Multimodal analgesia before thoracic surgery does not reduce postoperative pain†

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SUMMARY

Several reports have suggested that preoperative nociceptive block may reduce postoperative pain, analgesic requirements, or both, beyond the anticipated duration of action of the analgesic agents. We have investigated, in a double-blind, placebo-controlled study, pre-emptive analgesia and the respiratory effects of preoperative administration of a multimodal antinociceptive regimen. Thirty patients undergoing thoracotomy were allocated randomly to two groups. Before surgery, the treatment group (n = 15) received morphine 0.15 mg kg^{-1} i.m. with perphenazine 0.03 mg kg^{-1} i.m. and a rectal suppository of indomethacin 100 mg, while the placebo group (n = 15) received midazolam 0.05 mg kg^{-1} i.m. and a placebo rectal suppository. After induction of anaesthesia, the treatment group received intercostal nerve block with 0.5% bupivacaine and adrenaline 1:200000 (3 ml) in the interspace of the incision and in the two spaces above and two spaces below. The placebo group received identical injections but with normal saline only. The treatment group consumed significantly less morphine by patient-controlled analgesia in the first 6 h after operation, but the total dose of morphine consumed on days 2 and 3 after surgery was significantly greater in the treatment group. There were no differences between the groups in postoperative VAS scores (at rest or after movement), Pa_{CO_2} values or postoperative spirometry. However, pain thresholds to pressure applied at the side of the chest contralateral to the site of incision decreased significantly from preoperative values on days 1 and 2 after surgery in both groups. The results of this study do not support the preoperative use of this combined regimen for post-thoracotomy pain. (Br. J. Anaesth. 1994; **73**: 184–189)

KEY WORDS

Analgesic techniques. Analgesia: pre-emptive. Pain. post-operative. Surgery: thoracic

Recent reviews [1–3] and editorial comments [4–6] have examined the possibility that pre-emptive analgesia may have a role in the prevention of postoperative pain. We have reported recently a clinical study which tends to corroborate a clinical role of central neuronal plasticity [7] by demonstrating a small but significant decrease in postoperative pain and opioid consumption after thoracic surgery in patients who received extradural fentanyl before, rather than after, surgical incision.

The concept of "balanced analgesia" has received much attention recently [8, 9]. The simultaneous administration of several classes of analgesic agents affords the potential for enhancing the degree of analgesia, through additive actions [10], whilst minimizing the potential for dose-related adverse effects.

Preoperative parenteral opioids have been shown to increase the median time to the first request for postoperative analgesia in patients undergoing orthopaedic procedures [11] and lumbar disc surgery [12]. More recently, Richmond, Bromley and Woolf have shown that preoperative morphine, compared with late intraoperative morphine, reduced postoperative pain and early analgesic requirements after abdominal hysterectomy [13]. Preoperative local anaesthetic neural block with spinal anaesthesia [14], major peripheral nerve block [15, 16] or tissue infiltration [14, 17, 18] has resulted in an analgesic effect persisting long after the clinically anticipated duration of action of the local anaesthetic agents. Local anaesthesia administered before, as opposed to after, surgical incision has resulted in reduced postoperative analgesic requirements and improved

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postoperative pain scores [19]. While intercostal nerve block has not been examined before operation in patients undergoing thoracic surgery, the clinical effectiveness of the technique has been clearly demonstrated [20].

Although preoperative, compared with postoperative, administration of a non-steroidal anti-inflammatory drug (NSAID) has been associated with improved postoperative analgesia in patients undergoing oral surgery [21], a recent study of thoracic surgical patients found no advantage in commencing administration of indomethacin before, as opposed to after, surgery [22]. Nonetheless, in thoracic surgical patients, perioperative administration of NSAID has resulted in excellent analgesia comparable with low-dose opioid infusion [23], decreased pain scores [24, 25] and reduced opioid requirements [25, 26].

