David C. Warltier, M.D., Ph.D., Editor

Anesthesiology 2002; 96:725–41

A Qualitative and Quantitative Systematic Review of Preemptive Analgesia for Postoperative Pain Relief

The Role of Timing of Analgesia

Steen Møiniche, M.D., Henrik Kehlet, M.D., D.M.Sc.,† Jørgen Berg Dahl, M.D., D.M.Sc.‡*

THE concept of preemptive analgesia to reduce the magnitude and duration of postoperative pain was paved in 1983 by Woolf,[1] who showed evidence for a central component of postinjury pain hypersensitivity in experimental studies. Subsequently, an overwhelming amount of experimental data demonstrated that various antinociceptive techniques applied before injury were more effective in reducing the postinjury central sensitization phenomena as compared with administration after injury.[2] Finally, these promising experimental findings were taken into clinical testing of the hypothesis. Although early reviews of clinical findings were mostly negative,[3–5] there is still a widespread belief of the efficacy of preemptive analgesia among clinicians.

The definition of preemptive analgesia has varied, thereby causing confusion and misunderstanding of the concept.[6] Because the original observations in experimental studies suggested that timing of analgesic treatment was important to obtain efficient reduction of postinjury pain hypersensitivity phenomena, we performed an updated review of studies to compare the role of timing of analgesia *i.e.*, preoperative *versus* intraoperative or postoperative initiation of analgesia. In this review we are not considering studies designed to compare preemptive analgesia *versus* no treatment. We have only included double-blind, randomized, controlled trials of identical or very similar analgesic regimens, where the only difference between study groups was timing of analgesia.

This article is accompanied by an Editorial View. Please see: Hogan QH: No preemptive analgesia: Is that so bad? ANESTHESIOLOGY 2002; 96:526–7.

Methods

Literature Search

Reports of randomized controlled trials of preemptive analgesia for acute or chronic postoperative pain relief were systematically sought using the Cochrane Library 2000§ (www.cochrane.org) and the MEDLINE‖ (www.ncbi.nlm.nih.gov/PubMed/; 1966–2000) databases without language restriction. We used different search strategies with free text combinations, including the following search terms: preemptive analgesia, preemptive analgesia, prophylactic pain treatment, preoperative treatment, postoperative pain, postoperative analgesia, chronic pain, and long-term pain. The last search was performed on December 30, 2000. Reference lists of retrieved reports and review articles were hand-searched for additional papers. No abstracts, correspondences, or unpublished observations were included. Authors were not contacted for original data.

Inclusion and Exclusion Criteria and Data Extraction

Reports that were included consisted of double-blind randomized comparisons of identical or nearly identical analgesic regimens initiated before *versus* after surgical incision for postoperative pain relief with or without the use of a double dummy.

Reports that were excluded included trials of comparisons of preoperative treatment with placebo or no treatment, and trials of comparisons of preoperative with preoperative plus postoperative treatment. Such studies provide no evidence for a preemptive effect, *i.e.*, if timing of the initiation of the pain treatment is of importance.[5]

* Registrar, ‡ Consultant, Department of Anesthesiology, Herlev University Hospital. † Professor and Consultant, Department of Surgical Gastroenterology, Hvidovre University Hospital.

Received from the Department of Anesthesiology, Herlev University Hospital, Herlev, Denmark, and the Department of Surgical Gastroenterology, Hvidovre University Hospital, Hvidovre, Denmark. Submitted for publication April 16, 2001. Accepted for publication September 28, 2001. Supported by grant No. 22000947 from the Danish Medical Research Council, Copenhagen, Denmark (to Dr. Dahl).

Address correspondence to Dr. Møiniche: Department of Anesthesiology, Herlev University Hospital, DK-2730 Herlev, Copenhagen, Denmark. Address electronic mail to: moiniche@dadlnet.dk. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

§ Cochrane Library [database online]. Issue 4, 2001. Oxford. Update Software. Updated quarterly.

‖ MEDLINE [database online]. Bethesda: National Library of Medicine.

We developed standard data collection sheets to record details of trial design, interventions, and outcome measures for every trial. Each report meeting the inclusion criteria was read independently by two of the authors and scored using a three-item, 1–5 quality scale.[7] Consensus was subsequently achieved. If the reports were described as randomized, one point was given, and an additional point was given if the method of randomization was described and adequate (computer-generated, table of random numbers, *etc.*), but one point was deducted if randomization was inappropriate (alternate randomization, randomization according to weekday, *etc.*). If studies were described as double-blind, one point was given, and an additional point was given if blinding was described and appropriate (use of double-dummy, blinded pharmacy manufactured ampoules, *etc.*), but one point was deducted if blinding was inappropriate. Finally, reports that described the numbers and reasons for withdrawals were given one point. By definition, studies without randomization and blinding were excluded. Thus, the minimum score of an included clinical trial was 2, and the maximum score was 5.

Each trial was assessed for different measures of internal sensitivity. First, trials were checked for magnitude of pain intensity. Because it is difficult to detect an improvement with low or no pain, it was noted if pain scores were less than 30 mm on a visual analog scale (VAS) or less than moderate pain on a verbal rating scale or similar score.[8] Second, it was noted if a power calculation of the statistical tests was performed. Trials with sample sizes less than 10 patients per treatment group were not considered.[9]

Use of other intraoperative analgesic treatment (which in theory may preempt pain in the postsurgery treatment group) was noted but not regarded to invalidate the clinical relevance of trials, since common anesthetic practice often includes analgesic use (*e.g.*, intraoperative fentanyl).

Data on postoperative pain and analgesic consumption were extracted for each report. Finally, information about type of anesthesia (general, regional) and number of patients enrolled was taken from each report.

Data Handling

Qualitative analysis of postoperative effectiveness was evaluated by significant difference ($P < 0.05$ as reported in the original investigation) in pain relief using pain scores, time to first analgesic request, and consumption of supplementary analgesics between the presurgical and postsurgical treatment groups, and by assessment of the clinical importance of observed differences. The plot of L'Abbé *et al.*[9] of VAS pain scores with preemptive *versus* postsurgical regimens was used as a graphic means of exploring the consistency of efficacy and the homogeneity of the data whenever possible.

Quantitative analysis of combined data were intended by calculation of the weighted mean difference (WMD) of VAS pain scores between treatment groups (using the Review Manager software, version 4.0, the Cochrane Collaboration; The Nordic Cochrane Center, Copenhagen, Denmark). The weight given to each study in this analysis (*i.e.*, how much influence each study had on the overall results) was determined by the precision of its estimate by taking into account study size and SDs of the VAS scores in the individual trials. For the current use, a mean VAS for each treatment group was calculated in every trial from all available recordings performed within 24 h after surgery. Verbal rating pain scores and similar scores were converted to VAS pain scores (*e.g.*, a four-point verbal rating score including no, light, moderate, and severe pain was converted to 0, 25, 50, and 75 mm VAS, respectively). The possibility was recognized that data only would allow a qualitative analysis. Finally, the trials were stratified according to the type of drug (opioid, local anesthetic, *N*-methyl-D-aspartate [NMDA] receptor antagonist, nonsteroidal antiinflammatory drug [NSAID]), mode of administration (systemic, neuraxial, peripheral nerve block, or wound infiltration), and, if possible, to surgical procedure.

Results

Ninety-three randomized clinical trials of preincisional *versus* postincisional analgesic regimens for postoperative pain control were identified. Of these, 11 studies were excluded because of lack of appropriate blinding or randomization[10–18] or use of different analgesic doses preoperatively and postoperatively.[19,20] Two articles were not available through the Danish University Library (Copenhagen, Denmark) or the British Library[21,22] (London, United Kingdom), leaving 80 reports for analysis. Studies excluded are summarized in the Appendix.

The remaining studies could be divided into 20 trials of systemic NSAIDs, 8 trials of systemic opioids, 8 trials of systemic NMDA receptor antagonists, 24 trials of epidural, caudal, or intrathecal analgesia, and 20 trials of peripheral local anesthetic use (wound infiltration or nerve block) or combinations of treatment.

A total of 3,761 patients, of which 1,964 received preincisional treatment, were studied. The range of the number of patients included in the studies was 10 (in a crossover trial) to 128. The median quality score was 4 (range, 2–5) in trials with significant differences in pain relief between the treatment groups and 4 (range, 2–5) in trials with no significant differences. The percentage of trials with a significant finding in favor of preemptive analgesia did not differ between trials of high quality (score, 4–5) and trials of lower quality (score, 2–3) ($P = 0.67$, Fisher test). Details of included studies are shown in tables 1–7 and figures 1–4.

Table 1. Presurgical *versus* Postsurgical NSAID

Reference	Quality Score	N Pre/Post	Drug and Dose	Procedure	Pain Scores	Time to First Analgesic Request	Supplemental Analgesic Demand	Comments
Nordbladh *et al.*[31] (1991)	4	49/50	Diclofenac, 100 mg suppositories	Tonsillectomy	NS	$P < 0.05$	$P < 0.05$	Preemptive dose divided in two doses Time to first request prolonged 1.5 h Analgesic demand reduced by 28%
Nelson *et al.*[32] (1993)	3	22/19	Diclofenac, 75 mg × 2 oral 3–5 days preoperatively continued 7 days after surgery	Knee arthroscopy	NS	—	NS	Evaluated at day of surgery, day 1, and weeks 1, 3, and 8
Sandin *et al.*[33] (1993)	4	20/22	Diclofenac, 75 mg intramuscular	Knee arthroscopy	NS	—	NS	Intensity of pain scores low Evaluated hourly after weaning of epidural analgesia for 6 h and first postoperative day
Buggy *et al.*[30] (1994)	3	20/20	Diclofenac, 75 mg intravenous	Laparoscopic tubal ligation	NS	—	NS	Evaluated at 0.5, 1, 3, and 6 h
Bridgman *et al.*[27] (1996)	3	21 Crossover	Diclofenac, 100 mg oral	Third molar extractions	NS	—	Fixed	Intensity of pain scores low
Fletcher *et al.*[36] (1995)	5	20/20	Ketorolac, 60 mg intravenous	Total hip replacement	$P < 0.05$	—	$P < 0.05$	Pain scores significantly reduced in recovery room only, not 6, 12, 18, 24, 30, 36, 42, or 48 h after surgery Analgesic demand reduced by 6 mg of morphine during the first 6 h
Peduto *et al.*[41] (1995)	2	15/15	Ketorolac, 0.4 mg/kg	Nasal septoplasty	$P < 0.05$	—	Fixed	Pain scores significantly reduced during evaluation from 1 to 3 h after surgery
Rogers *et al.*[37] (1995)	5	30/28	Ketorolac, 10 mg intravenous	Abdominal hysterectomy	—	—	NS	PCA-morphine consumption evaluated at 2, 4, and 12 h
Rømsing *et al.*[38] (1998)	5	20/20	Ketorolac, 1 mg/kg (children aged 5–15)	Tonsillectomy	NS	—	(NS)	Demand of fentanyl reduced by 0.2 μg/kg until 1.5 h after surgery in the pre compared with the post group, not later
Parke *et al.*[39] (1995)	4	37/40	Ketorolac, 30 mg intravenous	Abdominal or vaginal hysterectomy	NS	—	NS	Evaluated 12 and 24 h after surgery
Cabell[42] (2000)	5	25/24	Ketorolac, 30 mg intravenous	Gynecologic laparoscopy	NS	—	NS	Evaluated until 24 h postoperatively Pain scores and analgesic demand higher in pre compared with post group
Vanlersberghe *et al.*[40] (1996)	2	30/30	Ketorolac, 30 mg intravenous	Minor orthopedic	NS	—	NS	Intensity of pain scores low Evaluated at 1, 2, 4, and 6 h after surgery
Likar *et al.*[44] (1998)	4	25/25	Ketoprofen, 100 mg intravenous + 12 mg/h for 48 h	Gynecologic laparotomy	NS	$P < 0.05$	NS	Time to first request prolonged 49 min Evaluated at 0.5, 1, 2, 3, 6, 9, 12, 18, 24, and 48 h
Likar *et al.*[43] (1997)	3	26/22	Ketoprofen, 2 mg/kg intravenous	Gynecologic laparotomy	NS	NS	NS	Evaluated at 0.5, 1, 2, 3, 6, 9, 12, 18, and 24 h
Bünemann *et al.*[34] (1994)	4	59/58	Naproxen, 1,100 mg oral	Minor orthopedic	NS	—	NS	
Sisk *et al.*[28] (1990)	3	36 Crossover	Naproxen, 550 mg oral	Third molar extraction	NS	—	—	Intensity of pain scores low No information about rescue analgesics
Sisk and Grover[29] (1989)	3	20 Crossover	Diflunisal, 1,000 mg oral	Third molar extraction	NS	—	—	Intensity of pain scores low No information about rescue analgesics
Flath *et al.*[35] (1987)	5	30/30	Flurbiprofen, 100 mg oral	Endodontic treatment	NS	—	NS	Intensity of pain scores low
Vogel *et al.*[45] (1992)	4	19/17	Ibuprofen, 600 mg oral	Periodontal surgery	NS	NS	NS	Intensity of pain scores low
Gustafsson *et al.*[26] (1983)	4	43 Crossover	Paracetamol, 1 g oral	Oral surgery	NS	NS	NS	

