The Efficacy of Preemptive Analgesia for Acute Postoperative Pain Management: A Meta-Analysis

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Whether preemptive analgesic interventions are more effective than conventional regimens in managing acute postoperative pain remains controversial. We systematically searched for randomized controlled trials that specifically compared preoperative analgesic interventions with similar postoperative analgesic interventions via the same route. The retrieved reports were stratified according to five types of analgesic interventions: epidural analgesia, local anesthetic wound infiltration, systemic *N*-methyl-D-aspartic acid (NMDA) receptor antagonists, systemic nonsteroidal antiinflammatory drugs (NSAIDs), and systemic opioids. The primary outcome measures analyzed were the pain intensity scores, supplemental analgesic consumption, and time to first analgesic consumption. Sixty-six studies with data from 3261 patients were analyzed. Data were combined by using a fixed-effect model, and the effect size index (ES) used was the standardized mean difference. When the data from all three outcome measures were combined, the ES was most pronounced for preemptive administration of epidural analgesia (ES, 0.38; 95% confidence interval [CI], 0.28–0.47), local anesthetic wound infiltration (ES, 0.29; 95% CI, 0.17–0.40), and NSAID administration (ES, 0.39; 95% CI, 0.27–0.48). Whereas preemptive epidural analgesia resulted in consistent improvements in all three outcome variables, preemptive local anesthetic wound infiltration and NSAID administration improved analgesic consumption and time to first rescue analgesic request, but not postoperative pain scores. The least proof of efficacy was found in the case of systemic NMDA antagonist (ES, 0.09; 95% CI, −0.03 to 0.22) and opioid (ES, −0.10; 95% CI, −0.26 to 0.07) administration, and the results remain equivocal.

(Anesth Analg 2005;100:757–73)

The concept of preemptive analgesia to reduce postoperative pain was founded on a series of successful animal experimental studies that demonstrated central nervous system plasticity and sensitization after nociception (1). Preemptive analgesia is defined as an antinociceptive treatment that prevents the establishment of altered central processing of afferent input, which amplifies postoperative pain (2). By decreasing the altered central sensory processing, preemptive analgesia is thought to consequently decrease the incidence of hyperalgesia and allodynia after surgery (3). It is important to consider this definition in clinical trials for determining the effectiveness of preemptive analgesia. The emphasis of preemptive analgesia is on the pathophysiologic phenomenon that it should prevent: altered sensory processing. Therefore, preemptive may not simply mean "before incision." An insufficient afferent blockade cannot be preemptive, even if it is administered before the incision.

Whether preemptive analgesic interventions are more effective than conventional regimens in managing acute postoperative pain remains controversial. Several reviews have addressed this question and have drawn fundamentally different conclusions. For example, some reviews have concluded that preemptive analgesia is effective as such (3,4), but some have concluded it to be effective only for certain analgesic drugs (5,6). Some analyses have attributed no beneficial effect to any drug (7), whereas some have postulated dependence on a range of factors (2,8,9), and some reviews have been unable to draw a final conclusion regarding efficacy (10–13). Therefore, it can be

Accepted for publication August 23, 2004.

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DOI: 10.1213/01.ANE.0000144428.98767.0E

0003-2999/05

stated that whereas the evidence on preemptive analgesia in animal studies is very convincing (14), results from human clinical studies remain inconsistent.

Many of the summaries of results of clinical studies of the above-mentioned reviews typically took the form of narrative reviews, which may have been subjective. Therefore, the purpose of this meta-analysis was to synthesize the data statistically from previous randomized and double-blind controlled trials to determine whether preemptive application of analgesic regimens is of superior efficacy in the treatment of acute postoperative pain as compared with the same analgesic regimens initiated after surgical incision. This was based on the original observations in experimental studies suggesting that the timing of analgesic regimens was important to obtain a reduction of postinjury pain hypersensitivity (1). In the event that the clinical studies yield comparable effects, we will then be able to report this effect more confidently.

Methods

This meta-analysis used the methods proposed by the Cochrane Collaboration (15). Full published reports of randomized controlled trials (RCTs) on preemptive analgesia for postoperative pain were sought in MEDLINE, EMBASE, CINAHL, and PubMed covering January 1987 to October 2003. A broad free-text search with restriction to publications in English was undertaken with all variants of terms. "Preemptive analgesia," "postoperative pain," "preoperative," and "preincisional" were entered as major subject headings, and "randomized controlled trial" was entered as a publication type selected from the dictionaries menu. Reference lists of retrieved reports and reviews were searched for additional trials. Unpublished reports and abstracts were not considered. Authors were not contacted for original data.

The retrieved reports were stratified according to the type of analgesics or interventions (local anesthetic wound infiltration, *N*-methyl-D-aspartic acid [NMDA] receptor antagonists, nonsteroidal antiinflammatory drugs [NSAIDs], and opioids), mode of administration (systemic, epidural, or wound infiltration), and surgical procedure.

Articles that met the following criteria were included in this meta-analysis: 1) comparison of the same analgesic intervention before and after surgical incision by the same route and 2) randomized and double-blind study design. Exclusion criteria were 1) comparison of preoperative treatment with placebo or no treatment, 2) comparison of preoperative treatment with a combination of preoperative plus postoperative treatment, and 3) comparison of different preoperative and postoperative treatment regimens.

Where possible, the following outcome measures data were extracted from the retrieved reports in the form of mean/median data plus dispersion values or dichotomous data:

1. Pain intensity in the form of the various pain scores, e.g., visual analog scale (VAS) scores during the first 24–48 postoperative hours.
2. Supplemental postoperative analgesic requirements.
3. Time to first rescue analgesic.

In cases in which trials reported outcome as graphs, the means and standard deviations were estimated from these graphs.

The quality of the included studies was assessed regarding the extent to which the RCT design, data collection, and statistical analysis minimized or avoided bias in treatment comparisons. A modification of a validated scale (16) was used to perform the quality assessment. This scale includes five items pertaining to description of randomization, appropriate blinding, dropouts and withdrawals, and other pain outcome measures. In brief, the following rules were applied to assess study quality:

1. Randomization—if the reports were described as randomized, one point was given. An additional point was given if the method of randomization was described and adequate, e.g., computer generated or a table of random numbers. However, one point was deducted if the method of randomization was inappropriate, e.g., randomization according to age or birthday.
2. Blinding—if the reports were described as double-blind, one point was given. An additional point was given if the blinding was described and appropriate, e.g., use of double-dummy. One point was deducted if blinding was inappropriate.
3. Patients' withdrawals—if the reports described the numbers and reasons for withdrawals, one point was given.
4. Pain intensity—to ensure that a clinically relevant effect could be detected, one point was given if the pain scores were $\geq$30 mm on a VAS or more than moderate on a verbal rating scale (VRS).
5. Sample size—studies that performed a power calculation to estimate the sample size required to detect the treatment difference were awarded one point. Furthermore, RCTs with a sample size of $\leq$10 were not considered in this meta-analysis (17).

According to these assessments, the minimum score of an included trial was 2, and the maximum was 7.

The statistical software Comprehensive Meta Analysis™ (Biosta Inc., NJ) was used for the synthesis of data from all the included studies. The meta-analysis consisted of a two-stage process. In the first stage, a summary statistic was calculated for each study. These values describe the treatment effects observed

in each individual study. In the second stage, a summary (pooled) treatment effect estimate was calculated as a weighted average of the treatment effects estimated in the individual studies. A weighted average is defined as follows:

$$\text{Weighted average} = \frac{\text{sum of (estimate} \times \text{weight)}}{\text{sum of weights}} = \frac{\sum T_i W_i}{\sum W_i},$$

where T_i is the treatment effect estimated in study i, W_i is the weight given to study i, and the summation is across all studies. In this meta-analysis, we were interested in the difference between the pain outcome variables of the patients between the two treatment groups (pretreatment and posttreatment). To perform meta-analyses of such data, the mean difference in the outcome variable between groups for each study was converted to an effect size (ES) by entering the mean values, the standard deviations, and the number of participants on whom the outcomes were assessed in each of the two groups into the software (18). The three outcome variables measured a single theoretical construct (pain experience). First, the ES for each outcome measure for all the studies for each intervention was combined, and a separate analysis on each outcome measure was performed. Second, the ES values of the three outcome measures for each intervention were combined mathematically into one. In addition, the significance tests for each included trial were combined.