The aim of this study was to investigate, in a double-blind, placebo-controlled study, if pre-incisional administration of a combined anti-nociceptive regimen (i.e. preoperative morphine i.m., preoperative rectal indomethacin and pre-incisional intercostal bupivacaine nerve blocks) would result in reduced postoperative pain, reduced opioid analgesic requirements and improved postoperative pulmonary function compared with administration of a placebo-controlled regimen (i.e. preoperative midazolam i.m., preoperative rectal placebo and pre-incisional intercostal saline).

PATIENTS AND METHODS

The study was approved by the Toronto Hospital Committee for Research on Human Subjects. Written informed consent was obtained from all patients before entering the study.

A power-based sample size estimation was performed [27]. Previous work in a similar patient population in our hospital indicated that the visual analogue scale rating at rest (VAS_R) at 24 h in the absence of pre-emptive analgesia and with i.v. morphine as the sole postoperative analgesic, was mean 4.9 (SD 0.69) [28]. Therefore, we anticipated a similar degree of postoperative pain in the control group. We hypothesized that our pre-emptive regimen would result in a reduction in the VAS of 50% in the treatment group at 24 h compared with the control group. Assuming a power of 0.80, and a type 1 error rate of 0.05, we estimated that a sample size of 30 patients (15 patients per group) would be required.

We studied adult patients undergoing elective lateral thoracotomy, ASA I or II. Exclusion criteria were age less than 18 yr or greater than 80 yr, preoperative analgesic use, symptomatic coronary artery disease, symptomatic peptic ulcer disease, uncontrolled hypertension, significant renal or hepatic impairment, congestive heart failure, cerebrovascular disease, allergy to study medications or a history of opioid addiction or postoperative confusional state.

A table of random numbers was used to allocate patients into either the treatment or control group. The particular group assignment for each prospective patient was then recorded in a separate numbered and sealed envelope, with only the patient's study number visible. The appropriate envelope was opened by an investigator (who had no further involvement with that patient) who administered the medications in accordance with the instructions in the envelope. The patients and all other personnel involved in subsequent patient management and assessment were completely blinded as to group allocation.

Preoperative assessment and management

The day before surgery, patients were interviewed by one of the members of the Acute Pain Research Unit. Baseline preoperative Spielberger state and trait anxiety assessments were completed [29]. Preoperative pain thresholds were assessed using an Algesiometer (Pressure Threshold Meter, Pain Diagnostics and Thermography Inc, Great Neck, NY, USA) on the skin overlying the lateral aspect of the fifth or sixth ribs contralateral to the proposed incision and noting (PSI) the level at which pain was first reported. Patients were introduced to the VAS [30] and instructed in the use of the i.v. patient-controlled analgesia (PCA) pump devices. All patients had baseline spirometric assessment of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) using a bedside spirometer (Respidyne model 5-7930, Sherwood Medical, Watertown, NY, USA).

Patients in group 1 received morphine 0.15 mg kg^{-1} i.m. with perphenazine 0.03 mg kg^{-1} i.m. and a rectal suppository of indomethacin 100 mg 60 min before surgery. Patients in group 2 received midazolam 0.05 mg kg^{-1} i.m. to produce mild sedation and thus maintain the blind and also received a placebo rectal suppository. No other anaesthetic premedications or analgesics were given.

Anaesthesia

General anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and fentanyl 1.0 μg kg^{-1} and maintained with isoflurane and nitrous oxide in oxygen, titrated to haemodynamic response. Fentanyl 1.0 μg kg^{-1} h^{-1} was given to all patients. The trachea was intubated with either a double-lumen or a single-lumen tube and bronchial blocker, after administration of either pancuronium or vecuronium 0.1 mg kg^{-1}. After induction of general anaesthesia and after the patients were placed in the lateral position, the treatment group received intercostal nerve block with 0.5% bupivacaine and adrenaline 1:200000 (3 ml) in the interspace of the planned incision, in addition to two spaces above and two spaces below. The placebo group received intercostal 0.9% saline (with no additives) 3 ml, in the interspace of the planned incision, in addition to two spaces above and two spaces below. When surgery was completed, residual neuromuscular block was antagonized with neostigmine 0.05 mg kg^{-1} and either atropine 0.02 mg kg^{-1} or glycopyrronium 0.006 mg kg^{-1} and the trachea was extubated when the patient was breathing spontaneously. The patient was transported to the postanaesthetic care unit (PACU) with supplementary oxygen by face mask ($F_{I_{O_2}}$ 0.5).