NSAID = nonsteroidal antiinflammatory drug; NS = no significant difference between treatment groups or no significant difference in favor of the preemptive treatment; $P < 0.05$ = significant difference between treatment groups in favor of the preemptive treatment; — = not evaluated; PCA = patient-controlled analgesia.

Table 2. Presurgical *versus* Postsurgical Intravenous Opioid

Reference	Quality Score	N Pre/Post	Drug and Dose	Procedure	Pain Scores	Time to First Analgesic Request	Supplemental Analgesic Demand	Comments
Richmond *et al.*[46] (1993)	4	23/21	Morphine, 10 mg	Abdominal hysterectomy	NS	—	$P < 0.05$	24-h PCA-morphine consumption 10 mg reduced (27% reduction)
Griffin *et al.*[50] (1997)	4	18/16	Alfentanil, 70 μg/kg	Abdominal hysterectomy	NS	NS	$P < 0.05$	PCA-morphine significantly reduced by 12 mg from 48–72 h, but not 0–6, 6–12, 12–24, or 24–48 h after surgery
Wilson *et al.*[51] (1994)	3	20/20	Alfentanil, 40 μg/kg	Abdominal hysterectomy	NS	—	NS	VAS significantly higher in pre compared with post group at 24 h
Fassoulaki *et al.*[49] (1995)	4	17/17	Fentanyl, 10 μg/kg	Abdominal hysterectomy	NS	—	Fixed	Evaluated at 0.5, 1, 1.5, 3, and 24 h VAS significantly higher in pre compared with post group for fentanyl
		17/17	Sufentanil, 1 μg/kg	Abdominal hysterectomy	NS	—	Fixed	
Mansfield *et al.*[47] (1996)	5	22/18	Morphine, 0.15 mg/kg	Abdominal hysterectomy	NS	—	NS	Evaluated at 1, 2, 4, 24, and 48 h
Sarantopoulos and Fassoulaki[52] (1996)	5	18/21	Sufentanil, 1 μg/kg	Abdominal hysterectomy	NS	—	NS	Evaluated before first analgesic, and at 4, 8, 12, and 24 h
Nagasaka *et al.*[53] (1996)	2	23/23	Pentazocine, 30 or 60 mg	Abdominal hysterectomy	NS	—	NS	Evaluated over 24 h
Millar *et al.*[48] (1998)	5	30/30	Morphine, 0.3 mg/kg	Abdominal hysterectomy	NS	—	NS	Evaluated at 1, 2, 4, 24, and 48 h

NS = no significant difference between treatment groups or no significant difference in favor of the preemptive treatment; $P < 0.05$ = significant difference between treatment groups in favor of the preemptive treatment; — = not evaluated; PCA = patient-controlled analgesia; VAS = visual analog scale.

Quantitative analysis was performed on the mean of VAS pain scores recorded within 24 h after surgery for each treatment modality. In five trials, verbal rating scores were converted to VAS scores (two trials of NSAID and three trials of local infiltration). Data on analgesic consumption and time to first analgesic request only allowed a qualitative analysis because of the variety of analgesics, doses, and outcome reporting used. Instead, any statistical difference between treatments regarding these measures was extracted from the original reports and documented in table format as performed previously for other qualitative systematic reviews.[23–25]

Acute Postoperative Pain

Nonsteroidal Antiinflammatory Drugs. Twenty trials comparing preincisional with postincisional NSAID or paracetamol[26] using a parallel or crossover design[26–29] were identified. Various odontologic, abdominal, and orthopedic procedures were studied. The NSAIDs were diclofenac,[27,30–33] naproxen,[28,34] flurbiprofen,[35] ketorolac,[36–42] ketoprofen,[43,44] diflunisal,[29] and ibuprofen[45] used in clinically relevant doses (table 1). Fentanyl,[30,31,33,36,38,39,42–44] alfentanil,[34,37] local anesthetics,[26–29,33,35,45] or nitrous oxide[30,31,36–44] were, as a part of the anesthesia, coadministered intraoperatively in all trials.

In two trials, pain scores were significantly improved immediately after surgery by preemptive compared with postoperative treatment.[36,41] In none of the other trials were improvements observed (fig. 1A). Quantitative analysis with the calculation of the WMD of VAS scores between treatment groups using a fixed-effect model (as test for heterogeneity was nonsignificant, $P = 0.78$) was not significant (WMD, 0 mm; 95% confidence interval [CI], −2 to 2 mm; fig. 2A) with 14 trials. In the remaining six trials, one of which showed reduced pain scores,[41] there was a lack of dispersion measures for the calculation.[27,31,35,37,41–42]

In one trial,[31] the number of patients needing rescue analgesics and time to first request was improved by 28% and 1.5 h, respectively. In two other studies, patient-controlled analgesia–morphine and time to first analgesic request were statistically improved by 6 mg over 6 h[36] and 49 min,[44] respectively. In none of the other trials was demand for supplementary analgesic different between treatment groups.

Power analysis of the statistical tests was only available in five trials,[30,34,36,40,44] with a power of 75–95% of detecting a difference of 15–25 mm VAS at the 5% significance level. Furthermore, intensity of pain scores was low in eight trials (< 30 mm VAS),[27–29,33,35–36,40,45] which might have impaired internal sensitivity.

Table 3. Presurgical *versus* Postsurgical Intravenous and Intramuscular NMDA Receptor Antagonists

Reference	Quality Score	N Pre/Post	Drug and Dose	Procedure	Pain Scores	Time to First Analgesic Request	Supplemental Analgesic Demand	Comments
Fu *et al.*[54] (1997)	4	20/20	Ketamine, 0.5 mg/kg + 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ intraoperatively	Major abdominal	NS	NS	$P < 0.05$	Cumulative morphine consumption reduced 40 mg over 48 h
Mathisen *et al.*[59] (1999)	5	20/20	(R)-ketamine, 1 mg/kg	Laparoscopic cholecystectomy	NS	—	NS	Evaluated at 0, 1, 2, 3, 4, and 24 h and after 7 days Intensity of pain scores low
Heinke and Grimm[56] (1999)	2	13/13	Ketamine, 0.5 mg/kg + 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ intraoperatively	Abdominal hysterectomy	NS	NS	NS	Pain evaluated at 1, 2, 3, 4, 5, and 6 h Analgesic demand over 24 h
Dahl *et al.*[58] (2000)	4	33/27	Ketamine, 0.4 mg/kg	Abdominal hysterectomy	NS	—	NS	Pain scores significantly higher in pre compared with post group early after surgery
Adam *et al.*[55] (1999)	5	64/64	Ketamine, 0.15 mg/kg	Total mastectomy	NS	NS	NS	PCA-morphine consumption significantly higher in pre compared with post group until 2 h after surgery
Meningaux *et al.*[57] (2000)	5	15/15	Ketamine, 0.15 mg/kg	Arthroscopic anterior cruciate ligament repair	NS	NS	NS	Evaluated every second to fourth hour until 48 h after surgery
Wu *et al.*[61] (1999)	2	30/30	Dextromethorphan, 40 mg intramuscular	Laparoscopic cholecystectomy	$P < 0.05$	$P < 0.05$	$P < 0.05$	Worst pain score reduced by 20 mm VAS Time to first request prolonged 11 h Total pethidine consumption reduced 57 mg over 48 h
Chia *et al.*[60] (1999)	4	30/30	Dextromethorphan, 5 mg/kg	Major abdominal	NS	—	$P < 0.05$	Morphine consumption reduced by 15.5 mg from 0–24 h and 17.6 mg from 24–48 h

NMDA = *N*-methyl-D-aspartate; NS = no significant difference between treatment groups or no significant difference in favor of the preemptive treatment; $P < 0.05$ = significant difference between treatment groups in favor of the preemptive treatment; — = not evaluated; PCA = patient-controlled analgesia; VAS = visual analog scale.

In conclusion, some aspects of postoperative pain control were improved by preemptive treatment in 4 of the 20 trials. Overall, the data demonstrated preemptive NSAIDs to be of no analgesic benefit when compared with postincisional administration of these drugs.

Intravenous Opioids. Eight trials with nine treatment arms were identified comparing preincisional with postincisional administration of morphine (10 mg or 0.15–0.3 mg/kg),[46–48] fentanyl (10 μg/kg),[49] alfentanil (40–70 μg/kg),[50,51] sufentanil (1 μg/kg),[49,52] or pentazocine (30–60 mg)[53] (table 2). In all trials, the surgical procedure was abdominal hysterectomy. In none of the trials was other intraoperative analgesics (beside the test drugs) administered except for nitrous oxide in all studies.

In no study were pain scores significantly reduced in the preemptive group (fig. 1B). In contrast, quantitative analysis of pain scores using a fixed-effect model ($P = 0.75$ in test for heterogeneity) revealed that the WMD in VAS scores between study groups was statistically significant in favor of the postoperative groups (5 mm; 95% CI, 1–9 mm; fig. 2B).

Supplementary analgesic consumption was significantly reduced in two studies in the preemptive group, averaging 10 mg morphine over 24 h[46] and 12 mg morphine[50] from 48 to 72 h, but not from 0 to 6, 6 to 12, 12 to 24, or 24 to 48 h postoperatively, rendering interpretation difficult. Time to first analgesic request was evaluated in only one trial[50] and was not different between study groups.

Intensity of pain scores was considered adequate (> 30 mm VAS) in all trials. However, in only three trials was power analysis of the statistical tests performed,[48–50] revealing an at least 80% power to detect a reduction in VAS scores of 20 mm[49,50] or decrease in opioid consumption of 30%[48] at the 5% significance level.

In conclusion, no improvement in postoperative pain control was observed after preemptive administration of systemic opioids.

