

## *Effects of a Nighttime Opioid Infusion with PCA Therapy on Patient Comfort and Analgesic Requirements after Abdominal Hysterectomy*

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Since pain during the early postoperative period can disrupt a patient's normal sleep pattern, we investigated the influence of a nighttime "basal" infusion of morphine on patient comfort, ability to sleep at night, restfulness, and analgesic requirements following elective abdominal hysterectomy. One hundred fifty-six adult women were randomly assigned to receive either patient-controlled analgesia (PCA) alone or PCA supplemented with a nighttime infusion of morphine  $1.0 \text{ mg} \cdot \text{h}^{-1}$ . The infusion was started in the postanesthesia care unit and continued until the morning after surgery. Subsequently, the infusion was used only during the nighttime hours (10 PM–8 AM). Patients in both treatment groups were able to self-administer supplemental bolus doses of morphine, 2 mg intravenously, as needed during the 72-h study period. The use of a nighttime morphine infusion did not significantly improve the patient's ability to sleep or to rest comfortably at night. Only 8% and 7% of patients in the control and infusion groups, respectively, found it inconvenient to self-administer bolus doses at night. In addition, the number of patient demands and supplemental bolus doses, opioid usage, and recovery parameters were similar in the two treatment groups. The use of a basal infusion resulted in six programming errors, and three patients required discontinuation of the infusion because of hemoglobin oxygen desaturation (i.e.,  $\text{SpO}_2 < 85\%$  for  $> 5 \text{ min}$ ). We concluded that the routine use of a continuous nighttime opioid infusion in combination with a standard PCA regimen failed to improve the management of postoperative pain, sleep patterns, or recovery profiles compared to PCA alone after abdominal hysterectomy. (Key words: Analgesia, postoperative: patient-controlled. Pain: postoperative. Patient-controlled analgesia.)

CHANGES have occurred in the routine management of postoperative pain as a result of technological advances in drug delivery systems. Newer patient-controlled analgesia (PCA) devices provide for more complex prescription programming capability. Theoretical advantages in maintaining an effective blood concentration of the analgesic medication have led to the increased use of background ("basal") infusions with standard intermittent PCA dosing regimens.<sup>1-6</sup> However, reports describing the

effectiveness of opioid infusion techniques when used with conventional PCA therapy have been highly variable.

In a recent study involving the use of 24-h/day continuous morphine infusions ranging from 0.5 to  $2 \text{ mg} \cdot \text{h}^{-1}$ , we were unable to demonstrate any advantage in using these infusion-plus-bolus regimens compared to PCA alone.<sup>4</sup> Patients who are alert and awake appear to have little difficulty managing their pain when using a conventional intermittent dosing PCA system after surgery. However, patients who are excessively sedated in the early postoperative period or who are trying to sleep at night may not self-administer adequate analgesic medication when using a traditional PCA delivery system.

We designed a randomized, controlled study to evaluate the safety and efficacy of two postoperative analgesic regimens. The control group was administered conventional postoperative PCA therapy, whereas the study group received a morphine infusion beginning in the postanesthesia care unit (PACU), which was continued after the day of surgery during the nighttime hours as a supplement to intermittent bolus doses "on demand." The two PCA techniques were compared with respect to the quality of pain relief, degree of sedation, restfulness, and opioid usage, as well as side effects and recovery profiles after abdominal hysterectomy.

### Materials and Methods

After obtaining written informed consent, 156 ASA physical status 1–3 adult women scheduled to undergo abdominal hysterectomy were randomly assigned to one of two postoperative analgesic treatment groups. The study protocol was approved by the Washington University Human Studies Committee. The theoretical basis for PCA therapy and the operational aspects of the Abbott Lifecare PCA® Plus infuser were explained to each patient at the time of the preoperative visit and were reviewed prior to initiating PCA therapy in the PACU. All patients were admitted to the same postsurgical ward after their operation and the nursing staff was familiarized with the use of this PCA device. In addition, the nurses received inservice training by the manufacturer's representative prior to the start of the study.

