

Preemptive Epidural Analgesia and Recovery From Radical Prostatectomy

A Randomized Controlled Trial

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Context.—Preemptive analgesia can decrease the sensitization of the central nervous system that would ordinarily amplify subsequent nociceptive input, but a clear demonstration of its clinical efficacy is necessary for it to become a routine component of acute pain therapy.

Objective.—To determine the impact of preemptive epidural analgesia on postoperative pain and other clinically important outcome variables after radical retropubic prostatectomy.

Design and Setting.—A block randomized double-blind clinical trial lasting 20 months at a single academic medical center.

Patients.—A total of 100 generally healthy and neurologically intact patients scheduled for radical retropubic prostatectomy for the treatment of prostate cancer in whom an epidural catheter for treating postoperative pain was to be placed prior to the induction of general anesthesia.

Interventions.—Epidural bupivacaine, epidural fentanyl, or no epidural drug was administered prior to induction of anesthesia and throughout the entire operation, followed by aggressive postoperative epidural analgesia for all patients.

Main Outcome Measures.—Daily pain scores during hospitalization and pain scores obtained 3.5, 5.5, and 9.5 weeks after hospital discharge.

Results.—The patients who received epidural fentanyl or bupivacaine prior to surgical incision (preemptive analgesia) experienced 33% less pain while hospitalized ($P=.007$). Pain scores in those receiving preemptive analgesia were significantly lower at 9.5 weeks ($P=.02$), but were not significantly different at 3.5 or 5.5 weeks. At 9.5 weeks, 32 (86%) of 37 patients receiving preemptive analgesia were pain-free compared with 9 (47%) of 19 control patients ($P=.004$). Patients receiving preemptive analgesia were more active 3.5 weeks after surgery ($P=.01$), but not at 5.5 or 9.5 weeks.

Conclusions.—Even in the presence of aggressive postoperative pain management, preemptive epidural analgesia significantly decreases postoperative pain during hospitalization and long after discharge, and is associated with increased activity levels after discharge.

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THE TREATMENT of postoperative pain is of justifiable public concern^{1,2} because appropriate perioperative pain therapy may decrease patient morbidity,^{3,4} improve patient satisfaction,⁵ and help prevent the development of chronic pain syndromes.^{6,7} These considerations underlie recent laboratory work that is be-

ginning to elucidate the physiologic basis of pain perception and modulation. Such studies⁸⁻¹¹ of nociception indicate that the timing of an analgesic regimen with respect to the onset of painful stimuli may play an important role in the perception of subsequent stimuli. By preventing sensitization of the central nervous system (CNS) by painful stimuli, appropriate interventions limit the response to future

For editorial comment see p 1114.

nociceptive input¹² and prevent a degree of CNS sensitization sufficient to enable normally painless stimuli to be experienced as pain.¹³ Preemptive analgesia^{14,15} describes the concept of decreasing pain perception and overall analgesic needs by use of a drug regimen capable of inhibiting CNS sensitization before the application of painful stimuli. Animal studies demonstrate that clinically adequate levels of general anesthesia produced by volatile anesthetics such as isoflurane do not prevent central sensitization by nociceptive impulses.¹⁶ This is of critical importance for appreciating the potential of preemptive analgesia in a surgical setting.

Some clinical trials of preemptive analgesia using intravenous analgesics,^{17,18} local anesthetic infiltration of the surgical site,^{19,20} peripheral nerve block,^{21,22} epidural administration of opioids and local anesthetics,²³⁻²⁷ and multimodality combinations^{28,29} indicate that preemptive administration of analgesics can lead to clinically appreciable analgesic effects. However, even preemptive analgesic regimens with positive results have varied in their efficacy, and the potential for

meaningful long-term benefits from preemptive analgesia remains controversial. Reasons for this varied efficacy^{30,31} may include incomplete blockade of CNS sensitization, a contribution to central sensitization from inadequately treated postoperative pain,¹⁵ and the potential overriding effect of peripheral nociceptor sensitization by tissue factors released in response to tissue injury.³²⁻³⁴

We hypothesized that preemptive epidural analgesia, initiated prior to a major surgical procedure with adequate doses of local anesthetic or opioid, would favorably impact short-term and long-term postoperative pain and would influence other postoperative outcome variables. Therefore, we examined the role of 2 preemptive epidural analgesic regimens in a uniform group of generally healthy patients undergoing radical retropubic prostatectomy, after which all patients, including those in the control group, received the same aggressive postoperative epidural analgesia initiated at the beginning of fascial closure.