Intravenous or Intramuscular *N*-methyl-D-aspartate Receptor Antagonists. Eight trials were identified comparing preincisional with postincisional ketamine[54–59] or dextromethorphan[60,61] in a variety of sur-

Table 4. Presurgical *versus* Postsurgical Single-dose Epidural Analgesic Regimens

Reference	Quality Score	N Pre/Post	Epidural Drug and Bolus Dose	Procedure	Pain Scores	Time to First Analgesic Request	Supplemental Analgesic Demand	Comments
Katz *et al.*[63] (1992)	4	15/15	Fentanyl, 4 μg/kg	Thoracic	$P < 0.05$	—	$P < 0.05$	Pain score significantly reduced at only 6 h, not 2, 4, 12, 24, or 48 h Analgesic demand significantly reduced only from 12–24 h, not 0–2, 2–4, 4–6, 6–12, or 24–48 h
Kundra *et al.*[65] (1997)	2	15/15	Morphine, 3 mg	Lumbar laminectomy	$P < 0.05$	$P < 0.05$	$P < 0.05$	VAS reduced maximally by 20 mm Time to first request prolonged by 11 h Total morphine reduced by 20.1 mg over 24 h
Gil *et al.*[68] (1998)	2	10/10	Morphine, 2–4 mg	Thoracic	$P < 0.05$	—	$P < 0.05$	VAS significantly reduced by 14 mm only at 18 h, not 1, 6, 12, or 24 h Epidural morphine reduced by 1.4 mg
Subramaniam *et al.*[71] (2000)	4	20/20	Morphine, 50 μg/kg	Thoracic and upper abdominal	NS	NS	NS	Epidural catheter placed lumbar for upper procedures in all groups Intensity of pain scores low (< 30 mm VAS)
		20/20	Morphine, 50 μg/kg + 0.1% bupivacaine, 10 ml		NS	NS	$P < 0.05$	Supplemental epidural morphine consumption reduced by 48% corresponding 8 mg over 5 days
Rockemann *et al.*[62] (1996)	4	48/48	1% Mepivacaine, 15–20 ml + morphine, 5 mg + diclofenac, 75 mg intramuscular + metamizole, 1 g intravenous	Major abdominal	NS	NS	$P < 0.05$	Morphine consumption reduced by 16 mg over 5 days Intensity of pain scores low (< 30 mm VAS)
Choe *et al.*[70] (1997)	2	30/30	Morphine, 2 mg + ketamine, 60 mg	Subtotal gastrectomy	NS	$P < 0.05$	$P < 0.05$	Time to first request prolonged mean 10 h 57 *versus* 90% of patients required supplemental analgesics
Richards *et al.*[69] (1998)	4	13/12	0.5% Bupivacaine, 15 ml + fentanyl, 50 μg	Abdominal hysterectomy	NS	—	NS	Evaluated at 1, 2, 4, 6, 12, 23, 24, 47, and 48 h
Katz *et al.*[64] (1994)	5	21/21	0.5% Bupivacaine, 15 ml	Lower abdominal	NS	—	$P < 0.05$	VAS NS but McGill pain score significantly reduced at 24 h PCA-morphine reduced by 16 mg over 24 h
Pryle *et al.*[66] (1993)	3	15/18	0.5% Bupivacaine, 15 ml	Abdominal hysterectomy	NS	—	NS	Evaluated at 5, 6, 23, and 24 h
Espinet *et al.*[67] (1996)	3	19/19	0.5% Bupivacaine, 20 ml + diclofenac, 100 mg rectal	Abdominal hysterectomy	NS	NS	NS	Morphine demand significantly larger in pre compared with post group

$P < 0.05$ = significant difference between treatment groups in favor of the preemptive treatment; — = not evaluated; NS = no significant difference between treatment groups or no significant difference in favor of the preemptive treatment; VAS = visual analog scale; PCA = patient-controlled analgesia.

Table 5. Presurgical *versus* Postsurgical Continuous Epidural Analgesic Regimens

Reference	Quality Score	N Pre/Post	Epidural Drug and Bolus Dose	Continuous Epidural Regimen	Procedure	Pain Scores	Time to First Analgesic Request	Supplemental Analgesic Demand	Comments
Wong *et al.*[72] (1997)	2	15/15	Morphine, 1.5 mg + ketamine, 20 mg	Morphine, 1 mg + ketamine, 10 mg + 0.32% lidocaine, 10 ml every 12 h	Total knee replacement	$P < 0.05$	$P < 0.05$	$P < 0.05$	VAS reduced by 15–20 mm at 6 and 12 h Time to first request prolonged 4.5 h Morphine reduced 3 mg/24 h
Obata *et al.*[77] (1999)	4	28/30	1.5% Mepivacaine, 4 ml	Mepivacaine, 4 ml/h	Thoracic	$P < 0.05$	—	NS	VAS reduced by 17 mm at operation day and days 2 and 3
Nakamura *et al.*[79] (1994)	2	30/30	2% Mepivacaine, 15 ml	Bupivacaine, 5 mg/h + fentanyl, 10 μg/h	Abdominal hysterectomy	$P < 0.05$	—	NS	VAS reduced by 17 and 8 mm at 4 and 24 h
Dahl *et al.*[74] (1992)	4	16/16	0.75% Bupivacaine, 9 ml + morphine, 2 mg	Bupivacaine, 10 mg/h + morphine, 0.2 mg/h for 72 h	Colonic surgery	NS	—	NS	Evaluated at 8, 10, 24, 30, 48, 54, and 72 h
Dahl *et al.*[75] (1994)	4	16/16	0.75% Bupivacaine, 18 ml + morphine, 2 mg	Bupivacaine, 5 mg/h until 24 h followed by 2.5 mg/h until 48 h + morphine, 0.2 mg/h	Total knee replacement	NS	—	NS	Evaluated 0.3, 1, 1.3, 2, 2.3, 3, and up to 7 days after operation
Aguilar *et al.*[73] (1996)	4	15/15	0.5% Bupivacaine, 8 ml	Bupivacaine, 0.125% + fentanyl, 6 μg/ml, 2 ml/h + PCEA	Thoracic	NS	—	NS	Low internal sensitivity due to no difference compared with a placebo control group Evaluated at 5, 10, 15, 20, 25, 30, 35, 40, and 45 h
Nonaka and Kashimoto[76] (1995)	2	20/20	1.5% Mepivacaine, 5 ml + buprenorphine, 0.1 mg	Mepivacaine, 17 mg/h + buprenorphine	Upper abdominal	NS	—	NS	Evaluated at 2, 24, 48, and 72 h
Flisberg *et al.*[78] (2000)	3	12/14	Pre group: 2% mepivacaine, 7–13 ml + morphine, 4 mg Post group: 0.25% bupivacaine, 6–12 ml + morphine, 4 mg	Bupivacaine, 10 mg/h + morphine, 0.5 mg/h for 3 days	Upper abdominal (Nissen antireflux repair)	NS	—	NS	Evaluated every morning and afternoon for 3 days

$P < 0.05$ = significant difference between treatment groups in favor of the preemptive treatment; — = not evaluated; NS = no significant difference between treatment groups or no significant difference in favor of the preemptive treatment; VAS = visual analog scale; PCEA = patient-controlled epidural analgesia.

gical procedures (table 3). Ketamine was administered in doses of 0.15–1 mg/kg and in two trials continued with intraoperative infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the preemptive group, of which one was negative and one positive.[54,56] Dextromethorphan was given in doses of 40 mg to 5 mg/kg (mean, 275 mg). Coadministered analgesic drugs included intraoperative fentanyl, alfentanil, or sufentanil in seven trials[55–61] and nitrous oxide in five trials.[54–58]

The worst pain score was significantly reduced by 20 mm VAS in one trial of dextromethorphan.[61] In the seven other trials, no effect on pain scores was observed (fig. 1C). The WMD calculated by use of a random-effect model ($P < 0.05$ in test for heterogeneity) was not significant (WMD, −2 mm; 95% CI, −8 to 4 mm; fig. 2C).

Supplementary analgesic consumption was significantly reduced by preemptive analgesia in three trials (one ketamine study[54] and the two dextromethorphan trials[60,61]) by 40–70%, corresponding to 15–25 mg morphine[54,60] and 57 mg pethidine[61] over a 24–48-h observation period. In the five other trials (of ketamine), no effect[56–59] or increased analgesic consumption[55] was

Table 6. Presurgical *versus* Postsurgical Caudal Analgesia in Children and Presurgical *versus* Postsurgical Intrathecal Anesthesia and Analgesia

Reference	Quality Score	N Pre/Post	Caudal Drug and Dose	Procedure	Pain Scores	Time to First Analgesic Request	Supplemental Analgesic Demand	Comments
Kundra *et al.*[83] (1998)	2	30/30	0.25% Caudal bupivacaine, 0.66 ml/kg + morphine, 0.02 mg/kg	Hernia repair	$P < 0.05$	—	$P < 0.05$	Total morphine consumption reduced by 1 mg over 24 h
Rice *et al.*[80] (1990)	3	20/20	0.25% Caudal bupivacaine, 0.5 ml/kg	Hernia repair, orchidopexy, hydrocelectomy	NS	NS	NS	
Holthausen *et al.*[81] (1994)	3	14/11	1% Caudal lidocaine, 0.5 ml/kg	Circumcision	NS	NS	NS	Cumulative pain scores significantly higher in pre compared with post group
Goodarzi[84] (1996)	2	10 Crossover	0.25% Caudal bupivacaine, 0.8 ml/kg	Club foot operation	—	NS	NS	
Ho *et al.*[82] (1997)	3	28/23	0.25% Caudal bupivacaine, 0.6 ml/kg	Hernia repair, orchidopexy circumcision	NS	—	NS	Evaluated 0.5, 1, and 3 h after operation and 4, 6, and 24 h after discharge
Dakin *et al.*[85] (1996)	3	19/19	0.5% Intrathecal bupivacaine, 3 ml hyperbaric	Abdominal hysterectomy	NS	NS	NS	Morphine consumption significantly higher in pre compared with post group from 0–12 h but not 0–24 h

$P < 0.05$ = significant difference between treatment groups in favor of the preemptive treatment; — = not evaluated; NS = no significant difference between treatment groups or no significant difference in favor of the preemptive treatment.

observed compared with the postincisional groups. Time to first analgesic request was evaluated in only one trial and was prolonged by 11 h by preemptive treatment.[61]

Power analysis was performed in three trials[55,57,60] and showed an 80% power to detect a difference of 30% or 5 mg/24 h of morphine at the 5% significance level. Intensity of pain scores were greater than 30 mm VAS in all except for one trial.[59]

In conclusion, no improvement in postoperative pain control was observed from preemptive systemic ketamine. Both studies on dextromethorphan were positive, but the data are too sparse to reach a definitive conclusion.

Epidural, Caudal or Spinal Regimens. Eighteen trials of presurgically *versus* postsurgically initiated epidural analgesic regimens were identified. These could be divided into trials of single-dose analgesic regimens[62–71] and trials of continuous analgesic regimens extending 24–72 h into the postoperative period.[72–79] Furthermore, five trials of caudal analgesia in children[80–84] and one trial of intrathecal anesthesia–analgesia[85] were found eligible for analysis.

Single-dose Epidural Analgesia. Ten trials with 11 treatment arms were identified comparing different preemptive *versus* postincisional single-dose epidural analgesic regimens. In four trials, epidural fentanyl (4 μg/kg)[63] and morphine (2–4 mg or 0.05 mg/kg)[65,68,71] were evaluated. In three trials,[64,66–67] epidural bupivacaine (0.5%, 15–20 ml) was studied, in three trials, combined epidural opioid (fentanyl or morphine) and local anesthetic (bupivacaine or mepivacaine),[62,69,71] and in one trial, epidural morphine (2 mg) plus ketamine (60 mg).[70] As a part of a balanced analgesic regimen, systemic NSAID was administered in two studies.[62,67] Coadministered analgesics included intraoperative alfentanil, fentanyl, or morphine in four trials[62,65,58,71] and nitrous oxide in eight trials.[62–66,69–71] Surgical procedures were major thoracic and abdominal (table 4).