Postoperative management and assessment

The patients were assessed immediately after arrival in the PACU. The time of arrival in the PACU was taken as 0 h after operation. Every 10 min the patients were asked: "Do you have pain?", and if so they were given a bolus dose of morphine 2.0 mg i.v. If at any time between these 10-min intervals, the patients indicated that they were in pain, or appeared to the investigator to be in pain, then an additional bolus dose of i.v. morphine 2.0 mg was given. When sufficiently alert, the patients used a PCA infusion device (Abbott Life Care II Infuser, Chicago, IL, USA) programmed to deliver boluses of i.v. morphine 1.5–2.0 mg, with a 6-min lockout period and a maximum dose of 30 mg in any 4-h period. Patients were encouraged to use the system for 72 h after operation.

VAS pain ratings at rest (VAS_R) were collected at 6, 12, 24, 48 and 72 h with a record of PCA morphine consumption. In addition, at 24, 48 and 72 h, the following measurements were recorded: VAS pain rating after movement (VAS_M) (i.e. sitting up and performing two maximal inspirations using an incentive spirometer) and bedside measurements of FVC and FEV_1. Contralateral pain thresholds, where local pressure sensitivity was assessed on the side opposite to the side of incision, were assessed on days 1 and 2 after surgery. Arterial blood samples were obtained for measurement of Pa_{CO_2} at 3, 6, 12 and 24 h after operation.

Statistical analysis

The investigators analysing the data were unaware of the identity of the groups until all the data were analysed. Parametric data are presented as mean (SD) and non-parametric data are presented as frequencies or percentages. Patient data were analysed using unpaired two-tailed *t* tests for parametric variables and Fisher's exact test for categorical data. Contralateral pain thresholds (CPT), VAS pain scores, PCA morphine consumption, Pa_{CO_2}, FVC and FEV_1 were analysed by two-way ANOVA (parametric analysis) with group as the between-group factor and time after surgery as the repeated measures factor. A significant main effect of time was further analysed by Tukey's HSD procedure [31]. A significant group × time interaction was analysed into simple main effects using a pooled mean square error term and Satterthwaite's adjusted degrees of freedom [32]. Where appropriate, significant simple main effects of time within groups were analysed further by Tukey's HSD procedure to determine the pattern of significant differences between pairs of means over time. Group means were used to estimate missing data. Statistical significance was assumed at $P < 0.05$.

RESULTS

There were no significant differences between the two groups in age, weight, sex, preoperative diagnosis, baseline anxiety assessments (STAI-T, STAI-S), baseline algesiometry or preoperative pulmonary function (FVC, FEV_1) (table I).

There were no significant differences between the groups in operative procedure, estimated operative blood loss, duration of surgery or total dose of intraoperative fentanyl (table II).

Mean PCA morphine consumption over the first 6 h after surgery (fig. 1) was slightly less in the treatment group compared with the control group (ANOVA group main effect, $P < 0.03$). VAS_R (fig. 2) and VAS_M (table III) pain scores were not significantly different between the groups at any time after surgery. In addition, cumulative consumption was greater at 72 h ($P < 0.05$, ANOVA) after surgery in the treatment group (185 (58) mg) compared with the control group (150 (32) mg). Power analysis of the VAS_R pain scores at 24 h after surgery revealed that the probability of detecting a significant difference in pain between the groups at this time (assuming such a difference existed) was 0.87. CPT to pressure decreased significantly ($P < 0.002$, ANOVA, time main effect) from preoperative values

TABLE I. *Preoperative patient data (mean (SD or range) or number). STAI-T and STAI-S Spielberger state and trait anxiety assessments, respectively; FVC = forced vital capacity and FEV_1 = forced expiratory volume in 1 s. No significant differences between groups*