A standardized general anesthetic technique was used, consisting of thiopental 3–5  $\text{mg} \cdot \text{kg}^{-1}$  intravenously (iv) and fentanyl 2–3  $\mu\text{g} \cdot \text{kg}^{-1}$  iv for induction, and isoflurane

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0.5–1.5% and nitrous oxide 70% in oxygen for maintenance of anesthesia. To provide analgesia during emergence from anesthesia, morphine 0.05–0.15 mg · kg<sup>-1</sup> iv was administered upon completion of the surgical procedure. In the PACU, morphine was administered in 2-mg iv bolus doses by the nursing staff until the patient appeared to be resting comfortably and was judged to be capable of using the PCA device.

The PCA device was connected to the patient's intravenous catheter prior to discharge from the PACU. The control (no infusion) group received morphine 2-mg iv bolus doses with a minimum lockout interval of 10 min. In addition to the intermittent bolus doses, the study group received a continuous (basal) morphine infusion of 1.0 mg · h<sup>-1</sup> iv. The basal infusion was started in the PACU when PCA therapy was initiated and continued through the first night after surgery. During the daytime (8:00 AM–10:00 PM), the infusion was discontinued and all patients received PCA bolus doses only. The programming of the PCA device was performed by the nurses on the postsurgical ward. As a result of the minimum (lockout) interval between successive bolus doses, the number of patient demands could exceed the number of delivered doses. Hemoglobin oxygen saturation (SpO<sub>2</sub>) by pulse oximetry was continuously monitored using a Nellcor Oximet<sup>®</sup> telemetry system while patients were resting in bed. An alarm was sounded at the nursing station when the SpO<sub>2</sub> decreased to < 85%. The desaturation alarm alerted the nursing staff to investigate the possibility of clinically significant desaturation secondary to PCA therapy. Therapeutic interventions (e.g., supplemental oxygen or changes in PCA dosage regimen) were undertaken if the SpO<sub>2</sub> remained < 85% for greater than 5 min.

Postoperative assessments included PCA usage (including number of patient demands, supplemental bolus doses delivered, and hourly morphine use) during the 72-h study period. Patients assessed their pain (no pain to worst pain imaginable), sedation (wide awake, alert to nearly asleep), fatigue (well rested to exhausted), discomfort (extremely comfortable to extremely uncomfortable), and anxiety (very relaxed to extremely nervous) at 8-h intervals using 100-mm linear visual analog scales (with 0 = none to 100 = maximal). Opioid-related side effects and recovery times (e.g., times to ambulation, resumption of liquid intake and solid diet, return of bowel function, discontinuation of PCA therapy, and hospital discharge) were recorded by the ward nurse. Assessment questionnaires were completed by the patients immediately following discontinuation of their PCA therapy (Appendix).

Provisions for changes in the PCA dosage regimen were as follows. 1) A nighttime infusion could be added for the control patients if they felt that the conventional PCA therapy failed to provide acceptable pain relief at night. 2) The nighttime infusion could be decreased by 50% or

discontinued if patients complained of excessive sedation (e.g., drowsiness or sleepiness) and/or the SpO<sub>2</sub> value at night was < 85% for a period of > 5 min. 3) The bolus dose could be decreased by 50% if patients complained of excessive daytime sedation.

## STATISTICAL ANALYSIS

Morphine usage, analog scores, and recovery times were analyzed using one-way analysis of variance (ANOVA) with a Bartlett's *post hoc* test to determine differences between the two groups. The Wilcoxon rank-sum nonparametric test was used to compare median values for visual analog scores and number of supplemental bolus doses in the two treatment groups. Chi-square testing was used to analyze discrete variables. Repeated measures of ANOVA and Student's *t* test with Bonferroni's correction for multiple comparisons were used to evaluate changes in morphine usage over time within each treatment group. A *P* value < 0.05 was considered statistically significant. A power analysis revealed that the study population was sufficiently large for an 85% probability of achieving a statistically significant difference (*P* < 0.05) in morphine use between the basal infusion and control groups if an actual difference of at least 0.5 mg · h<sup>-1</sup> had existed. Data are reported as medians (and interquartile ranges) or mean values ± SD (in tables) and ± SEM (in fig. 1).