The outcome variables used for combining results were the pain intensity scores during the first 24–48 h, total supplemental postoperative analgesic consumption, and time to first analgesic. Because the outcome measures data were entered as mean, standard deviation, and P value of the difference between treatment groups, the effect size index (ES) for this meta-analysis is the standardized mean difference (SMD). The ES is expressed in standardized units. A positive ES indicates that preemptive analgesia is effective, and a negative value indicates that preemptive analgesia is ineffective. Therefore, a point estimate of 0 indicates no effect, values more than 0 reflect a better outcome for the pretreated group, and values <0 reflect a better outcome of the posttreated group. If the point estimate and confidence interval (CI) were more than 0, the study would meet the criterion for statistical significance (α was set at 0.05). If the CI overlapped 0, the P value would exceed 0.05, and the study would not be statistically significant. Results of our meta-analyses are graphically displayed in Forrest plots (19).

Each of the three outcome variables was analyzed separately. In the case of preemptive analgesia being effective for that outcome variable as evidenced by the overall point estimate, it was decided that preemptive treatment should reduce that pain outcome measure by at least 10% of points to be clinically useful. These "percentage points" are units relative to the standard deviations of the outcome measure. This tells us whether the intervention is more effective for the outcome. Forrest plots were plotted for each outcome measure and for each different type of analgesic intervention.

There will always be confounding covariates (study population, age, sex, type of surgery, quality of study, and publication year) and manipulation, and these may affect the analysis. Fixed-effects models were used throughout, unless statistical heterogeneity was observed by the Cochran Q test ($P < 0.05$). When heterogeneity was significant, random-effects models were used. Potential publication bias was not assessed with funnel plots because these tests have been shown to be unhelpful (20). A Mann-Whitney U-test was also used to assess the relationships between positive and negative trials and quality scores.

Results

The literature search identified 102 RCTs of preemptive analgesia for acute postoperative pain. Of these, 36 trials were excluded because they did not meet the inclusion criteria; these are summarized in Appendix 1 (21–56).

Subsequently, 66 RCTs, with a total of 3261 patients, were included in this meta-analysis (Tables 1–5). These 66 studies were stratified into 5 groups according to surveyed intervention as follows: 1) 19 trials of epidural analgesia (57–75), 2) 15 trials of peripheral local anesthetic infiltrations (76–90), 3) 7 trials of systemic NMDA receptor antagonists (91–97), 4) 17 trials of systemic NSAIDs (98–114), and 5) 8 trials of systemic opioids (115–122). Not all the 66 trials used all 3 outcome measures (pain intensity, supplemental analgesic, and time to first analgesic) that were needed for the meta-analysis. Some used only one or two of the outcome measures. A total of 50 trials used pain intensity, 44 trials used supplemental analgesic, and 28 trials used time to first analgesic as 1 of the outcome measures.

The median quality score for the studies that favored pretreatment was 4 (range, 2–7) and was 4 (range, 2–7) for studies that favored posttreatment. The percentage of trials that favored pretreatment did not differ from that which favored posttreatment (Mann-Whitney U-test; $P = 0.7$). There was also no significant difference between the higher-quality (range, 5–7) trials and lower-quality (range, 2–4) trials ($P = 0.44$).

The data from the RCTs of each of the five stratified analgesic intervention groups were synthesized separately to obtain a combined value that reflects the ES for each of the pain outcome measures (Figs. 1–3). Finally, data from all three outcome measures were

Table 1. Epidural/Caudal Preemptive Studies (19 RCTs; 905 Patients)

Reference	Quality score	Sample size (before/after)	Intervention	Procedure	Pain intensity	Supplemental analgesic	Time to first analgesic
Katz (57)	7	45/49	Epidural lidocaine + fentanyl	Gynecologic surgery	VAS, NS	PCA morphine, $P = 0.0009$	—
Esmaoglu (58)	3	20/20	Epidural fentanyl	Abdominal surgery	VAS, $P < 0.05$ favoring control	PCA fentanyl, NS	—
Aida (59)	6	28/31	Epidural morphine	Orthopedic surgery	VAS, $P < 0.005$	PCA morphine, $P < 0.005$	—
Subramaniam (60)	5	20/20	Epidural morphine + bupivacaine	Abdominal and thoracic surgery	VAS, NS	PCA morphine, $P < 0.0001$	$P < 0.0001$
Aida (61)	6	42/46	Epidural morphine	Limb and breast surgery	VAS, $P < 0.001$	PCA morphine, $P < 0.001$	—
Obata (62)	5	35/35	Epidural mepivacaine	Thoracotomy	VAS, $P < 0.05$	Indomethacin suppositories, NS	—
Kundra (63)	6	30/30	Caudal bupivacaine	Herniography in children	Objective pain scale, $P < 0.05$	IM morphine, $P < 0.05$	$P < 0.05$
Richards (64)	4	25/25	Epidural bupivacaine + fentanyl	Hysterectomy	VAS, NS	PCA morphine, NS	—
Wong (65)	4	15/15	Epidural ketamine + morphine	Total knee replacement	VAS, $P < 0.05$	PCA morphine, $P < 0.05$	$P < 0.05$
Choe (66)	4	30/30	Epidural morphine + ketamine	Gastrectomy	—	IM morphine, $P < 0.05$	$P < 0.01$
Kundra (67)	4	15/15	Epidural morphine	Lumbar laminectomy	VAS, $P < 0.05$	IV morphine, $P < 0.05$	$P < 0.05$
Aguilar (68)	4	15/15	Epidural bupivacaine	Thoracic surgery	VAS, NS	PCA fentanyl, NS	—
Dahl (69)	6	16/16	Epidural bupivacaine + morphine	Total knee arthroscopy	VAS, NS	IV morphine, NS	—
Holthusen (70)	5	14/11	Caudal lidocaine	Circumcision in children	Children's Hospital of Eastern Ontario Pain Scale, NS	PO paracetamol, NS	NS
Rockemann (71)	6	27/23	Epidural mepivacaine + morphine	Abdominal surgery	VAS, NS	PCA morphine, $P = 0.002$	NS
Katz (72)	7	21/21	Epidural bupivacaine	Abdominal surgery	VAS, $P = 0.003$	PCA morphine, $P = 0.001$	—
Pryle (73)	4	15/18	Epidural bupivacaine	Abdominal surgery	VAS, NS	PCA morphine, $P < 0.05$ favoring control	—
Dahl (74)	6	16/16	Extradural bupivacaine + morphine	Abdominal surgery	VAS, NS	—	—
Rice (75)	5	20/20	Caudal bupivacaine	Herniography in children	Pediatric objective pain scale, NS	—	NS

VAS = visual analog scale; PCA = patient-controlled analgesia; RCT = randomized controlled trials; NS = not significant; PO = by mouth.

combined for each analgesic intervention to give a final ES (Fig. 4). Below are the details for the analyses.

Pain Intensity Outcome Measure

In the included studies, various different types of pain scales were used for preemptive studies, including the VAS, VRS, numerical rating scale, and objective pain scale (in the case of young children). Of the 50 trials reporting pain intensity as an outcome measure, there were 13 epidural, 11 local anesthetic, 7 NMDA antagonist, 12 NSAID, and 7 opioid studies. The results are summarized in the Forrest plot in Figure 1.

Epidural Analgesic RCTs. Thirteen RCTs with a total of 653 patients comparing preincisional versus postincisional epidural analgesia were included (Table 1). Of the 13 RCTs, 7 were statistically significant favoring pretreatment, whereas the other 6 were reported as not significant. Figure 1 shows that the 13 studies had a combined ES of +0.25, with a CI of +0.10 to +0.41. The combined *P* value is 0.002.