	Treatment group	Control group
Sex (M:F)	5:10	8:7
Age (yr)	54.6 (19–75)	58.9 (46–72)
Weight (kg)	69.4 (10.9)	74.8 (11.7)
STAI-T	37.4 (8.9)	36.8 (2.8)
STAI-S	44.5 (11.2)	43.9 (12.0)
FVC (litre)	3.2 (1.2)	3.1 (0.8)
FEV_1 (litre)	2.2 (0.8)	2.4 (0.8)

TABLE II. *Operative data (mean (SD) or number). No significant differences between groups*

	Treatment group	Control group
Duration (min)	202 (41)	205 (47)
Blood loss (ml)	325 (228)	389 (343)
Fentanyl (μg)	249 (79)	257 (86)
Pulmonary surgery (*n*)	12	14
Oesophageal surgery (*n*)	3	1

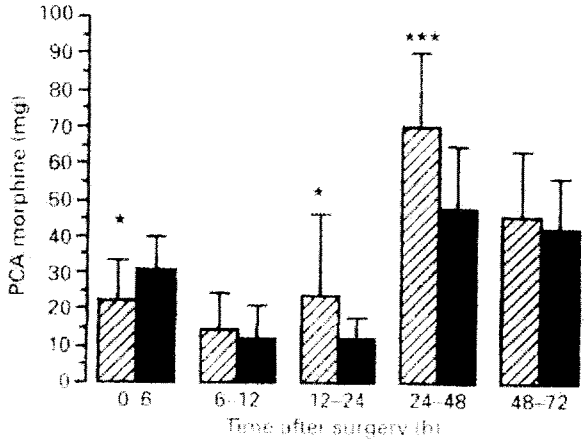

FIG. 1. PCA morphine consumption (mean, SD) in the treatment (▨) and control (■) groups after operation, with limits that correspond to when VAS_R pain assessments were obtained. $*P < 0.05$, $***P < 0.0001$

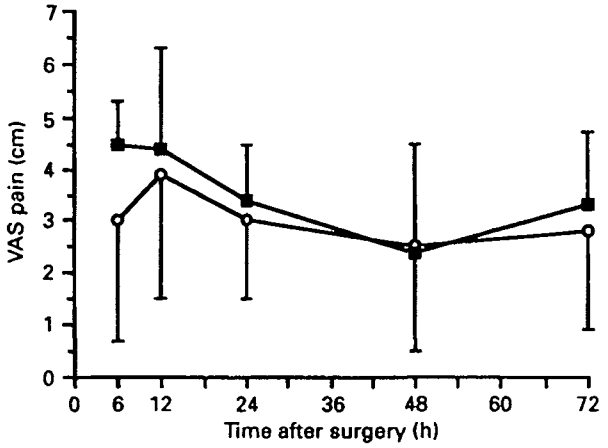

FIG. 2. Mean (SD) VAS pain scores in the treatment (○) and control (■) groups.

TABLE III. *Postoperative VAS pain scores after movement (VAS_M) (mean (SD)). No significant differences between groups at any time*

	Treatment group	Control group
VAS_M		
24 h	4.0 (2.2)	4.9 (3.2)
48 h	3.3 (2.4)	2.8 (2.7)
72 h	4.1 (2.1)	4.3 (1.7)

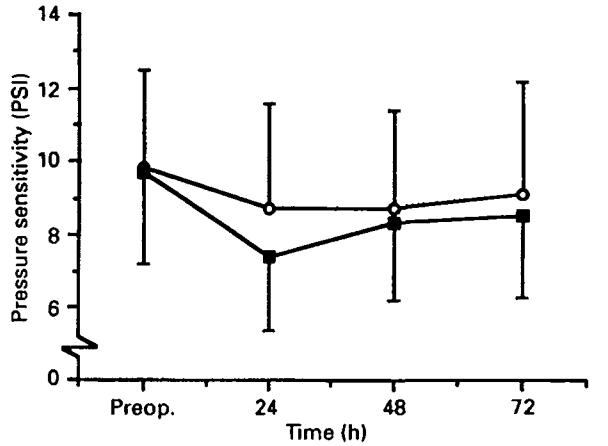

FIG. 3. Mean (SD) contralateral pain thresholds (pounds per square inch (PSI)) for the treatment (○) and control (■) groups in response to pressure applied to the skin overlying the lateral aspect of the fifth or sixth rib contralateral to the incision.

to postoperative values at 24 h ($P < 0.01$, Tukey's test) and 48 h ($P < 0.05$, Tukey's test) after surgery, but there was no significant difference between the groups in CPT over time (fig. 3).