Epidural Opioid Regimens. Pain scores were significantly reduced over 24 h by preemptive analgesia in one trial,[65] but only at six[63] and 18 h,[68] respectively, and not at 2, 4, 8, 10, 24, or 48 h postoperatively in two[63,68] of a total of four trials–treatment arms.[63,65,68,71] Analgesic demand was significantly reduced between 12 and 50%[65,68] and by 14 mg of patient-controlled analgesia–morphine from 12–24 h[63] in the preemptive groups in three trials.

Epidural Local Anesthetic Regimens. Visual analog scale pain scores were not different between study groups in any of three trials.[64,66–67] Patient-controlled analgesia–morphine consumption in the preemptive group was significantly reduced by 16 mg over 24 h in one trial[64] but significantly higher in another trial.[67]

Combined Epidural Regimens. Pain scores were not different between study groups in any of four trials–treatment arms.[62,69–71] Analgesic demand or number of patients requesting analgesics was significantly reduced between 33 and 48% in the preemptive groups in two trials[70,71] but only by 16 mg over 96 h in another trial.[62]

Table 7. Presurgical *versus* Postsurgical Wound Infiltration, Peripheral Nerve Block, and Intraperitoneal Instillation with Local Anesthetics

Reference	Quality Score	N Pre/Post	Drug and Dose	Procedure	Pain Scores	Time to First Analgesic Request	Supplemental Analgesic Demand	Comments
Ke *et al.*[101] (1998)	5	20/29	0.5% Bupivacaine, 10 ml above and below fascia	Gynecologic laparoscopy	$P < 0.05$	$P < 0.05$	NS	McGill score (0–5) significantly reduced by 1.1 at 24 but not 2 or 4 h after surgery Time to first request prolonged 4 h
Ejlersen *et al.*[86] (1992)	5	19/18	1% Lidocaine, 40 ml incisional	Hernia repair	NS	$P < 0.05$	$P < 0.05$	Evaluated hourly until 6 h after surgery Time to first request prolonged 1 h 58 *versus* 98% received supplemental analgesics in pre *versus* post group
Dierking *et al.*[87] (1992)	3	16/16	1% Lidocaine, 5 ml + 0.5% 40 ml	Hernia repair	NS	NS	NS	Inguinal field block Evaluated at 1, 2, 4, 6, 8, and 24 h, and on the seventh day
Dahl *et al.*[91] (1996)	4	28/22	0.25% Bupivacaine, 1 mg/kg	Hernia repair	NS	NS	NS	Intensity of pain scores low until 2 h after surgery Pain scores significantly reduced at 0.5 h, not at 1 or 2 h or at discharge
Turner and Chalkiadis[88] (1994)	4	29/32	1.5% Lidocaine, 15 ml in subcutis and muscle	Appendectomy	NS	—	NS	Low internal sensitivity as pre and post group not significantly different from placebo Evaluated at days 1 and 2
O'Hanlon *et al.*[96] (2000)	4	36/38	0.5% Bupivacaine, 10 ml	Breast biopsy	NS	NS	NS	Evaluated at 0.5, 1, 2, and 4 h
Campbell *et al.*[95] (1997)	4	40/40	0.5% Bupivacaine, 4 + 1 ml	Third molar surgery	NS	—	Fixed	Intensity of pain scores low Evaluated at 6 h and days 1, 3, and 6
Campbell and Kendrick[94] (1997)	4	40 Crossover	0.5% Bupivacaine, 4 ml	Third molar surgery	NS	—	Fixed	Intensity of pain scores low
Bourget *et al.*[93] (1997)	4	52/60	0.25% Bupivacaine, 40 ml	Various laparotomies	NS	—	NS	Significantly higher pain scores at day 1 in pre compared with post group
Victory *et al.*[90] (1995)	3	18/19	0.5% Bupivacaine, 40 ml	Abdominal hysterectomy	NS	—	NS	Low internal sensitivity as pre and post group not significantly different from placebo Evaluated at 4, 8, 24, 48, and 96 h
Badner *et al.*[92] (1996)	4	28/27	0.5% Bupivacaine, 30 ml intraarticular	Total knee replacement	NS	—	NS	
Ørntoft *et al.*[89] (1994)	5	12/12	0.25% Bupivacaine, 8 ml	Tonsillectomy	NS	—	NS	Low internal sensitivity as pre and post group not significantly different from placebo Evaluated at 4 h, days 1, 2, 3, and 8
Molliex *et al.*[97] (1996)	4	23/22	0.25% Bupivacaine, 9 ml	Tonsillectomy	NS	—	NS	Evaluated at 1, 5, 9, 13, 17, and 21 h after surgery
Likar *et al.*[98] (1999)	5	20/19	0.75% Ropivacaine, 6 ml	Tonsillectomy	NS	NS	NS	At certain time point, significantly higher pain scores in pre compared with post group
Elhakim and Abdel Hay[99] (1995)	3	25/25	10% Lidocaine spray, 4 mg/kg	Tonsillectomy	NS	—	—	Intensity of pain scores low
Podder *et al.*[100] (2000)	3	10/10	0.25% Bupivacaine, 4 ml	Tonsillectomy	NS	—		
Huffnagle *et al.*[102] (1996)	4	11/12	0.5% Bupivacaine, 10 + 10 ml ilioinguinal and iliohypogastric block	Cesarean delivery	(NS)	—	NS	Evaluated at 6, 12, 24, 48, and 96 h after surgery Pain scores at 24 h significantly reduced by 6 mm VAS in pre compared with post group
Altintas *et al.*[103] (2000)	3	25/24	0.25% Bupivacaine, 2 ml/kg in axillary block	Hand and forearm surgery	NS	—	NS	Pain scores significantly higher in pre compared with post group at 10 h only Analgesic demand significantly higher in pre compared with post group
Doyle and Bowler[104] (1998)	4	15/15	0.5% Bupivacaine, 40 ml intercostal nerve blocks in spaces 2–11 + morphine, 10 mg intravenous and diclofenac, 75 mg intramuscular	Thoracotomy	$P < 0.05$	—	NS	Pain scores significantly decreased during vital capacity breath test only, not at rest
Pasqualucci *et al.*[105] (1996)	4	26/28	0.5% Bupivacaine, 20 ml intraperitoneal at upper surface liver and gallbladder bed	Laparoscopic cholecystectomy	$P < 0.05$	—	$P < 0.05$	VAS reduced by 10 mm Demand of ketorolac reduced by 32 mg over 24 h

$P < 0.05$ = significant difference between treatment groups in favor of the preemptive treatment; NS = no significant difference between treatment groups or no significant difference in favor of the preemptive treatment; — = not evaluated; VAS = visual analog scale.

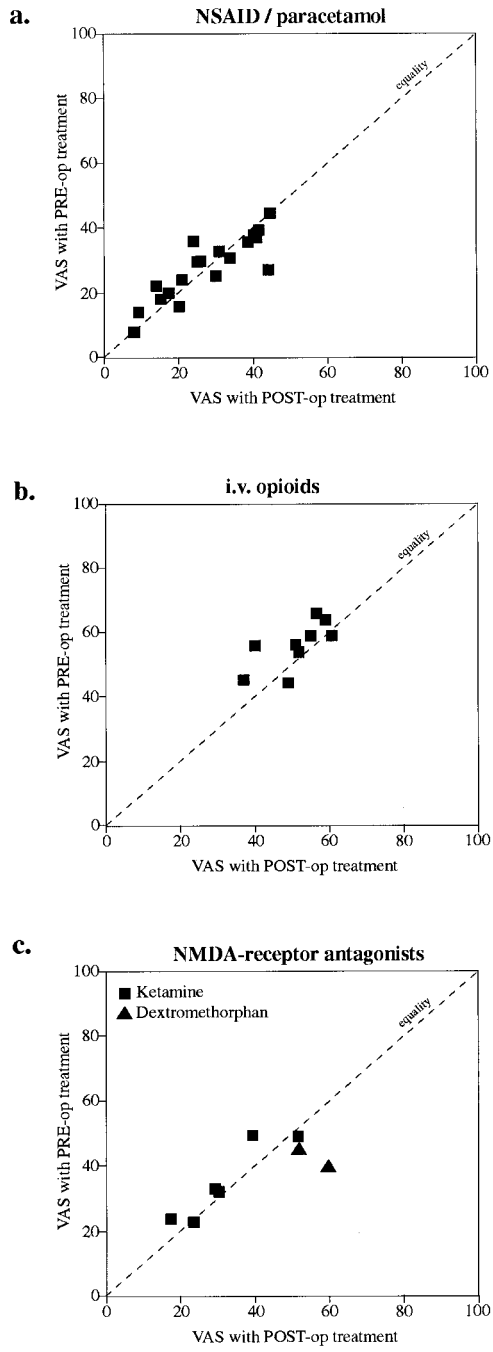

Fig. 1. Mean visual analog scale (VAS) pain scores over 24 h for preemptive *versus* postincisional treatment. Each point represents an individual trial.[9] (*A*) Nonsteroidal antiinflammatory drugs (NSAIDs)–paracetamol. Results from the 19 trials where pain scores were available (all except reference 37). (*B*) Intravenous opioids. Results from the nine treatment arms. (*C*) *N*-methyl-D-aspartate (NMDA) receptor antagonists. Each square represents an individual study of ketamine, and each triangle represents an individual study of dextromethorphan.

Quantitative analysis, which was only possible with seven trials (eight treatment arms) because of lack of dispersion measures, revealed a nonsignificant WMD of mean VAS pain scores recorded over 24 h of −4 mm (95% CI, −9 to 2 mm; random effect mode; $P = 0.04$ in test for heterogeneity; figs. 3A and 4A). In two of the three trials not included in the WMD calculation,[67–68,70] no significant difference in VAS was observed at any time during the postoperative course supporting the quantitative estimate.

Power analysis of the statistical tests revealing a 90% power was available in two trials,[63,67] although without

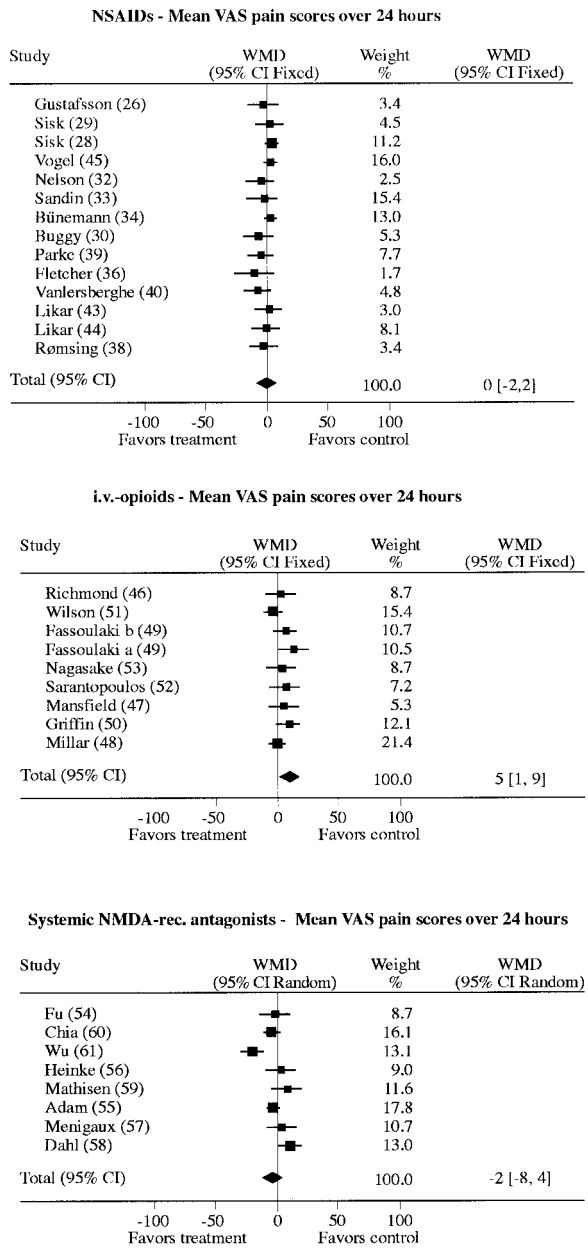

Fig. 2. Weighted mean difference (WMD) with 95% confidence intervals (CIs, horizontal lines) of visual analog scale (VAS) pain scores recorded within 24 h after surgery between the preemptive and postincisional groups in the different regimens (*A–C*). "Fassoulaki a" and "Fassoulaki b" indicate the two treatment arms in this study. "Total" at the bottom of each regimen indicates the results from pooling all the trials. The different sizes of squares in the figure and the numbers under the subheading "Weight" at the right of the figure indicate the weight the individual trials had in the analysis within each regimen, taking into account study size and SDs of VAS scores.