Local Anesthetic RCTs. Eleven RCTs with a total of 535 patients comparing preincisional versus postincisional peripheral local anesthetic wound infiltration were included (Table 2). Of the 11 RCTs, 5 were statistically significant favoring pretreatment, whereas the other 6 were reported as not significant or significantly favored posttreatment. Figure 1 shows that the 11 studies have a combined ES of +0.10, with a CI of −0.07 to +0.27. The combined *P* value is 0.26.

NMDA Antagonist RCTs. Seven RCTs with a total of 418 patients comparing preincisional versus postincisional systemic NMDA antagonists were included

Table 2. Local Anesthetic Infiltration Preemptive Studies (15 RCTs; 671 Patients)

Reference	Quality score	Sample size	Intervention	Procedure	Pain intensity	Supplemental analgesic	Time to first analgesic
Mahfouz (76)	6	15/15	LA block	Retina detachment surgery	—	PO paracetamol, $P < 0.001$	$P < 0.001$
Reuben (77)	5	20/20	LA—intraarticular bupivacaine	Arthroscopic knee surgery	VAS, NS	PO paracetamol, $P = 0.02$	$P < 0.001$
Kristin (78)	4	15/15	LA bupivacaine peribulbar block	Vitreoretinal surgery	VAS, $P < 0.05$	—	—
Gill (79)	6	19/19	LA bupivacaine field block	Herniorrhaphy	VAS, NS	PO diclofenac, NS	—
Altintas (80)	6	25/24	LA bupivacaine axillary block	Hand surgery	Faces pain scale, $P < 0.05$ favoring control	NS	—
Hanlon (81)	6	36/38	LA bupivacaine wound infiltration	Breast biopsy	VAS, NS	—	NS
Fischer (82)	4	35/35	LA bupivacaine	Herniography	VAS, $P < 0.05$	Ibuprofen, $P < 0.05$	—
Ke (83)	6	20/19	LA bupivacaine wound infiltration	Laparoscopy	McGill Present Pain intensity scale, $P < 0.05$	PO ibuprofen, $P < 0.05$	$P < 0.05$
Molliex (84)	6	24/23	LA bupivacaine wound infiltration	Tonsillectomy	VAS, NS	PO paracetamol, $P < 0.05$ favoring control	—
Pasqualucci (85)	4	30/30	LA bupivacaine infiltration	Laparoscopic cholecystectomy	VAS, $P = 0.01$	IV ketorolac, $P = 0.05$	—
Dahl (86)	5	28/22	LA bupivacaine	Hernioplasty in children	Objective pain scale, $P = 0.03$	IV meperidine, NS	—
Huffnagle (87)	6	11/12	LA bupivacaine	Cesarean	VAS, NS	PCA morphine, NS	—
Orntoft (88)	4	12/12	LA bupivacaine	Tonsillectomy	VAS, NS	PO aspirin, NS	—
Turner (89)	6	30/30	LA lidocaine	Appendectomy	VAS, NS	PCA pethidine, NS	—
Ejlersen (90)	6	19/18	LA lidocaine	Hernioplasty	VAS, NS	PO paracetamol, $P < 0.05$	$P < 0.05$

LA = Local anesthetic; VAS = visual analog scale; PCA = patient-controlled analgesia; RCT = randomized controlled trials; NS = not significant; PO = by mouth.

(Table 3). Of the seven RCTs, only two were statistically significant, whereas the other five were reported as not significant. Figure 1 shows that the seven studies have a combined ES of 0.0, with a CI of −0.19 to +0.20. The combined *P* value is 0.97. The 0.0 point estimate indicates that preemptive NMDA antagonists have no effect on postoperative pain intensity scores.

NSAID RCTs. Twelve RCTs with a total of 617 patients compared preincisional versus postincisional systemic NSAIDs (Table 4). Of the 12 RCTs, 6 were statistically significant favoring pretreatment, whereas the other 6 were reported as not significant or significantly favored posttreatment. Figure 1 shows that the 12 studies have a combined ES of +0.14, with a CI of −0.02 to +0.30. The combined *P* value is 0.09.

Opioid RCTs. Seven RCTs with a total of 324 patients comparing preincisional versus postincisional systemic opioids were included (Table 5). Of the seven RCTs, only one was statistically significant favoring pretreatment, whereas the other six had been reported as not significant or significantly favored posttreatment. Figure 1 shows that the 7 studies have a combined ES of −0.24, with a CI of −0.01 to -0.41. The combined *P* value is 0.39.

Supplemental Analgesic Outcome Measure

The supplemental analgesics taken included patient-controlled analgesia; IM or IV morphine, meperidine, and fentanyl; and oral paracetamol or NSAIDs. Of the 66 included trials, 44 trials used postoperative supplemental analgesic consumption as an outcome measure for assessing the efficacy of the treatment groups. There were 13 epidural, 8 local anesthetic, 7 NMDA antagonist, 12 NSAID, and 4 opioid trials. The results are summarized in the Forrest plot in Figure 2.

Epidural Analgesic RCTs. Thirteen RCTs with a total of 640 patients comparing preincisional versus postincisional epidural analgesia were included (Table 1). Of the 13 RCTs, 10 were statistically significant favoring pretreatment, whereas the other 3 were reported as not significant. The 13 studies have a combined ES of +0.58, with a CI of +0.42 to +0.74. The

Table 3. *N*-Methyl-D-Aspartic Acid Antagonist Preemptive Studies (7 RCTs; 418 Patients)

Reference	Quality score	Sample size	Intervention	Procedure	Pain intensity	Supplemental analgesic	Time to first analgesic
Helmy (91)	7	20/20	IM dextromethorphan	Abdominal surgery	VAS, $P < 0.05$	PCA meperidine, $P < 0.001$	$P < 0.001$
Dahl (92)	4	33/27	IV ketamine	Hysterectomy	VAS, NS	IV ketobemidone, NS	—
Menigaux (93)	7	15/15	IV ketamine	Orthopedic surgery	VAS, NS	PCA morphine, NS	—
Adam (94)	7	64/64	IV ketamine	Mastectomy	VAS, NS	PCA morphine, $P = 0.04$ favoring control group	NS
Chia (95)	7	30/30	IV dextromethorphan	Abdominal surgery	VAS, NS	PCA morphine, $P < 0.01$	—
Wu (96)	4	30/30	IM dextromethorphan	Laparoscopic cholecystectomy	VAS, $P < 0.0001$	IM meperidine, $P < 0.00001$	$P < 0.001$
Mathisen (97)	6	20/20	IV ketamine	Laparoscopic cholecystectomy	VAS, NS	PCA meperidine, NS	—

RCT = Randomized controlled trials; VAS = visual analog scale; PCA = patient-controlled analgesia; NS = not significant.

schematic in Figure 2 shows that the majority of the studies are within the pretreatment effective range, and the CI for all 14 studies includes the combined ES of +0.58. The combined *P* value is $<10^{-8}$, a highly significant difference favoring pretreatment.

Local Anesthetic RCTs. Eight RCTs with a total of 360 patients comparing preincisional versus postincisional peripheral local anesthetic wound infiltration were included (Table 2). Of the eight RCTs, five were statistically significant favoring pretreatment, whereas the other three were reported as not significant. The eight studies have a combined ES of +0.44, with a CI of +0.23 to +0.65. The combined *P* value is 0.00006.

NMDA Antagonist RCTs. Seven RCTs with a total of 418 patients comparing preincisional versus postincisional systemic NMDA antagonists were included (Table 3). Of the seven RCTs, three were statistically significant favoring pretreatment, whereas the other four were reported as not significant or significantly favored posttreatment. The seven studies had a combined ES of +0.17, with a CI of −0.24 to +0.37. The combined *P* value is 0.09.

NSAID RCTs. Twelve RCTs with a total of 582 patients comparing preincisional versus postincisional systemic NSAIDs were included (Table 4). Of the 12 RCTs, 8 were statistically significant favoring pretreatment, whereas the other 4 were reported as not significant. The 12 studies have a combined ES of +0.48, with a CI of +0.31 to +0.65. The combined *P* value is 0.00000003, a highly significant difference favoring pretreatment.

Opioid RCTs. Four RCTs with a total of 194 patients comparing preincisional versus postincisional systemic opioids were included (Table 6). Two of the RCTs were reported as statistically significant favoring pretreatment, and the other two were reported as not significant. The four studies have a combined ES of +0.23, with a CI of −0.06 to +0.52. The combined *P* value is 0.12.