## Results

One hundred fifty-six women were enrolled in the study from February, 1990 until January, 1991. The two treatment groups were comparable with respect to demographic variables (table 1). The total intraoperative fentanyl, morphine, and PACU morphine dosages were also similar in the two groups. Four patients in each group were unable to complete the entire 72-h study period. In the control group, PCA was prematurely discontinued as a result of severe pruritus (*n* = 2) and persistent nausea

TABLE 1. Demographic Data for the PCA Treatment Groups

	Control	Nighttime Infusion
Number (n)	78	78
Age (yr)	47 ± 12	46 ± 11
Height (cm)	161 ± 08	162 ± 08
Weight (kg)	73 ± 18	76 ± 23
ASA physical status (1/2/3)	33/42/3	25/50/3
Duration of surgery (min)	168 ± 55	164 ± 69
Intraoperative fentanyl (μg)	217 ± 96	215 ± 83
Intraoperative morphine (mg)	6.4 ± 4.3	7.5 ± 8.7
PACU morphine (mg)	3.7 ± 4.6	5.4 ± 5.3

Data are expressed as mean values ± SD. *P* values < 0.05 were considered statistically significant.

PCA = patient-controlled analgesia. PACU = postanesthesia care unit.

( $n = 2$ ). In the infusion group, 3 patients required discontinuation of PCA therapy because of excessive sedation with sustained  $SpO_2 < 85\%$  for  $> 5$  min, and 1 patient experienced severe pruritus.

The average hourly morphine use (mean  $\pm$  SD) on the day of surgery (from time of PACU discharge until 10:00 PM) was significantly greater ( $P < 0.05$ ) for the infusion group ( $3.8 \pm 1.6 \text{ mg} \cdot \text{h}^{-1}$ ) compared to control patients receiving no infusion ( $3.0 \pm 1.8 \text{ mg} \cdot \text{h}^{-1}$ ). After the initial daytime period, patients in both groups used similar hourly doses of morphine (control  $2.0 \pm 1.4 \text{ mg} \cdot \text{h}^{-1}$  and infusion  $2.3 \pm 1.3 \text{ mg} \cdot \text{h}^{-1}$ ) for the remainder of the 72-h study period. Compared to the control group, the presence of a continuous nighttime infusion of morphine did not significantly decrease the number of demands or supplemental bolus doses (table 2). The ratio of delivered doses to demands from 8 AM until 10 PM ranged from  $0.67 (\pm 0.28)$  on the day of surgery to  $0.90 (\pm 0.22)$  during the 3rd postoperative day; however, it did not differ between the two study groups. Similarly, there were no significant differences in the ratio of hourly PCA doses demanded to the actual doses delivered on the day of surgery and during the nighttime hours (10 PM–8 AM) between the two treatment groups during the 72-h study period (table 3).

Compared to the conventional intermittent PCA dosing technique, the use of a continuous nighttime opioid infusion did not significantly decrease the postoperative pain analog scores (fig. 1). Overall, 59% of the patients in the control group and 65% of the infusion group patients reported sleeping well during the first three nights after surgery. Excessive activity and noise in their hospital room, as well as the unfamiliar surroundings, were the most common reasons cited for difficulty sleeping in both groups (68% vs 64%). The occurrence of nocturnal awakenings secondary to pain were also similar in both groups. In the control group, 59% of patients reported awakening in pain and needed to administer a mean of  $2.4 (\pm 1.8)$  nighttime bolus doses. Similarly, 53% of nighttime infusion patients reported awakening in pain and needed to

TABLE 2. Hourly PCA Bolus Doses during the Day of Surgery and During the Nighttime Hours (10 PM to 8 AM)

	Control	Nighttime Infusion
Day of surgery	1.3 (0.8–3.8)	1.4 (0.8–5.0)
Night of surgery	0.9 (0.5–1.5)	0.8 (0.5–1.2)
Night of POD 1	0.6 (0.5–1.2)	0.6 (0.3–1.0)
Night of POD 2	0.5 (0.3–0.9)	0.5 (0.2–0.8)

Data are expressed as medians (and interquartile ranges).  $P$  values  $< 0.05$  were considered statistically significant.

