit analyses, should be included in reports of postthoracotomy analgesia. Attempts should be made

to conduct clinical investigations that would maximize the yield of clinically useful data, make real advances in the field, and possibly reduce the number of redundant studies and patients enrolled therein.

Appendix

Aim of Study

It is fundamental that the primary question be selected, defined and stated in advance to optimize proper design and to ensure the validity of subsequent statistical analysis.[191] This criterion was scored as *clear* if the aim was clearly described and as *not clear* if there was no statement of aim or if the issue was equivocal.

Entry Criteria

It is essential to define and report the population under study.[191] Insufficient information about entry criteria makes interpretation of intergroup outcome comparisons potentially ambiguous. When entry criteria are not specified it is difficult for readers to compare the work with other published data in a meaningful way. This criterion was rated *clear* if both inclusion and exclusion criteria were clearly provided and *not clear* if only inclusion or exclusion criteria were described or if no comment was made regarding entry criteria.

Study Design

The quality, accuracy and validity of results can differ appreciably depending on whether the study was carried out prospectively or retrospectively. In fact, the clinical trial has been defined as a prospective study.[191] Each study design was rated as *prospective, retrospective,* or *unclear.*

Controls

This is an area of possible confusion for two reasons. First, because there is no "gold standard" or ideal therapy for postthoracotomy pain, there is no standard control treatment against which other forms of therapy have been compared in published studies. Second, the validity of control data depends in part on whether the study was conducted in a prospective or retrospective fashion. In a prospective study, the control group may consist of contemporaneously studied patients (concurrent controls). Alternatively, control group data may be drawn from the medical records of patients treated before the current treatment group (historic controls). Although historically controlled trials are associated with greater degrees of sensitivity, their biases are inherent and not correctable.[192] A prospective design with a concurrent control group is recommended for evaluating the efficacy of new modes of therapy.[21,192] Studies including two or more treatment conditions were considered controlled studies. In retrospective studies, the controls are historic by definition, whether their data were obtained concurrent with or before the data from the treatment group. Thus, the status of the control group was rated *concurrent, historic,* or *absent,* or as *not clear* when it was difficult to decipher.

Treatment Regimens

It is imperative that the treatment regimens for clinical studies be described in detail.[25,193] The complete anesthetic and analgesic regimen should be described in detail to ensure that any effect—or lack of effect—on postoperative pain, can be correctly attributed to the specific intervention under investigation, rather than simply occurring as a result of differences in potentially dissimilar nonstandardized anesthetic-analgesic techniques. This criterion was coded as *clear* if the analgesic regimens and doses during preoperative, intraoperative and postoperative care were outlined in sufficient detail to enable replication. It was coded as *not clear* if the description of the regimens were incomplete or not clear.

Randomization

The importance of randomization lies in three main areas.[191] First, the potential for bias in subject allocation is eliminated.[194] Second, baseline characteristics and demographic data are likely to be comparable between the groups with respect to known and unknown variables (especially with larger sample sizes). Third, the validity of subsequent statistical analysis may be enhanced.[191] This criterion was coded *yes* if the title, abstract, or text contained a statement that allocation of patients to treatment was performed according to a randomization plan; *no* was entered if patients were not allocated randomly to treatment or if the method of allocation was not mentioned.

Blinding of Study

Blinding eliminates a potential source of bias in a clinical trial. At a minimum, blinding should include administration of the therapeutic intervention and evaluation of the response outcome measures.[16] This criterion was coded as follows: *double-blind* if clearly neither the patient, the caregivers, nor study personnel involved in patient assessment and data collection were aware of the group to which the patients were allocated; *single-blind* if either the patients or the research personnel assessing the patients were aware of the group allocation; *not blind* if the study was either obviously not blind or if the issue of blinding was not addressed; and *not clear* if the issue of blinding was not clear from the text.

