

# Postoperative Morphine Use and Hyperalgesia Are Reduced by Preoperative but Not Intraoperative Epidural Analgesia

## Implications for Preemptive Analgesia and the Prevention of Central Sensitization

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**Background:** The aim of this study was to evaluate the postoperative morphine-sparing effects and reduction in pain and secondary mechanical hyperalgesia after preincisional or postincisional epidural administration of a local anesthetic and an opioid compared with a sham epidural control.

**Methods:** Patients undergoing major gynecologic surgery by laparotomy were randomly assigned to three groups and studied in a double-blinded manner. Group 1 received epidural lidocaine and fentanyl before incision and epidural saline 40 min after incision. Group 2 received epidural saline before incision and epidural lidocaine and fentanyl 40 min after incision. Group 3 received a sham epidural control (with saline injected into a catheter taped to the back) before and 40 min after incision. All patients underwent surgery with general anesthesia.

**Results:** One hundred forty-one patients completed the study (group 1, n = 45; group 2, n = 49; group 3, n = 47). Cumulative patient-controlled analgesia morphine consumption at 48 h was significantly lower ( $P = 0.04$ ) in group 1 ( $89.8 \pm 43.3$  mg) than group 3 ( $112.5 \pm 71.5$  mg) but not group 2 ( $95.4 \pm 60.2$  mg), although the hourly rate of morphine consumption between 24 and 48 h after surgery was significantly lower ( $P < 0.0009$ ) in group 1 ( $1.25 \pm 0.02$  mg/h) than group 2 ( $1.41 \pm 0.02$  mg/h). Twenty-four hours after surgery, the visual analog scale pain score on movement was significantly less intense ( $P = 0.005$ ) in group 1 ( $4.9 \pm 2.2$  cm) than group 3 ( $6.0 \pm 2.6$  cm) but not group 2 ( $5.3 \pm 2.5$  cm), and the von Frey pain threshold near the wound was significantly higher ( $P = 0.03$ ) in

group 1 ( $6.4 \pm 0.6$  log mg) than in group 3 ( $6.1 \pm 0.8$  log mg) but not group 2 ( $6.2 \pm 0.7$  log mg).

**Conclusions:** Preincisional administration of epidural lidocaine and fentanyl was associated with a significantly lower rate of morphine use, lower cumulative morphine consumption, and reduced hyperalgesia compared with a sham epidural condition. These results highlight the importance of including a standard treatment control group to avoid the problems of interpretation that arise when two-group studies of preemptive analgesia (preincisional vs. postsurgery) fail to find the anticipated effects.

DESPITE the controversy over the efficacy of preemptive analgesia,<sup>1-5</sup> there is a growing body of well-controlled studies showing that preoperative blockade of noxious surgical inputs *via* the epidural route reduces pain and analgesic consumption after the pharmacological action of the target agents has worn off.<sup>6-12</sup> The results of these studies support the idea that the noxious events associated with surgery induce a state of central neural sensitization in the spinal cord (and possibly more rostral sensory structures). After surgery, the flow of afferent input impinges on these sensitized neurons, which then amplify the peripheral signal and transmit it onward to the brain. The pain that accompanies these events is therefore more painful than otherwise would have been had the spinal cord cells been blocked at the time of surgery. Preoperative epidural analgesia minimizes central sensitization and consequently lessens the intensity of the postoperative pain experience.<sup>13</sup>

In the present study, we evaluated the postoperative morphine-sparing and pain-reducing effects of preemptive epidural administration of both an opioid and a local anesthetic. The use of these two agents capitalizes on their combined actions in reducing central sensitization.<sup>14</sup> On the basis of our previous studies using an opioid<sup>6</sup> and a local anesthetic,<sup>7</sup> we hypothesized that postoperative pain scores and postoperative morphine requirements after major abdominal gynecologic surgery would be reduced by a combination of general anesthesia plus preincisional lumbar epidural fentanyl and lidocaine when compared with general anesthesia plus postincisional lumbar epidural fentanyl and lidocaine.

The controversy over preemptive analgesia extends beyond the issue of efficacy. More fundamentally, it involves the very definition of the phenomenon.<sup>5,15,16</sup>

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This has been partially resolved by distinguishing between preventive analgesia and preemptive analgesia<sup>5,17</sup> and by defining preemptive analgesia in a broad (presurgical analgesic administration *vs.* no treatment) or narrow (presurgical *vs.* postsurgical analgesic administration) sense.<sup>18</sup> The focus on demonstrating that pretreatment is more effective than the same treatment administered after incision or after surgery (*i.e.*, preemptive analgesia) has sidetracked progress since inclusion of a control condition (*e.g.*, saline given before and after incision) has been ignored.<sup>19</sup> Two-group studies that fail to demonstrate a superiority of the preincisional treatment over the postincisional or postsurgical treatment are inherently flawed because it is not known whether the absence of an effect reflects the relative efficacy of postoperative blockade or the inefficacy of preoperative blockade in reducing central sensitization.<sup>5</sup> Therefore, the second aim of the study was to compare postoperative pain and opioid consumption in patients who received general anesthesia plus epidural fentanyl and lidocaine before or after incision with a standard treatment control group that received general anesthesia alone (plus a sham epidural agent). We hypothesized that postoperative pain and morphine consumption would be lowest in the preincisional group and highest in the control group.

Finally, factors other than the nature of surgery and perioperative analgesia can affect postoperative pain. Psychosocial variables including extent of social support, mental health status, degree of optimism, coping style, and mood all have been shown to influence pain experience of varying durations,<sup>20,21</sup> but they have not been evaluated in studies of preemptive analgesia. Assessment of psychosocial variables would provide information on the extent to which the observed preemptive analgesic effects are attributable to the preemptive intervention *versus* (pre)existing differences in psychosocial factors among the groups. Assessment of these factors also may help to shed light on the processes involved in recovery from postsurgical pain.<sup>15,22</sup>

## Materials and Methods

Approval to carry out the study was obtained from the University Health Network Research Ethics Board (Toronto, Ontario, Canada). All patients gave written informed consent to participate before enrolling in the study.

Patients scheduled for major gynecologic surgical procedures by laparotomy were eligible for recruitment into the study. Inclusion criteria were American Society of Anesthesiologists (ASA) physical status I-II, age between 19 and 75 yr, weight between 45 and 90 kg, height between 150 and 175 cm, body mass index less than or equal to 30, and able to speak and read English. Exclu-

sion criteria were contraindications to epidural anesthesia or iv patient-controlled analgesia (PCA) with morphine, ASA physical status of more than II, history of major psychiatric disorder, history of substance use disorder, and current opioid use.