PCA = patient-controlled analgesia. POD = postoperative day.

TABLE 3. Ratio of Hourly PCA Doses Demanded to Actual Doses Delivered during the Day of Surgery and during the Nighttime Hours (10 PM to 8 AM)

	Control	Nighttime Infusion
Day of surgery	$0.67 \pm 0.28$	$0.75 \pm 0.29$
Night of surgery	$0.79 \pm 0.23$	$0.72 \pm 0.27$
Night of POD 1	$0.78 \pm 0.21$	$0.84 \pm 0.22$
Night of POD 2	$0.83 \pm 0.22$	$0.81 \pm 0.26$

Data are expressed as mean values  $\pm$  SD.  $P$  values  $< 0.05$  were considered statistically significant.

PCA = patient-controlled analgesia. POD = postoperative day.

administer  $2.2 (\pm 1.0)$  bolus doses. Difficulty sleeping secondary to pain was reported in 18% and 15% of the patients in the control and infusion groups, respectively. Only 8% and 7% of patients in the control and infusion

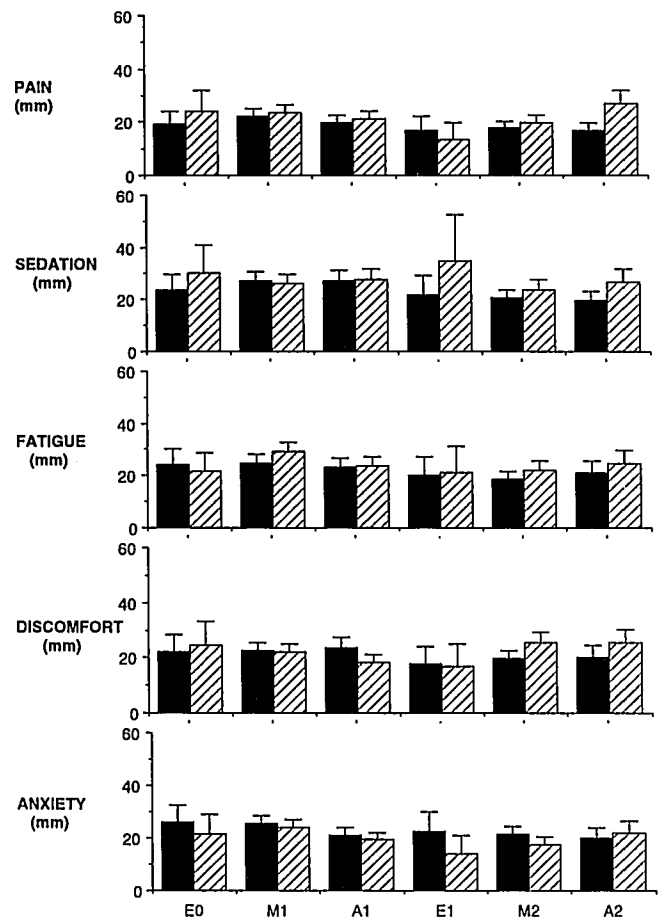


FIG. 1. Postoperative interval analog scores for pain, sedation, fatigue, discomfort, and anxiety on a scale (millimeters) from 0 = none to 100 = maximal. Solid bar = control group (no infusion); hatched bar = nighttime infusion. EO = evening of surgery; M1 = morning of postoperative day (POD) 1; A1 = afternoon of POD 1; E1 = evening of POD 1; M2 = morning of POD 2; A2 = afternoon of POD 2. Values are mean  $\pm$  SEM.  $P < 0.05$  was considered significant.

groups, respectively, stated that self-administering PCA doses during the night was inconvenient.

In the control and infusion group, 76% and 82% respectively, reported being able to rest comfortably during the nighttime hours. Visual analog scores for sedation, fatigue, discomfort, and anxiety were also similar in the two treatment groups (fig. 1). Exclusive of the day of surgery, 50% of patients in each group reported feeling wide awake during the daytime hours. Drowsiness during the daytime was reported by only 12% and 14% of the patients in the two study groups. Opioid-related side effects (table 4) and changes in therapy secondary to side effects were uncommon in both groups (table 5). Only two patients (3%) in the control group required addition of an infusion to improve their postoperative analgesia. More than 95% of the patients felt that their pain relief was adequate and would choose to use PCA therapy again in the future.