Evaluation of Pain

To claim that an intervention has reduced postoperative pain, some measurement of the painful experience must be obtained. This statement may seem obvious, but several studies of postthoracotomy pain have referred to the benefits of specific interventions in terms of their pain relieving effects even though pain was not measured at any point after surgery (see table 3). Studies purporting to report on the efficacy of analgesic regimens should provide evidence of an assessment of pain or pain relief. The quantification of postoperative analgesics should not be substituted as a measure of pain[195] as patients may differ with respect to experience of various nonanalgesic effects of administered analgesics, or may have different pain thresholds requiring administration of additional analgesia. The use of postoperative spirometric indices or physiotherapy performance scores also should not be substituted for a measure of pain even though they may correlate with postoperative pain or analgesia. The pain measurement tools used should have demonstrated reliability and validity.

Pain measurement may be classified as *patient-rated,* when the patient records or reports his or her pain, or as *observer-rated.* Because pain is a subjective experience[196] patient-rated reports of pain are preferred to observer reports. In some situations, such as in pre-

verbal children or adults with impaired communication skills, observer-rated methods (*e.g.,* behavioral assessments) may be appropriate.[197] Observer-rated methods may yield data that correlate closely with patient-rated pain scores, but these methods should not replace patient-ratings if the patient is capable of rating his or her pain.[197] Despite good correlation between physicians' rating and patients' rating of patients' pain experience, actual agreement may be low: physicians consistently underestimated the patients' reported pain.[198] Other studies have demonstrated a lack of concordance in pain as rated by patients compared with that rated by nursing personnel.[199,200]

The criterion for evaluation of pain was scored as follows: *patient-rated,* when patients rated their pain, or if the description was not explicit, in which a referenced patient-rated pain scale was used; *observer-rated,* in which personnel and not the patients evaluated the pain; *none,* when pain assessment was not reported; and *not clear,* when the method of evaluating pain was not clear.

Analgesic Use

In addition to reporting a measure of pain experience, many studies report the quantity and nature of analgesic medication administered to the study groups. These data are obtained to enable comparisons of analgesic efficacy: relatively more efficacious regimens should reduce analgesic requirements. The analgesic agents may be administered by systemic or regional routes, may consist of a variety of analgesic drug classes, and the administration may be controlled either by the patient or by the health-care personnel.

Although many of the problems of measurement and validation in the area of pain assessment have been researched, little is known about the optimal approach to the assessment or standardization of postoperative analgesic consumption. Indeed Taenzer[201] reported a very low correlation between analgesic consumption and postoperative pain scores as assessed by a variety of patient-rated scoring systems suggesting that factors other than actual postoperative pain intensity determine the consumption of postoperative analgesics.[202,203] A recent suggestion[204] for combining PCA use and pain score data in an integrated fashion may assist in the interpretation of results of studies that report these two variables.

The nature of the analgesic agent and route of administration depend on the study design and the clinical circumstances. In addition, some studies report total analgesic consumption, time to first analgesic request, total number of doses received or total consumption between pain ratings. These differences in reported data make comparisons between studies difficult. However, where clinical conditions and considerations of study design permit, studies assessing postoperative pain should ideally have analgesic use controlled by patients, and should at a minimum report some measure of analgesic consumption. For the purposes of this review, analgesic use was classified as *patient-controlled* if a PCA system was used and the data on analgesic consumption were reported. It was rated as *non–patient-controlled* if a non-PCA method was used or the method was not specified but data on analgesic consumption were reported. *No data* was recorded where data on postoperative analgesic consumption were not reported.

Power Analysis

Increasing concern has arisen over the appropriate reporting of so-called "negative trials" (trials in which data analysis of outcome measures fail to yield test statistics that equal or exceed the critical value required to reject the null hypothesis at a specified α). Failure to reject the null hypothesis when it is false yields a type II error, with the result that a true effect is not detected.[205,206] Although the true "state of affairs" is never known, the probability of failing to reject the null hypothesis when it is false (a type II error) may be assessed for a given α, effect size, measure of variation, and sample size. Clinical studies reporting "negative results" should therefore include an estimation of the power of the statistical test, documenting the type I error rate (α), the magnitude of the clinical effect, a measure of variation and the sample size. Therefore this criterion was coded as *present* when a power analysis was reported. It was coded as *not required* in the case of a positive outcome (the null hypothesis regarding pain or analgesic use was rejected) and as *absent* when not reported, in the case of a negative outcome, or in the case of a single group case series for which comparative data or analysis is obviously not possible.