### *Randomization and Blinding Procedures*

A randomization schedule was computer generated by a biostatistician (not otherwise involved in the study) and provided to the hospital pharmacist who prepared and dispensed drugs for clinical trials. The randomization schedule specified the group (1, 2, or 3) to which each prospective patient would be allocated upon enrollment in the trial. An opaque envelope containing the patient number and group assignment was prepared, sealed, and numbered for each patient by the hospital pharmacist.

A standard volume of lidocaine, fentanyl, and preservative-free saline for epidural and intravenous administration was prepared in separate syringes, coded for blinding purposes, numbered, and dispensed by the hospital pharmacy on the day of surgery. The pharmacist who dispensed the study medications was not involved in any other aspect of the study.

All patients and personnel involved in patient management and data collection were unaware of the group to which the patient had been allocated. The anesthesiologist in charge of the case was aware of group allocation for control group patients and was not involved in postoperative management or data collection.

### *Pain Assessment Instruments*

**Visual Analog Scale (VAS).** The VAS provides a simple, efficient, and minimally intrusive measure of pain intensity that has been used widely in research settings where a quick index of pain is required and to which a numerical value can be assigned.<sup>23</sup> The VAS consists of a 10-cm horizontal line with the two endpoints labeled "no pain" and "worst possible pain." The patient is required to mark the 10-cm line at a point that corresponds to the present level of pain intensity. The distance in centimeters from the low end of the VAS and the patient's mark are used as a numerical index of pain intensity. Pain was assessed with patients at rest (VAS-R) and after standard mobilization (VAS-M) by asking patients to roll from a supine to a side-lying position and perform two maximal inspirations before rating their pain.

**McGill Pain Questionnaire (MPQ).** The MPQ was developed by Melzack<sup>24</sup> to obtain quantitative and qualitative measures of the experience of pain. The MPQ yields two global scores, the pain rating index and the present pain intensity, which have been found to provide valid and reliable measures of pain.<sup>23,24</sup> The pain rating index is the sum of the rank values of the words chosen from 20 sets of qualitative words, each set con-

taining two to six adjectives that describe the sensory, affective, and evaluative properties of pain. The lists of pain descriptors are read to the patients who are asked to choose the word in each category that best describes their pain at the moment. The present pain intensity is rated on a scale of 0–5 as follows: 0 = none; 1 = mild; 2 = discomforting; 3 = distressing; 4 = horrible; and 5 = excruciating.

**von Frey Filaments.** Secondary mechanical hyperalgesia to punctate stimulation applied to the skin was assessed using von Frey filaments (Smith & Nephew Rolyan, Menomonee Falls, WI) that consist of a set of 20 individual nylon filaments of equal length (38 mm) ranging from 0.06 to 1.14 mm in diameter. Each filament has been assigned a value that represents the logarithm of the force (in mg) required to bend it maximally when pressed against the skin. To minimize the assessment burden on the patients, we used every other filament beginning with the smallest (0.06 mm). On each trial, a filament was applied to the designated point on the skin for approximately 1 s with the patient's eyes closed. Trials were separated by an interval ranging from 5 to 15 s to reduce the likelihood of anticipatory responses. Filaments were applied in ascending serial order. Pain threshold was defined by the value (force in log mg) associated with the filament that patients first reported as being uncomfortable or painful. Pain thresholds were obtained from two regions of the body: a control site on the inner forearm and a test site approximately 10 cm from the wound dressing.

#### *Measures of Psychosocial Functioning*

The following control measures were administered before and/or after surgery to determine comparability among groups on psychosocial characteristics.

**Mental Health Inventory (MHI).** The MHI<sup>25</sup> is a self-administered questionnaire that measures symptoms of psychologic distress and well-being. The present study used an 18-item version of the MHI that consists of a total score and five subscales: anxiety, depression, loss of behavioral or emotional control, positive affect, and interpersonal ties.<sup>26</sup> Subjects responded to each of the 18 statements on the basis of how often "in the past month" they had had each symptom. Each statement is accompanied by a 6-choice response set ranging from 1 (all of the time) to 6 (none of the time). The total score, which we report in the present study, ranges from 0 to 108, with higher scores indicative of better mental health. The MHI was administered during the preadmission visit, on the day of the operation prior to surgery, and 24 and 48 h after surgery. The time frame over which ratings were made was modified to read "in the past 24 h" for administration of the MHI on the day of surgery and at 24 and 48 h after surgery. Internal reliability of the MHI by Cronbach  $\alpha$  ranged from 0.36 to 0.88.

**Mood Questionnaire (MQ).** The MQ is a 26-item stress scale that has been shown to be a reliable measure of acute distress.<sup>27,28</sup> Each item was rated on a 5-point scale ranging from "not at all" to "extremely" based on the feelings that patients were currently experiencing. Higher scores indicate increased distress. The questionnaire showed good internal consistency at each time point (Cronbach  $\alpha$  ranged from 0.65 to 0.74).

**Impact of Event Scale.** The impact of event scale<sup>29,30</sup> is a 15-item self-report scale that assesses the two most common categories of responses to stressful events: intrusion (intrusively experienced ideas, images, feelings, or bad dreams) and avoidance (consciously recognized avoidance of certain ideas, feelings, or situations). This scale assesses effectiveness of adaptation to a stressful, traumatic event (e.g., anticipation of major surgery). Factor analysis of scale items yielded two relatively distinct factors, reflecting intrusive thoughts and avoidant behavior.<sup>30</sup> In the present study, the internal consistency estimates measured by Cronbach  $\alpha$  were 0.81 and 0.80 for intrusive thoughts and avoidant behavior, respectively.

**Schedule of Recent Experiences (SRE).** The SRE is based on a social readjustment scale developed by Holmes and Rahe.<sup>31</sup> The SRE was used as a control variable for varying levels of chronic stress in patients' lives. Patients completed a modified version of the SRE. This inventory measures both the frequency of life change events and their perceived impact over the past 6 months. Chronic stress has been found to be related to changes in baseline physiologic levels<sup>32</sup> as well as changes in health-related behaviors.<sup>33</sup>

**Life Orientation Test (LOT).** The LOT<sup>34</sup> is a 13-item questionnaire that measures dispositional optimism in terms of expectations and beliefs about the world. Patients rated the degree to which they agreed or disagreed with each item using a 5-point scale (0 = strongly disagree to 4 = strongly agree). Sample items include "In uncertain times, I usually expect the best"; "If something can go wrong for me, it will"; "I'm always optimistic about my future." Four filler items were included. The LOT is scored as a single factor with higher scores reflecting greater optimism (scale range, 0–36). The internal consistency estimate for the LOT was 0.42.

