

Does ketorolac produce preemptive analgesic effects in laparoscopic ambulatory surgery patients?

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The purpose of this study was to determine whether intravenous ketorolac tromethamine could produce preemptive analgesia in patients undergoing laparoscopic gynecologic surgical procedures. Each patient's response to pain was measured by the mechanical visual analogue scale (M-VAS) and total analgesic use.

By using a double-blind design, 49 patients were randomized into the preemptive group (n = 25), which received ketorolac preoperatively, or the control group (n=24), which received ketorolac at the conclusion of surgery. Comparisons in pain scores using the M-VAS were made at 6 intervals in the postanesthesia care unit and 24 hours after the procedure. Further comparisons of the total fentanyl use and total postoperative oral analgesic requirements were analyzed.

The preemptive group experienced higher pain scores and postoperative fentanyl use. Only the pain change from baseline between the 2 groups was statistically significant. Total fentanyl use and postoperative oral analgesic use was not statistically significant. Clinically, the preemptive administration of ketorolac to patients undergoing laparoscopic gynecologic surgery did not demonstrate preemptive analgesic effects.

Key words: Ambulatory surgery, ketorolac, preemptive analgesia.

Introduction

The ambulatory surgical setting has been reported to be the fastest growing service among US hospitals.¹ During the past decade, outpatient procedures surpassed the total number of inpatient procedures.² An essential factor in treating ambulatory surgery patients is successfully controlling their postoperative pain. By preventing postoperative pain and emesis, the timely discharge of ambulatory patients can be ensured since both of these sequelae may cause an unanticipated overnight admission.³ With inadequate pain control, a patient's discharge may be delayed. Challenges exist concerning the care of the ambulatory surgery patient because the primary method of managing surgical pain is via opioids; however, these drugs have multiple adverse effects that may prevent or delay discharge the same day. These effects include respiratory depression, sedation, nausea, vomiting, and urinary retention. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a possible treatment for postoperative pain.⁴ Ketorolac, the only NSAID available in the intravenous form, offers an alternative to opioids since NSAIDs do not cause sedation or respiratory depression (Figure 1).

Preemptive analgesia⁵ is a new concept for

providing pain relief (Figure 2). This term suggests that an analgesic given before a painful stimulus will prevent or reduce subsequent pain. A noxious injury, such as surgery in which tissue damage occurs, causes a “hypersensitivity” response that initially peaks and then decreases over time. This occurs because not only are the myelinated A- δ and unmyelinated C fibers stimulated by the painful insult, but a central change also occurs. This second mechanism of central sensitization involves a change in the excitability of neurons in the spinal cord. This progressive change in the spinal cord excitability results in a “wind-up” phenomenon that can manifest as a hypersensitivity state that outlasts the duration of the initial injury.⁵

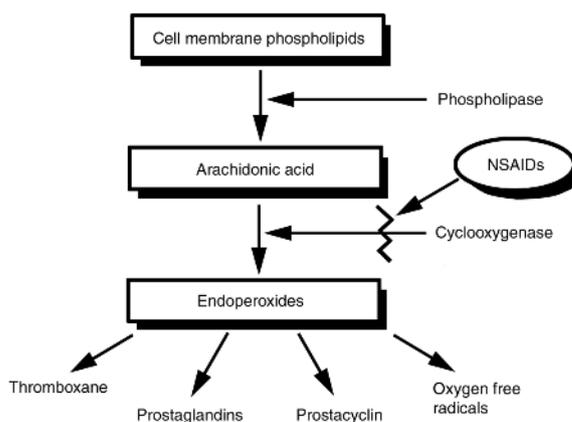
The value of preemptive analgesia for treating postoperative pain has been studied by several investigators; however, inconsistencies in the overall design of these studies has created questions about the significance of the results. Despite such criticism, preoperative epidural administration of bupivacaine and morphine clearly reduced phantom limb pain in amputees.⁶ Preincisional infiltration of the surgical wound with a local anesthetic also provided better postoperative analgesia than postincisional infiltration among patients undergoing elective herniotomy.⁷ The preoperative administration of NSAIDs also has decreased the postoperative requirement for opioid analgesics in patients who have undergone laparoscopic surgery.⁸⁻¹²

Most of these studies revealed an analgesic intervention before surgery was better than no intervention at all. These results led researchers to

conclude that preemptive analgesia was demonstrated.¹³ The positive results suggested a clinical benefit. Evidence for or against preemptive analgesic effects must require a control of the same intervention made both before and after surgery (Figure 3). Few studies have followed such a design.