Prestudy Comparability of Groups

Pretreatment differences may make subsequent outcome analyses ambiguous. Despite precautions, intergroup differences in demographic and clinical data due to sampling error can occur, and when they do, they are obvious sources of bias.

Presentation of demographic data allows the reader to assess the characteristics of the sample of patients studied as opposed to those eligible for inclusion. This is clearly of importance when extrapolating the results of a study to a broader population.[191] In this section, studies were categorized as *comparable* where minimum demographic data (age and sex) for each study group were presented, and statistical analysis indicated that the groups did not differ significantly (on these variables or on others if more than two were measured). Studies were rated as *not comparable* where statistical analysis revealed a significant difference between the groups. *No analysis* indicated that (1) minimum demographic data were provided without statistical comparison or reference to statistical significance, or (2) the study design used a single group of patients and demographic data were presented. *Data absent* was recorded where no demographic information was presented. *Not clear* was recorded where either the nature of the statistical comparisons or the data could not be ascertained, or if data describing fewer than the minimum demographic variables were presented.

Report of Adverse Effects

The issue of adverse effects is of particular importance because subjects enrolled in pharmacologic studies represent a population of patients whose clinical course is subject to particular scrutiny in a detailed and standardized manner. Therefore, documentation of adverse effects allows practicing physicians to better assess the risks and benefits of a given intervention for a particular patient under their care. In most cases, adverse effects will be of interest to readers.[24] Because of the wide spectrum of possible adverse effects associated with the different modalities, we recorded whether adverse effects related to analgesic techniques or agents were mentioned. This criterion was rated as *yes* if adverse effects were mentioned and *no* if they were not.

Patient Withdrawals

It is important for many of the same reasons, that details of patient follow up be provided. Patients may be excluded from analysis for any number of reasons.[24] This may result in bias regardless of whether

patients are excluded from treatment or control groups. This can bias the study outcome, depending on the reasons for withdrawal and the group from which withdrawal occurred. In addition, the possibility exists that patients may be withdrawn from a study because of an adverse event that was not disclosed. This criterion was scored as follows: *no withdrawals* where this was explicitly stated, *reasons given* where there were withdrawals and the reasons for withdrawal were documented, *no reasons given* where there were withdrawals but without documented reason, or *no comment* where no specific mention was made of withdrawals.

Data Presentation

Data should be presented in a format that allows the reader to assess the magnitude and degree of variability of the observed effects. This requirement can be achieved by presenting a measure of central tendency (mean, median, or mode) and dispersion (range, standard deviation, standard error of the mean, or confidence intervals) for variables with ordinal, integral or ratio-scale properties. For categorical data, modal values, fractions, frequencies or percentages should be presented for each outcome variable. This criterion was rated as *complete* when the above specifications were met for measures of pain and analgesic requirement (or one of these if only that variable was reported). It was rated *incomplete* when the data were partial (*e.g.*, only a measure of central tendency or variation, when both could have been presented). *None* was used where a study did not present descriptive statistics of pain or analgesic requirements.

Statistical Procedures

The question of appropriate statistical treatment of clinical outcome data has been addressed in the general medical[22-24,207] and anesthesiology[208-210] literature. Although there are numerous concerns about statistical analysis, two questions were critical for the current criteria. (1) Were the statistical procedures used clearly described or referenced? (2) Were the statistical procedures used appropriately? For the purposes of this review, assessment of the statistical methods was restricted to analyses of outcome variables dealing specifically with pain and analgesic consumption. This criterion was rated as *clear* where documentation of the statistical procedures specifically relating to pain and analgesia (or pain or analgesic data where only one of these variables was reported) was provided and the analyses were appropriate to the design and data. The criterion was rated as *none* where statistical analysis was not described, and *not clear* in all other cases. Standard textbooks of biostatistics were used to determine the appropriateness of the statistical procedures evaluated.[211-213]

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