**The Brief-COPE.** Coping tendency or style was measured with the Brief-COPE.<sup>35</sup> The Brief-COPE is a validated 24-item version of the original COPE<sup>36,37</sup> that measures a set of conceptually distinct coping strategies with the following subscales: active coping, positive reframing, planning, use of social support, turning to religion, acceptance, use of humor, venting, denial, behavioral disengagement, self-distraction, and alcohol and/or drug use. The internal reliability of most items is adequate, ranging from 0.69 to 0.90. For the present study, we combined the active coping, planning, and positive reframing subscales for a measure of active coping and the

denial and self-distraction subscales for a measure of avoidant coping.

**Medical Outcomes Study Social Support Survey.** Social support was measured using the Medical Outcomes Study social support survey<sup>38</sup> that was developed with the SF-36 quality of life index and other Medical Outcomes Study measures in one of the largest and most comprehensive studies of health status in the chronically ill. The scale focuses on the perception of the availability of functional support. Patients rate the perceived availability of emotional or informational support, tangible support, positive interactions, and affectional support. In the present study, we report the total score. The internal consistency of the questionnaire was high ( $\alpha = 0.92$ ).

### Procedures

**Preoperative Assessments.** A member of the research team approached prospective patients at their preadmission appointment approximately 7–10 days before surgery. Patients were informed of the nature of the study, screened for eligibility, and recruited if interested. Following informed written consent, patients completed the preassessment battery of questionnaires that included the MHI, MQ, impact of event scale, SRE, LOT, Brief-COPE, and the Medical Outcomes Study social support survey. Resting measures of systolic and diastolic blood pressure and heart rate were obtained.

On the morning of surgery, patients completed the MHI and MQ prior to administration of the midazolam premedication and placement of the epidural catheter. Resting systolic blood pressure, diastolic blood pressure, and heart rate were obtained. A research nurse drew up the appropriate volume of each drug from the coded syringes that had been prepared and dispensed by the pharmacy.

### Anesthesia

**Epidural Anesthesia and Analgesia.** Patients in groups 1 and 2 had an epidural catheter inserted prior to induction of general anesthesia. The procedure was performed in a sterile manner using a 17-gauge epidural needle and a 20-gauge epidural catheter. Using the loss of resistance technique, the epidural catheter was placed *via* the L2–L3 or L3–L4 interspaces and advanced 3–4 cm into the epidural space. The position of the catheter was confirmed with a test dose of 3–5 ml lidocaine, 1.5%, with epinephrine, 1:200,000, to exclude intrathecal or intravascular placement.

Patients in group 3 underwent a sham epidural procedure prior to induction of general anesthesia. The anesthesiologist went through all the motions of placing an epidural catheter, including prepping and cleansing the skin, infiltrating the skin and interspinous regions with 2–3 ml lidocaine (2%), applying pressure as if inserting the needle, simulating loss of resistance, and threading of the catheter. The epidural needle was removed, and the exposed length of catheter was wrapped in gauze

and taped to the patient's back. A test dose of 3–5 ml normal saline was injected into the catheter that drained into the gauze.

All patients were told that the test dose might produce a wet and cold feeling in the lower back at the site of the catheter and were asked to indicate if they felt any numbness in their toes or had a metallic taste in the mouth. Sensory and motor assessments were completed in all patients 1 and 5 min after administration of the test dose and at 15-min intervals thereafter. A research nurse assisted with the epidural placement and completed all sensory and motor assessments. This nurse was not involved in data collection or postoperative care.

**Group 1 (Preincision).** After placement of the epidural catheter and administration of the test dose, group 1 received a bolus injection of epidural lidocaine, 2% (12 ml plus 0.8 ml for each inch of height above 60 in), with epinephrine, 1:200,000, followed by a bolus injection of 4  $\mu\text{g}\cdot\text{kg}^{-1}$  epidural fentanyl (50  $\mu\text{g}\cdot\text{ml}^{-1}$ ). Forty minutes after incision, patients in group 1 received two consecutive bolus injections of epidural saline. The first contained 12 ml saline plus 0.8 ml saline/in of height. The second contained 0.08 ml saline/kg of weight. The iv syringes for group 1 contained normal saline (0.04  $\text{ml}\cdot\text{kg}^{-1}$ ).

**Group 2 (Postincision).** After placement of the epidural catheter and administration of the test dose, group 2 received two consecutive epidural bolus injections of normal saline. The first contained 12 ml saline (plus 0.8 ml/in of height). The second contained 0.08  $\text{ml}\cdot\text{kg}^{-1}$  saline. Forty minutes after incision, patients in group 2 received a bolus injection of epidural lidocaine, 2% (12 ml plus 0.8 ml for each inch of height above 60 in), with epinephrine, 1:200,000, followed by a bolus injection of 4  $\mu\text{g}\cdot\text{kg}^{-1}$  epidural fentanyl (50  $\mu\text{g}\cdot\text{ml}^{-1}$ ). The iv syringes for group 2 contained normal saline (0.04  $\text{ml}\cdot\text{kg}^{-1}$ ).

**Group 3 (Control).** After placement of the sham epidural catheter and administration of the test dose, group 3 received (into the epidural catheter taped onto their back) two consecutive bolus injections of saline and another two consecutive bolus injections of saline 40 min after incision. The first injection contained 12 ml saline plus 0.8 ml/in of height. The second injection contained 0.08 ml saline/kg of weight. The iv syringes for group 3 contained fentanyl (1  $\mu\text{g}\cdot\text{kg}^{-1}$ , 25  $\mu\text{g}\cdot\text{ml}^{-1}$ ).

**General Anesthesia.** Patients received iv midazolam, 1–3 mg, as sedation for placement of the epidural catheter. General anesthesia was induced with thiopental (4–6  $\text{mg}\cdot\text{kg}^{-1}$ ). Patients received iv fentanyl (1  $\mu\text{g}\cdot\text{kg}^{-1}$ , 25  $\mu\text{g}\cdot\text{ml}^{-1}$  in group 3) or iv normal saline (0.04  $\text{ml}\cdot\text{kg}^{-1}$  in groups 1 and 2) at induction. Intubation followed the administration of vecuronium (0.08–1.0  $\text{mg}\cdot\text{kg}^{-1}$ ), rocuronium (0.6–0.9  $\text{mg}\cdot\text{kg}^{-1}$ ), or succinylcholine (1.0–1.5  $\text{mg}\cdot\text{kg}^{-1}$ ). Every 40 min beginning 40 min after incision, patients in groups 1 and 2 received iv saline

(0.04 ml·kg<sup>-1</sup>), and patients in group 3 received iv fentanyl (1 μg·kg<sup>-1</sup>, 25 μg·ml<sup>-1</sup>). General anesthesia was maintained with 60% N<sub>2</sub>O in O<sub>2</sub> and isoflurane. Vecuronium was used for neuromuscular blockade. Vasoactive agents (β blockers, vasodilators, and vasopressors) were used as required to maintain hemodynamic parameters within ±20% of mean preoperative baseline values. Neuromuscular blockade was reversed with neostigmine (0.05 mg·kg<sup>-1</sup>) and glycopyrrolate (0.02 mg·kg<sup>-1</sup>) at the conclusion of the surgery. The trachea was extubated after emergence and upon resumption of spontaneous breathing. Patients received supplemental O<sub>2</sub> by mask and were transported to the postanesthetic care unit.