Postoperative Pa_{CO_2} values did not differ significantly between the two groups. Postoperative FEV_1 and FVC were expressed as percentages of preoperative values and did not differ significantly between groups.

There were no allergic or other reactions to any of the study medications or study techniques.

DISCUSSION

The results of the present study did not confirm our hypothesis that pretreatment with a multimodal analgesic regimen consisting of i.m. morphine, rectal indomethacin and intercostal bupivacaine would result in decreased pain, analgesic consumption, or both, beyond the expected clinical duration of action of the agents.

This study supports other studies which failed to confirm a clinical role for pre-emptive analgesia in general surgical [33, 34] and thoracic surgical [22] patients. Apart from the possible ineffectiveness of the pre-emptive analgesic regimen *per se*, several factors may explain the clinically negative outcome. First, the intercostal blocks were not tested and even assuming complete intercostal nerve block, potential afferent input mediated by phrenic, vagal and sympathetic nerves [35] may not be blocked. However, the blocks were performed by experienced thoracic anaesthetists and it is unlikely that a significant number would have been ineffective. Second, the indomethacin and morphine doses may have been inadequate. However, pharmacokinetic data [36, 37] suggest that the timing and routes of administration used in this study would result in maximal pre-incisional plasma concentrations. Third, the uniform use of intraoperative fentanyl as part of a standard balanced anaesthetic regimen in all patients might theoretically have contributed an equivalent pre-emptive analgesic effect in both groups [38] thus reducing differences in pain scores between the groups. Although our group initially raised concerns about the possible pre-emptive analgesic effects of intraoperative opioids [38, 39], these concerns are not shared by others [40]. The possibility that the intraoperative use of isoflurane may have confounded the interpretation of the results by interfering with the processes of central sensitization seems unlikely in the light of a recent report by Abram and Yaksh [41]. These authors found that spinal morphine, but not inhaled isoflurane (1 % or 2.5 %), significantly inhibited phase 2 flinching in the formalin rat paw model, suggesting that isoflurane (unlike morphine) had no effects on post-injury central facilitation of afferent processing [41].

The lower consumption of opioids in the treatment group during the early postoperative period was anticipated. This period was between 230 and 590 min after administration of the preoperative regimen. Therefore, the residual effects of intercostal bupivacaine [42], rectal indomethacin [36] and i.m. morphine [37] may explain the apparent early postoperative analgesia in the treatment group, as indicated by less use of morphine by PCA. After 6 h it is possible that the convergence of PCA morphine consumption in the two groups reflected progressively diminishing effective concentrations of the drugs used in the pre-emptive regimen.

The increased opioid consumption at 24–72 h in the patients treated with the preoperative analgesic regimen was statistically significant. The magnitude of the differences observed may not be clinically important, in that the pretreated group self-administered approximately 1.0 mg h^{-1} of morphine more than the control group. Nonetheless, this finding is of some interest in the light of the study by Richmond, Bromley and Woolf [13] who found that patients pretreated with preoperative morphine

reported more severe movement-associated pain at 48 h after surgery compared with patients treated with late intraoperative morphine.

In a recent editorial on the subject of pre-emptive analgesia, McQuay [5] raised the possibility that the use of opioids to pre-empt postoperative pain may lead to acute tolerance when administered to patients who are not yet experiencing pain. Acute tolerance has been demonstrated in human subjects after administration of fentanyl [43] and may be associated with opioids of higher potency [44, 45]. This may explain in part why a pre-emptive analgesic effect was demonstrated with pre-incisional extradural fentanyl in our previous study [7], but not in the current study, where pre-incisional i.m. morphine was used.