The timing of analgesia may have potential importance in the management of postoperative

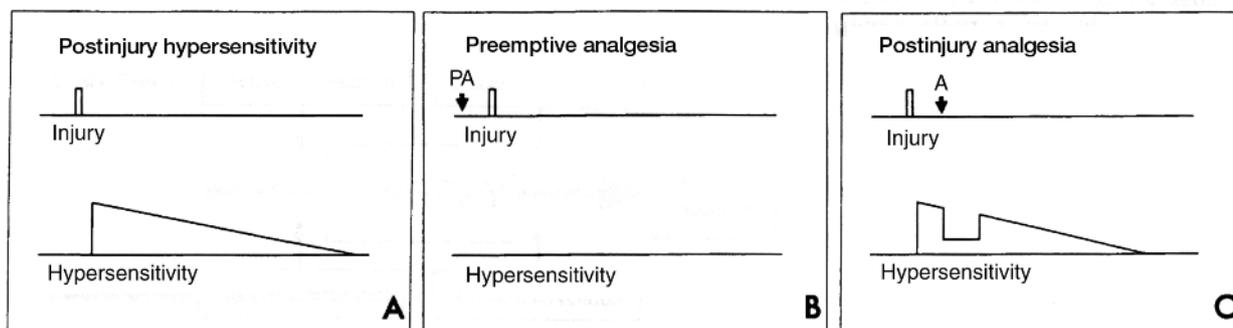
Figure 1. The proposed mechanism of action of the nonsteroidal anti-inflammatory drugs (NSAIDs)



NSAIDs block the enzyme, cyclooxygenase, which is essential for the synthesis of prostaglandins and thromboxanes.

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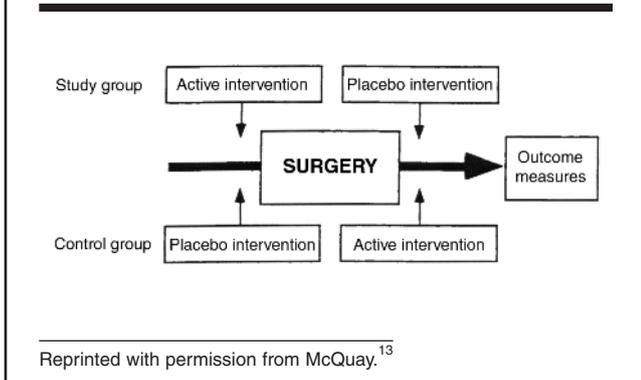
Figure 2. Preemptive analgesia



A simple model of the rationale behind single-treatment preemptive analgesia. Injury triggers central sensitization, leading to a prolonged hypersensitivity state (A). A preemptive analgesic (PA) prevents the induction of the central sensitization, preempting the postinjury hypersensitivity (B). Postinjury analgesia (A) has a much diminished effect on an established state of hyperexcitability.

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Figure 3. The recommended study design for determining whether a preemptive analgesic effect is present



pain.¹⁴ Preempting pain is essential for managing postoperative pain.⁵ With few studies investigating preemptive analgesia with optimal study designs, more research is necessary. Profound benefits to all surgical patients could occur if properly conducted studies revealed improved pain control by using preemptive analgesia. The present study investigated whether the NSAID, ketorolac, produces a preemptive analgesic effect in patients undergoing ambulatory laparoscopic surgery.