**Postoperative Analgesia.** Patients were assessed immediately upon arrival in the postanesthetic care unit and were connected to a PCA pump system (Abbott Life Care Infuser, Abbott Laboratories, Chicago, IL; or Graseby 3300 PCA Pump, Graseby Medical, Watford, Herts, UK). If patients complained of pain, a research nurse blind to group allocation administered a loading dose of 4 mg morphine. Every 5 min, patients were asked whether they were in need of pain relief. An affirmative response was followed by a 1.0- to 1.5-mg iv bolus of morphine. This procedure was repeated until the patients were alert enough to begin self-administration using the PCA pump button. The PCA pump was set to deliver a 1.0- to 1.5-mg iv bolus dose of morphine with a lockout time of 5 min, a maximum dose of 40 mg in any 4-h period, and no continuous background infusion. This regimen was overseen by the Acute Pain Service and was continued on the ward for 48 h during which no other analgesics were administered. Morphine consumption in milligrams was calculated on an hourly basis from hard copy records (Abbott TRW Printer, Model TP 40, Abbott Laboratories, Chicago, IL) of the 48-h study period.

#### Measurement of Postoperative Pain, Mental Health, and Mood

VAS-R was measured 3, 6, 12, 24, and 48 h after surgery. VAS-M, MPQ, MHI, and MQ were administered 24 and 48 h after surgery. von Frey pain threshold (in log mg force) was assessed at 24 and 48 h after surgery by application of monofilaments to the skin 10 cm from the wound dressing and at a control site on the forearm.

#### Sample Size Calculation and Power Estimation

Power calculations were carried out with data from our previous study of preemptive analgesia<sup>7</sup> using mean cumulative morphine consumption (mg) for the preincisional (55 mg) and postincisional (71 mg) groups and an SD of 28 mg. In that study, the reduction in morphine consumed amounted to 30% savings in favor of the preincisional group. Standard power calculations<sup>39</sup> indicated that with 45 patients per group and an SD of 28 mg there would be a power of approximately 80% to detect a difference between 71 and 55 mg. Since a three-group

trial of this sort would be analyzed using general linear modeling techniques or ANOVA and a global F test adopted to protect against multiple comparisons, two Monte Carlo simulations<sup>40</sup> of 10,000 trials each were carried out under the following two conditions assuming 45 patients per group and an SD of 28 mg: (1) preincision mean of 55 mg, postincision mean of 71 mg, and control mean of 85 mg and (2) preincision mean of 55 mg, postincision mean of 71 mg, and control mean of 71 mg, with two-group comparisons being undertaken only if the omnibus F test was statistically significant ( $\alpha = 0.05$ , two-sided). The results of the Monte Carlo simulations showed that even when the second condition was assumed, a sample size of 45 patients per group provided a power of 80%. The power was found to be 99% when the first condition was assumed.

#### Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS for Windows, release 9.0, SPSS, Chicago, IL) and Primer of Biostatistics: The Program<sup>41</sup> (Version 4.0, McGraw Hill, New York, NY). Background demographic data and clinical variables were compared using ANOVA (for parametric variables) and chi-square test for two-way tables (for frequency data).

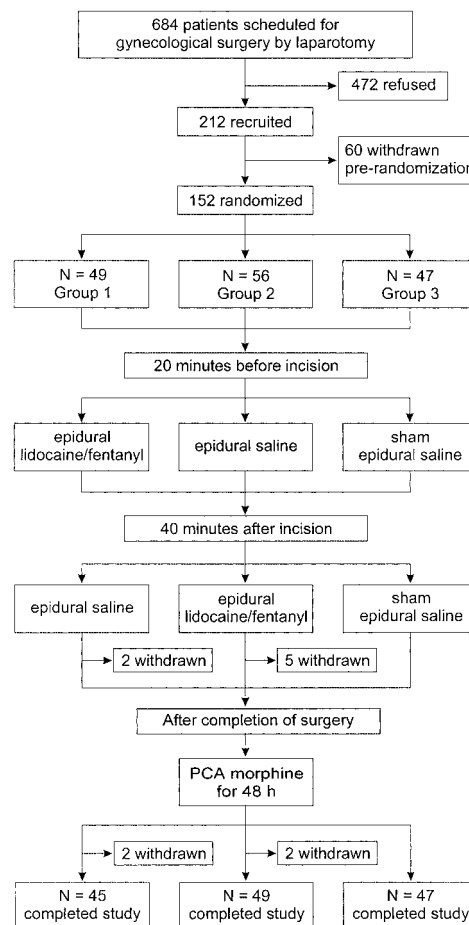


Fig. 1. Chart of study design and patient flow.

**Table 1. Demographic and Clinical Variables**

Variable	Group 1 (Preincision)	Group 2 (Postincision)	Group 3 (Control)
Age (yr)	44 ± 8.9	47 ± 10.6	44 ± 9.6
Height (cm)	163 ± 5.7	163 ± 7.7	163 ± 7.2
Weight (kg)	69 ± 11.9	70 ± 12.8	69 ± 12.1
Frequency of ASA status (1:2:3)	27:18	27:21:1	27:19:1
Pain history (%)	27	45	30
Days between preadmission and surgery	10 ± 12.1	9 ± 5.5	8 ± 6.3
Midazolam premedication (mg)	1.5 ± 0.72	1.6 ± 0.73	1.5 ± 0.69
Epidural test dose (ml)	3.5 ± 0.93	3.7 ± 1.0	3.5 ± 0.91
Time (min) between test dose and first epidural syringes	22 ± 25.8	24 ± 25.5	19 ± 22.9
Time (min) between first epidural syringes and incision	21 ± 7.2	20 ± 5.7	21 ± 6.1
Time (min) between incision and second epidural syringes	39 ± 6.5	40 ± 2.4	40 ± 0.5
iv fentanyl (μg)	0.0 ± 0.0	15.1 ± 28.7	253 ± 116.3
Epidural fentanyl (μg)	280 ± 47.4	275 ± 63.4	0.0 ± 0.0
Epidural lidocaine, 2% (ml)	15.7 ± 1.8	15.6 ± 2.2	0.0 ± 0.0
Surgery duration (min)	93 ± 37.7	85 ± 32.5	98 ± 37.1
Fluid intake (ml)	2385 ± 693	2156 ± 739	2183 ± 1106
Fluid loss (ml)	348 ± 341	431 ± 1056	373 ± 417
Blood loss (ml)	343 ± 257	313 ± 201	426 ± 461

Data are mean ± SD unless otherwise stated.