We aimed to lessen the postoperative diminution in pulmonary function invariably observed in this population [20, 28]. The development of post-operative pulmonary dysfunction after thoracic surgery is complex [35]. Previous studies of analgesia after thoracotomy have documented lesser diminution in post-thoracotomy pulmonary function in those patients receiving more efficacious analgesic regimens [20,28]. Our findings of no differences between the groups in terms of FVC and FEV_1 are consistent with the findings of no differences in pain scores.

A recent study has examined the role of an anti-analgesic system which may operate by modulating endogenous opioid systems [46]. The authors found that trained rats, when exposed to a signal indicating safety, demonstrated reversal of conditioned analgesia. These safety signals reversed the effects of systemically and spinally administered morphine, and the anti-analgesic effect appeared to be mediated through cholecystokinin receptors located in the spinal cord. It is possible, though as yet untested, that such a system is operational in humans, and that the abolition or early treatment of intense post-operative pain, may result in an increased requirement for subsequent postoperative analgesics.

Increases in arterial Pa_{CO_2} are the hallmark of respiratory depression. We hypothesized that patients treated with the pre-emptive analgesic regimen would experience less pain, consume less morphine by PCA, or both. A recent study demonstrated that although a regional technique (paravertebral bupivacaine infusion) reduced the amount of systemic opioid required after thoracotomy, this had no effect on the frequency of arterial haemoglobin desaturation [47]. However, the authors did not report Pa_{CO_2} values. We found that although the pretreated patients consumed slightly more morphine by PCA, this was not accompanied by any evidence of elevation in mean Pa_{CO_2} values.

Local pain thresholds to pressure applied at the side of the chest contralateral to the site of proposed incision decreased significantly from preoperative values on days 1 and 2 after surgery. This finding is consistent with other clinical observations that hyperalgesia develops in body regions which are distant from the area of deep tissue injury [48] and that flexion reflex thresholds are lowered in patients after gynaecological laparotomy [49]. The lack of a difference between the two groups in discomfort threshold on days 1 and 2 after surgery implies that hyperalgesia (relative to preoperative values) is not dependent solely on nociceptive inputs at the time of surgery and that inputs from the wound after surgery may be responsible for the development and maintenance of postoperative contralateral hyperalgesia. Moreover, as discomfort thresholds were obtained from a body region that did not sustain injury or tissue damage, the reduced threshold after surgery on the side *contralateral* to the incision suggests that a peripheral mechanism is unlikely (e.g. nociceptor sensitization) and supports the idea that a centrally mediated process of sensitization may be responsible for the contralateral postoperative hyperalgesia.