A total of six programming errors were recorded during the study in the nighttime infusion group. Two patients were given the continuous infusion but no bolus dose capability; one patient received a basal infusion that was only one half of the intended rate; two patients received two- and five-fold overdoses due to incorrect programming of the drug concentration; and one patient received ten times the prescribed infusion dose when the PCA device was reprogrammed after the battery expired during the early morning hours. All six of these patients were excluded from our data analysis.

Analysis of postoperative recovery parameters revealed no significant differences between the two treatment groups with respect to times to ambulation ( $24 \pm 5$  h in the control group *vs.*  $24 \pm 3$  h in the infusion group), return of bowel function ( $39 \pm 18$  *vs.*  $47 \pm 32$  h), initial oral intake ( $71 \pm 32$  *vs.*  $76 \pm 51$  h), resumption of regular diet ( $106 \pm 43$  *vs.*  $109 \pm 58$  h), or hospital discharge ( $130 \pm 43$  *vs.*  $137 \pm 64$  h).

### Discussion

Despite the theoretical advantages of maintaining a minimum plasma opioid concentration with a continuous

TABLE 4. Percentage of Patients with Opioid-related Side Effects during the 72-h Study Period

	Control	Nighttime Infusion
Nausea	28 (19)	22 (18)
Pruritus	16 (7)	11 (4)
Dizziness	0 (0)	0 (0)
Excessive sedation	1 (1)	1 (1)
Confusion	1 (1)	1 (1)

The number in parentheses indicates the percentage of all patients requiring therapy for side effects. *P* values <0.05 were considered significant.

TABLE 5. Incidence of Changes in the PCA Dosage Regimen as a Result of Side Effects or Inadequate Analgesia

	Control	Nighttime Infusion
Side effects		
Bolus decreased	1/78 (1%)	1/78 (1%)
Infusion decreased	NA	1/78 (1%)
PCA discontinued	4/78 (5%)	4/78 (5%)
Inadequate pain relief		
Bolus increased	0/78 (0%)	0/78 (0%)
Infusion increased	2/78 (3%)*	0/78 (0%)

*P* values <0.05 were considered significant.

NA = not applicable.

\* In the control group (no infusion), a nighttime infusion was added to improve postoperative analgesia.

infusion as part of a standard PCA regimen, recent clinical studies<sup>2,4,5</sup> have been unable to demonstrate a benefit in using a "basal" infusion with PCA. Although nighttime infusions are commonly used in conjunction with PCA therapy,<sup>5</sup> the use of a nighttime opioid infusion to supplement PCA has not been evaluated in a controlled fashion. These data suggest that there is no advantage in the routine use of a continuous nighttime opioid infusion to supplement the traditional intermittent PCA bolus-dosing method after this lower abdominal procedure. We were unable to demonstrate a decrease in the number of nocturnal awakenings secondary to pain, improvement in analgesic effectiveness, patient comfort or overall restfulness, quality of sleep, side effects, or recovery profile when a nighttime infusion was used in combination with intermittent bolus PCA therapy.

The inherent safety of a PCA delivery system results from the fact that the patient determines when additional analgesic medication is needed. If a patient becomes excessively sedated (or somnolent), the number of supplemental PCA bolus doses should decrease, thereby reducing the risk of opioid-induced respiratory depression. Whenever a patient is obligated to receive a minimum dose of opioid medication *via* a continuous infusion as part of a PCA bolus-plus-infusion regimen, the inherent safety of the technique is diminished.<sup>7</sup> Because of marked individual variability in postoperative opioid requirements, some of the patients receiving continuous opioid infusions will inevitably receive more analgesic medication than they would have demanded from a conventional PCA delivery system. In addition, the potential for programming errors is increased when multiple changes are required in the PCA prescription.<sup>8</sup> This study was carried out on a single gynecologic surgery nursing ward. The nurses on this postsurgical ward had been using this PCA device for more than 2 yr before we started the study and had received inservice training by the manufacturer's

representative prior to the study and by the pain research nurse during the 11-month study period.

