Anesthesiology
73:381–385, 1990

# *Effect of Epinephrine on Intrathecal Fentanyl Analgesia in Patients Undergoing Postpartum Tubal Ligation*

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**Eighty women receiving spinal anesthesia for postpartum tubal ligation were entered into a double-blind, randomized protocol studying the effects of epinephrine on intrathecal fentanyl-induced postoperative analgesia. All patients received 70 mg hyperbaric lidocaine with either 0.2 mg epinephrine (LE), 10 μg fentanyl (LF), epinephrine and fentanyl (LFE), or 0.4 ml saline (L). Onset and regression of anesthesia, degree of intraoperative comfort, incidence of pruritus, and extent of postoperative analgesia were evaluated. The simultaneous administration of epinephrine and fentanyl prolonged the duration of complete analgesia (137 ± 47 min (LFE); 76 ± 32 min (LE); 85 ± 44 min (LF); 65 ± 36 min (L)) and the duration of effective analgesia (562 ± 504 min (LFE); 227 ± 201 min (LE); 203 ± 178 min (LF); 198 ± 342 min (L)). Administration of epinephrine decreased the incidence of pruritus associated with intrathecal fentanyl (1/18 (LFE); 1/21 (LE); 8/19 (LF); 2/19 (L)). (Key words: Pain; postoperative. Analgesics, intrathecal: fentanyl. Sympathetic nervous system, catecholamines: epinephrine.)**

INTRASPINAL OPIOIDS are widely used in the management of acute postoperative pain. Lipid-soluble opioids such as fentanyl are used in an attempt to provide analgesia while reducing the incidence and severity of potential bothersome side effects.[1,2] The addition of epinephrine enhances postoperative analgesia obtained after a relatively small dose (*i.e.*, 25 μg) of epidural fentanyl[3] and after a repeated dose of epidural fentanyl.[4] However, side effects, especially pruritus, are more frequent.[3,4] In animals, the simultaneous intrathecal administration of an alpha-adrenergic agonist and opioid has been shown to increase analgesia in a multiplicative fashion.[5,6,7] This study was designed to investigate acute postoperative analgesia after the administration of epinephrine or fentanyl or a combination of these in patients receiving lidocaine spinal anesthesia for postpartum tubal ligation.

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Received from the Department of Anesthesiology, University of Maryland School of Medicine, University of Maryland Hospital, Baltimore, Maryland. Accepted for publication March 21, 1990. Presented in abstract form at the Meeting of the American Society of Regional Anesthesia, Boston, Massachusetts, 1989; at the Meeting of the Society for Obstetric Anesthesia and Perinatology, Seattle, Washington, 1989; and at the Meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, 1989.

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## Methods

Eighty ASA physical status-1 or -2 patients electing spinal anesthesia for postpartum tubal ligation gave written informed consent to a protocol approved by the Human Volunteers Research Committee. Patients with a history of drug abuse were excluded from the study.

Patients were assigned to receive one of four intrathecal study drug solutions according to a computer-generated random number list. All study drug solutions were prepared by an anesthesiologist uninvolved with the administration of anesthesia or in observation of the patient. Seventy milligrams of commercially prepared lidocaine 5%/dextrose 7.5% (Abbott, Chicago, IL) were mixed with either: 0.4 ml preservative-free normal saline (group L); 0.2 mg (0.2 ml) epinephrine plus 0.2 ml saline (group LE); 10 μg (0.2 ml) fentanyl plus 0.2 ml saline (group LF); or 10 μg fentanyl plus 0.2 mg epinephrine (group LFE). The total volume of study drug injectate was 1.8 ml.