Time to First Analgesic Outcome Measure

A total of 28 trials used time to first analgesic as an outcome measure for assessing the efficacy of treatment. There were nine epidural, seven local anesthetic, four NMDA antagonist, six NSAID, and two opioid studies. Time to first analgesic was defined as the time from the end of surgery to the first rescue analgesic request. The results are summarized in the Forrest plot in Figure 3.

Epidural Analgesic RCTs. Nine RCTs with a total of 368 patients comparing preincisional versus postincisional epidural analgesia were included (Table 1). Of the nine RCTs, five were statistically significant favoring pretreatment, whereas the other four were reported as not significant or significantly favored posttreatment. The nine studies have a combined ES of +0.31, with a CI of +0.10 to +0.52. The combined *P* value is 0.004.

Local Anesthetic RCTs. Seven RCTs with a total of 306 patients comparing preincisional versus postincisional peripheral local anesthetic wound infiltration were included (Table 2). Of the seven RCTs, five were statistically significant favoring pretreatment, whereas the other two were reported as not significant. The seven studies have a combined ES of +0.44, with a CI of +0.21 to +0.68. The combined *P* value is 0.0002.

NMDA Antagonist RCTs. Four RCTs with a total of 258 patients comparing preincisional versus postincisional systemic NMDA antagonists were included (Table 3). Of the four RCTs, two were statistically significant favoring pretreatment, whereas the other two were reported as not significant. The four studies

Table 4. NSAID Preemptive Studies (16 RCTs; 875 Patients)

Reference	Quality score	Sample size	Intervention	Procedure	Pain intensity	Supplemental analgesic	Time to first analgesic
Ong (98)	6	30/30	IV ketorolac	Oral surgery	VAS, $P = 0.003$	PO paracetamol, $P = 0.007$	$P = 0.005$
Reuben (99)	7	20/20	PO rofecoxib	Arthroscopic knee surgery	VAS, $P = 0.005$	PO paracetamol, $P = 0.0001$	$P = 0.001$
Priya (100)	4	25/25	IV ketoprofen	Breast surgery	VAS, NS	IM morphine, $P = 0.0001$	$P = 0.0001$
Norman (101)	7	23/25	IV ketorolac	Ankle surgery	VAS, $P = 0.02$	PCA morphine, NS	—
Rosaeg (102)	4	20/20	IV ketorolac + intraarticular morphine	Arthroscopic knee surgery	VAS, NS	PCA morphine, $P < 0.05$	—
Nagatsuka (103)	4	41/41	Rectal diclofenac	Oral surgery	VAS, NS	Data unclear	—
Colbert (104)	4	37/40	IV tenoxicam	Breast biopsy	VAS, $P = 0.02$	IM meperidine, $P = 0.007$	$P = 0.004$
Romsing (105)	4	19/18	IV ketorolac	Tonsillectomy	Children poker chip tool pain score, NS	PO paracetamol, $P < 0.05$	—
Hanlon (106)	4	20/20	PO piroxicam	Laparoscopic surgery	VAS, $P < 0.05$	PO paracetamol, $P = 0.04$	$P = 0.03$
Vanlersberghe (107)	4	30/30	IV ketorolac	Orthopedic surgery	VAS, NS	PCA morphine, NS	NS
Fletcher (108)	7	20/20	IV ketorolac	Orthopedic surgery	VAS, $P = 0.03$	PCA morphine, $P = 0.01$	—
Rogers (109)	7	30/28	IV ketorolac	Hysterectomy	Not measured	PCA morphine, $P = 0.49$, NS	—
Buggy (110)	3	20/20	IM diclofenac	Laparoscopic tubal ligation	VAS, $P = 0.58$, NS	IM morphine, $P = 0.6$, NS	NS
Nelson (111)	4	22/19	PO diclofenac	Knee arthroscopy	VAS, NS	PO codeine, NS	—
Murphy (112)	3	22/28	Indomethacin suppositories	Thoracotomy	VAS, NS	IV papavertetum, NS	—
Sisk (113)	4	36/36	PO naproxen	Oral surgery	VAS, NS	—	—
Sisk (114)	4	20/20	PO diflunisal	Oral surgery	VAS, NS	—	—

RCT = randomized controlled trials; VAS = visual analog scale; PCA = patient-controlled analgesia; NSAID = nonsteroidal antiinflammatory drug; PO = by mouth; NS = not significant.

have a combined ES of +0.12, with a CI of −0.13 to +0.37. The combined *P* value is 0.34.

NSAID RCTs. Six RCTs with a total of 307 patients comparing preincisional versus postincisional systemic NSAIDs were included (Table 4). Of the six RCTs, five were statistically significant favoring pretreatment, whereas the other was reported as not significant. The six studies have a combined ES of +0.68, with a CI of +0.44 to +0.91. The combined *P* value is $<10^{-8}$, a highly significant difference favoring pretreatment.

Opioid RCTs. Two RCTs with a total of 74 patients comparing preincisional versus postincisional systemic opioids were included (Table 5). Both RCTs were reported as not significant. The two studies have a combined ES of −0.34, with a CI of −0.81 to +0.13. The combined *P* value is 0.16.

Combined Three Outcome Measures

The three outcomes were combined to achieve an ES for each group of analgesic interventions (Fig. 4).

Epidural RCTs. A total of 37 combined outcome variables in 19 trials were analyzed. They had a combined ES of +0.38, with a CI of +0.28 to +0.47. The combined *P* value is $<10^{-8}$, a highly significant difference favoring pretreatment.

Local Anesthetic RCTs. A total of 26 combined outcome variables in 15 trials were analyzed. They had a combined ES of +0.29, with a CI of +0.17 to +0.40. The combined *P* value is 0.000001.

NMDA Antagonist RCTs. A total of 16 combined outcome variables in 7 trials were analyzed. They had a combined ES of +0.09, with a CI of −0.03 to +0.22. The combined *P* value is 0.12.

NSAID RCTs. A total of 30 combined outcome variables in 17 trials were analyzed. They had a combined ES of +0.39, with a CI of +0.27 to +0.48. The combined *P* value is $<10^{-8}$, a highly significant difference favoring pretreatment.

Opioid RCTs. A total of 13 combined outcome variables in 8 trials were analyzed. They had a combined ES of −0.10, with a CI of −0.26 to +0.07. The combined *P* value is 0.25.

Table 5. Opioid Preemptive Studies (8 RCTs; 392 Patients)

Reference	Quality score	Sample size	Intervention	Procedure	Pain intensity	Supplemental analgesic	Time to first analgesic
Doyle (115)	6	15/15	IV morphine + LA bupivacaine	Thoracic surgery	VAS, $P < 0.05$	PCA morphine, NS	—
Millar (116)	6	30/30	IV morphine	Hysterectomy	VAS, NS	PCA morphine, NS	—
Griffin (117)	5	17/17	IV alfentanil	Abdominal surgery	VAS, NS	PCA morphine, $P < 0.02$	NS
Sarantopoulos (118)	6	20/20	IV sufentanil	Hysterectomy	VAS, NS	IM pethidine, NS	NS
Fassoulaki (119)	6	34/34	IV fentanyl	Hysterectomy	VAS, NS	—	—
Wilson (120)	4	20/20	IV alfentanil	Hysterectomy	VAS, NS	PCA morphine, NS	—
Mansfield (121)	3	30/30	IV alfentanil	Hysterectomy	VAS, NS	PCA morphine, NS	—
Richmond (122)	6	39/21	IM morphine	Hysterectomy	VAS, NS	PCA morphine, $P < 0.05$	—

RCT = randomized controlled trials; LA = local anesthetic; VAS = visual analog scale; PCA = patient-controlled analgesia; NS = not significant.

Discussion

This meta-analysis was conducted to assess the ability of preemptive analgesic interventions to attenuate postoperative pain scores, decrease supplemental postoperative analgesic requirements, and prolong the time to first rescue analgesia. The main result is that with these outcome measures, preemptive analgesia showed an overall beneficial effect in selected analgesic regimens that was most pronounced after epidural analgesia, local wound infiltrations, and systemic NSAID administration.