METHODS

Patients

In a protocol approved by the Committee on Studies Involving Human Beings at the University of Pennsylvania, Philadelphia, and outlined in Figure 1, all patients scheduled for radical retropubic prostatectomy for the treatment of organ-contained prostate cancer were considered for inclusion in the study. When study personnel were available, patients who had consented to an anesthetic plan consisting of general anesthesia with an epidural catheter to be placed prior to induction of general anesthesia were invited to participate if they were without gross neurologic impairment, any type of chronic painful condition, or cardiovascular conditions (eg, severe valvular heart disease, coronary artery disease) that, in the judgment of the attending anesthesiologist, might proscribe 1 or more arms of the protocol.

Study Protocol

Written informed consent was obtained by 1 of the investigators on the day of surgery. Patients were aware that medication administered intraoperatively through the epidural catheter was being varied within the bounds of current institutional practice, but were not informed of the specific treatment arms.

Baseline Measures.—A research assistant, who was blinded with respect to the eventual treatment assignment, obtained demographic data, administered a health survey (subset of the Health Status Questionnaire; Interstudy/Qual-

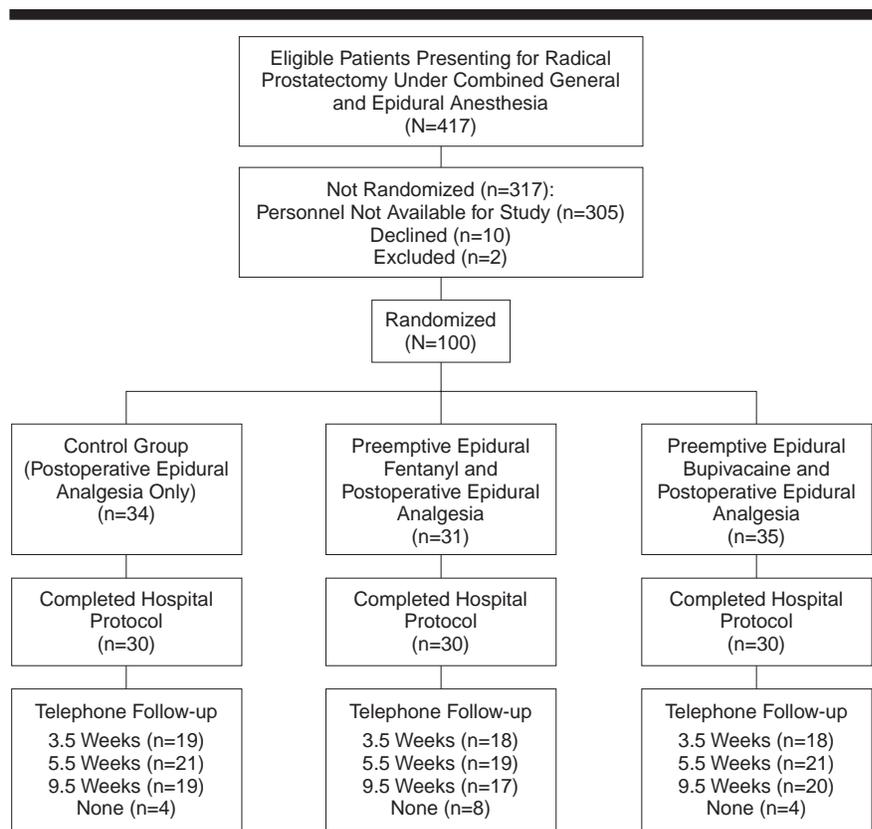


Figure 1.—Flowchart for the clinical trial. Two eligible patients were excluded because of coronary artery disease such that the attending anesthesiologist judged that the patient would benefit from a dose of intravenous fentanyl at induction in order to blunt the hemodynamic response to intubation. Reasons for dropping out of the hospital-based portion of the study include alterations in the surgical schedule after patient randomization (n=3), epidural catheter function not within parameters of the protocol (n=3), patient remained intubated postoperatively for reasons unassociated with the study (n=2), inadvertent use of a nonsteroidal anti-inflammatory drug in a patient who was experiencing no difficulties with pain control (n=1), and patient withdrawal (n=1). Although an attempt was made to contact all subjects completing the hospital-based portion of the study, not all patients could be contacted or were willing to participate further in the study. The number of subjects who provided data when contacted by telephone is indicated for the different times at which contact was initiated. The number of subjects who provided no data after discharge from the hospital is also indicated.

ity Quest Inc, Excelsior, Minn),³⁵ measured the oxygen saturation of hemoglobin with a pulse oximeter (Nellcor; Hayward, Calif) while the patient was breathing room air, and performed pulmonary function tests (PC-Flow⁺; Spirometrics Inc, Auburn, Me). The health survey consisted of 10 questions that assessed activity on a 3-point scale, 1 that assessed bodily pain on a 6-point scale, and 1 that assessed the extent to which bodily pain interfered with normal work on a 5-point scale. After obtaining this information, the patient was randomized to 1 of 3 treatment groups according to a block randomized design in which 10 groups of 9 subjects each were to complete the hospital-based portion of the study. The research assistant presented the attending anesthesiologist with a sealed envelope indicating the particular treatment assignment, and left the treatment area prior to the unsealing of the envelope and the performance of additional steps in the protocol. Individu-

als other than the attending and resident anesthesiologists were not informed of the particular treatment group to which the patient was assigned.