**Primary Outcome Variable.** Cumulative morphine consumption at 48 h was analyzed by ANOVA followed by contrasts among the group means. Both an intention-to-treat analysis and a protocol-compliant analysis were performed.

**Secondary Outcome Variables.** VAS-R and VAS-M pain scores and von Frey pain threshold were analyzed by ANOVA or analysis of covariance. The regression lines relating cumulative morphine consumption and time were compared pairwise by ANOVA for the three groups by first testing the overall coincidence of the regression lines.<sup>41</sup> If the overall coincidence differed, the slopes and intercepts were compared by a *t* test using the Bonferroni type I error rate correction for multiple comparisons ( $\alpha$ /number of tests). MPQ total pain rating index and MPQ present pain intensity were analyzed by nonparametric Kruskal-Wallis ANOVA of ranks.

**Control Variables.** Psychosocial variables were analyzed by two-way repeated-measures multivariate ANOVA using group as the independent-samples factor and time as the repeated-measures factor.

All data presented are mean ± SD unless otherwise specified.  $P \leq 0.05$  was considered statistically significant.

## Results

### *Patient Withdrawals*

Between August 1995 and August 2000, 684 patients were approached and screened for interest in participating in the study (fig. 1). Of these patients, 212 were recruited into the study. In total, 60 patients dropped out or were withdrawn prior to randomization between the day of recruitment and the day of surgery: 38 decided against participating on the day of the operation prior to surgery stating that they were apprehensive about the upcoming operation or epidural placement; 10

had their procedure canceled on the day of surgery; 7 were excluded on the morning of surgery prior to epidural placement due to a change in ASA physical status from 2 to 3; and 5 could not have the epidural catheter placed. In addition, seven patients were withdrawn during surgery due to intraoperative protocol violations, and four were withdrawn after surgery due to apnea and chest wall rigidity upon extubation requiring reintubation, faulty PCA equipment, and nausea and back pain. Thus, 141 patients completed the study: 45 in group 1, 49 in group 2, and 47 in group 3. Data up to the time of patient withdrawal are included in the statistical analyses.

### *Prerandomization Dropouts and Withdrawals*

Baseline demographic and psychosocial data were compared between patients who dropped out or were withdrawn prior to randomization and a random sample of participants who completed the study. There were no significant differences among the groups in any variable.

### *Preoperative Demographic, Clinical, and Psychosocial Variables*

There were no significant differences among the groups in demographic or clinical data (tables 1 and 2). Similarly, preoperative baseline values for all psychosocial variables were comparable across groups (table 3).

Thus, at the time of the preadmission interview approximately 1 week before surgery, the groups were well matched in terms of demographics, clinical variables, mental health (MHI), mood (MQ), use of avoidant and active coping strategies (Brief-COPE), optimistic disposition (LOT), intrusive thoughts and avoidant behaviors (impact of event scale), frequency of and adjustment to stressful life events (SRE), and level of social support (Medical Outcomes Study social support survey).

**Table 2. Frequency of Diagnosis, Surgical Procedure and Type of Incision**

	Group 1 (Preincision)	Group 2 (Postincision)	Group 3 (Sham Epidural)
Diagnosis			
Fibroids	23	20	22
Cancer (endometrial, uterine, cervical, ovarian)	7	10	9
Mass (uterine, pelvic, ovarian)	6	9	7
Other (ovarian cyst, pelvic pain, endometriosis, menorrhagia, enlarged ovaries)	8	10	8
Surgical procedure			
Total abdominal hysterectomy	26	24	26
Radical hysterectomy	4	6	6
Subtotal hysterectomy	4	6	4
Other (abdominal myomectomy, salpingoophorectomy, ovarian cystectomy)	11	13	11
Type of incision			
Horizontal	24	16	19
Midline	21	33	28

Data no. of patients.

### Preoperative and Intraoperative Biomedical Data

The groups did not differ significantly with respect to the time between the test dose of lidocaine and the injection of the first epidural syringes, the time between injection of the first epidural syringes and skin incision, the duration of surgery, or other relevant intraoperative variables. Groups 1 and 2 did not differ significantly in the total volume of epidural lidocaine or dose of epidural fentanyl received (table 1).

### PCA Morphine Consumption

There was no appreciable difference in the results of the intention-to-treat analyses and the protocol-compliant analyses. Data and results of significance tests reported below are therefore based on the intention-to-treat analyses.

Cumulative PCA morphine consumption at 24 and 48 h was significantly lower ( $P < 0.04$ ) in group 1 ( $57.1 \pm 26.4$  and  $89.8 \pm 43.3$  mg, respectively) than in

group 3 ( $72.7 \pm 47.7$  and  $112.5 \pm 71.5$  mg, respectively) but not in group 2 ( $59.0 \pm 37.6$  and  $95.4 \pm 60.2$  mg, respectively). In addition, group 2 used significantly less morphine than group 3 at 24 h ( $P = 0.04$ ) but not at 48 h ( $P = 0.08$ ). The mean difference in morphine consumption of 23 mg between group 1 and group 3 over the 48-h period translates into a reduction of 20%. The number of PCA requests that did not result in a bolus of morphine (*i.e.*, requests made during the 5-min lockout period) did not differ significantly among the groups.

Table 4 shows PCA morphine consumption between intervals when pain at rest was assessed. Morphine consumption during the first 3 h after surgery was significantly greater in the control group than in the other two groups (which did not differ), reflecting the continued analgesic action of the epidural fentanyl and lidocaine in the preincisional and postincisional groups.