Pain intensity measures rated by the patient have been described as one of the most reliable estimates of treatment efficacy (123). In this meta-analysis, preemptive epidural analgesia could reduce postoperative pain intensity by approximately 25% points (ES, +0.25; 95% CI, 0.10–0.41). Therefore, it can be concluded that, according to the currently available data, preemptive epidural analgesia is effective and clinically useful in reducing postoperative pain intensity scores. In contrast, effects of preemptive local anesthesia and NSAID administration on postoperative pain intensity did not reach levels of statistical significance sufficient to draw a positive conclusion, even though a trend toward reduced postoperative pain scores was noted in the NSAID cohort. Synthesis of preemptive systemic opioid and NMDA antagonist analgesia yielded a negative and zero ES, respectively, suggesting that these preemptive treatments are not effective in reducing postoperative pain intensity scores.

Furthermore, it has been shown that total analgesic consumption is perhaps the most adequate outcome measure for showing a true preemptive effect (124). Preemptive epidural analgesia proved effective in reducing supplemental analgesic consumption, featuring a very large ES (ES, +0.58; 95% CI, 0.42–0.74), and the entire range of the CI exceeds our *a priori* criterion of at least 10%. Similarly, it could be concluded that preemptive local anesthetics (ES, +0.44; 95% CI, 0.23–0.65) and NSAIDs (ES, +0.48; 95% CI, 0.31–0.64) are clinically useful in reducing supplemental analgesic consumption. The preemptive administration of systemic NMDA antagonists and opioids was not shown to elicit a significant beneficial effect. Reducing the supplemental analgesia by approximately 44% to 58% by using preemptive analgesic techniques is clinically useful. Thus, there may be an economic facet that favors the incorporation of preemptive analgesia into the clinical routine. Although it has been stated that the difference in the requirement for postoperative supplemental analgesic consumption is not an important medical issue, provided that adequate doses are available when the need arises (125), in today's climate of financial constraints on health care expenditure, it is important to consider the economic effect of adopting preemptive analgesia with the potential of reducing overall postoperative analgesic requirements. Forty-four percent to 58% less postoperative analgesic consumption for surgical patients could mean that a large sum of money could be saved through adopting the technique of preemptive analgesia, which essentially does not add any additional cost to the existing armamentarium of pain management other than changing the timing of administration. This is significant because this effect was observed not only for more costly and time-consuming interventions, such as epidural analgesia, but also for NSAIDs and local anesthesia.

Time to the first rescue analgesic request was used in many of the included trials as an outcome measure. In this meta-analysis, we could show that preemptive epidural analgesia was clinically useful in prolonging the time to first analgesic request (ES, 0.31; 95% CI, 0.10–0.52). Similarly, local anesthesia (ES, 0.44; 95% CI, 0.21–0.68) and NSAID (ES, 0.68; 95% CI, 0.44–0.91) administration are clinically useful in prolonging the time to first analgesic intake. In contrast, the administration of NMDA antagonists and systemic opioids

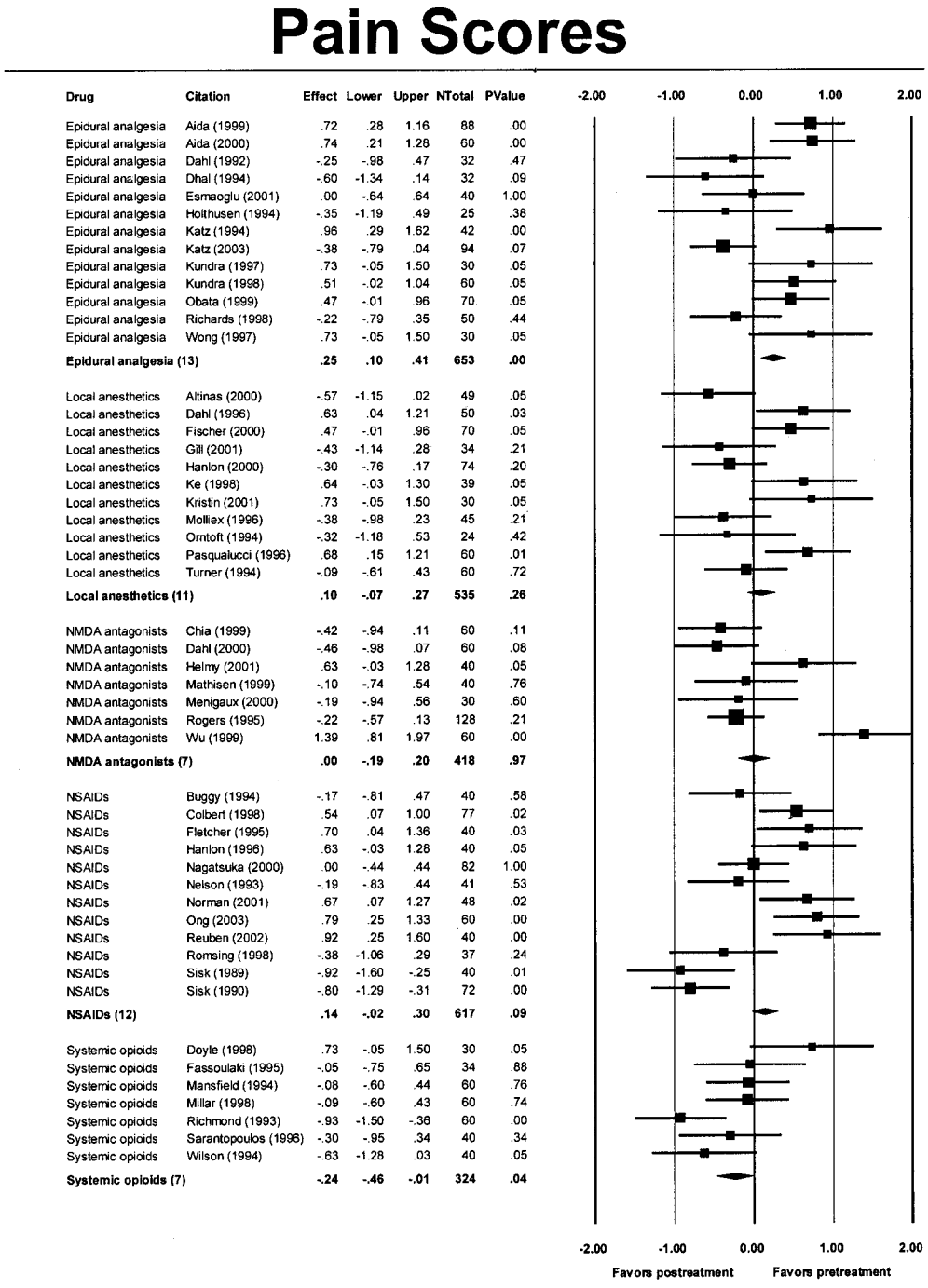

Figure 1. Forrest plot for pain intensity scores. The plot displays the study, sample size, effect size (standardized mean difference), confidence interval, and *P* value. The estimated effect of preemptive treatment compared with control is expressed in standardized units (point estimate and effect size). At the right, the point estimate and 95% confidence interval are displayed on a Forrest plot. The different sizes of squares indicate the weight the individual trials had in the analysis within each analgesic regimen, taking into account sample size and standard deviations. The diamonds indicate the results from pooling all the trials of each analgesic regimen. NSAID = nonsteroidal antiinflammatory drug; NMDA = *N*-methyl-D-aspartic acid.

did not yield effects consistent enough to draw conclusions regarding their clinical utility. Although it has been stated that the time to first analgesic intake is probably less accurate for assessing the preemptive effect and that a decreased time to first analgesic request is not a treatment problem provided that timely medication is available when the need arises (125), there is potential clinical usefulness for prolonging the