Epidural Placement.—After administration of sufficient intravenous sedation with fentanyl citrate and midazolam to make the procedures tolerable, an arterial catheter was placed and blood samples were obtained for the determination of cortisol levels and hematologic parameters. A lumbar epidural catheter was placed with the patient sitting. The catheter was tested for subarachnoid or intravascular placement with 3 mL of a solution of 1% lidocaine containing 1:100 000 epinephrine. If deemed necessary by the attending anesthesiologist, additional test doses of lidocaine were permitted in order to confirm catheter placement. The patient was placed in the supine position and prepared for anesthetic induction. Patients in group 1 (control group) received no additional drugs through their epidural catheters until

the beginning of fascial closure. Patients in group 2 (fentanyl group) received fentanyl citrate, 4 µg/kg diluted with preservative-free saline to a total volume of 20 mL via the epidural catheter prior to anesthetic induction, and were maintained with fentanyl citrate, 0.75 µg/kg diluted to a total volume of 13 mL with preservative-free saline, every 2 hours. Patients in group 3 (bupivacaine group) received a solution of 0.5% bupivacaine containing 1:200 000 epinephrine and sodium bicarbonate, 0.005 mEq/mL. The bupivacaine solution was administered in divided doses to a total volume of 20 mL. Anesthetic induction was delayed in this group until a sensory level to at least the fourth thoracic dermatome (T4) could be demonstrated by pinprick. The anesthesiologist was free to administer additional doses of the bupivacaine solution to reach this point. Patients were unaware that obtaining a sensory level at this time was characteristic of a particular treatment arm of the protocol. Typically, members of the surgical team were not present until after induction of general anesthesia. Thereafter, the subjects in group 3 received at least 13 mL of the same local anesthetic mixture every 2 hours. The anesthesiologist was free to administer additional local anesthetic to the members of group 3 to attenuate any hemodynamic response to surgery.

Course of Anesthesia.—Induction of general anesthesia was accomplished with sodium thiopental, 3 to 5 mg/kg, and vecuronium bromide, 0.1 mg/kg. Isoflurane in air and oxygen was used for maintenance of general anesthesia. Additional vecuronium bromide was titrated to maintain an adequate level of muscle relaxation. Intravenous fluid therapy consisted of physiologic saline with up to 1 L of 6% hetastarch, 5% albumin, and up to 4 U of previously banked autologous blood. Ephedrine and phenylephrine were permitted to maintain an adequate blood pressure as judged by the attending anesthesiologist. Blood samples were obtained for the determination of plasma cortisol concentrations 2, 4, and 6 hours after incision, and on the morning of the first postoperative day. Blood samples for the measurement of hematologic parameters and coagulation indices were also obtained immediately after incision, 2 and 4 hours after incision, 2 hours after extubation, and on the first postoperative morning.

Postoperative Pain Management.—At the beginning of fascial closure, all subjects received 5 mg of preservative-free morphine sulfate, 1 mg/mL mixed with 8 mL of 2% lidocaine, via the epidural catheter. At the conclusion of surgery, the isoflurane was discontinued, neuromuscular blockade was reversed,

and the patient was extubated on satisfactory emergence from general anesthesia. Subjects in the control and fentanyl groups whose epidural catheter was shown not to be functioning as indicated by the lack of sensory block in the postanesthesia care unit were dropped from the study. Subjects in the bupivacaine group who did not have a T4 sensory level or higher when first examined in the postanesthesia care unit were dropped from the study. Patient-controlled epidural analgesia was initiated in the postanesthesia care unit for all patients by a member of the acute pain service, who followed the standard institutional protocol. This consisted of an infusion of 0.01% preservative-free morphine sulfate and 0.05% bupivacaine, 5 to 10 mL/h, with self-administered bolus doses of 3 to 5 mL and a lockout period of 20 to 30 minutes. Opioids other than those administered through the epidural catheter were not administered per routine while the epidural catheter was in place, although they were permitted if epidural analgesia was judged to be inadequate. The epidural catheter was typically removed on the second or third postoperative day, once oral intake was well tolerated and pain well controlled. Oral analgesics were then used for pain relief under the supervision of a member of the urologic service. Nonsteroidal anti-inflammatory drugs were not administered at any time.