Materials and methods

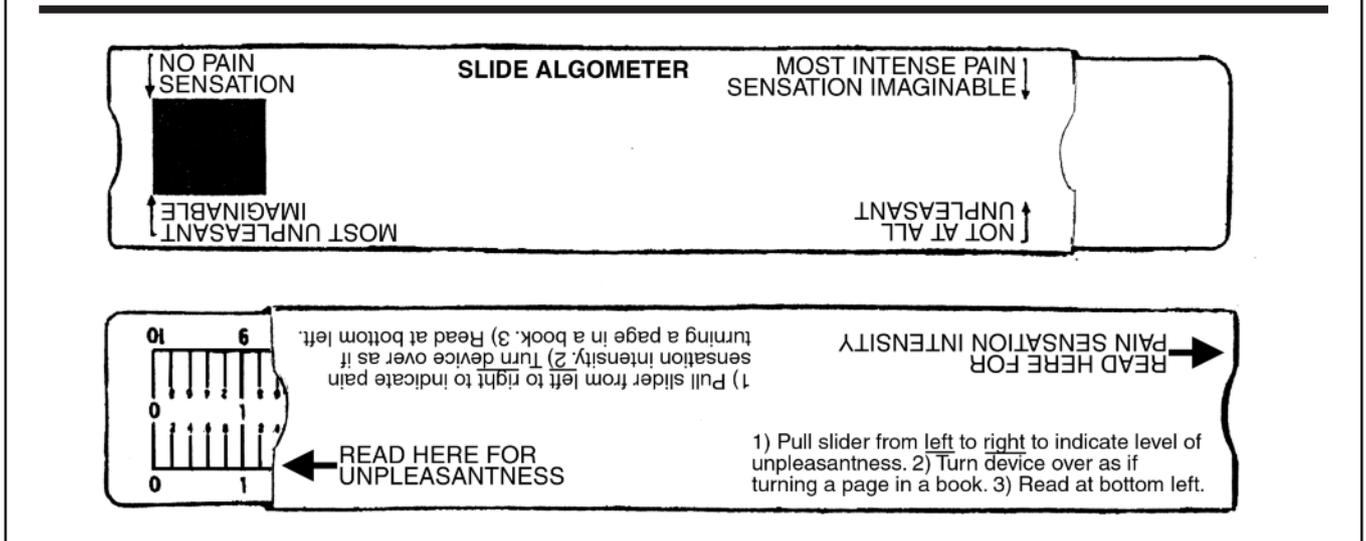
Approval was obtained from the institutional review board, and written informed consent was obtained from 51 women, ASA physical status I or II, between the ages of 18 and 65 years who were

scheduled to undergo laparoscopic gynecologic procedures in the ambulatory surgery center at a large mid-Atlantic university teaching hospital. Only healthy patients with ASA physical status I or II were included in the study. Patients with clinically significant renal, hepatic, or cardiopulmonary disease that placed them in the ASA physical status III or IV were excluded. In addition, any woman who was pregnant, lactating, addicted to drugs or alcohol, or hypersensitive to aspirin or NSAIDs or had a history of peptic ulcer disease or gastrointestinal problems was excluded from the study.

Upon entry into the study, each participant was randomized by a computer-generated number sequence to 1 of 2 treatment groups. Patients in group 1 (n = 25) received intravenous (IV) ketorolac, 30 mg, when they entered the operating room and 1 mL IV isotonic sodium chloride at the completion of surgery. Patients in group 2 (n = 24) received IV isotonic sodium chloride, 1 mL, before surgery and IV ketorolac, 30 mg, after surgery.

Patients were enrolled in the study in the holding area on the day of surgery. At this time, a 15-cm mechanical visual analogue scale (M-VAS) with the endpoints of *no pain sensation* and *most intense pain sensation imaginable* was explained to minimize errors in using the scale (Figure 4). When properly used, the visual analogue scale (VAS) has been heralded as a reliable, valid, and sensitive self-report measure for studying subjective patient experiences.^{15,16} After this instruction, the patients then moved the slider from left to right to demonstrate their level of discomfort preoperatively. A discharge

Figure 4. Mechanical visual analogue scale



sheet with a 15-cm VAS was also shown and explained to the patients so they could use it to reveal their pain score 24 hours after the surgery. Further instructions were given to document the number of pain pills consumed after their discharge from the ambulatory surgery facility.