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REFERENCES

1. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain* 1993; 52: 259–285.
2. Dahl JB, Kehlet H. The value of pre-emptive analgesia in the treatment of postoperative pain. *British Journal of Anaesthesia* 1993; 70: 434–439.
3. Woolf CJ, Chong M. Preemptive analgesia—Treating post-operative pain by preventing the establishment of central sensitization. *Anesthesia and Analgesia* 1993; 77: 362–379.
4. Bush DJ. Pre-emptive analgesia. Local anaesthesia given before general anaesthesia may reduce the severity of postoperative pain. *British Medical Journal* 1993; 306: 285–286.
5. McQuay HJ. Pre-emptive analgesia. *British Journal of Anaesthesia* 1992; 69: 1–3.
6. Katz J. Preop analgesia for postop pain. *Lancet* 1993; 342: 65–66.
7. Katz J, Kavanagh BP, Sandler AN, Nierenberg H, Boylan JF, Friedlander M, Shaw BF. Preemptive analgesia: Clinical evidence of neuroplasticity contributing to post-operative pain. *Anesthesiology* 1992; 77: 439–446.
8. Dahl JB, Rosenberg J, Dirkes WE, Mogensen T, Kehlet H. Prevention of postoperative pain by balanced analgesia. *British Journal of Anaesthesia* 1990; 64: 518–520.
9. Kehlet H. Surgical stress: The role of pain and analgesia. *British Journal of Anaesthesia* 1989; 63: 189–195.
10. Dahl JB, Kehlet H. Non-steroidal anti-inflammatory drugs: Rationale for use in severe postoperative pain. *British Journal of Anaesthesia* 1991; 66: 703–712.
11. McQuay HJ, Carroll D, Moore RA. Post-operative orthopaedic pain—the effect of opiate premedication and local anaesthetic blocks. *Pain* 1988; 33: 291–295.
12. Kiss IE, Kilian M. Does opiate premedication influence postoperative analgesia? A prospective study. *Pain* 1992; 48: 157–158.
13. Richmond CE, Bromley LM, Woolf CJ. Preoperative morphine pre-empts postoperative pain. *Lancet* 1993; 342: 73–75.
14. Tverskoy M, Cozacov C, Ayache M, Bradley EL, Kissin I. Postoperative pain after inguinal herniorrhaphy with different types of anesthesia. *Anesthesia and Analgesia* 1990; 70: 29–35.
15. Ringrose NH, Cross MJ. Femoral nerve block in knee joint surgery. *American Journal of Sports Medicine* 1984; 12: 398–402.
16. Bugedo GJ, Cárcamo CR, Mertens RA, Dagnino JA, Muñoz HR. Preoperative percutaneous ilioinguinal and iliohypogastric nerve block with 0.5% bupivacaine for post-