Outcomes Measures

Each postoperative morning, pain scores were determined on a 100-mm visual analog scale (VAS)³⁶ while the patient was at rest, analgesic use was recorded, the oxygen saturation of hemoglobin was determined with a pulse oximeter while the patient was breathing room air, pulmonary function tests were administered, milestones such as the start of patient ambulation were recorded, and significant complications such as angina, pneumonia, renal dysfunction, or admission to the intensive care unit were sought by chart review and patient interview. Testing was usually performed by a research assistant blinded with respect to treatment group. However, on occasion, an anesthesiologist who did not participate in the patient's care and who was blinded with respect to treatment group obtained the postoperative data. An attempt to contact all patients who had completed the hospital-based portion of the study was made by telephone 3.5, 5.5, and 9.5 weeks after the operation. The telephone contact included administering the same health survey as that which was given preoperatively. At 3.5 and 5.5 weeks, this health survey inquired as to the patient's status over the

immediate past 2 weeks; at 9.5 weeks, the patient's status over the immediate past 4 weeks was sought. The telephone survey was performed by a research assistant blinded with respect to the treatment assignment.

Laboratory Studies

Total cortisol levels were determined by radioimmunoassay (Coat-A-Count; Diagnostic Products Corporation, Los Angeles, Calif), and are reported as the average of a single assay performed on duplicates of 2 separate blood samples for each point in time. The whole blood prothrombin time, whole blood partial thromboplastin time, platelet count, hemoglobin level, whole blood fibrinogen level, and thromboelastogram (Thromboelastograph; Haemoscope Corporation, Morton Grove, Ill) were determined using standard techniques.

Statistical Analysis

The number of patients in each group was determined by using a power analysis based on postoperative pain variance taken from an earlier study of preemptive analgesia.²⁵ This analysis indicated that a study with 2 groups of 30 subjects would detect, with a probability of .80, a difference of 12 mm between groups in the VAS measure of postoperative pain at a significance level of .05.

Demographic data were analyzed using 1-way analysis of variance, the Kruskal-Wallis test for analysis of variance by ranks, and the Fisher exact test (2-tailed). Cortisol levels, hematologic parameters, pulmonary function, and VAS pain scores were analyzed using 2-way repeated-measures analysis of variance. Post hoc tests were performed using the least significant difference test. Analgesic use was analyzed by using a multivariate analysis of variance after use of the transformation $\log(1 + x)$ on the dependent variables. The differences between preoperative and postoperative categorical pain and activity scores were analyzed with the Kruskal-Wallis test for analysis of variance by ranks (1-way). The number of patients with residual pain at the conclusion of the study period was analyzed with the Fisher exact test (2-tailed). The time until the achievement of postoperative milestones was analyzed using the Gehan generalized Wilcoxon test for multiple samples. Unless otherwise indicated, all significance levels are reported for the combination of the fentanyl and bupivacaine groups (preemptive group) vs the control group. In all cases, a *P* value less than .05 was considered significant.

RESULTS

Over a period of 20 months, from April 1994 to December 1995, 100 patients

Table 1.—Demographic Data and Intraoperative Parameters of Patients Completing Hospital-Based Portion of Study*

Categories	Control Group (n=30)	Fentanyl Group (n=30)	Bupivacaine Group (n=30)	P Value†
Age, y	60.1 (5.9)	59.5 (6.1)	61.4 (7.4)	.83
ASA physical status score (range: 0-5)	2 (0)	2 (0)	2 (0)	.28
Goldman score ³⁷ (range: 0-49)	3 (0)	3 (0)	3 (0)	.15
Intravenous fentanyl, µg‡	39 (50)	75 (95)	43 (64)	.21
Intravenous midazolam, mg‡	1.1 (0.8)	1.2 (0.7)	1.3 (1.4)	.55
Lidocaine test dose, mL§	3.2 (0.6)	3.0 (0.7)	3.1 (1.0)	.58
Fluid use, crystalloid, L	5.8 (1.9)	5.7 (2.0)	6.2 (2.1)	.65 (.39)
Fluid use, colloid, L	.35 (.44)	.45 (.59)	.49 (.51)	.30 (.26)
Transfusion-packed red blood cells, L	.25 (.37)	.31 (.61)	.29 (.45)	.62 (.68)
Phenylephrine use, mg¶	.13 (.25)	.27 (.94)	.24 (.42)	.69 (.79)
Ephedrine use, mg¶#	20.9 (18.9)	11.5 (14.3)	38.5 (30.9)	.47 (.01)
Total sodium thiopental, mg	455 (128)	424 (88)	423 (83)	.17 (.26)
Total vecuronium bromide, mg	21.7 (5.6)	20.1 (6.8)	20.7 (5.0)	.31 (.45)
Dural punctures, n**	1 (3.3)	0 (0)	1 (3.3)	.99 (.99)

*Continuous data are reported as mean (SD); ordinal data (American Society of Anesthesiologists [ASA] physical status and Goldman scores) are reported as median (quartile range); and frequency data (dural punctures) are reported as the number (percentage) of events.