By using the random number sequence, the study drugs were prepared by a registered nurse who did not participate in the study. Each syringe contained 1 mL of ketorolac or 1 mL of normal saline. Since ketorolac has a slightly yellowish color, each syringe was labeled by covering the area where the drug was visible to maintain the double-blind nature of the study.

The same general anesthetic was administered to both groups for induction and intubation: midazolam, 1 to 2 mg; d-tubocurarine, 3 mg; fentanyl, 1 to 2 $\mu\text{g}/\text{kg}$; propofol, 1 to 2.5 mg/kg; and succinylcholine, 1.5 mg/kg. Maintenance was achieved with an oxygen-nitrous oxide mixture and a continuous infusion of propofol at 100 to 200 $\mu\text{g}/\text{kg}$ per minute. Additional doses of propofol 20 to 40 mg or isoflurane were administered if needed. "Rescue" doses of fentanyl, 12.5 to 25 μg IV, also were given intraoperatively if the patient's vital signs revealed a hemodynamic change that indicated a sympathetic response to pain. The same dose of fentanyl was given postoperatively if the patient voiced discomfort in the postanesthesia care unit (PACU). If pain control was not obtained with fentanyl in the PACU, morphine, 2 to 4 mg IV, was given. Ondansetron, 4 mg, or droperidol, 0.625 mg, was given for nausea or vomiting.

The researcher or nurses who assisted with the data collection asked each patient to use the M-VAS to measure her pain intensity level on admission to the PACU and every 15 minutes for 4 times, followed by every 30 minutes for 2 times or up to discharge, whichever occurred first. The initial pain level at times was difficult to obtain for sleepy patients whose consciousness was clouded with anesthesia. One limitation of the M-VAS is the variability of each patient's ability to use the slide algometer, which was completely dependent on their level of alertness after surgery.

At the time of discharge, instructions were repeated about record keeping for the prescribed analgesic for discharge. A 15-cm VAS on a piece of paper also was given to the patients to record their 24-hour pain scores. The patients were instructed to place a mark on the paper 24 hours after the surgery. After placing the mark, they were asked to turn the bottom edge of the paper up to meet the endpoints of the scale and to note the number between 0 and 10 that correlated to their mark.

The investigator telephoned the subject the following day to obtain the VAS score and the number of analgesics taken since discharge from the ambulatory surgery unit.

Data were analyzed by several methods. Continuous variables such as age, weight, length of surgery, and total preoperative and postoperative fentanyl use were analyzed with the *t* test. Chi square contingency tables also were used to evaluate the independence of categorical variables, such as the number of oral analgesics and NSAIDs taken at home. Analysis of the patient's perceived pain upon arrival to the PACU, every 15 minutes for the first hour, every 30 minutes for the second hour, and at 24 hours after the surgery was evaluated using a repeated measures analysis of covariance or ANCOVA. A *P* value of $<.05$ was established as indicating statistical significance.

Results

Of the 51 subjects who consented, the data for 2 were excluded from statistical analysis because the proposed laparoscopic procedure progressed to an open laparotomy. Homogeneity between the 2 groups was examined. The groups were similar in age ($P>.05$, *t* test), weight ($P>.05$, *t* test), and ASA physical status classification ($P>.05$, χ^2). The length of surgery also was analyzed and found to be similar ($P>.05$, *t* test). No statistically significant differences existed between the groups relative to these characteristics.

Laparoscopic bilateral tubal ligation or diagnostic laparoscopy with lysis of adhesions were the major surgical procedures for the patient population. Several of the patients underwent additional gynecologic procedures that included ovarian cystectomy, drainage of ovarian cysts, endometrial ablation, and biopsies. Each group was categorized into the various types of laparoscopic procedures. The *t* test indicated the surgical procedure was independent of the group ($P>.05$).

The basic statistical method used to analyze the pain variable was ANCOVA. Since several of the patients in each group had a baseline pain score of more than 0, the baseline pain score was the covariate. Group 1 had a mean baseline score of 0.252, and group 2 had a mean baseline pain score of 0.158. Analysis by this method avoided being misled by chance differences in preoperative pain levels.