herniorrhaphy pain management in adults. *Regional Anesthesia* 1990; 15: 130–133.
17. Ågren K, Engquist S, Danneman A, Feychting B. Local versus general anaesthesia in tonsillectomy. *Clinical Otolaryngology* 1989; 14: 97–100.
18. Jebeles JA, Reilly JS, Gutierrez JF, Bradley EL, Kissin I. The effect of pre-incisional infiltration of tonsils with bupivacaine on the pain following tonsillectomy under general anesthesia. *Pain* 1991; 47: 305–308.
19. Ejlersen E, Bryde Anderson H, Eliasen K, Mogensen T. A comparison between preincisional and postincisional lidocaine infiltration and postoperative pain. *Anesthesia and Analgesia* 1992; 74: 495–498.
20. Chan VWS, Chung F, Cheng DCH, Seyone C, Chung A, Kirby TJ. Analgesic and pulmonary effects of continuous intercostal nerve block following thoracotomy. *Canadian Journal of Anaesthesia* 1991; 38: 733–739.
21. Dupuis R, Lemay H, Bushnell MC, Duncan GH. Preoperative flurbiprofen in oral surgery: A method of choice in controlling postoperative pain. *Pharmacotherapy* 1988; 8: 193–200.
22. Murphy DF, Medley C. Preoperative indomethacin for pain relief after thoracotomy: Comparison with postoperative indomethacin. *British Journal of Anaesthesia* 1993; 70: 298–300.
23. Jones RM, Cashman JN, Foster JMG, Wedley JR, Adams AP. Comparison of infusions of morphine and lysine acetyl salicylate for the relief of pain following thoracic surgery. *British Journal of Anaesthesia* 1985; 57: 259–263.
24. Keenan DJM, Cave K, Langdon L, Lea RE. Comparative trial of rectal indomethacin and cryoanalgesia for control of early postthoracotomy pain. *British Medical Journal* 1983; 287: 1335–1337.
25. Pavy T, Medley C, Murphy DF. Effect of indomethacin on pain relief after thoracotomy. *British Journal of Anaesthesia* 1990; 65: 624–627.
26. Merry AF, Wardall GJ, Cameron RJ, Peskett MJ, Wild CJ. Prospective, controlled, double-blind study of i.v. temoxicam for analgesia after thoracotomy. *British Journal of Anaesthesia* 1992; 69: 92–94.
27. Stolley PD, Strom BL. Sample size calculations for clinical pharmacology studies. *Clinical Pharmacology and Therapeutics* 1986; 39: 489–490.
28. Shulman M, Sandler AN, Bradley JW, Young PS, Brebner J. Post-thoracotomy pain and pulmonary function following epidural and systemic morphine. *Anesthesiology* 1984; 61: 569–575.
29. Spielberger CD, Gorsuch RL, Lushene RE. *STAI Manual for the State–Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press Inc, 1970.
30. Revills I, Robinson IO, Rosen M, Hogg MIJ. The reliability of a linear analogue for evaluating pain. *Anaesthesia* 1976; 31: 1191–1198.
31. Winer BJ. *Statistical Principles in Experimental Design*. New York: McGraw-Hill, 1971; 196–198.
32. Winer BJ. *Statistical Principals in Experimental Design*. New York: McGraw-Hill, 1971; 514–603.
33. Dahl JB, Hansen BL, Hjortsø NC, Erichsen CJ, Møiniche S, Kehlet H. Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery. *British Journal of Anaesthesia* 1992; 69: 4–8.
34. Dierking GW, Dahl JB, Kanstrup J, Dahl A, Kehlet H. Effect of pre- *vs* postoperative inguinal field block on postoperative pain after herniorrhaphy. *British Journal of Anaesthesia* 1992; 68: 344–348.
35. Conacher ID. Pain relief after thoracotomy. *British Journal of Anaesthesia* 1990; 65: 806–812.
36. Huskisson EC, Taylor RT, Burson D, Chuter PJ, Dudley Hart F. Evening indomethacin in the treatment of rheumatoid arthritis. *Annals of Rheumatic Disease* 1970; 29: 393–396.
37. Stanski DR, Greenblatt DJ, Lowenstein E. Kinetics of intravenous and intramuscular morphine. *Clinical Pharmacology and Therapeutics* 1978; 24: 52–59.
38. Katz J, Kavanagh BP, Sandler AN. Does pre-operative fentanyl administration influence post-operative analgesia? *Pain* 1992; 51: 123–124.
39. Katz J, Kavanagh BP, Sandler AN. Effect of preoperative opioid administration on postoperative pain. *British Journal of Anaesthesia* 1992; 69: 424.
40. Dahl JB, Kehlet H, Dierking G, Dahl A, Kanstrup J. Effect of preoperative opioid administration on postoperative pain. *British Journal of Anaesthesia* 1992; 69: 424–425.
41. Abram SE, Yaksh TL. Morphine, but not inhalational anesthesia blocks post-injury facilitation. *Anesthesiology* 1993; 78: 713–721.
42. Delilkan AE, Lee CK, Yong NK, Ganedran A. Post-operative local analgesia for thoracotomy with direct bupivicaine intercostal blocks. *Anaesthesia* 1973; 28: 561–567.
43. McQuay HJ, Bullingham RES, Moore RA. Acute opiate tolerance in man. *Life Sciences* 1981; 28: 2513–2517.
44. Gebhart GF. Some mechanistic insights into opioid tolerance. *Anesthesiology* 1990; 73: 1065–1066.
45. Sosnowski M, Yaksh TL. Differential cross tolerance between intrathecal morphine and sufentanil in the rat. *Anesthesiology* 1990; 73: 1141–1147.
46. Wiertelak EP, Maier SF, Watkins LR. Cholecystokinin anti-analgesia: Safety cues abolish morphine analgesia. *Science* 1992; 256: 830–833.
47. Entwhistle MD, Roe PG, Sapsford DJ, Berrisford RG, Jones JG. Patterns of oxygenation after thoracotomy. *British Journal of Anaesthesia* 1991; 67: 704–711.
48. Hardy JD, Wolff HG, Goodell H. Experimental evidence on the nature of cutaneous hyperalgesia. *Journal of Clinical Investigation* 1950; 29: 115–140.
49. Dahl JB, Erichsen CJ, Fuglsang-Frederiksen A, Kehlet H. Pain sensation and nociceptive reflex excitability in surgical patients and human volunteers. *British Journal of Anaesthesia* 1992; 69: 117–121.