Figure 2 shows cumulative morphine consumption for the three groups across postoperative day 1 (0–24 h)

**Table 3. Scores on Measures of Social Support and Psychologic and Emotional Functioning Obtained at the Preadmission Visit Approximately 1 Week Before Surgery**

Psychosocial measure	Group 1 (Preincision)	Group 2 (Postincision)	Group 3 (Control)
Mental health inventory-18	$84.3 \pm 10.6$	$85.8 \pm 14.8$	$83.8 \pm 13.1$
Mood questionnaire	$28.2 \pm 8.0$	$27.9 \pm 7.6$	$27.4 \pm 11.5$
Brief-COPE			
Avoidant coping	$7.9 \pm 2.7$	$7.9 \pm 3.1$	$7.5 \pm 2.2$
Active coping	$16.1 \pm 5.4$	$16.2 \pm 4.8$	$16.4 \pm 4.2$
Life orientation test—optimism	$13.5 \pm 4.0$	$14.5 \pm 3.3$	$14.1 \pm 3.6$
Impact of event scale			
Intrusive thoughts	$10.4 \pm 8.4$	$8.6 \pm 6.8$	$11.3 \pm 8.6$
Avoidant behaviors	$12.2 \pm 9.6$	$10.0 \pm 8.0$	$12.6 \pm 8.7$
Total score	$22.7 \pm 16.9$	$18.5 \pm 13.2$	$23.8 \pm 16.3$
Schedule of recent experiences			
Total no. of events	$5.2 \pm 3.4$	$6.0 \pm 4.7$	$4.4 \pm 4.0$
Total adjustment score	$244 \pm 204$	$220 \pm 228$	$249 \pm 248$
Medical Outcomes Study social support survey	$76.4 \pm 11.4$	$75.8 \pm 14.5$	$75.1 \pm 11.5$

Data are mean  $\pm$  SD.

**Table 4. PCA Morphine Consumption (mg) within Intervals Bounded by Times when Pain at Rest Was Assessed**

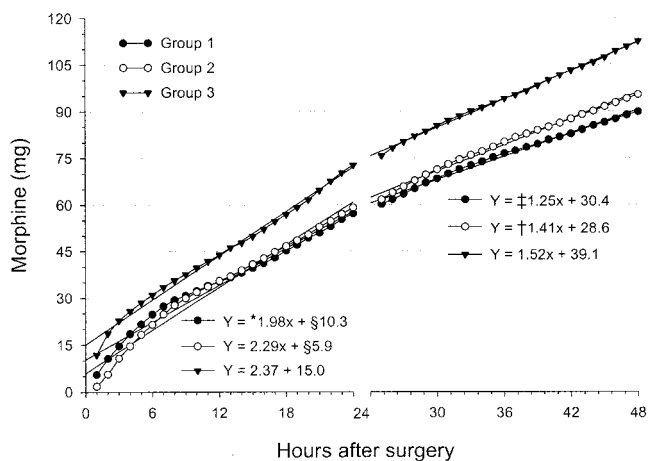
Time Interval (h) after Surgery	Group 1 (Preincision)	Group 2 (Postincision)	Group 3 (Control)
0–3	14.6 ± 9.4	10.7 ± 10.0	22.7 ± 15.3*
3–6	10.0 ± 7.2	10.7 ± 7.6	8.2 ± 7.5
6–12	10.6 ± 6.4	14.0 ± 9.8	12.8 ± 12.4
12–24	21.8 ± 10.9	23.6 ± 16.4	28.9 ± 21.0
24–48	31.8 ± 22.7	35.6 ± 28.0	38.8 ± 28.3

Data are mean ± SD.

\*  $P < 0.004$  compared with group 1 and  $P < 0.0009$  compared with group 2.

PCA = patient-controlled analgesia.

and day 2 (25–48 h) as well as the best-fitting linear regression lines relating cumulative morphine consumption and time. On day 1, the hourly rate (mean ± SEM) of morphine consumption was significantly lower ( $P < 0.003$ ) in group 1 ( $1.98 \pm 0.07$  mg/h) than group 3 ( $2.37 \pm 0.05$  mg/h) but not group 2 ( $2.29 \pm 0.07$  mg/h). On day 2, the hourly rate for each group differed significantly ( $P < 0.0009$ ) from the others (group 1,  $1.25 \pm$



**Fig. 2.** An hour-by-hour plot of cumulative patient-controlled analgesia (PCA) morphine consumption for each group showing the best-fitting least squares regression line calculated separately for day 1 (0–24 h) and day 2 (25–48 h). Each regression line accounts for at least 98% ( $r^2$ ) of the total variance. The significantly higher Y intercept for group 3 versus group 1 and group 2 on day 1 reflects the greater morphine requirements for the control group upon arriving in postanesthetic care unit due to the absence of active epidural analgesia ( $P < 0.0009$  for Bonferroni corrected tests of the intercept comparing group 1 with group 3 and group 2 with group 3 on day 1). Despite these initial differences, the hourly rate of morphine consumption was significantly lower for group 1 than group 3 across the 2-day study period and for group 2 than group 3 on day 2, reflecting the benefits of preincisional and postincisional epidural analgesia. In addition, on day 2, the rate of morphine consumption was significantly lower for group 1 than group 2, reflecting a late preemptive analgesic effect. The rate of morphine consumption across the 2 days was lower by approximately 17% among group 1 compared with group 3. Bonferroni corrected significance tests of the regression line slope compared the following: group 1 versus group 2 and group 1 versus group 3 on day 1,  $*P < 0.003$ ; group 1 versus group 2 and group 1 versus group 3 on day 2,  $\ddagger P < 0.0009$ ; and group 2 versus group 3 on day 2,  $\uparrow P < 0.0009$ .

**Table 5. VAS Pain Scores at Rest and McGill Pain Questionnaire PRI-T, PPI, and NWC**

	Group 1 (Preincision)	Group 2 (Postincision)	Group 3 (Control)
VAS pain score at rest			
3 h	5.3 ± 2.2	4.6 ± 2.7	5.4 ± 2.6
6 h	4.8 ± 2.7	5.4 ± 2.3	4.8 ± 2.5
12 h	3.9 ± 2.4	3.9 ± 2.0	3.9 ± 2.4
24 h	3.1 ± 1.9	2.7 ± 2.1	2.9 ± 2.2
48 h	1.9 ± 1.6	1.7 ± 1.7	2.1 ± 2.1
McGill pain questionnaire (24 h)			
PRI-T	19.8 ± 12.0	20.1 ± 11.1	20.8 ± 12.1
PPI	2.0 ± 0.7	1.8 ± 0.9	1.8 ± 1.0
NWC	11.7 ± 7.6	12.1 ± 6.9	13.1 ± 8.0
McGill pain questionnaire (48 h)			
PRI-T	15.7 ± 11.1	16.9 ± 12.5	16.0 ± 13.1
PPI	1.6 ± 0.9	1.5 ± 0.8	1.5 ± 0.9
NWC	9.0 ± 7.2	10.0 ± 8.0	10.2 ± 9.1

Data are mean ± SD.