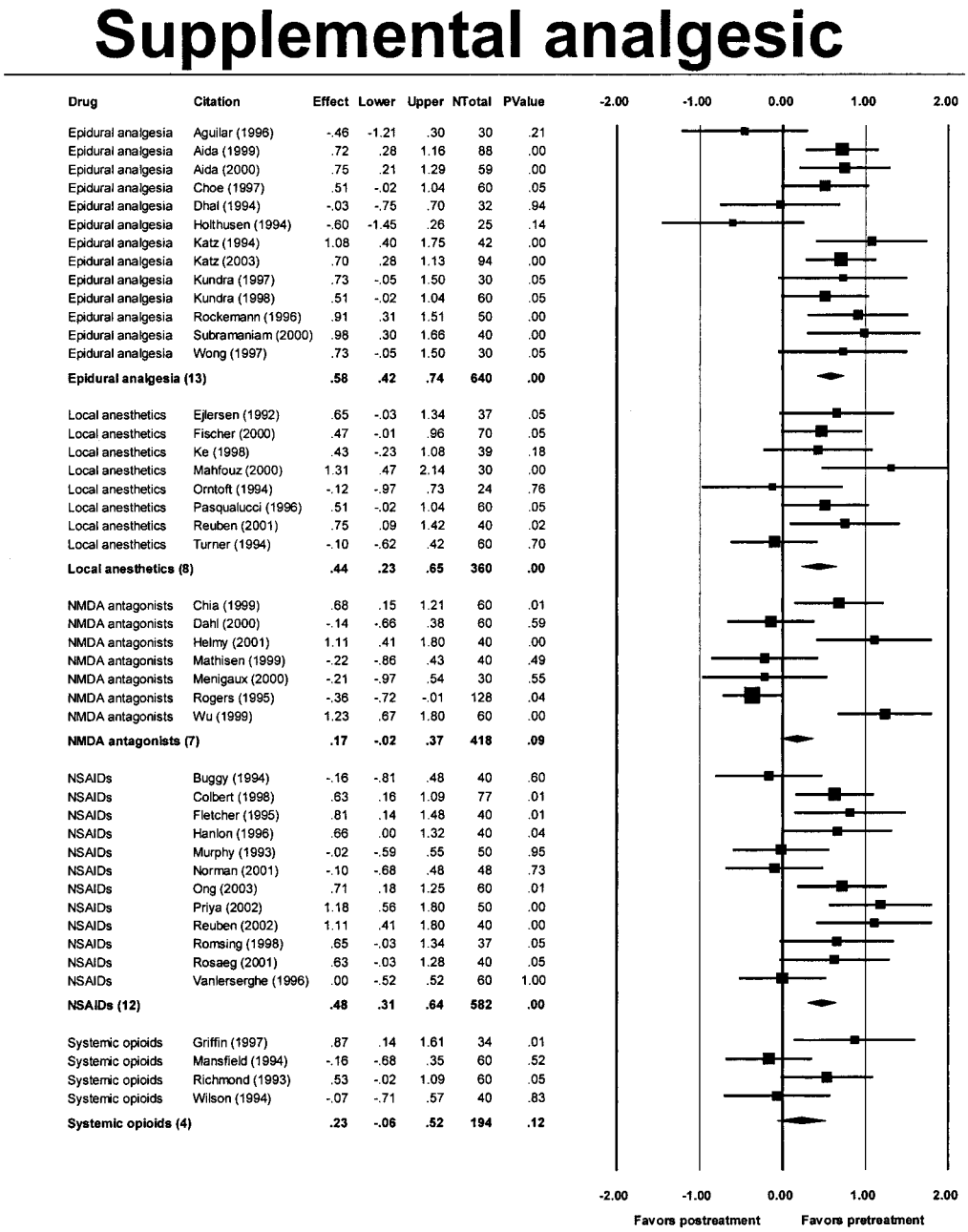

Figure 2. Forrest plot for the supplemental analgesic consumption. The different sizes of squares indicate the weight the individual trials had in the analysis within each analgesic regimen, taking into account sample size and standard deviations. The diamonds indicate the results from pooling all the trials of each analgesic regimen. NSAID = nonsteroidal antiinflammatory drug; NMDA = *N*-methyl-D-aspartic acid.

time to the first analgesic request. Prolonging the time to first analgesic request means that the analgesic duration has outlasted the pharmacological duration of action of the drug. In theory, this is a technique of increasing the duration of analgesia without increasing the dosage or dosing frequency. Often, this would translate into less pain, less total analgesic consumption, and better patient comfort. As an example, ketorolac administered before surgery for impacted third-molar surgery has a mean analgesic duration of 8.9 hours, compared with 6.9 hours when given after surgery (98). This is clinically significant, because pain for this type of procedure is usually most severe between six to eight hours after the surgery (126).

Considering the efficacy of the individual interventions, it can be stated that preoperative epidural analgesic treatment is more effective in managing acute postoperative pain, attenuating pain scores, decreasing the total supplemental analgesic consumption, and prolonging the time to first rescue analgesic.

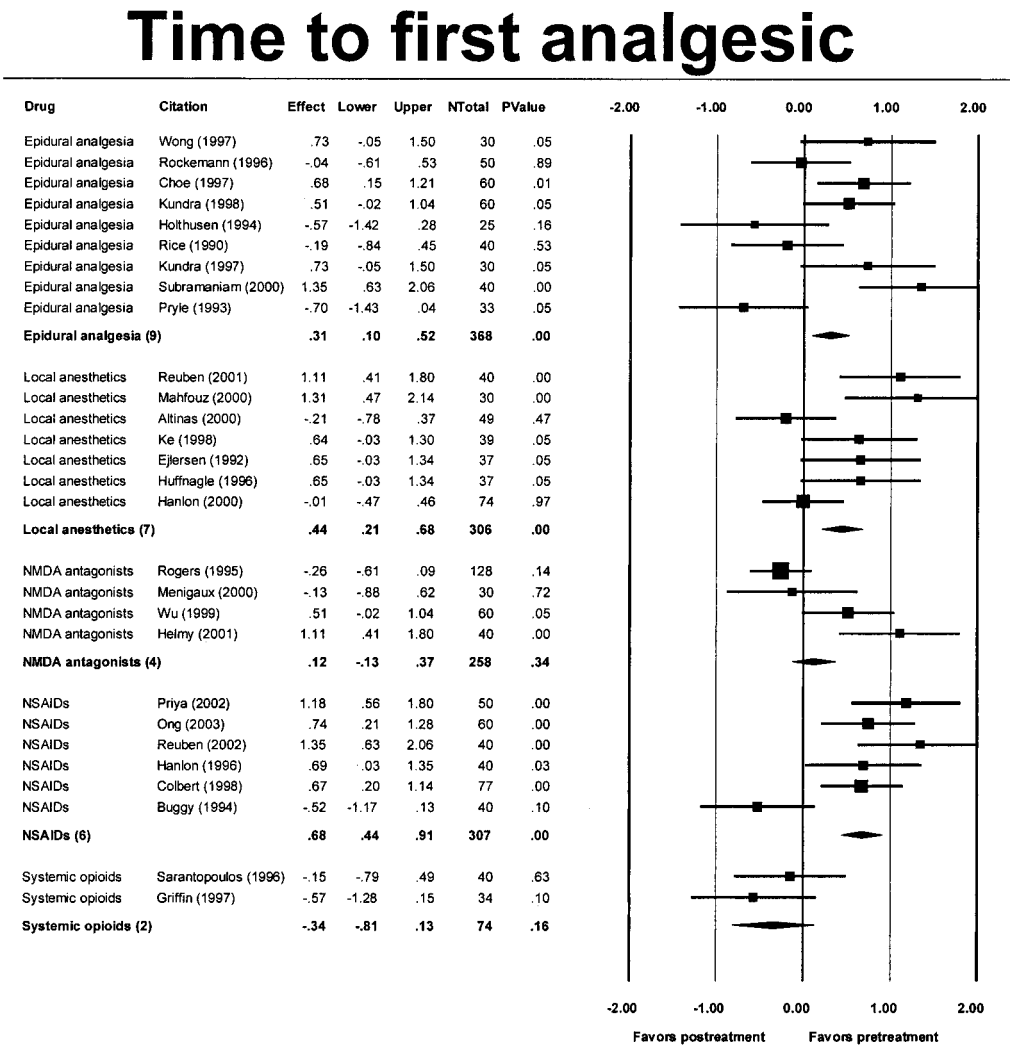

Figure 3. The Forrest plot for the time to first analgesic request. The different sizes of squares indicate the weight the individual trials had in the analysis within each analgesic regimen, taking into account sample size and standard deviations. The diamonds indicate the results from pooling all the trials of each analgesic regimen. NSAID = nonsteroidal antiinflammatory drug; NMDA = *N*-methyl-D-aspartic acid.