†P values are reported for preemptive group vs control group and, in parentheses, for bupivacaine group vs control group as determined by 1-way analysis of variance, the Kruskal-Wallis test by ranks, and the Fisher exact test for continuous, ordinal, and frequency data, respectively.

‡Medications were administered prior to anesthetic induction to make procedures tolerable.

§Total volume of local anesthetic test dose used to place epidural catheter.

||Fluid therapy during surgery.

¶Vasopressors administered during surgery to support blood pressure.

#Ephedrine use is also noted to be significantly different between the bupivacaine and fentanyl subgroups ($P < .001$).

**No patient in the study was treated for a dural puncture headache.

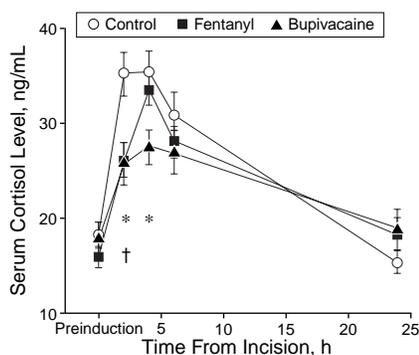


Figure 2.—Total serum cortisol levels (mean \pm SEM) obtained preoperatively, intraoperatively, and on the morning of the first postoperative day. Overall, the cortisol levels of those receiving preemptive analgesia are significantly different when compared with the control group ($P < .001$). An asterisk indicates a significant difference ($P < .001$) for the bupivacaine group vs the control group, and a dagger indicates a significant difference ($P < .001$) for the fentanyl group vs the control group.

were randomized to 1 of the 3 treatment groups (Figure 1). Patient characteristics³⁷ and intraoperative parameters are summarized in Table 1.

Cortisol levels during the perioperative period (Figure 2) differed significantly between the preemptive group and the control group ($P < .001$). Two hours after incision, the cortisol response of the fentanyl group was suppressed with respect to the control group to the same extent as in the bupivacaine group ($P < .001$). Two hours later, there was no difference in the fen-

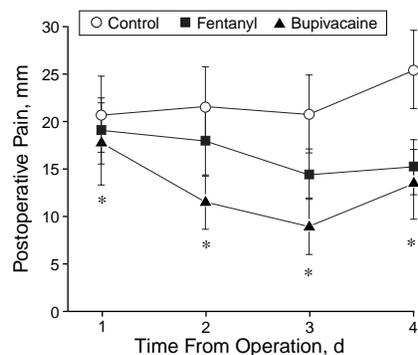


Figure 3.—Postoperative pain while hospitalized (mean \pm SEM) as measured on a 100-mm visual analog scale (VAS), with 0 indicating no pain. Overall, those receiving preemptive analgesia experienced significantly less pain when compared with the control group ($P = .007$), and significant differences (asterisks) were present on each postoperative day ($P = .05$ on the first postoperative day and $P < .002$ on postoperative days 2-4). Significant differences for the bupivacaine group vs the control group were present for each postoperative day ($P = .02$ on the first postoperative day and $P < .002$ for postoperative days 2-4). A significant difference for the fentanyl group vs the control group ($P = .009$) was present on the fourth postoperative day.

tanyl group compared with the control group, while the bupivacaine group continued to show significant suppression ($P < .001$). By the morning of the first postoperative day, serum cortisol had returned to baseline in all groups. As shown in Table 1, intraoperative fluid use and transfusion requirements for the entire surgical procedure were not significantly different between groups. Sig-

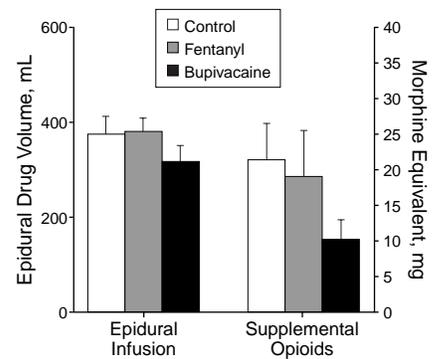


Figure 4.—Total postoperative analgesic use (mean \pm SEM) during hospitalization for each patient group and route of administration. The epidural solution contained 0.01% preservative-free morphine sulfate and 0.05% bupivacaine. The morphine equivalent of opioids not administered through the epidural catheter was obtained by converting each dose to its equivalent of intravenous morphine. Although overall analgesic use did not differ between the preemptive and control groups ($P = .18$), a significant difference was present between the bupivacaine group and the control group ($P = .05$), but not between the bupivacaine group and the fentanyl group ($P = .11$).

nificantly more ephedrine was administered to the bupivacaine group compared with the control group ($P = .01$) and the fentanyl group ($P < .001$). Coagulation indices (not shown) did not differ significantly among groups.