NWC = number of words chosen; PPI = present pain intensity; PRI-T = total pain rating index; VAS = visual analog scale.

0.02 mg/h; group 2,  $1.41 \pm 0.02$  mg/h; group 3,  $1.52 \pm 0.01$  mg/h).

#### Postoperative Pain and Hyperalgesia

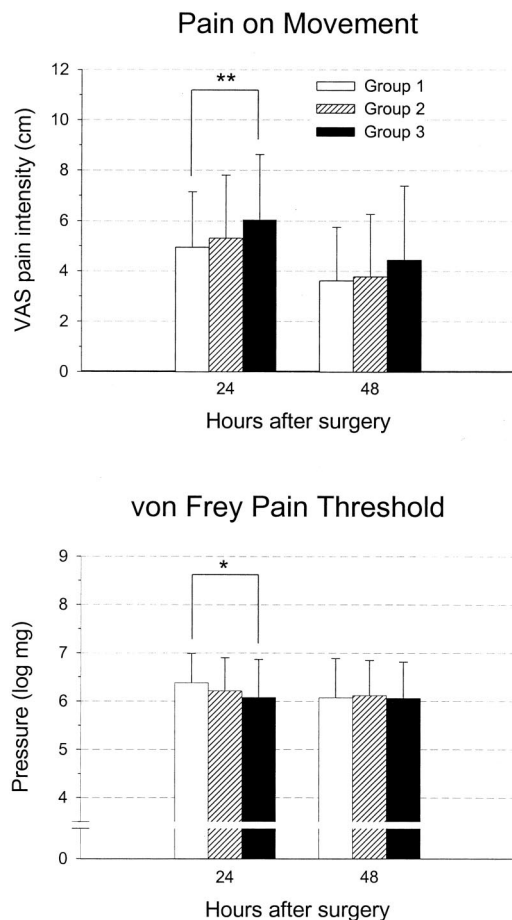
Pain scores measured with the patient in a resting position (VAS-R and MPQ total pain rating index) showed no significant differences among the groups, consistent with appropriate use of the PCA pump (table 5). However, group 1 reported significantly less pain in response to standardized movement (VAS-M) than did group 3 at 24 h ( $P = 0.005$ ) but not at 48 h ( $P = 0.07$ ) after surgery (fig. 3). Similarly, at 24 h but not at 48 h, the von Frey pain threshold, assessed 10 cm from the wound dressing, was significantly lower in group 3 than in group 1 ( $P = 0.03$ ), revealing the presence of secondary mechanical hyperalgesia in the control group relative to the preincisional group (fig. 3). There were no significant differences among the groups in the von Frey pain threshold applied at the control site on the inner forearm at 24 or 48 h after surgery.

#### Postoperative Mental Health and Mood

Scores on the MHI and MQ subscales did not differ significantly among the groups on the day of the procedure before surgery or on the 2 days after surgery, suggesting that the observed differences in pain and morphine consumption were not due to differences in mental health or mood (data not presented).

#### Complications and/or Adverse Events

One patient in group 1 developed severe nausea and low back pain and withdrew from the study. One patient



**Fig. 3.** Visual analog scale (VAS) pain scores after standardized movement and pain thresholds in response to von Frey monofilaments applied 5 cm from the edge of the wound dressing 24 and 48 h after surgery. Data are mean and SD. \*\* $P < 0.005$  and \* $P < 0.03$  for group 1 versus group 3 by ANOVA.

in group 2 developed apnea and chest wall rigidity upon extubation and was reintubated and ventilated for 2 h.

## Discussion

The results of the present study show that blocking or attenuating noxious inputs using a combination of epidural fentanyl and lidocaine before incision reduces the rate and amount of morphine consumption, pain on movement, and secondary mechanical hyperalgesia compared with a sham epidural control. The results are consistent with the hypothesis that the combined actions of preincisional epidural fentanyl and lidocaine interrupted transmission to the spinal cord of high-intensity inputs arising from incision and subsequent noxious surgical events and therefore prevented the development of a state of central sensitization or hyperexcitability in dorsal horn neurons.<sup>13</sup> By contrast, group 3 received the full brunt of the noxious injury barrage: in the absence of the neuroprotective effect of the epidural agents, central sensitization was induced by surgery and

maintained by postoperative inflammatory inputs from the wound. In the hours and days after surgery, peripheral input to the sensitized spinal cord generated by normal activities was amplified, leading to increased morphine requirements and more intense pain on movement (primary hyperalgesia) as well as in response to punctate stimulation applied to uninjured tissue near the wound dressing (secondary hyperalgesia). The neurophysiology underlying these effects has been well described and involves an *N*-methyl-D-aspartate-mediated increase in dorsal horn neuron activity that follows the corelease of neuropeptides and excitatory amino acids from C fiber primary afferent terminals during tissue damage and inflammation.<sup>13,42</sup>

The results cannot be due the direct analgesic effects of the agents given preoperatively. The differences in hyperalgesia and morphine consumption in group 1 were observed between 24 and 48 h after surgery, long after the expected clinical duration of actions of epidural fentanyl and lidocaine. Moreover, the same agents given by the same route to group 2 did not produce equivalent reductions in pain and morphine consumption when compared with group 3, even though they were given to group 2 after incision, approximately 1 h later than in group 1. Therefore, the most likely explanation for these findings is that the preoperative administration of fentanyl and lidocaine blocked the deleterious effects of surgery on spinal neural processing and minimized development of central sensitization relative to group 3.

The pattern of results in the present study suggests that the development of postoperative central sensitization in group 2 also may have been attenuated to some degree by the postincisional blockade, since group 2 morphine consumption (fig. 2) and VAS-M pain scores (fig. 3) were in between the scores of the other groups. This is also supported by the significantly lower rate of morphine self-administration in group 2 compared with group 3 on day 2, possibly by the significantly lower cumulative morphine consumption between these groups at 24 h, and by the absence of significant differences between the two drug treatment groups. These findings suggest that notwithstanding the sensitizing effects of an unchecked injury barrage during the first 40 min of surgery, postincisional blockade confers some protection from the subsequent development of central sensitization.

Comparison of regression line slopes among the groups provided additional information that is otherwise not available from analysis of cumulative morphine consumption or morphine consumed within specified intervals. Higher morphine consumption in group 3 at 3 h after surgery (table 4) was attributed to the ongoing actions of lidocaine and fentanyl in groups 1 and 2. These initial differences complicate interpretation of the significant differences in cumulative morphine consumption unless they are accompanied by similar differ-

ences in interval morphine and/or rate of consumption.<sup>5</sup> In the present study, differences among the groups in rate of consumption on day 2 provided evidence for the preventive (group 1 *vs.* group 3 and group 2 *vs.* group 3) and preemptive analgesic (group 1 *vs.* group 2) effects of the epidural regimen.