One variable factor that was impossible to completely eliminate was the use of local anesthetics at the trocar sites. Some surgeons insisted on using 5 to 10 mL of bupivacaine at the end of the procedure, while others used a local anesthetic

despite saying preoperatively that a local anesthetic would not be given. Since 8 (32%) of the patients in group 1 and 9 (38%) of the patients in group 2 received local anesthetic at the end of the procedure, it became essential to consider 2 factors in the analysis: group and local. After determining that the interaction of the covariate with the 2 factors was similar, the repeated measures of ANCOVA for pain was completed.

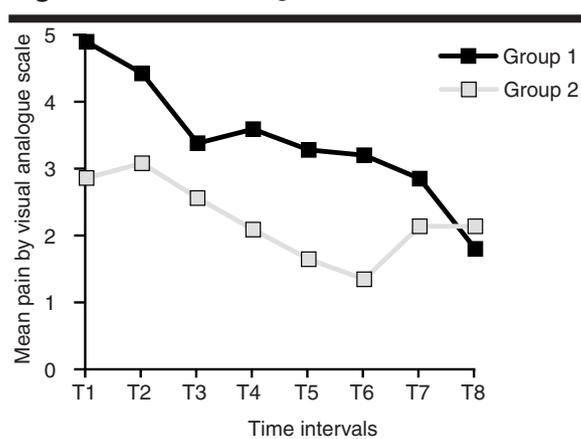
First, the between-group effect tested the hypothesis that there was no difference in the mean pain scores over time after adjusted for the baseline covariate. The 2 groups did not have equal means, which revealed a difference between the groups. The between-local effect tested the hypothesis that the mean pain score (adjusted for the covariate) of the patients who received a local anesthetic at the end of surgery was equal to the mean score for the patients who did not receive a local anesthetic. With $P=.935$, statistical significance was not reached.

The within-time effect tested the hypothesis that the mean pain scores of the 2 groups were equal at each point in time. This effect reached statistical significance, $P<.001$, indicating that the means were not the same at each point in time. This finding was not surprising because pain was expected to decrease over time. Determining whether the pattern of change over time was the same in both groups was the most crucial objective. This was obtained from the time-by-group interaction effect. Statistical significance was reached ($P=.01$), indicating that the pattern of change over time was not the same for both groups. This lack of parallelism between the groups is shown in Figure 5. Group 1 (preoperative ketorolac) had pain scores that were higher initially, dropped suddenly at first, and increased at 45 minutes after admission to the PACU, and dropped slowly thereafter. For group 2 (postoperative ketorolac), pain scores increased slightly at 15 minutes after admission to the PACU and then dropped rapidly. At 24 hours after surgery, the 2 groups experienced similar pain levels.

Postoperative fentanyl use was compared between the groups. No difference in the perioperative narcotic dose was revealed ($P=.424$, t test), and no difference in postoperative fentanyl use was shown, but this difference approached statistical significance ($P=.101$, t test).

The remaining variables were all categorical and were analyzed by means of the χ^2 test of independence. Some surgeons injected local anesthetic at the end of the procedure. The use of local anesthetic did not differ between the 2 groups ($P>.05$).

Figure 5. Pain change from baseline*



Time intervals:

- T1 = Admission to postanesthesia care unit
- T2 = 15 minutes after admission
- T3 = 30 minutes after admission
- T4 = 45 minutes after admission
- T5 = 60 minutes after admission
- T6 = 90 minutes after admission
- T7 = 120 minutes after admission
- T8 = 24 hours after surgical procedure

*Group 1 received ketorolac given before surgery; group 2 received ketorolac at conclusion of surgery.