Other interventions, such as local anesthesia and NSAID intake, failed to elicit significant effects in all outcome measures but did affect selected variables (Table 6). As for the latter interventions, the relatively large CI regarding ES on pain intensity suggests that additional information may be required to establish the role of these analgesics in reducing pain intensity scores. The least proof of efficacy was found in the case of systemic NMDA antagonist and opioid administration.

Our findings are therefore largely at odds with a recent systematic review (7) of preemptive analgesia, which did not find a beneficial effect on postoperative pain intensity scores. We believe that Moiniche et al. (7) have done a good job in reviewing the topic, and it is probably neither us nor Moiniche et al. who are wrong, because a number of studies have been published since 2000 that may have substantially changed the overall picture. This meta-analysis included 10 recent trials from 2001 to 2003 (58,59,76,79,91,98–102) that were not included in Moiniche et al.'s review, which included only studies published up to 2000 (7). Furthermore, the methods and data used were different from our present meta-analysis. In Moiniche et al.'s review, all the scores in the different pain scales were converted into a single VAS score, such that the scores could be combined. The weighted mean difference (WMD) was calculated by using this converted pain score for each group of analgesic interventions. In contrast, our meta-analysis used the SMD in lieu of WMD as the ES. This allowed us to combine and analyze the data without having to convert. WMD is a

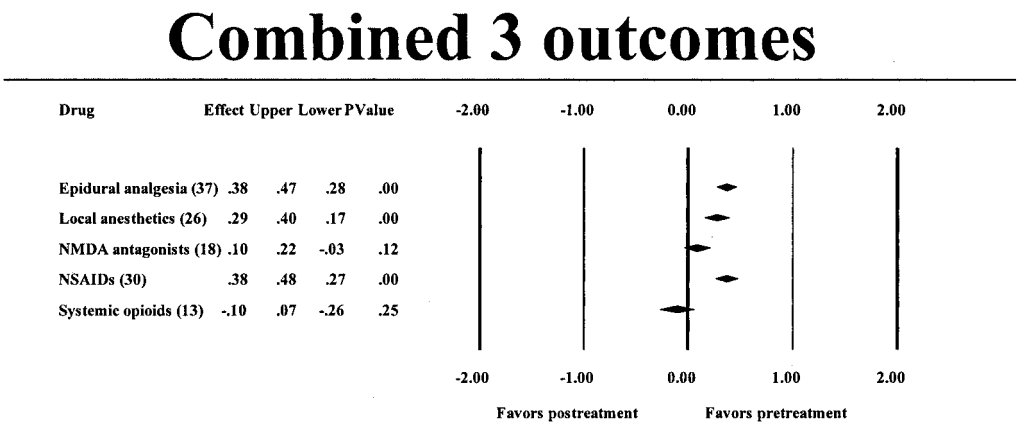

Figure 4. Forrest plot for all three combined outcomes. Diamonds indicate the results from pooling all the trials of each analgesic regimen. NSAID = nonsteroidal antiinflammatory drug; NMDA = *N*-methyl-D-aspartic acid.

standard statistic that measures the absolute difference between mean values in two groups in a clinical trial. It estimates the amount by which the treatment changes the outcome on average. However, it is important to note that this method assumes that all of the trials have measured the outcome on the same scale. Conversely, SMD is used as a summary statistic in meta-analysis when the trials all assess the same outcome but measure it in a variety of ways. When an outcome (such as pain) is measured in a variety of ways across studies (by using different scales), it may not be possible to directly compare or combine study results in a meta-analysis. By expressing the effects as a standardized value (SMD), the results can be combined because they have no units. Moiniche et al.'s review also included several studies that were excluded from this meta-analysis for reasons of methodological deficiencies (Appendix 2) (36,40,42,44,45). The present meta-analysis featured stricter inclusion criteria, as reflected by the fact that we evaluated only 66 (64%) of 102 potentially eligible trials, whereas Moiniche's review included 80 (86%) of 93 potential studies (7).

One possible caveat of preemptive analgesia may be the theoretical risk of complications when certain drugs are administered before surgery. This is exemplified by the possible increased risk of intraoperative and postoperative bleeding problems from the use of preoperative NSAIDs. However, existing data from RCTs on the incidence of perioperative bleeding complications caused by NSAIDs have been conflicting (127). A recent meta-analysis concluded that the evidence that NSAIDs increase the incidence of bleeding after surgery is ambiguous (128).

The differences in the efficacy of the individual analgesic interventions for a preemptive effect may be due to the degree of sufficiency of the afferent blockade, the nature of the pain, and its inflammatory component. Preemptive analgesia cannot be effective if the analgesic intervention is not adequate. The analgesic interventions need to produce a sufficiently dense and long duration of blockade for them to block the transmission of noxious afferent information from the periphery to the spinal cord and brain (2). In this respect, it appears that systemic opioids do not provide a sufficiently dense and long duration of blockade of spinal nociception to prevent central sensitization. In contrast, epidural analgesia can provide the sufficiently dense blockade required for a positive outcome. In addition, it has been suggested that if preemptive analgesia extends its duration into the postoperative period, then prevention of pain hypersensitivity could be even more pronounced. For acute postoperative pain, inflammatory mediators and nociceptive input should be kept inhibited well into the postoperative period. Central sensitization may not be prevented if the treatment is terminated too early.

Table 6. Effects of Various Preemptive Treatment Regimens on Surrogate Outcome Measures

Variable	Pain score	Analgesic consumption	Time to rescue analgesic
Epidural	+	+	+
Local anesthesia	?	+	+
NMDA antagonist	0	?	?
NSAID	?	+	+
Opioids	0	?	?

+ = positive effect; 0 = no beneficial effect; ? = meta-analysis of currently available studies yielded no unequivocal finding; NMDA = *N*-methyl-D-aspartic acid; NSAID = nonsteroidal antiinflammatory drugs.

In conclusion, on the basis of the surrogate outcome measures "postoperative pain scores," "total analgesic consumption," and "time to first rescue analgesic," this meta-analysis demonstrates the possible efficacy of preemptive analgesia to improve postoperative acute pain management in selected analgesic regimens. The ES was most pronounced for preemptive administration of epidural analgesia, local anesthetic wound infiltration, and NSAIDs. Although preemp-

tive epidural analgesia resulted in consistent improvements in all three outcome variables, preemptive local anesthetic wound infiltration and NSAID administration improved analgesic consumption and time to first rescue analgesia, but not postoperative pain scores. The least proof of efficacy was found in the case of systemic NMDA antagonist and opioid administration, and the results remain equivocal.