The foregoing is consistent with the idea that central sensitization is triggered not only by incision but also by noxious inputs arising from intraoperative tissue damage as well as from postoperative inflammatory inputs and ectopic activity in the case of nerve damage.<sup>5,43</sup> It is not known to what extent each of these factors contributes to central sensitization for any given surgical procedure or patient, but we do know that prevention of central sensitization does not require that an intervention be initiated before surgery.<sup>2,5</sup> Recent studies have shown that pain and analgesic consumption are reduced to a clinically significant extent even when the analgesic intervention is started after surgery, in the context of an unchecked injury barrage due to incision and other noxious intraoperative events.<sup>44,45</sup>

Perhaps the most relevant aspect of the present study to the field of preemptive analgesia is the critical importance of including a standard treatment control group in studies of preemptive analgesia.<sup>5</sup> The classic definition of preemptive analgesia, which requires identical treatment before *versus* after incision or surgery, is incomplete since without a standard treatment control group significant effects may go undetected. The inclusion of a control group in the present study made it possible to demonstrate the benefits of preventive analgesia<sup>5</sup> in the face of what otherwise would have been another negative study of preemptive analgesia. Two other studies have evaluated the preemptive analgesic effects of an epidural opioid and a local anesthetic in women undergoing abdominal gynecologic procedures.<sup>46,47</sup> Neither study found significant differences in pain or analgesic use between the preincisional and postincisional groups. However, there is no way of determining whether the absence of differences between the groups was due to the relative efficacy of postoperative blockade (as in the present study) or the inefficacy of preoperative blockade in preventing central sensitization.<sup>5</sup> The continued use of incomplete designs that consist of a postincisional or postsurgical condition without a true placebo condition (or a control group that receives treatment both before and after surgery) will hinder progress in preemptive analgesia, since negative results leave us with no idea of the significance of the preoperative intervention relative to a group that does not receive the target treatment.

Although the differences in pain and morphine consumption observed in the present study are statistically significant, the clinical significance of these effects is relatively modest. For example, a comparison of the preincisional group with the sham epidural control group showed that the difference in the rate of mor-

phine self-administration between 24 and 48 h after surgery was 0.27 mg/h and the mean difference in VAS-M pain score was 1.0 cm at its maximum 24 h after surgery. Finally, the von Frey pain thresholds revealed the presence of reduced secondary mechanical hyperalgesia, but the magnitude of the effect was small. These latter data are consistent with other studies that have examined the effects of preoperative analgesia on sensory changes after major surgery.<sup>48-50</sup>

The opioid-sparing effect and reduced hyperalgesia observed in the present study were not due to differences in mood or mental health, since the three groups did not differ significantly on a comprehensive battery of psychologic, emotional, and social inventories measuring mood state, anxiety, depression, or positive affect at any point during the postoperative period under study. Similarly, baseline measures of social support, mode of coping, level of optimism, degree of chronic stress, and adaptation to stressful situations were comparable among the three groups, indicating that the groups were well matched on these control variables and making it unlikely that their contribution to the postoperative pain experience differentially affected the three groups.

There are limitations to the present study. Group 2 received the active agents intraoperatively and not postoperatively, which would have provided greater nociceptive input in group 2. Thus, the present design compared an early and late start to surgical antinociception. The choice of fentanyl and lidocaine and the decision to administer the second set of epidural syringes 40 min after incision were based on the duration of action of these agents relative to the average duration of the surgical procedure. To maintain the blinding of patients and the research nurses who collected pain scores, it was necessary to choose a drug combination whose effects would be waning by the end of surgery and arrival in the postanesthetic care unit. This combination of drugs and their timing of administration may have reduced the magnitude of the potential difference in the rate of morphine consumption observed between groups 1 and 2. First, the epidural fentanyl and lidocaine dose in group 1 was administered 20 min before incision so that approximately 113 min had elapsed by the time the patients arrived in the postanesthetic care unit and the PCA pump was connected (table 1). Therefore, it is possible that the waning epidural blockade toward the end of the operation allowed a process of spinal cord sensitization to begin. In contrast, the epidural blockade in group 2 was initiated approximately 60 min after group 1 and lasted that much longer into the postoperative period. This is supported by the finding that morphine consumption in the first 3 h after surgery was lowest in group 2, and it was not until 6 h after surgery that group 1 consistently began self-administering smaller doses of morphine.

The choice of agents and their timing of administration therefore may have contributed to the initiation of late intraoperative or early postoperative central sensitization in group 1 as well as a reduction in morphine consumption in the early hours after surgery in group 2 by virtue of the prolonged epidural blockade. The magnitude of the preemptive analgesic effect between groups 1 and 2 might have been increased had we combined an opioid with a longer-lasting local anesthetic, such as bupivacaine, and run a continuous infusion until the end of surgery. These considerations are consistent with the idea that intraoperative and postoperative noxious inputs make separate contributions to the process of central sensitization.<sup>19</sup> In spite of the suggestion that central sensitization may have been initiated in the late intraoperative and early postoperative periods in group 1, the significantly lower rate of morphine consumption in this group compared with the other two groups between 24 and 48 h after surgery is evidence that this late sensitization was not of sufficient magnitude to surpass the central sensitizing effects of the afferent injury barrage brought about by incision and the subsequent noxious intraoperative events in groups 2 and 3.

Another limitation is the use of PCA morphine consumption as the primary outcome measure in a study in which the main hypothesis concerns development of central sensitization and hyperalgesia. Allowing pain to fluctuate by holding constant the level of postoperative analgesics administered would have been a more direct test of the hypothesis,<sup>5</sup> but this was not possible given that PCA is standard practice for postoperative pain management at our institutions.

In summary, administration of a single dose of epidural lidocaine and fentanyl before incision reduced pain on movement, secondary mechanical hyperalgesia, and cumulative morphine consumption after abdominal gynecologic surgery when compared with a sham epidural control. Preincisional epidural analgesia also reduced the hourly rate of cumulative morphine consumption compared with epidural analgesia administered after incision and the sham epidural control. Although the magnitude of these effects was modest, they demonstrate the dynamic and plastic nature of postoperative nociceptive processing in the central nervous system. Preoperative blockade followed by prolonged blockade of noxious inputs well into the postoperative period may prove to be the most effective way of managing postoperative pain,<sup>2,51</sup> since the contribution to central sensitization of both noxious intraoperative inputs and postoperative inflammatory inputs may be prevented.

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