Patients in all groups had excellent pain control³⁸ for the first 4 days of hospitalization, as indicated by mean VAS pain scores of 21 mm \pm 1.8 mm (mean \pm SEM), 16 mm \pm 1.4 mm, and 12 mm \pm 1.5 mm for the control, fentanyl, and bupivacaine groups, respectively. Thus, the group with the highest pain level had a pain score of only 21% of the maximum pain score of 100. Despite excellent overall pain control, VAS pain scores during hospitalization (Figure 3) were significantly lower for those patients who received preemptive analgesia compared with the control group ($P = .007$), and significant differences were observed on each postoperative day. Overall, these differences represented a 33% reduction in pain scores during hospitalization for the members of the preemptive group. When the treatment groups were evaluated individually, the trend toward decreased VAS pain scores for the fentanyl group compared with the control group reached statistical significance only on the fourth postoperative day ($P = .009$, Figure 3). The trend toward less pain in the bupivacaine group compared with the fentanyl group did not reach statistical significance ($P = .28$), and significant differences were not seen between the 2 preemptive subgroups on individual hospital days.

Table 2.—Postoperative Milestones and Complication Rates During Hospitalization*

Milestones	Control Group (n=30)	Fentanyl Group (n=30)	Bupivacaine Group (n=30)	P Value†
Tracheal extubation, min	-18.8 (14.4)	-15.8 (7.5)	-18.0 (7.7)	.96 (.54)
Removal of nasogastric tube, h	14.8 (6.9)	15.6 (7.7)	13.0 (6.1)	.46 (.39)
Out of bed to chair, h	38.0 (20.5)	39.6 (7.4)	36.2 (8.6)	.78 (.64)
Ambulating, h	52.1 (16.4)	55.9 (22.6)	48.9 (14.7)	.41 (.10)
First flatus, h	61.5 (20.1)	73.6 (26.8)	65.6 (27.0)	.15 (.76)
First bowel movement, h	62.1 (41.7)	58.8 (52.8)	65.8 (44.2)	.36 (.48)
Discharge from hospital, h	134.4 (37.9)	134.0 (36.0)	128.6 (25.3)	.66 (.65)
Complications, n (%)‡	2 (6.7)	4 (13.3)	4 (12.9)	.49 (.67)

*Postoperative milestones are reported as mean (SD). All times are given with respect to the arrival of the patient in the postanesthesia care unit after completion of surgery.

†P values for postoperative milestones and complication rates are reported for preemptive group vs control group and, in parentheses, for bupivacaine group vs control group. These were determined using the Gehan generalized Wilcoxon test for multiple samples and the Fisher exact test.

‡There were 3 episodes of electrocardiographic changes consistent with myocardial ischemia unassociated with myocardial infarction (1 in the control group and 2 in the fentanyl group); there was 1 uncomplicated myocardial infarction in the bupivacaine group and 1 myocardial infarction complicated by congestive failure in the bupivacaine group (this individual remained intubated, could not participate in the hospital-based portion of the study, and was dropped as indicated in Figure 1, but is included here in reporting the number of complications); there were 2 episodes of new-onset atrial fibrillation unassociated with myocardial infarction (control and fentanyl groups), 1 episode of mild congestive heart failure in the bupivacaine group, 1 patient in the fentanyl group who experienced some postoperative dyspnea and was transferred to the intensive care unit pending negative studies for myocardial infarction and pulmonary embolus, and 1 patient in the bupivacaine group who was somnolent with a normal respiratory rate and received naloxone.

Table 3.—Outcomes After Discharge From Hospital*

Parameter	Control	Fentanyl	Bupivacaine	P Value†
Preoperative				
Pain (range: 1-6)	1 (0)	1 (0)	1 (0)	...
Interference with work (range: 1-5)	1 (0)	1 (0)	1 (0)	...
Activity (range: 10-30)	30 (1)	30 (1)	30 (1)	...
3.5 Weeks After Surgery				
Pain (range: 1-6)	2 (2)	3 (2)	2 (3)	.74 (.84)
Interference with work (range: 1-5)	2 (1)	2 (1)	2 (1)	.65 (.52)
Activity (range: 10-30)	22 (7)	27 (3)	27 (6)	.01‡ (.02‡)
5.5 Weeks After Surgery				
Pain (range: 1-6)	2 (1)	2 (1)	2 (1)	.83 (.61)
Interference with work (range: 1-5)	1 (1)	1 (1)	1 (1)	.46 (.28)
Activity (range: 10-30)	28 (6)	28 (6)	28 (3)	.76 (.86)
9.5 Weeks After Surgery				
Pain (range: 1-6)	2 (1)	1 (0)	1 (0)	.02‡ (.03‡)
Interference with work (range: 1-5)	1 (1)	1 (0)	1 (0)	.11 (.18)
Activity (range: 10-30)	29 (2)	29 (2)	29 (3)	.67 (.95)

*Data are reported as median (quartile range).