All patients received 30 ml oral Bicitra (Willen, Baltimore, MD) and 1 l intravenous lactated Ringer's solution. Pulse oximetry, continuous electrocardiography, and blood pressure (automated noninvasive oscillometric cuff) were monitored. Patients were placed in the right lateral decubitus position (with thoracolumbar spine parallel to the floor) for midline subarachnoid insertion of a 26-G Quincke type spinal needle through a 20-G introducer at the second or third lumbar interspace. The patient was placed in the sitting position only after unsuccessful attempts at subarachnoid needle insertion with the patient in decubitus. The patient was placed supine immediately after the injection of study drug. Supplemental oxygen was administered. Systemic arterial blood pressure was measured every minute for 15 min immediately after induction of spinal anesthesia and at least every 2.5 min thereafter. Hypotension, defined as a greater than 25% decrease in arterial pressure from preanesthetic level, was treated with incremental intravenous ephedrine and crystalloid infusion. Systemic arterial blood pressure was measured at least every minute during hypotensive episodes and until the patient blood pressure was stable. The position of the operating room table was manipulated to aid in surgical exposure only after a 15-min interval from intrathecal injection had elapsed. Intraoperative intravenous sedation was not provided.

The rostral dermatome level of sensory anesthesia to pin prick was determined. Motor block of the lower ex-

TABLE 1. Patient Assessment Scales

| |
|---|
| Motor Block |
| 0 = Voluntary movement of the hip, knee and ankle |
| 1 = Voluntary movement of the knee and ankle |
| 2 = Voluntary movement distal to the ankle only |
| 3 = No voluntary movement of the ankle, knee or hip |
| Intraoperative Discomfort |
| 0 = No complaints of discomfort |
| 1 = Transient discomfort, one epidose, no supplemental analgesia requested |
| 2 = Transient discomfort, more than one epidose, no supplemental analgesia requested |
| 3 = Continual discomfort and/or supplemental analgesia given |
| Prutitus |
| 0 = None |
| 1 = Facial, patient without complaint |
| 2 = Generalized, patient without complaint |
| 3 = Patient with complaint, treatment requested |

tremities was measured according to a four-point scale modified after Bromage[8] (Table 1). Observations and measurements were recorded at 1, 2, 3, 4, 5, 10, and 15 min after the injection of the study drug and every 15 min thereafter until complete regression of spinal anesthesia. The quality of intraoperative analgesia was assessed by the observer on a four-point scale (Table 1). The degree of pruritus was assessed by the observer on a four-point scale (Table 1).

Each patient evaluated analgesia on a 0–10 linear visual analog pain ruler at the end of surgery and every 15 min thereafter until the first request for supplemental analgesia. Patient-requested supplemental analgesia was administered prn *per* surgical postoperative orders. There was no attempt to influence the surgeon's choice, dose, or route of administration of analgesic. A patient was discharged from the postanesthesia care unit only when sacral regression of sensory anesthesia to pin prick and full return of lower extremity motor function were observed.

The following times were measured beginning at intrathecal injection of study drug: time until peak rostral dermatome sensory anesthesia; time until two-segment dermatome regression of the sensory anesthesia; time until sacral regression of sensory anesthesia; time until complete motor block of the lower extremities (score = 3); time until full return of lower extremity motor function (score = 0); time until a pain score other than zero; and time until the patient's first request for supplemental analgesia.

Two arbitrary conventions were made. First, if the patient complained of intraoperative discomfort (score = 1 or 2) and the first postoperative pain score was 0, then the duration of a 0 pain score continued until the time that a non-0 postoperative pain score was reported. If the patient complained of intraoperative discomfort (score = 1 or 2) and the first postoperative pain score was other than zero, then the duration of a 0 pain score was truncated at the time of intraoperative complaint. Second, the time until the first request for analgesia was recorded as 1440 min for those patients not requesting any supplemental analgesia at 24 h after intrathecal injection of study drug. At 24 h after injection, cumulative doses of analgesics were converted to milligram morphine equivalents.[9]

The specific gravity of each of the four study solutions was measured on a Bosch S2000/30 densitometer balance. The *p*H of each of the four study solutions was measured on a Nova STP5 (Waltham, MA)

Data were subjected to analysis of variance with Tukey's studentized range test, chi-squared analysis, Fisher's exact test, and the log-rank test for comparison of Kaplan-Meier survival curves where applicable. A $P < 0.05$ was considered significant. Results are expressed as means ± SD.