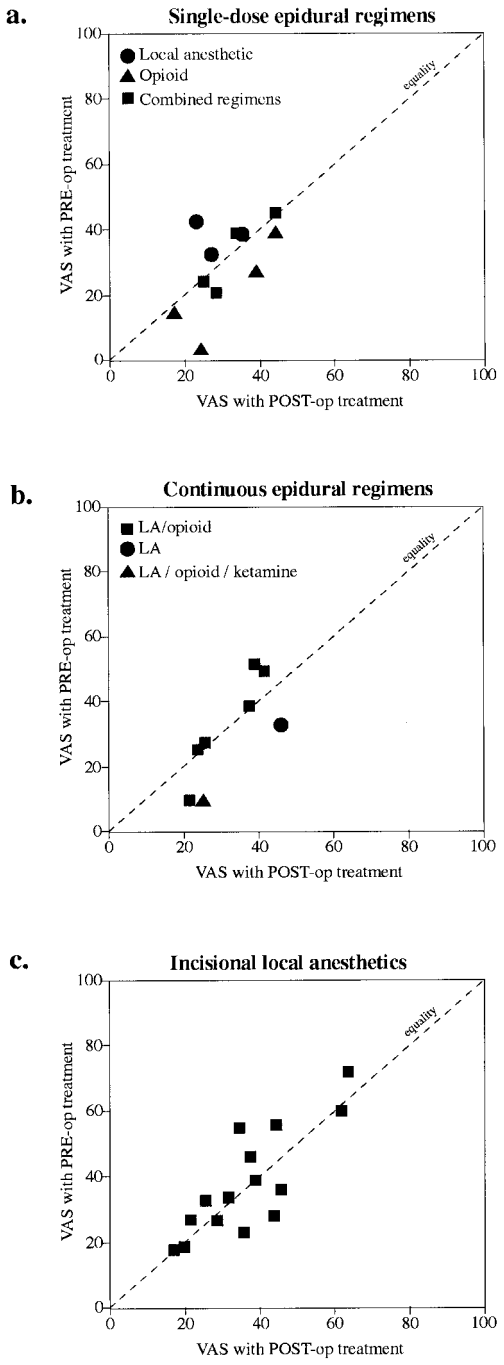

Fig. 3. Mean visual analog scale (VAS) pain scores over 24 h for preemptive *versus* postincisional treatment. Each point represents an individual trial.[9] (*A*) Single-dose epidural regimens. Results from the 11 treatment arms. (*B*) Continuous epidural regimens extending into the postoperative period. Results from the eight studies. LA = local anesthetic. (*C*) Local anesthetic wound infiltration. Results from the 15 trials where pain scores were available.

information of the minimal relevant difference (*e.g.*, number of millimeters VAS), not to be overlooked. Furthermore, in one negative[62] and one positive[68] trial, low pain scores may have impaired internal sensitivity.

In conclusion, the quantitative analysis of mean VAS pain scores showed no significant reduction by preemptive single-dose epidural analgesia with opioid, local anesthetic, or a mixture. However, significant reductions in analgesic demand were demonstrated in 7 of 11 treatment arms.

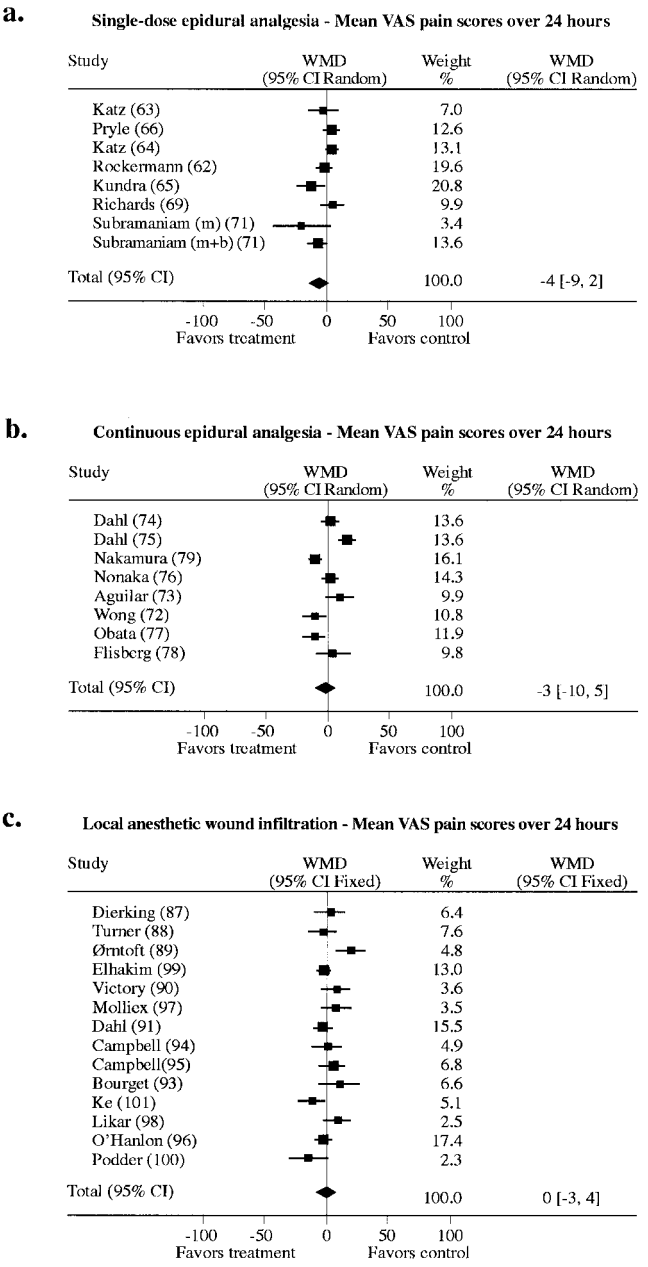

Fig. 4. Weighted mean difference (WMD) with 95% confidence intervals (CIs, horizontal lines) of visual analog scale (VAS) pain scores recorded within 24 h after surgery between the preemptive and postincisional groups in the different regimens (*A–C*). "Subramaniam m" and "Subramaniam m+b" indicate the two treatment arms in this study[71] with epidural morphine and morphine plus bupivacaine, respectively. "Total" at the bottom of each regimen indicates the results from pooling all the trials. The different sizes of squares in the figure and the numbers under the subheading "Weight" at the right of the figure indicate the weight the individual trials had in the analysis within each regimen, taking into account study size and SDs of VAS scores.

Continuous Epidural Analgesia. Eight trials were identified[72–79] comparing different preemptive *versus* postincisional initiated continuous epidural regimens that extended 24–72 h into the postoperative period.

The regimens investigated included bolus epidural bupivacaine (0.5–0.75%, 8–18 ml)[73–75] plus morphine (2 mg),[74,75] epidural mepivacaine (1.5–2%, 4–15 ml)[76–79] plus morphine (4 mg)[78] or buprenorphine (0.1 mg),[76] and bolus epidural morphine (1.5 mg) plus ketamine (20 mg).[72] These were in the postoperative course followed by continuous epidural bupivacaine (5–10 mg/h) plus morphine (0.2–0.5 mg/h) or fentanyl (10–12 μg/h),[73–75,78,79] epidural mepivacaine (17–60 mg/h)[76,77] plus buprenorphine, and by combined epidural morphine (1 mg), ketamine (10 mg), and lidocaine (32 mg) every 12 h.[72] Coadministered analgesics consisted of fentanyl or alfentanil[73–75,78] and nitrous oxide[72,74–79] in four and seven trials, respectively. The surgical procedures were thoracotomy, major abdominal, and total knee replacement. For details, see table 5.

Visual analog scale pain scores were significantly reduced at certain time points in three trials within the first 72 h,[72,77,79] ranging between 8 and 17 mm on a VAS scale. No differences between groups were observed in the other trials (fig. 3B). Quantitative analysis of WMD of mean VAS scores recorded within 24 h was not significant (WMD, −3 mm; 95% CI, −10 to 5 mm; calculated using a random-effect model as $P = 0.0002$; fig. 4B). Supplemental patient-controlled analgesia–morphine consumption was significantly reduced by 3 mg over 24 h in only one trial.[72]

Intensity of pain scores was considered adequate (> 30 mm VAS) in negative trials[73–76,78] and not a cause of possible insensitivity (although low [< 30 mm VAS] in two of the positive trials).[72,79] Power analysis was performed in only four trials,[73,75,77–78] revealing an 80% power to detect a 12–23-mm difference in VAS at the 5% significance level.

In conclusion, the results showed no overall improvement in postoperative pain relief with preemptive *versus* postincisional continuous epidural analgesia.

Caudal and Intratheal Analgesia. Five trials comparing preemptive with postincisional caudal block were identified.[80–84] The analgesics–anesthetics investigated were bupivacaine (0.25%, 0.5–0.8 ml/kg)[80,82–84] plus morphine (0.02 mg/kg),[83] and lidocaine (1%, 0.5 ml/kg).[81] In none of the trials was other intraoperative analgesics administered except for nitrous oxide in all studies. The surgical procedures consisted of hernia repair, orhidopexy, circumcision, and operation for club foot deformities (table 6).

Only in the trial of combined caudal bupivacaine and morphine[83] pain scores and analgesic demand were significantly reduced by the preemptive treatment, ranging 50% and 1 mg of morphine over a 24-h observation period. In no other trials were differences between treatment groups observed.[80–82,84]

In one trial, preoperative spinal bupivacaine (15 mg) was compared with an identical postsurgical treatment in patients undergoing abdominal hysterectomy with general anesthesia.[85] No difference in pain scores were observed between treatment groups, but morphine consumption was significantly greater from 0 to 12 h after surgery in the preemptive compared with the postincisional group.

In conclusion, preemptive treatment was ineffective in four of five studies of caudal block and in the one study of intrathecal block.

Peripheral Local Anesthetics. Twenty trials comparing preemptive with postincisional application of peripheral local anesthetics were found eligible for analysis. These could be divided into trials of wound infiltration, peripheral nerve block, and intraperitoneal infiltration.

Wound Infiltration. Sixteen trials compared preoperative incisional local anesthetics with similar postincisional administration.[86–101] Bupivacaine (0.25–0.5%), ropivacaine (0.75%), and lidocaine (1–1.5%) were administered in volumes between 4 and 45 ml depending on the extent of the surgical incision and type of procedure. Intraoperative fentanyl or alfentanil and nitrous oxide were coadministered in 10[87–90,92,93,96–98,101] and 13 studies,[86–91,94,95,97–101] respectively. Evaluated surgical procedures were hernia repair, appendectomy, hysterectomy, tonsillectomy, total knee replacement, laparoscopy, breast biopsy, and odontologic surgery (table 7).