†P values for preemptive group vs control group and, in parentheses, for bupivacaine group vs control group as determined by the Kruskal-Wallis test by ranks. Ellipses indicate data not applicable.

‡Denotes significant differences.

Total postoperative epidural and non-epidural analgesic use is shown in Figure 4 (non-epidural opioid analgesics were converted to equivalent intravenous doses of morphine sulfate^{39,40}). Although overall analgesic use was not significantly different between those patients receiving preemptive analgesia and those in the control group ($P=.18$), analgesic use by the bupivacaine group was significantly less than that of the control group ($P=.05$), but not significantly less than that of the fentanyl group ($P=.11$).

Although differences were observed over time, statistically significant differences between groups were not detected for forced vital capacity, forced expiratory volume in 1 second, room-air oxygen saturation, or maximum daily tem-

perature (data not shown). The times at which hospital milestones occurred, including tracheal extubation, nasogastric tube removal, ambulation, return of bowel function, and discharge from the hospital, also did not differ significantly among groups, nor did the complication rate differ significantly (Table 2).

After discharge from the hospital, significant differences in activity scores (Table 3) were noted at 3.5 weeks ($P=.01$), but not at 5.5 or 9.5 weeks. Categorical pain scores (Table 3) were not significantly different at 3.5 weeks or 5.5 weeks. However, at 9.5 weeks there was a significant difference between the preemptive and control groups ($P=.02$). The distribution of categorical VAS pain scores at 9.5 weeks (Figure 5) indicated that 32 (86%) of 37 patients from the fen-

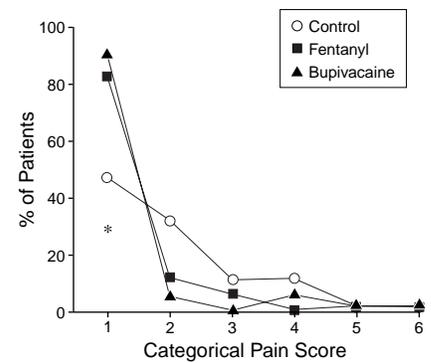


Figure 5.—Distribution of categorical pain scores 9.5 weeks after hospital discharge. Categorical pain scores range from 1 to 6, with a score of 1 corresponding to no pain and a score of 6 corresponding to very severe pain. An asterisk indicates a significant difference for those who received preemptive analgesia compared with the control group ($P=.004$).

tanyl and bupivacaine groups available for follow-up reported no pain compared with 9 (47%) of 19 for the control group ($P=.004$). At that time, the extent that pain was reported to interfere with work (Table 3) was not significant ($P=.11$). Patients available for follow-up at the time of the telephone surveys were no different from those who were not available for follow-up based on the level of pain they experienced during hospitalization ($P=.67$ at 3.5 weeks, $P=.93$ at 5.5 weeks, and $P=.81$ at 9.5 weeks). The patients who were lost to follow-up on discharge from the hospital did not differ from those who were not lost to follow-up based on their hospital-based VAS pain scores ($P=.87$).

COMMENT

This study shows that administration of specific analgesic regimens through an epidural catheter prior to skin incision is associated with long-term benefits in generally healthy patients undergoing major lower abdominal surgery. Although there was a trend toward increased efficacy of preemptive bupivacaine treatment compared with preemptive fentanyl treatment, this difference did not reach statistical significance.

Our finding of long-term benefit with respect to postoperative pain is consistent with animal studies¹¹ and with clinical findings that preemptive analgesia decreases phantom limb pain following amputation.^{6,7} Moreover, the reductions in pain experienced by these patients were consistent with the trend toward their decreased use of analgesics while hospitalized and in their increased activity after discharge from the hospital. The percentage of patients in the control group who continued to experience low

levels of residual pain is similar to that reported for other types of surgery.^{41,42}

The improvement in activity levels 3.5 weeks after the operation was not associated with a significant reduction in pain levels. Our interpretation of these data is that, unless otherwise motivated, patients will be active only to the point of discomfort, and this leads to uniform pain scores despite differences in activity. We speculate that the intergroup differences observed in categorical pain scores 9.5 weeks after surgery occurred as a result of the patients beginning to fully resume routine activities, including employment, even if some degree of discomfort was induced by these activities. The age and general health of the patients in this study did not preclude their employment and patients were generally told to allow 6 weeks for recovery from the operation.