## Results

Of the eighty patients entered into the study, two patients receiving fentanyl and saline as study drug were excused from the protocol because local anesthesia was infiltrated for skin incision in one and because there was a failed spinal anesthetic in the other. One patient receiving fentanyl and epinephrine was excused from the protocol during surgery due to lack of cooperation. Patient characteristics of age, height, weight, and parity were the similar in all groups (Table 2). Seventy-one patients had subarachnoid anesthesia induced while in the right lateral decubitus position, and six while in the sitting position (Table 2).

TABLE 2. Patient Characteristics

| | L (n = 19) | LE (n = 21) | LF (n = 19) | LFE (n = 18) | Significance |
|---|---|---|---|---|---|
| Age (yr) | 25 ± 4.3 | 25 ± 3.4 | 26 ± 4.4 | 28 ± 5.4 | NS |
| Height (cm) | 158 ± 7.0 | 160 ± 6.5 | 159 ± 4.5 | 160 ± 6.5 | NS |
| Weight (kg) | 76 ± 24.5 | 73 ± 16.5 | 75 ± 15.3 | 74 ± 7.9 | NS |
| Parity | 2.9 ± 1.0 | 2.9 ± 1.0 | 3.1 ± 1.0 | 2.6 ± 1.0 | NS |
| Patient position for spinal | | | | | |
| No. decubitus | 17 | 20 | 17 | 17 | NS |
| No. sitting | 2 | 1 | 2 | 1 | |

NS = no significant difference between patient groups.

TABLE 3. Characteristics of Spinal Anesthesia

| | L (n = 19) | LE (n = 21) | LF (n = 19) | LFE (n = 18) | Significance |
|---|---|---|---|---|---|
| Peak dermatome of sensory anesthesia | C7 ± 3 | C8 ± 2 | C8 ± 2 | C8 ± 2 | NS |
| Time to peak sensory anesthesia (min) | 21 ± 16 | 16 ± 10 | 14 ± 10 | 18 ± 11 | NS |
| Time to 2-segment regression (min) | 67 ± 23 | 77 ± 29 | 71 ± 23 | 83 ± 33 | NS |
| Time to sacral regression (min) | 145 ± 34 | 194 ± 26* | 156 ± 42 | 214 ± 56* | $P < 0.0005$ |
| Time to complete motor block (min) | 5.1 ± 3.1 | 3.1 ± 1.9 | 3.8 ± 2.8 | 5.1 ± 3.9 | NS |
| Time to complete motor recovery (min) | 108 ± 37 | 146 ± 41* | 106 ± 36 | 156 ± 53* | $P < 0.0005$ |
| Incidence of intraoperative discomfort (no. scores = 1, 2, or 3) | 4 | 3 | 3 | 2 | NS |
| Patients requiring ephedrine (%) | 57 | 61 | 47 | 61 | NS |

* Different as compared to patient groups L, LF.

NS = no significant difference between patient groups.

There were no differences found among patient groups in: peak rostral dermatome level of sensory anesthesia attained; time to peak rostral sensory dermatome level of anesthesia; time to two-segment dermatome regression of sensory anesthesia; and time to onset of complete motor block of the lower extremities (Table 3). The time to sacral dermatome regression of sensory anesthesia to pin prick as well as the time to complete return of lower extremity motor function was prolonged only in those patients who received intrathecal epinephrine (Table 3). There was no difference in the time to sacral dermatome regression of sensory anesthesia or the time to complete return of lower extremity motor function among patients who received intrathecal epinephrine and fentanyl or intrathecal epinephrine alone. There were no differences found among patient groups in: percentage of patients requiring ephedrine, duration of hypotension; milligram dose of ephedrine administered; or the quality of intraoperative analgesia (Table 3).

The time to a pain score other than 0 (time of complete analgesia) was prolonged only in the patient group that received fentanyl and epinephrine (Table 4). The time until the patient's first request for analgesia (time of effective analgesia) was prolonged only in the patient group that received fentanyl and epinephrine (Table 4 and Figure 1). Three patients receiving fentanyl and epinephrine and one patient receiving saline as the study drug did not request any postoperative analgesia for 24 h. There were no differences between the patient groups in 24-h narcotic requirement (Table 4).