Pain scores were significantly reduced 24 h after surgery in the preemptive group in one trial[101] and at certain time points in the postincisional group in two other trials.[93,98] In the other trials, no differences in pain scores between groups were observed (fig. 3C).

Quantitative analysis was only performed with 14 trials because of lack of dispersion measures in the last two trials.[86,92] Using a fixed-effect model ($P = 0.29$), the WMD of VAS pain scores between treatment groups was nonsignificant (WMD, 0 mm; 95% CI, −3 to 4; fig. 4C).

Analgesic demand was significantly reduced by 50% over a 6-h observation period in one trial,[86] and time to first analgesic request was prolonged by 4 h in another trial[101] in the preemptive compared with the postsurgical treatment groups. In none of the other trials were significant differences observed between study groups.

A number of studies suffered from low internal sensitivity because of low pain scores in either group.[94,95,99] Furthermore, statistical power analysis was only performed in seven of the trials,[86,90,93–97] revealing an 80–90% power of detecting a difference of 10–15 mm VAS. In summary, there is no evidence for improved pain relief with preemptive local anesthetic wound infiltration compared with a similar postincisional administration.

Peripheral Nerve Blocks and Intraperitoneal Local Anesthetic. Three trials investigated an ilioinguinal iliohypogastric nerve block in patients undergoing cesarean delivery,[102] axillary block in hand or forearm surgery,[103] and intercostal nerve block in patients undergoing thoracotomy.[104] In the latter study, preincisional *versus* postincisional intravenous morphine and intramuscular diclofenac was coadministered using a multimodal approach[104] (table 7).

No significant difference in pain relief was observed after cesarean section, but results were difficult to interpret because of technical difficulties in obtaining a sufficient block in the preemptive group and because of low pain scores in either group.[102] In the trial of axillary block, postoperative pain and analgesic demand were improved in the postincisional compared with the preemptive group.[103] In contrast, pain scores were reduced during a vital capacity breath test but not at rest, and analgesic demands were not improved by preemptive *versus* postincisional treatment in the trial of thoracotomy.[104]

Finally, pain scores and demand for supplementary ketorolac were reduced by 10 mm VAS and 13 mg, respectively, in the preemptive treatment group from 8 to 24 h after surgery in one trial of topical intraperitoneal 0.5% bupivacaine.[105] In conclusion, the limited data available do not allow conclusions as to a positive effect of preemptive analgesia with peripheral nerve blocks or intraperitoneal local anesthetic.

Chronic Postoperative Pain

Only one study was available comparing preemptive *versus* postincisional continuous epidural mepivacaine in patients undergoing thoracotomy.[77] Pain scores and the percentages of pain-free patients were improved in the preemptive group at 3 and 6 months after surgery in a fashion parallel to findings on acute pain scores.

Overall Conclusion

Statistical improvements in postoperative pain relief by the preemptive compared with the postincisional treatment were observed in some parameters or time points in 24 of 80 (82 treatment arms) trials. Quantitative analyses of WMD of average VAS pain scores recorded within 24 h after surgery were in no case significant in favor of the preemptive treatment.

The review revealed a lack of evidence for preemptive treatment with NSAIDs, intravenous opioids, intravenous ketamine, peripheral local anesthetics, and caudal analgesia to be of any benefit with respect to postoperative pain relief compared with a similar postincisional treatment. Results from trials of single-dose epidural treatment were inhomogeneous, with more than half of the trials showing statistically significant, but in most cases small, improvements with preemptive analgesia. Results from a third of the trials of continuous epidural analgesia demonstrated, at certain time points, statistically improved pain relief or analgesic demand by preemptive treatment, but overall interpretation of all continuous epidural regimens did not support the hypothesis that preemptive analgesia is of greater benefit than analgesia administered after the onset of the surgical procedure.

Discussion

We tested the clinical evidence for timing of analgesia to improve postoperative pain control in the early and long-term postoperative period in this systematic review. Only trials designed to compare similar preincisional and postincisional treatment were included, excluding a number of studies from the analysis.[19,20] We chose to include a statistical combination of data from the independent trials in a quantitative analysis in addition to the qualitative systematic review. This was done to produce a single estimate of the effect of the intervention and to help resolve disparities between conflicting studies.[106] However, only data on pain scores could be quantitatively analyzed. For the quantitative analysis, we chose to use recordings of average pain scores within the first 24 h postoperatively as we considered this to be a clinically relevant measure and a way to overcome difficulties if only one of several recordings were found significant in an individual study. This analysis may therefore have overlooked potential positive findings within the immediate postoperative period or during the next few postoperative days. With these assumptions, our qualitative and quantitative analysis should be viewed together to achieve an overall synthesis of the results.

A concern was the lack of internal sensitivity and power in some of the negative studies. Validity criteria for the included studies was a number of 10 or more patients per treatment group.[9] Internal sensitivity was evaluated with respect to pain intensity, since it has been recognized that it is difficult to detect an improvement with low or no pain.[8] Furthermore, similar pain scores in study groups receiving active treatment may reflect similar analgesic effects or no effects at all. Inclusion of a placebo group in the comparison would solve the problem with similar or low pain scores.[107] Although pain intensity was low in some trials, and because only rather few trials on preemptive analgesia did include a placebo group, we did not exclude such trials from the analysis, but instead documented studies with low pain scores in the Results and in the tables.

Criticism has previously been raised against a number of negative studies in which both study groups received intraoperative opioid.[108] Such treatment may have caused a similar preemptive effect in both the preoperative and postoperative treatment groups and thereby contributed to the lack of difference in postoperative pain control between groups. Furthermore, various anesthetics have been demonstrated to suppress spinal

sensitization in experimental studies.[109] However, such studies have not been excluded from our analysis, since the objective was to investigate if preemptive techniques combined with conventional intraoperative management, which often includes intraoperative opioids or nitrous oxide, can improve postoperative pain control. Although trials were quality assessed, potential pitfalls in individual trials, such as inadequacy of used statistics, may have remained unidentified. Finally, pooling of data from a class of analgesics (*e.g.*, NSAIDs) may blur a possible effect of one specific agent (*e.g.*, ketorolac). However, no such pattern was observed.

A total of 80 trials meeting the strict inclusion and exclusion criteria were identified. The trials were divided into those of NSAIDs, intravenous opioids, parenteral NMDA receptor antagonists, epidural analgesia (single dose or continuous), caudal analgesia, and peripheral local anesthetics. A common feature of the analysis was that timing of analgesia did not influence the quality of postoperative pain control, whatever the type of preemptive analgesia. This conclusion may have clinical relevance. It implies that NSAIDs should not routinely be given preemptively because of the lack of enhanced analgesic effects and because of potential adverse effects such as increased intraoperative bleeding with the preoperative treatment compared with postoperative treatment.

With regard to NMDA receptor antagonists, trials of ketamine were uniformly negative, while the only two existing studies of dextromethorphan were positive of a preemptive effect. Further data are obviously needed to allow a final conclusion as to the clinical recommendation of preemptive treatment with dextromethorphan.

Pain control was, at certain time points, improved by preemptive analgesia in 7 of 11 treatment arms of trials of single-dose epidural analgesia. However, validity and clinical relevance was questionable in several cases and difficult to interpret. Results were therefore considered to reveal a lack of evidence for any important effect (rather than evidence for lack of effect) with preemptive analgesia. Preemptive continuous epidural treatment extending into the postoperative period might theoretically have an improved capacity to reduce nociceptive input and thereby central neuroplasticity caused not only by incision and on-going surgery but also by postsurgical inflammation. However, the results were uniformly negative. In the few studies with improved analgesia, this was only observed at certain time points and not in the overall quantitative analysis. An explanation for the negative findings of continuous epidural regimens may be that, despite continuous treatment, it was insufficient to prevent the development and maintenance of injury-induced central sensitization.

It is widely assumed that preemptive analgesia may reduce the risk of developing chronic postoperative pain. This assumption may be supported by data suggesting that patients with high intensity of acute postoperative pain scores also have a higher risk of developing a chronic pain state.[110] In the only trial to compare the effect of identical preincisional *versus* postincisional treatment[77] on long-term pain, the percentage of patients with pain at 6 months postoperatively was significantly reduced. Obviously, more data are needed, and in other trials of preemptive treatment *versus* no treatment in prostatectomy,[20] thoracotomy,[111] or amputation,[112] only one demonstrated an effect on chronic postoperative pain.[20] However, in this study,[20] the follow-up rate was low (65%) and with a diversity between pain and activity scores at the different follow up intervals, making interpretation difficult.

It may be considered surprising and disappointing that the overall conclusion of this systematic review has been negative as to a potential beneficial effect of preemptive analgesia on postoperative pain. The issue of preemptive analgesia for postoperative pain relief has been a topic of several articles and editorials, in which terminology and definition has varied, thereby creating much of the controversy about this concept.[6,108,113] The concept has been further complicated by mixing results from trials of preincisional *versus* postincisional treatment and trials of pretreatment *versus* no treatment.[6] A number of suggestions have been offered to explain negative results: outcome measurement problems, too low or too high noxious stimulation induced by the surgical procedure, insufficient afferent blockade–analgesia, insufficient central inhibition, and insufficient duration of the treatment.[6,108,113,114] The current analysis of clinical trials has only focused on one aspect of this discussion, namely, whether timing of conventional analgesic therapy, *i.e.*, preinjury *versus* postinjury initiation of analgesia, has a clinically significant impact on postoperative pain relief. One conservative conclusion that may be drawn from this review is that there is no need for further trials to investigate the role of timing of preemptive single-dose (short-lasting) analgesic treatment on the postoperative pain pattern. Furthermore, only three of eight trials investigating preemptive continuous epidural treatment extending into the postoperative period demonstrated improved pain relief at certain time points. Thus, overall results are also negative when timing is considered as the variable in prolonged analgesic treatment. It is important to realize, however, that these conclusions do not preclude a possible beneficial effect of an aggressive, perioperative, analgesic intervention on short- and long-term pain after surgery. We suggest that future studies redirect their focus from timing of perioperative analgesia (preemptive analgesia) to protective analgesia, aimed at the prevention of pain hypersensitivity (pathologic pain). These studies should investigate the effects of intensive and prolonged, multimodal analgesic ("protective") interventions *versus* less aggressive, conventional perioperative analgesia on immediate and late postoperative pain.

Appendix: Excluded Trials

Reference	Intervention	Reason	Overall Result
Murphy and Medley[11] (1993)	NSAID	Not blinded	Negative
Colbert *et al.*[10] (1998)	NSAID	Blinding unclear	Positive
Romej *et al.*[19] (1996)	Paracetamol	Different pre (oral) and post (rectal) doses	Positive
Mansfield *et al.*[12] (1994)	Intravenous alfentanil	Single-blind	Negative
Kucuk *et al.*[15] (1998)	Epidural ketamine	Not blinded	Negative
Wu *et al.*[13] (2000)	Epidural bupivacaine–morphine–ketamine	Single-blind	Positive
Gottschalk *et al.*[20] (1998)	Epidural fentanyl and epidural bupivacaine	Postoperative treatment group received no preoperative and intraoperative epidural bolus dose	Positive
Sakaguchi *et al.*[18] (1998)	Continuous epidural bupivacaine–morphine	No information about blinding	Negative
Gunter *et al.*[14] (1990)	Caudal bupivacaine	Blinding unclear	Negative
Ringrose and Cross[16] (1984)	Femoral nerve block	Not randomized or blinded	Positive
Shah *et al.*[17] (1997)	Paravertebral block	Not randomized (historic control)	Negative
Uckunkaya *et al.*[22] (1995)	Epidural clonidine	Not available	Negative
Pjevic *et al.*[21] (1999)	Intravenous pethidine	Not available	Negative

NSAID = nonsteroidal antiinflammatory drug.