We did not observe significant treatment differences in pulmonary function, complication rates, coagulation indices, bowel function, or the achievement of postoperative milestones. Postoperative pulmonary function is largely determined by preoperative pulmonary function, the location of the surgical incision, and the quality of postoperative pain control.⁴³ Considering the excellent health of our subjects and the quality of pain control achieved, it should not be surprising that no treatment differences in postoperative pulmonary function were observed.

This protocol was designed to test the hypothesis that the use of preemptive analgesia contributes to meaningful improvements in postoperative pain. As such, it was necessary to use a treatment regimen of sufficient potency that the process of central sensitization would be adequately attenuated,³¹ and to use a protocol that controlled for technical failures in the ability to deliver preemptive analgesic therapy or postoperative epidural analgesia. This last consideration motivated assessment of the adequacy of epidural catheter function as part of the protocol. A potentially overwhelming factor might have been sensitization of the peripheral nociceptors by tissue injury.³²⁻³⁴ Since anti-inflammatory drugs may modulate this sensitization, such drugs were not permitted in this protocol. Thus, it is conceivable that failure to appropriately modulate peripheral sensitization could mask beneficial effects of preemptive blockade at the more central components of the pain pathway. However, the uniformly good quality of pain control suggests that sensitization of the peripheral nervous system was not a major factor.

It has been argued that good pain control in the immediate postoperative pe-

riod is an important component of preemptive analgesia by its continued inhibition of CNS sensitization to intense postoperative pain.¹⁵ In this sense, our control group may have benefited substantially from an aggressive postoperative analgesic regimen initiated prior to emergence from general anesthesia. However, in the preemptive groups, the postoperative analgesic regimen may have played an essential role in preserving the benefits produced by the administration of pain therapy prior to the surgical incision. Thus, it cannot be certain that preemptive epidural analgesia will lead to benefits in the presence of postoperative pain management that is less aggressive than was used in the current protocol.

It would have been desirable to have assessed patients at more frequent intervals after discharge from the hospital. Our choices represented a compromise with respect to intrusiveness and also took into account the fact that patients were discharged with a urinary drainage catheter in place, which was removed approximately 2 weeks later. Since its presence might have limited activity, the first assessment was made at 3.5 weeks.

Although it would have been ideal to blind the anesthesiologist caring for the patient during the surgical procedure, this is not truly possible. Titration of local anesthetic administered through the epidural catheter is an essential component of effective epidural anesthesia, and the acute sensory blockade and autonomic response⁴⁴ to epidural local anesthetic administration made the members of this group apparent to the anesthesiologist. Furthermore, the attenuated physiological response to the surgical incision and decreased anesthetic requirements without a substantial decrease in blood pressure during surgery helped distinguish patients receiving epidural fentanyl from the other groups, although these changes were not as marked as for the group receiving epidural bupivacaine.

Although other persons involved in the patients' care were not informed of patient assignment to the various treatment groups, this information could have been obtained through detailed examination of the intraoperative anesthetic record. However, if members of the acute pain or urologic services availed themselves of this information, there is no evidence that it affected postoperative pain management. The trend toward similar or decreased analgesic use in the treatment groups (Figure 4) demonstrates that the decreases in pain seen in these groups were not the result of more liberal analgesic administration.

Not all eligible patients were given the opportunity to enroll in the study be-

cause of logistical issues, but few refused to do so when presented with the opportunity (Figure 1). Logistical considerations prevented the participation of 3 patients who were enrolled in the study and randomized just prior to unexpected revisions in the surgical schedule. Two patients from the bupivacaine group were dropped because adequate sensory blockade could not be obtained preoperatively in 1 case and postoperatively in another. Even if these 2 patients remained within the study, and were found not to be pain-free at the conclusion of the study period, our conclusions would remain unaltered ($P=.01$). Several additional patients were dropped from the hospital-based portion of the study, although only 1 was at the initiative of the patient. In another instance, the inadvertent and potentially confounding administration of a nonsteroidal anti-inflammatory drug was a break with our established protocol that was not in any way related to the quality of pain management, but was rather the arbitrary decision of a junior member of the surgical team. In 2 other cases, complications, whose inclusion (Table 2) does not affect the lack of significant differences in complication rates, precluded the acquisition of appropriate data. In 2 additional instances, patients in the control group were found to have inadequately functioning epidural catheters on arrival in the postanesthesia care unit. Since epidural catheter failure could lead to inadequate pain management in these patients, the inclusion of the patients would have biased this study against the control group.

In summary, our data show that preemptive administration of epidural analgesics can lead to long-term decreases in postoperative pain and earlier resumption of normal activities. These differences were observed even though all subjects received an aggressive postoperative epidural analgesic regimen initiated well before the end of surgery and maintained for several postoperative days.

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