Even though the nursing staff had considerable experience with this PCA device, six documented programming errors occurred during the course of this investigation. With one exception,<sup>§</sup> the errors were detected before significant adverse clinical effects occurred. Given the lack of any obvious improvement in patient outcome, our data suggest that the routine use of a nighttime (basal) infusion is not justified. The risk of opioid-induced respiratory depression as a result of a programming error and/or enhanced patient sensitivity (e.g., in the elderly population),<sup>8</sup> appears to negate any potential benefit in this surgical population.

Our group<sup>4</sup> and others<sup>2,5</sup> have failed to demonstrate any obvious advantage in the routine use of a continuous opioid infusion to supplement conventional PCA therapy. In our opinion, the intrinsic risk in using a nighttime infusion requires justification on the basis of improved patient comfort, sleep, restfulness (or less exhaustion), diminished anxiety, or fewer nocturnal sleep disturbances secondary to pain. This carefully controlled study failed to demonstrate any clinical advantage in routinely prescribing a nighttime opioid infusion to supplement intermittent bolus PCA therapy following abdominal hysterectomy. In fact, patients did not feel that self-administration of PCA bolus doses during the nighttime hours was inconvenient.

Although these data were carefully collected according to a rigorously controlled protocol, there were limitations in the study design: 1) the liquid crystal display on the PCA device and the need to alter the PCA program twice each day did not allow the protocol to be performed in a double-blinded fashion, and 2) the patient population included only women undergoing abdominal hysterectomy. Thus, the results of this study may not apply to all post-surgical patient populations. Investigator bias as a result of the unblinded study design was minimized by using only objectively collected data.

In conclusion, these data do not support the theoretical advantage in maintaining a constant background infusion during the nighttime hours in this postoperative patient population. Following lower abdominal operations, we recommend that PCA therapy be started with a conventional intermittent dosing regimen and that a continuous nighttime infusion be considered only if pain at night is controlled inadequately. For the use of sophisticated, computer-based, programmable PCA devices, we rec-

ommend that *two* individuals familiar with the device be present during the actual programming of PCA prescription changes. Prior to instituting newer types of analgesic therapy, carefully controlled studies should be performed to determine the risk-benefit ratio. Future studies should examine the use of basal infusion techniques in patients undergoing upper abdominal and major orthopedic procedures.

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## Appendix: Posttherapy Patient Questionnaire

1. Have you slept well at night since the operation?
  - A. No
  - B. Yes
2. The most common cause of difficulty sleeping after the operation was:
  - A. Pain and discomfort
  - B. Activity in the room
  - C. Unfamiliar surroundings
  - D. Need to push the PCA button
  - E. Other (specify)

§ The patient who received a 10-fold overdose due to a programming error required treatment with naloxone and ventilatory support for 5 days in the ICU to treat aspiration pneumonia.

3. Did you ever awaken from sleep at night just because you were in pain and needed an additional dose of pain medicine?
  - A. No
  - B. Yes (How many times per night?)
4. Was self-administering pain medicine from the PCA device during sleeping hours inconvenient?
  - A. No
  - B. Yes (Describe)
5. Were you able to rest comfortably at night?
  - A. No
  - B. Yes
6. Excluding the day of the operation, which of the following best describes how sleepy you felt during the daytime after your operation?
  - A. Wide awake
  - B. Slightly drowsy
  - C. Moderately drowsy
  - D. Very drowsy
7. Would you say that your pain has been "adequately" treated since the operation?
  - A. No
  - B. Yes
8. If you had to undergo the same operation in the future, what method would you choose to provide pain relief after surgery?
  - A. Definitely choose the self-administered (PCA) device
  - B. Probably choose the self-administered (PCA) device
  - C. Not care which pain method was used
  - D. Probably choose to have the usual intramuscular "shots"
  - E. Definitely choose to have the usual intramuscular "shots"