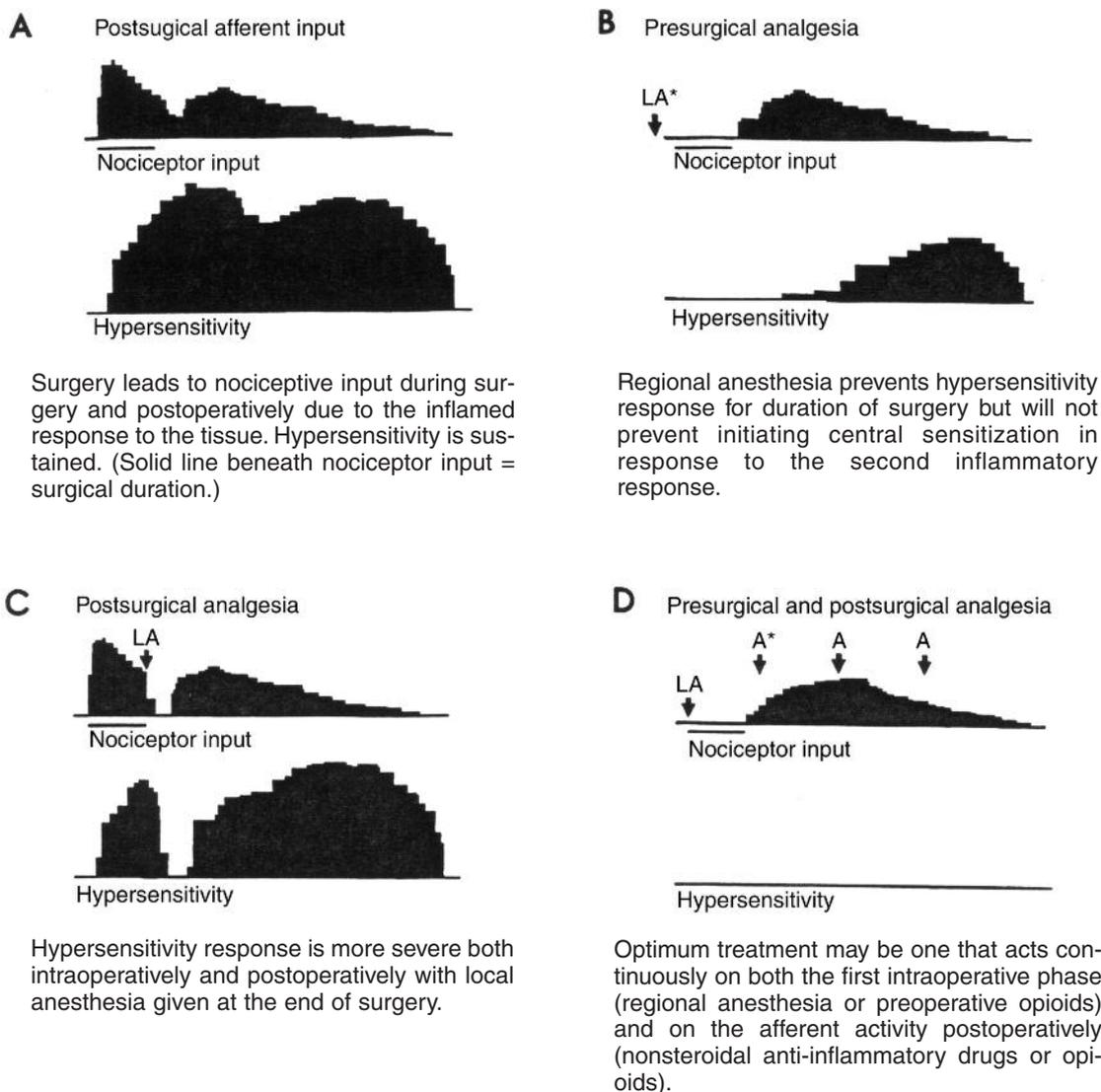
Several patients required an additional narcotic postoperatively because fentanyl failed to control their pain. Generally, morphine was given; however, 1 patient received meperidine hydrochloride since she had pain and shaking chills. The use of intravenous narcotics postoperatively did not differ between the groups ($P>.05$, χ^2).

The postoperative oral analgesic requirements of the groups also were studied. Each patient received a prescription for acetaminophen, 300 mg, and codeine phosphate, 39 mg, or acetaminophen, 325 mg, and oxycodone hydrochloride, 5 mg. Several patients also received a prescription for an NSAID, such as ibuprofen. The use of oral analgesics taken after discharge by group was not statistically significant ($P>.05$, χ^2). The use of NSAIDs postoperatively between groups also was non-significant ($P>.05$, χ^2). A final analysis between postoperative oral analgesic use and local anesthetic administration did not reveal a difference between the groups ($P>.05$, χ^2).