References

1. Woolf CJ: Evidence for a central component of postinjury pain hypersensitivity. Nature 1983; 308:386–8
2. Coderre TJ, Catz J, Vaccarino AL, Melzack R: Contribution of central neutoplasticity to pathological pain: Review of clinical and experimental evidence. Pain 1993; 52:259–85
3. Woolf CJ, Chong M-S: Preemptive analgesia: Treating postoperative pain by preventing the establishment of central sensitisation. Anesth Analg 1993; 77: 362–79
4. Dahl JB, Kehlet H: The value of pre-emptive analgesia in the treatment of postoperative pain. Br J Anaesth 1993; 70:434–9
5. McQuay HJ: Pre-emptive analgesia: A systematic review of clinical studies. Ann Med 1995; 27:249–56
6. Kissin I: Preemptive analgesia. ANESTHESIOLOGY 2000; 93:1138–43
7. Jadad AR, Moore A, Carrol D, Jenkinson C, Reynold DJ, Gavaghan DJ, McQuay HJ: Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996; 17:1–12
8. Collins SL, Moore RA, McQuay HJ: The visual analogue pain intensity scale: what is moderate pain in millimeters? Pain 1997; 72:95–7
9. L'Abbé K, Detsky AS, O'Rourke K: Meta-analysis in clinical research. Ann Intern Med 1987; 107:224–33
10. Colbert ST, O'Hanlon DM, McDonnel C, Given FH, Keane PW: Analgesia in day case breast biopsy: The value of pre-emptive tenoxicam. Can J Anaesth 1998; 45:217–22
11. Murphy DF, Medley C: Preoperative indomethacin for pain relief after thoracotomy: Comparison with postoperative indomethacin. Br J Anaesth 1993; 70:298–300
12. Mansfield M, Meikle R, Millar C: A trial of pre-emptive analgesia. Influence of timing of peroperative alfentanil on postoperative pain and analgesic requirements. Anaesthesia 1994; 49:1091–3
13. Wu CT, Yeh CC, Yu JC, Lee MMS, Tao PL, Ho ST, Wong CS: Pre-incisional epidural ketamine, morphine and bupivacaine combined with epidural and general anaesthesia provides pre-emptive analgesia for upper abdominal surgery. Acta Anaesthesiol Scand 2000; 44:63–8
14. Gunter JB, Forestner JE, Manley CB: Caudal epidural anesthesia reduces blood loss during hypospadias repair. J Urol 1990; 144:517–9
15. Kucuk N, Kizilkaya M, Tokdemir M: Preoperative epidural ketamine does not have a postoperative opioid sparing effect. Anesth Analg 1998; 87:103–6
16. Ringrose NH, Cross MJ: Femoral nerve block in knee joint surgery. Am J Sports Med 1984; 12:398–402
17. Shah R, Sabanathan S, Richardson J, Mearns A, Bembridge J: Continuous paravertebral block for post thoracotomy analgesia in children. J Cardiovasc Surg 1997; 38:543–6
18. Sakaguchi H, Tashiro T, Koga T, Naomi I, Matsumoto S, Kubota F, Ushijima K, Kano T: Effects of pre- vs postoperative commencement of epidural analgesia on postoperative pain relief and comfort: A study of preemptive analgesia. Kumamoto Med J 1998; 46:13–20
19. Romej M, Voepel-Lewis T, Merkel SI, Reynolds PI: Effect of preemptive acetaminophen on postoperative pain scores and oral fluid intake in pediatric tonsillectomy patients. AANAJ 1996; 64:535–40
20. Gottschalk A, Smith DS, Jobes DR, Kennedy SK, Lally SE, Noble VE, Grugan KF, Seifer HA, Cheung A, Malkowitcz B, Gutsche BB, Wein AJ: Preemptive epidural analgesia and recovery from radical prostatectomy: A randomised controlled trial. JAMA 1998; 279:1076–82
21. Pjevic M, Komarecvic M, Kovacevic S, Jovanovic L, Gajic S: Pre-emptive analgesia in cholecystectomy using pethidine. Med Pregl 1999; 52:485–8
22. Uckunkaya N, Haci I, Bilgin H, Sahin S: Does clonidine have pre-emptive effects. Agri Dergisi 1995; 7:17–21
23. Kalso E, Tramèr MR, Carroll D, McQuay HJ, Moore RA: Pain relief from intra-articular morphine after knee surgery: A qualitative systematic review. Pain 1997; 71:127–34
24. Tramèr MR, Williams JE, Carrol D, Wiffen PJ, Moore RA, McQuay HJ: Comparing analgesic efficacy of non-steroidal anti-inflammatory drugs given by different routes in acute and chronic pain: A qualitative systematic review. Acta Anaesthesiol Scand 1998; 42:71–9
25. Møiniche S, Mikkelsen S, Wetterslev J, Dahl JB: A qualitative systematic review of incisional local anesthesia for postoperative pain relief after abdominal operations. Br J Anaesth 1998; 81:377–83
26. Gustafsson I, Nyström E, Quiding H: Effect of preoperative paracetamol on pain after oral surgery. Eur J Clin Pharmacol 1983; 24:63–5
27. Bridgman JB, Gillgrass TG, Zacharias M: The absence of any pre-emptive analgesic effect for non-steroidal anti-inflammatory drugs. Br J Oral Maxillofac Surg 1996; 34:428–31
28. Sisk AL, Grover BJ: A comparison of preoperative and postoperative naproxen sodium for suppression of postoperative pain. J Oral Maxillofac Surg 1990; 48:674–8
29. Sisk AL, Mosley RO, Martin RP: Comparison of preoperative and postoperative diflunisal for suppression of postoperative pain. J Oral Maxillofac Surg 1989; 47:464–8
30. Buggy DJ, Wall C, Carton EG: Preoperative or postoperative diclofenac for laparoscopic tubal ligation. Br J Anaesth 1994; 73:767–70
31. Nordbladh I, Ohlander B, Björkman R: Analgesia in tonsillectomy: A double-blind study on pre and post-operative treatment with diclofenac. Clin Otolaryngol 1991; 16:554–8
32. Nelson WE, Henderson RC, Almekinders LC, DeMasi RA, Taft TN: An evaluation of pre-and postoperative nonsteroidal antiinflammatory drugs in patients undergoing knee arthroscopy: A prospective, randomized, double-blind study. Am J Sport Med 1993; 21:510–6
33. Sandin R, Sternlo JE, Stam H, Brodd B, Björkman R: Diclofenac for pain relief after arthroscopy: A comparison of early and delayed treatment. Acta Anaesthesiol Scand 1993; 37:747–50
34. Bünemann L, Thorshauge H, Herlevsen P, Iversen AD, Nielsen FB: Analgesia for outpatient surgery: Placebo versus naproxen sodium (a non-steroidal anti-inflammatory drug) given before or after surgery. Eur J Anaesth 1994; 11:461–4
35. Flath RK, Hicks ML, Dionne RA, Pelleu GB: Pain suppression after pulpectomy with preoperative flurbiprofen. J Endodontics 1987; 13:339–47
36. Fletcher D, Zetlaoui P, Monin S, Bombart M, Samii K: Influence of timing on the analgesic effect of intravenous ketorolac after orthopedic surgery. Pain 1995; 61:291–7
37. Rogers JE, Fleming BG, Macintoch KC, Johnston B, Morgan-Hughes JO: Effect of timing of ketorolac administration on patient-controlled opioid use. Br J Anaesth 1995; 75:15–8
38. Rømsing J, Østergaard D, Walther-Larsen S, Valentin N: Analgesic efficacy

and safety of preoperative versus postoperative ketorolac in paediatric tonsillectomy. Acta Anaesthesiol Scand 1998; 42:770–5

39. Parke TJ, Lowson SM, Uncles DR, Daughtery MO, Sitzman BT: Pre-emptive versus post- surgical administration of ketorolac for hysterectomy. Eur J Anaesthesiol 1995; 12:549–53

40. Vanlersberghe C, Lauwers, Camu F: Preoperative ketorolac administration has no preemptive analgesic effect for minor orthopaedic surgery. Acta Anaesthesiol Scand 1996; 40:948–52

41. Peduto VA, Toscano A, D'Uva R, Piga M: Profilassi con ketorolac del dolore acuto postoperatorio. Minerva Anestesiol 1995; 61:367–72

42. Cabell CA: Does ketorolac produce preemptive analgesic effect in laparoscopic ambulatory surgery patients. AANA J 2000; 68:343–9

43. Likar R, Krumpholz R, Mathiaschitz K, Pipam W, Burtscher M, Ozegovic G, Breschan C, Bernatzky G, Sittl R: The preemptive action of ketoprofen: Randomized, double-blind study with gynecologic operation. Anaesthesist 1997; 46: 186–90

44. Likar R, Krumpholz, Pipam W, Sadjak A, Kapral S, Forsthuber E, Bernatzky G, List FW: Randomized, double-blind study with ketoprofen in gynecologic patients: Preemptive analgesia study following the Breivik-Stubhaug design. Anaesthesist 1998; 47:303–10

45. Vogel RI, Desjardins PJ, Major KV: Comparison of presurgical and immediate postsurgical ibuprofen on postoperative periodontal pain. J Periodontol 1992; 63:914–8

46. Richmond CE, Bromley LM, Woolf CJ: Preoperative morphine pre-empts postoperative pain. Lancet 1993; 342:73–5

47. Mansfield MD, James KS, Kinsella J: Influence of dose and timing of administration of morphine on postoperative pain and analgesic requirements. Br J Anaesth 1996; 76:358–61

48. Millar AY, Mansfield MD, Kinsella J: Influence of timing of morphine administration on postoperative pain and analgesic consumption. Br J Anaesth 1998; 81:373–6

49. Fassoulaki A, Sarantopoulos C, Zotou M, Papoulia D: Preemptive opioid analgesia does not influence pain after hysterectomy. Can J Anaesth 1995; 42:109–13

50. Griffin MJ, Hughes D, Knaggs A, Donnelly MB, Boylan JF: Late-onset preemptive analgesia associated with preincisional large-dose alfentanil. Anesth Analg 1999; 85:1317–21

51. Wilson RJ, Leith S, Jackson IJ, Hunter D: Pre-emptive analgesia from intravenous administration of opioids. Anaesthesia 1994; 49:591–3

52. Sarantopoulos C, Fassoulaki A: Sufentanil does not preempt pain after abdominal hysterectomy. Pain 1996; 65:273–6

53. Nagasaka H, Taguchi M, Mizumoto Y, Hori K, Hayashi K, Sugai M, Murakami Y, Oohara K, Matsumoto I, Hori T: Pre-emptive analgesia from intravenous administration of opioid: No effect with pentazocine. Masui 1996; 45:750–5

54. Fu ES, Miguel R, Scharf JE: Preemptive ketamine decreases postoperative narcotic requirements in patients undergoing abdominal surgery. Anesth Analg 1997; 84:1086–90

55. Adam F, Libier M, Oszustowicz T, Lefebvre D, Beal J, Meynadier J: Preoperative small-dose ketamine has no preemptive analgesic effect in patients undergoing total mastectomy. Anesth Analg 1999; 89:444–7

56. Heinke VW, Grimm D: Präemptive effekte durch ko-analgesie mit ketamin bei gynäkologischen laparotomien? Anesthesiol Reanim 1999; 24:60–4

57. Menigaux C, Fletcher D, Dupont X, Guinard B, Guirimand F, Chauvin M: The benefit of intraoperative small-dose ketamine on postoperative pain after anterior cruciate ligament repair. Anesth Analg 2000; 90:129–35

58. Dahl V, Ernoe PE, Steen T, Raeder JC, White PF: Does ketamine have preemptive effects in women undergoing abdominal hysterectomy procedures? Anesth Analg 2000; 90:1419–22