Appendix 1. Excluded Trials (36 RCTs; 1986 Patients)

Reference	Sample size (before/after)	Intervention	Procedure	Reason for exclusion
Beilin (21)	21/20	Epidural analgesia	Hysterectomy	Different drugs used for posttreatment and pretreatment
Burmeister (22)	20/20	Epidural ropivacaine	Abdominal surgery	Different before and after doses
Neustein (23)	15/15	Epidural bupivacaine + fentanyl	Thoracic surgery	Control was saline
Flisberg (24)	12/14	Epidural mepivacaine + morphine versus epidural bupivacaine + morphine	Abdominal surgery	Comparing different drugs
Kirdemir (25)	10/10	Epidural ketamine and neostigmine	Abdominal surgery	Comparing pretreatment of 2 different drugs
Vaida (26)	15/15	Epidural bupivacaine	Hysterectomy	Control was nothing
Wu (27)	20/20	Epidural ketamine, morphine, bupivacaine	Abdominal surgery	Single-blind
Gottschalk (28)	30/30	Epidural bupivacaine + fentanyl	Prostatectomy	Control was nothing
Kucuk (29)	49/49	Epidural ketamine	Abdominal surgery	Nonblind
Rockemann (30)	54/56	Epidural bupivacaine + sufentanil	Abdominal surgery	Different doses of preoperative versus postoperative epidural drugs
Williams-Russo (31)	131/131	Epidural bupivacaine	Total knee replacement	Control was nothing
Moiniche (32)	21/21	Epidural bupivacaine/morphine	Orthopedic surgery	Control was nothing
Cerfolio (33)	66/53	LA—bupivacaine infiltration	Thoracic surgery	Control was saline
Maestroni (34)	30/30	LA—ropivacaine infiltration	Laparoscopic cholecystectomy	Control was nothing
Gatt (35)	10/10	LA—intraarticular bupivacaine	Orthopedic surgery	Control was nothing
Campbell (36)	32/32 (crossover)	LA—bupivacaine infiltration + IV tenoxicam + alfentanil	Oral surgery	The major argument in this model was that the unilateral biochemical changes after ipsilateral injury may have a bilateral effect. These biochemical changes may explain the difficulty in identifying any benefits of preemptive analgesia
Hoard (37)	11/23	LA—bupivacaine infiltration	Hip surgery	Control was nothing
Ke (38)	25/25	LA—bupivacaine	Gynecologic surgery	Study was published in 2 journals
Ko (39)	20/20	LA—lidocaine infiltration	Appendectomy	Control was nothing
Campbell (40)	40/40 (crossover)	LA—bupivacaine infiltration	Oral surgery	Major flaw in study design. Pain was measured with VAS at 6 h, 1 d, and 6 d after surgery. This model is not suitable in this study as pain for this type of surgery is usually only moderate to severe at 6 to 8 h after surgery
Pedersen (41)	20/20 (crossover)	LA—lidocaine nerve block	Leg surgery	Control was nothing
Elhakim (42)	25/25	LA—topical lidocaine spray	Tonsillectomy	Topical lidocaine is ultra short-acting; measuring pain at 24 h would make no difference
Wu (43)	45/15	NMDA antagonist—dextromethorphan	Abdominal surgery	Control was not dextromethorphan but chlorpheniramine
Fu (44)	20/20	NMDA antagonist—ketamine	Abdominal surgery	The major flaw is that markedly differing ketamine dosages were administered to the preincisional versus postincisional group
Tverskoy (45)	9/9	NMDA antagonist—ketamine	Hysterectomy	Control was nothing
Oztekin (46)	20/20	NSAID—rectal diclofenac	Tonsillectomy	Control was nothing
Hanlon (47)	37/36	NSAID—IV tenoxicam	Breast biopsy	Comparing 30 min before surgery versus at the induction of anesthesia
Mixter (48)	100	NSAID—IV ketorolac	Laparoscopic surgery	Control was nothing
Espinet (49)	20/20	NSAID—IM diclofenac	Hysterectomy	Data not clear in report. Graphs were of poor quality
Romej (50)	14/14	PO and rectal paracetamol	Tonsillectomy	Pretreatment with oral paracetamol, but posttreatment with rectal paracetamol
Sandin (51)	20/22	NSAID—IM diclofenac	Arthroscopy	Data not clear in report. Graphs were of poor quality
Vogel (52)	20/20	NSAID—PO ibuprofen	Oral surgery (periodontal surgery)	Data not clear in report. Graphs were of poor quality
Flath (53)	28/30	NSAID—PO flubiprofen	Oral surgery (pulpectomy)	Data not clear in report. Graphs were of poor quality
Chiaretti (54)	14/14	Opioid—fentanyl	Pediatric neurosurgery	Control was nothing
Motamed (55)	13/12	Opioid—morphine	Open knee surgery	Control was nothing
Collis (56)	16/22	Opioid—morphine	Hysterectomy	Different preoperative versus postoperative morphine was given

LA = local anesthetic; VAS = visual analog scale; RCT = randomized controlled trials; NMDA = *N*-methyl-D-aspartate; NSAID = nonsteroidal antiinflammatory drug; PO = by mouth.

Appendix 2. Detailed Reasons for Exclusion of Trials in Moiniche's Review

Reference	Sample size (before/after)	Intervention	Procedure	Reason for exclusion
Campbell (36, 40)	32/32 (crossover) 40/40 (crossover)	LA—bupivacaine infiltration + IV tenoxicam + alfentanil LA—bupivacaine infiltration	Oral surgery Oral surgery	In both studies, the study design was similar, using a crossover design with bilaterally symmetrical oral surgery under general anesthetic. Patients acted as their own controls and were allocated randomly to have surgery start on one side as preemptive and followed by the other side as control during the same occasion. Outcome measure was assessed between the 2 sides using the VAS at 6 h and 1, 3, and 6 d after surgery. There was no difference in the pain scores at any time. The major flaw in this study is that this model is not suitable for the analgesic tested. In this model, moderate to severe pain occurs only during the first 12 h after surgery, with a peak intensity after about 6 to 8 h. The analgesic effect of bupivacaine infiltration for third-molar surgery has been reported to be about 8 to 10 h. At 6 h, the bupivacaine is definitely still working well, and at 1, 3, and 6 d after surgery, there may be no pain to compare. Pain should have been assessed hourly for the first 12 h. In addition, both the preemptive and control sides in the same patient were operated on on the same occasion, making it difficult to interpret the results. The major argument was that the unilateral biochemical changes after ipsilateral injury may have a bilateral effect. These biochemical changes may explain the difficulty in identifying any benefits of preemptive analgesia. To avoid this problem, it would be better to operate on the preemptive and control sides on separate occasions with an adequate washout period
Fu (44)	20/20	NMDA antagonist—ketamine	Abdominal surgery	This study evaluated the preemptive effect of IV ketamine in a sample of 40 patients undergoing different abdominal surgeries. They compared a preincisional ketamine 0.5 mg/kg IV bolus followed by a ketamine infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ versus ketamine 0.5 mg/kg IV bolus alone without the infusion after skin closure. Outcome measure was assessed by VAS at rest and total PCA morphine consumption over the first 2 d. They found that the preemptive group had significantly less morphine consumption but no difference in the pain scores. The flaw in this study is that markedly differing ketamine dosages were administered to the pre- versus postincisional group. Any benefits may be due to the larger dosage of the analgesic rather than the preemptive effect. In addition, different surgical procedures with different severity of surgical stress were compared
Tverskoy (45)	9/9	NMDA antagonist—ketamine	Hysterectomy	This study evaluated the preemptive effect of fentanyl and ketamine in a sample of 27 patients undergoing hysterectomy. They compared preincisional fentanyl with preincisional ketamine and control (nothing). Pain intensity (VAS) and postoperative analgesic consumption were measured. The major flaw in this study was that the control was nothing. There should be 2 control groups receiving postincisional fentanyl and ketamine. In addition, the sample size was fewer than 10 per group
Elhakim (42)	25/25	LA—topical lidocaine spray	Tonsillectomy	This study evaluated the preemptive effect of topical lidocaine spray on 75 children aged between 4 and 6 years undergoing tonsillectomy with or without adenoidectomy. There were 3 groups: preincisional topical lidocaine spray, postincisional lidocaine spray, and nothing. Preincisional intramuscular ketamine and rectal diclofenac were also given. Pain was assessed by using the VAS at 0.5, 1, and 24 h after awakening from general anesthesia. No preemptive analgesic effect was found. The results showed that fairly large numbers of patients in each group (up to 21) were asleep at 0.5 to 1 h of the investigation period. The validity of using the VAS on these young sleepy patients may be questioned. In addition, it has been proposed that the blockade of pain needs to be of sufficient strength and duration for any preemptive analgesic effect. Topical lidocaine is ultra short-acting and a weak analgesic, and measuring pain at 24 h would probably not be able to detect any difference

LA = Local anesthetic; NMDA = *N*-methyl-D-aspartic acid; VAS = visual analog scale; PCA = patient-controlled analgesia.

The authors thank V. T. W. Fan, MD, Department of Oral & Maxillofacial Surgery, Faculty of Dentistry, National University of Singapore, for reviewing the manuscript.

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