Discussion

The results of the present study confirm that preoperative administration of ketorolac did not produce preemptive analgesic effects. In fact, the data revealed that patients given ketorolac at the

Figure 6. Model illustrating why single-treatment preemptive analgesia may be insufficient for managing post-operative pain*



* LA indicates local anesthetics; A indicates analgesia.
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conclusion of surgery had significantly less pain according to scores on the M-VAS. These were the only data that were statistically significant. All other comparisons of narcotic use between the 2 groups were not statistically significant. The only data that approached a level of significance of $P < .05$ were those for the postoperative fentanyl use while in the PACU. Since group 1, who received the preemptive medication, had higher pain scores than group 2, a higher consumption of

fentanyl would be expected since their pain was greater. The increased fentanyl use accurately correlated with the group with greater pain.

Since NSAIDs prevent the formation of prostaglandins, which have been identified as mediators of inflammation, one would think that an NSAID would decrease the inflammatory process. By reducing the inflammatory process, the hypersensitivity state should decrease. Therefore, pain should decrease. Since the preemptive

group had greater pain postoperatively, one must conclude that other mechanisms are occurring. Other possible mechanisms initiate new questions that can initiate more research to understand the complex subject of pain.

One possible explanation is that surgery leads to nociceptive input both before and after surgery (Figure 6). Woolf and Chong⁵ suggest that both phases of nociceptor input have the capacity to induce central sensitization. Thus, a single preemptive treatment may not be sufficient to eliminate completely the postoperative pain hypersensitivity because it could be induced by the second phase of nociceptor input. The most effective treatment would aim at eliminating the effects of both the first and second phases of afferent output. This could be achieved by administering a preemptive analgesic before and after surgery, thus, continuously preempting the establishment of central sensitization. Group 1 in the present study seemed to follow the pattern in Figure 6B quite well. Instead of a local anesthetic, an NSAID was given preoperatively. Notice the hypersensitivity response that follows the higher pain scores of group 1. Group 2, which had the lower pain scores, follows the pattern in Figure 6D fairly consistently. Woolf and Chong's theory may have merit as researchers attempt to understand the complexities of pain and how to best manage it.

Since few studies compare the use of an NSAID before and after surgery, it is difficult to compare present results with earlier research. One study found that the preoperative use of an NSAID before tubal ligation did not decrease the postoperative analgesic requirements or nonnarcotic analgesia use.¹⁷ The authors proposed that perhaps other factors besides prostaglandins mediate postoperative pain in patients undergoing laparoscopic tubal sterilization. This is also a viable explanation for results of the present study. The possibility of laparoscopic surgery inducing different types of pain from the incision, the insufflation of carbon dioxide, and the inflammatory effects of manipulating or ligating the fallopian tubes must be considered. The key to understanding this lies in further research targeting the various areas that create a hypersensitivity response and studying which drugs to give and when to give them.

The concept of preemptive analgesia is not one on which researchers fully agree. Various study designs have altered the opportunity to compare different studies. The present study questions the veracity of the preemptive analgesic model. Blocking prostaglandins at different times within

the surgical period is one possible approach to managing pain. Further research that combines the preemptive analgesic concept with the proposed theory of 2 hypersensitivity responses may provide more insight into effectively managing postoperative pain. With such research, the complexities of the subject of pain may be further clarified.

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ACKNOWLEDGMENTS

I acknowledge Jim P. Embrey, CRNA, PhD, former director of research, Virginia Commonwealth University School of Nurse Anesthesia, Richmond, Va; John T. Beeston III, thesis committee chairman and assistant director of research, Virginia Commonwealth University School of Nurse Anesthesia; Terry W. Hurt, MD, who developed this research idea; Sue LeGrande, CRNA, MSNA, who initially started the data collection; Ted Carron, statistician; and the nurses, nurse anesthetists, and anesthesiologists at the Medical College of Virginia Hospital Ambulatory Surgery Center, Richmond, Va, who assisted with this research project.