The incidence of pruritus in the patient group that received fentanyl alone was increased. Those patients that received epinephrine in addition to fentanyl had an incidence of pruritus similar to the groups that did not receive fentanyl (Table 5).

The specific gravity of each of the study solutions was 1.026. The *p*H of each of the four study solutions was 6.75.

## Discussion

The addition of epinephrine but not fentanyl to intrathecal lidocaine prolonged the regression of sensory anesthesia to the first sacral dermatome and the recovery of complete motor block by about 1 h. Neither the addition of epinephrine nor the addition of fentanyl prolongs two-segment dermatome regression of sensory anesthesia. These observations correspond well to the results of Chambers *et al.*,[10] Moore *et al.*,[11] and Spivey.[12]

Our results demonstrate that only the simultaneous intrathecal administration of fentanyl and epinephrine prolongs the duration of complete analgesia and the duration of effective analgesia. The incidence of pruritus seen with the addition of intrathecal fentanyl in this study was similar

TABLE 4. Characteristics of Analgesia

| | L (n = 19) | LE (n = 21) | LF (n = 19) | LFE (n = 18) | Significance |
|---|---|---|---|---|---|
| Duration of pain score = 0 (min) | 65 ± 36 | 76 ± 32 | 85 ± 44 | 137 ± 47* | $P < 0.0005$ |
| Time to first request for supplemental analgesia (min) | 198 ± 342 | 227 ± 201 | 203 ± 178 | 562 ± 504* | $P < 0.005$ |
| Range | (48–1440) | (44–825) | (23–840) | (105–1440) | |
| Quantiles | (60, 73, 107) | (120, 150, 270) | (123, 150, 240) | (195, 255, 1005) | |
| 24-h opioid requirements (mg morphine equiv.) | 10 ± 8 | 8 ± 4 | 10 ± 7 | 8 ± 13 | NS |

* Different as compared to all other patient groups.

NS = no significant difference between patient groups.

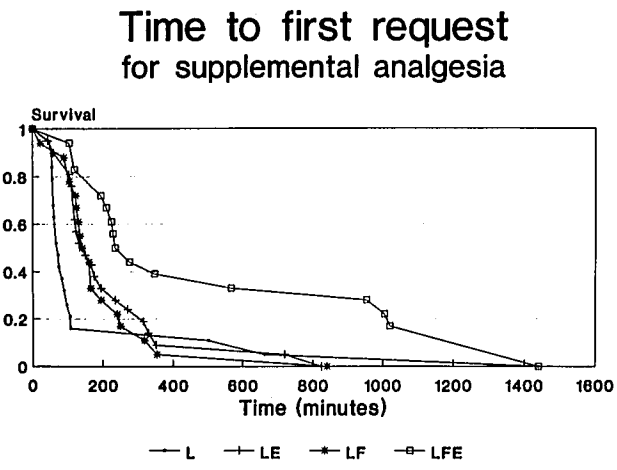


FIG. 1. Kaplan-Meier survival curves showing duration of effective analgesia for patients receiving L, LE, LF, or LFE. Survival is the proportion of each study drug group not yet requesting supplemental analgesia as a function of time. Time zero is intrathecal injection of study drug. Time to first request for supplemental analgesia for LFE is different from L, LE, and LF. $P < 0.005$.

to that seen in other reports.[3,4] The addition of epinephrine nullified the pruritic effect of intrathecal fentanyl.

Lipid-soluble opioids are quickly absorbed after intrathecal administration. The vasoconstricting effects of epinephrine may delay vascular absorption of fentanyl in the spinal cord, presenting a larger amount of opioid to bind opiate receptors. This greater chance for opioid–receptor interaction may produce more effective analgesia but should also increase the incidence of pruritus if greater cerebrospinal fluid concentration of opioid is correlated with pruritus. In the absence of serial measurements of fentanyl blood concentrations after intrathecal fentanyl administration, the contribution of epinephrine-induced vasoconstriction to prolonged analgesia cannot be easily determined.