59. Mathisen LC, Aasbø, Ræder J: Lack of pre-emptive analgesic effect of (R)-ketamine in laparoscopic cholecystectomy. Acta Anaesthesiol Scand 1999; 43:220–4

60. Chia Y, Liu K, Chow L, Lee T: The preoperative administration of intravenous dextromethorphan reduces postoperative morphine consumption. Anesth Analg 1999; 89:748–52

61. Wu C-T, Yu J-C, Yeh C-C, Liu S-T, Li, C-Y, Ho S-T, Wong C-S: Preincisional dextromethorphan treatment decreases postoperative pain and opioid requirement after laparoscopic cholecystectomy. Anesth Analg 1999; 88:1331–4

62. Rockemann MG, Seeling W, Bischof C, Börshughaus D, Steffen P, Georgiff M: Prophylactic use of epidural mepivacaine/morphine, systemic diclofenac and metamizole reduces postoperative morphine consumption after major abdominal surgery. ANESTHESIOLOGY 1996; 84:1027–34

63. Katz J, Kavanagh BP, Sandler AN, Nierenberg H, Boylan JF, Friedlander M, Shaw BF: Preemptive analgesia: Clinical evidence of neuroplasticity contributing to postoperative pain. ANESTHESIOLOGY 1992; 77:439–46

64. Katz J, Clairoux M, Kavanagh BP, Roger S, Nierenberg H, Redahan C, Sandler AN: Pre-emptive lumbar epidural anaesthesia reduces postoperative pain and patient-controlled morphine consumption after lower abdominal surgery. Pain 1994; 59:395–403

65. Kundra P, Gurnani A, Bhattacharya A: Preemptive epidural morphine for postoperative pain relief after lumbar laminectomy. Anesth Analg 1997; 85: 135–8

66. Pryle BJ, Vanner RG, Enriquez N, Reynolds F: Can pre-emptive lumbar epidural blockade reduce postoperative pain following lower abdominal surgery. Anaesthesia 1993; 48:120–3

67. Espinet A, Henderson DJ, Faccenda KA, Morrison LMM: Does pre-incisional thoracic extradural block combined with diclofenac reduce postoperative pain after abdominal hysterectomy. Br J Anaesth 1996; 76:209–13

68. Gil GM, Aguado RG, Rosso MT, Alarcón L, Olba FA, Armengod AC, Sanfrancisco JMP, Real FG: Estudio comparativo entre morfina epidural lumbar preventiva o postincisional en cirugía resectiva pulmonar: Informe preliminar. Rev Esp Anesthesiol Reanim 1998; 45:384–8

69. Richards JT, Read JRM, Chambers WA: Epidural anaesthesia as a method of pre-emptive analgesia for abdominal hysterectomy. Anaesthesia 1998; 53:296–8

70. Choe H, Choi Y-S, Kim Y-H, Ko S-H, Choi H-G, Han Y-J, Song H-S: Epidural morphine plus ketamine for upper abdominal surgery: Improved analgesia from preincisional administration. Anesth Analg 1997; 84:560–3

71. Subramaniam B, Pawar DK, Kashyap L: Pre-emptive analgesia with epidural morphine or morphine and bupivacaine. Anaesth Intensive Care 2000; 28:392–8

72. Wong C-S, Lu C-C, Cherng C-H, Ho S-T: Pre-emptive analgesia with ketamine, morphine and epidural lidocaine prior to total knee replacement. Can J Anaesth 1997; 44:31–7

73. Aguilar JL, Rincón R, Domingo V, Espachs P, Preciado MJ, Vidal F: Abscence of an early pre-emptive effect after thoracic extradural bupivacaine in thoracic surgery. Br J Anaesth 1996; 76:72–6

74. Dahl JB, Hansen BL, Hjortsø NC, Ericsen CJ, Møiniche S, Kehlet H: Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery. Br J Anaesth 1992; 69:4–8

75. Dahl JB, Daugaard JJ, Rasmussen B, Egebo K, Carlsson P, Kehlet H: Immediate and prolonged effects of pre- versus postoperative epidural analgesia with bupivacaine and morphine on pain at rest and during mobilisation after total knee arthroplasty. Acta Anaesthesiol Scand 1994; 38:557–61

76. Nonaka A, Kashimoto S: Does pre-operative epidural buprenorphine improve postoperative pain? Pain Clin 1996; 9:41–8

77. Obata H, Saito S, Fujita N, Fuse Y, Ishizaki K, Goto F: Epidural block with mepivacaine before surgery reduces long-term post-thoracoctomy pain. Can J Anaesth 1999; 46:1127–32

78. Flisberg P, Törnebrandt K, Walther B, Lundberg J: A comparison of the effects on postoperative pain relief of epidural analgesia started before or after surgery. Eur J Anaesthesiol 2000; 17:627–33

79. Nakamura T, Yokoo H, Hamakawa T, Takasaki M: Preemptive analgesia produced with epidural analgesia administered prior to surgery. Masui 1994; 43:1024–8

80. Rice LJ, Pudimat MA, Hannallah RS: Timing of caudal block placement in relation to surgery does not affect duration of postoperative analgesia in paediatric ambulatory patinets. Can J Anaesth 1990; 37:429–31

81. Holthausen H, Eichwede F, Stevens M, Willnow U, Lipfert P: Preemptive analgesia: comparison of preoperative with postoperative caudal block on postopertaive pain in children. Br J Anaesth 1994; 73:440–2

82. Ho JWS, Khambatta HJ, Pang LM, Siegfred RNM, Sun LS: Preemptive analgesia in children: Does it exist. Reg Anesth 1997; 22:125–30

83. Kundra P, Deepalakshmi K, Ravishankar M: Preemptive caudal bupivacaine and morphine for postoperative analgesia in children. Anesth Analg 1998; 87:52–6

84. Goodarzi M: The effect of perioperative and postoperative caudal block on pain control in children. Paediatr Anaesth 1996; 6:475–7

85. Dakin MJ, Osinubi OYO, Carli F: Preoperative spinal bupivacaine does not reduce postoperative morphine requirement in women undergoing total abdominal hysterectomy. Reg Anesth 1996; 21:99–102

86. Ejlersen E, Andersen H B, Eliasen K, Mogensen T: A comparison between pre- and postincisional lidocaine infiltration on postoperative pain. Anesth Analg 1992; 74:495–8

87. Dierking G, Dahl J B, Kanstrup J, Dahl Aa, Kehlet H: The effect of pre- versus postoperative inguinal field block on postoperative pain after herniotomy. Br J Anaesth 1992; 68:344–8

88. Turner GA, Chalkiadis G: Comparison of preoperative with postoperative lignocaine infiltration on postoperative analgesic requirements. Br J Anaesth 1994; 72:541–3

89. Ørntoft S, Løngren A, Møiniche S, Dahl JB: A comparison of pre- and postoperative tonsillar infiltration with bupivacaine on pain after tonsillectomy: A pre-emptive effect? Anaesthesia 1994; 94:151–4

90. Victory RA, Gajraj NM, Van Elstraete A, Pace NA, Johnson ER, White PF: Effect of preincision versus postincision infiltration with bupivacaine on postoperative pain. J Clin Anesth 1995; 7:192–6

91. Dahl V, Ræder JC, Ernø PE, Kovdal A: Pre-emptive effect of pre-incisional infiltration of local anaesthesia on children undergoing hernioplasty. Acta Anaesthesiol Scand 1996; 40:847–51

92. Badner NH, Bourne RB, Rorabeck CH, MacDonald SJ, Doyle JA: Intra-articular injection of bupivacaine in knee-replacement operations: Results of use for analgesia and for preemptive blockade. J Bone Joint Surg 1996; 78:734–8

93. Bourget JL, Clark J, Joy N: Comparing preincisional with postincisional bupivacaine infiltration in the management of postoperative pain. Arch Surg 1997; 132:766–9

94. Campbell WI, Kendrick RW: Pre-emptive analgesia using local anaesthesia: A study in bilaterally symmetrical surgery. Br J Anaesth 1997; 79:657–9

95. Campbell WI, Kendrick RW, Ramsay-Baggs P, McCaughey W: The effect of pre-operative administration of bupivacaine compared with its postoperative use. Anaesthesia 1997; 52:1212–6

96. O'Hanlon DM, Colbert ST, Keane PW, Given FH: Preemptive bupivacaine offers no advantage to postoperative wound infiltration in analgesia for outpatient breast biopsy. Am J Surg 2000; 180:29–32

97. Molliex S, Haond P, Baylot D, Prades JM, Navez M, Elkhoury Z, Auboyer C: Effect of pre- vs postoperative tonsillar infiltration wih local anesthetics on postoperative pain after tonsillectomy. Acta Anaesthesiol Scand 1996; 40: 1210–5

98. Likar R, Morianz U, Wieser S, Schabus H, Spacek A, Koppert W, Sittl R: Präemptive analgesie mit ropivacain bei tonsillektomien im erwachsenealter. Anaesthesist 1999; 48:373–8

99. Elhakim M, Abdel Hay H: Comparison of preoperative with postoperative topical lidocaine spray on pain after tonsillectomy. Acta Anaesthesiol Scand 1995; 39:1032–5

100. Podder S, Wig J, Malhotra SK, Sharma S: Effect of pre-emptive analgesia on self-reported and biological measure of pain after tonsillectomy. Eur J Anaesth 2000; 17:319–4

101. Ke RW, Portera SG, Bagous W, Lincoln SR: A randomized, double-blinded trial of preemptive analgesia in laparoscopy. Obstet Gynecol 1998; 92:972–5

102. Huffnagle HJ, Norris MC, Leighton BL, Arkoosh VA: Ilioinguinal iliohypogastric nerve blocks: Before or after cesarean delivery under spinal anesthesia? Anesth Analg 1996; 82:8–12

103. Altintas F, Bozkurt P, Ipek N, Yücel A, Kaya G: The efficacy of pre- versus postsurgically axillary block on postoperative pain in paediatric patients. Paediatr Anaesth 2000; 10:23–8

104. Doyle E, Bowler GMR: Pre-emptive effect of multimoal analgesia in thoracic surgery. Br J Anaesth 1998; 80:147–51

105. Pasqualucci A, De Angelis V, Contardo R, Colò F, Terrosu G, Donini A, Pasetto A, Bresadola F: Preemptive analgesia: Intraperitoneal local anesthetic in laparoscopic cholecystectomy. ANESTHESIOLOGY 1996; 85:11–20

106. Jadad AR: Meta-analysis in pain releif: A valuable but easily misused tool. Curr Opin Anaesth 1996; 9:426–9

107. McQuay HJ, Moore RA: An Evidence-based Resource For Pain Relief. Oxford, Oxford University Press, 1998, pp 14–8

108. Katz J: Pre-emptive analgesia: Evidence, current status and future directions. Eur J Anaesthesiol 1995; 12(suppl 10):8–13

109. O'Conner TC, Abram SE: Inhibition of nociception-induced spinal sensitization by anesthetic agents. ANESTHESIOLOGY 1995; 82:259–66

110. Perkins F, Kehlet H: Chronic pain as an outcome of surgery: A review of predictive factors. ANESTHESIOLOGY 2000; 93:1123–33

111. Katz J, Jackson M, Kavanagh BP, Sandler AN: Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. Clin J Pain 1996; 12:50–5

112. Nikolajsen L, Ilkjær S, Christensen JH, Krøner, K, Jensen TS: Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. Lancet 1997; 350:1353–7

113. Kissin I: Preemptive analgesia: Why its effect is not always obvious. ANESTHESIOLOGY 1996; 84:1015–9

114. Dahl JB: Neuronal plasticity and pre-emptive analgesia: Implications for the management of postoperative pain. Dan Med Bull 1994; 41:434–42