Alternatively, the addition of epinephrine may potentiate intrathecal opioid analgesia. The addition of both epinephrine to intrathecal fentanyl and clonidine to intrathecal morphine suppressed noxiously evoked activity of feline wide-dynamic-range neurons in a multiplicative fashion.[5,6] Many neurotransmitters, including enkephalins, endorphins, and epinephrine, play a role in neuraxial processing of nociceptive impulses, probably at the level of the wide-dynamic-range neurons.[13] If sufficient inhibitory modulation occurs, a noxious stimuli is felt as a sensory modality other than pain, such as pressure or pruritus.[13] Inhibitory modulation provided by combination epinephrine and fentanyl may eliminate pruritus. This mechanism may explain both prolongation of analgesia and the decrease in pruritus seen in the current study.

This study demonstrates efficacy in post-tubal ligation analgesia when an intrathecal combination of epinephrine and fentanyl is used, by assessing duration of a 0 pain score and the time to first opioid request. However, there was no difference in 24-h opioid requirements among patient groups even though there was a 5-h delay in time to first patient request for analgesia in patients receiving the combination intrathecal fentanyl and epinephrine. Reporting 24-h opioid requirements by conversion of the many analgesics in use today to "milligram morphine equivalents" is fraught with problems especially when drugs other than morphine and even oral analgesics are used. As the study was designed, we could not justify medicating all patients with parenteral opioids. Forty-five per cent of our patients received parenteral opioids for postoperative analgesia; the remainder, oral opioid analgesics. The apparent discrepancy in analgesic requirements is due most probably to the lack of complete control over the postoperative medication orders. Perhaps comparison of 12-h opioid requirements would have been different.

It is surprising that the addition of 10 μg fentanyl without epinephrine did not produce a significant degree of postoperative analgesia. Hunt *et al.* have demonstrated that as little as 6.25 μg intrathecal fentanyl provides effective analgesia after hyperbaric bupivacaine spinal anesthesia in patients undergoing cesarean delivery.[2] In a study of patients undergoing postpartum tubal ligation, good postoperative analgesia was obtained with 20 μg and 40 μg fentanyl given with intrathecal hyperbaric lidocaine.[14] It appears that additional dose–response studies are needed to define the minimum effective dose of intrathecal fentanyl in specific postoperative patient populations with respect to the type of surgery as well as the local anesthetic used for spinal anesthesia.

Enthusiastic clinical application of these results to routine anesthetic management must be tempered by the number of additional drug ampules (two) that need to be properly ordered, identified, and prepared for mixture. The possibility of human error in drug identification as



TABLE 5. Pruritus

| | L (n = 19) | LE (n = 21) | LF (n = 19) | LFE (n = 18) | Significance |
|---|---|---|---|---|---|
| Incidence of pruritus (scores = 0, 1, 2, 3, respectively) | 2 (17, 2, 0, 0) | 1 (20, 1, 0, 0) | 8* (11, 6, 2, 0) | 1 (17, 1, 0, 0) | $P < 0.005$ |

* Different as compared to all other groups.

NS = no significant difference between patient groups.

well as an increased chance of contamination exist. The relatively small volumes (0.2 ml) of drug that are mixed raises the additional possibility of dose errors.

The mean duration of effective analgesia lasted approximately 9 h. The risk of delayed respiratory depression after the intrathecal administration of drugs to prolong opioid-induced analgesia is unknown. The possible complication of respiratory depression leading to arrest must be considered after the administration of any opioid.[15,16]

In summary, simultaneous intrathecal administration of epinephrine (0.2 mg) and fentanyl (10 μg) prolongs postoperative analgesia after postpartum tubal ligation in patients receiving hyperbaric lidocaine subarachnoid anesthesia. Epinephrine (0.2 mg) or fentanyl (10 μg), when given alone, do not produce effective postoperative analgesia. Epinephrine decreases the incidence of pruritus associated with intrathecal fentanyl. Enhanced postoperative analgesia and decreased incidence of pruritus are obtained at the expense of a moderately prolonged recovery of sensory and motor function after lidocaine spinal anesthesia.

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