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Intrathecal Sufentanil for Labor Analgesia

Effects of Added Epinephrine

William R. Camann, M.D., Beth H. Minzter, M.D.,† Roger A. Denney, M.D.,‡ Sanjay Datta, M.D.§*

Background: **Intrathecal sufentanil has been found to provide profound analgesia during labor. Epinephrine, when added to various local anesthetic agents or opioids, may modify the analgesic profile and incidence of side effects. The authors sought to determine the effect of adding 0.2 mg epinephrine to 10 μg sufentanil when administered for analgesia during labor.**

Methods: **Forty women during active labor received 10 μg intrathecal sufentanil either with (n = 20) or without (n = 20) 0.2 mg epinephrine in a randomized, blinded fashion. A combined spinal–epidural technique was used in which a 25-G Whitacre spinal needle was passed through a standard 17-G epidural needle. After injection of the study drug, an epidural catheter was passed, but no local anesthetics were given. Analgesia was quantitated using visual analog scores, as well as time elapsed until first request for additional analgesia *via* the epidural catheter (0.25% bupivacaine). The incidence and severity of pruritus, nausea, and somnolence were assessed.**

Results: **The duration (median, range) of analgesia was 90 (40–310) min in the plain sufentanil group (SUF) and 90 (45–230) min in the sufentanil–epinephrine (SUF–EPI) group (*P* = NS). The onset of analgesia was rapid (within 5 min) in both groups and visual analog scores did not differ at any observation point between groups. The incidence of pruritus was 80% (16/20) in the SUF group, and 45% (9/20) in the SUF–EPI group (*P* = 0.05). Four patients in the SUF group rated the pruritus as severe *versus* none in the SUF–EPI groups (*P* = 0.05). Seven patients (35%) in the SUF–EPI group experienced nausea, *versus* none in the SUF group (*P* = 0.004). No patient developed hypotension, motor blockade, fetal heart rate abnormalities, excessive sedation, or postdural puncture headache.**

Conclusions: **Intrathecal sufentanil 10 μg, both with and without epinephrine, provided rapid-onset, albeit short-duration, analgesia during labor. Epinephrine did not prolong the duration of intrathecal sufentanil analgesia. The addition of epinephrine increased the incidence of nausea and decreased the incidence and severity of pruritus. (Key words: Analgesics, opioid: sufentanil. Anesthesia, obstetric. Anesthetic techniques: spinal. Pain, labor.)**

This article is accompanied by a Highlight. Please see this issue of ANESTHESIOLOGY, page 23A.

* Assistant Professor of Anesthesia, Harvard Medical School.

† Instructor in Anesthesia, Harvard Medical School.

‡ Staff Anesthesiologist, Fairfax Hospital.

§ Professor of Anesthesia, Director of Obstetric Anesthesia, Harvard Medical School.

From the Department of Anesthesia, Brigham and Women's Hospital, Harvard Medical School; and Fairfax Hospital, Falls Church, Virginia. Accepted for publication January 25, 1993.

Address reprint requests to Dr. Camann: Department of Anesthesia, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, Massachusetts 02115.

INTRASPINAL administration of lipid-soluble opioids may have a useful role during provision of analgesia for labor and delivery. Avoiding local-anesthetic side effects (motor blockade, hypotension) while providing effective analgesia represents a distinct advantage for the use of intraspinal opioids. A number of recent investigations have shown that intraspinal sufentanil affords profound analgesia of 1–3 h duration during labor.[1–4] The addition of epinephrine to both spinal and epidural opioids has been shown to modify the analgesic profile and incidence of side effects in a variety of clinical settings.[5–11] This study was designed to assess the effects of epinephrine (0.2 mg) added to intraspinal sufentanil (10 μg) during labor.

Materials and Methods

Forty ASA physical status 1 or 2 parturient patients requesting epidural analgesia during active labor were enrolled in the study. All patients were at term, had uncomplicated pregnancies, and had normal fetal heart tracings. All gave written informed consent to an institutionally approved human research protocol. When patients first requested analgesic medication, the following combined spinal–epidural technique was utilized. The patient was positioned in the right or left lateral decubitus and the usual aseptic preparation and draping was performed. A $4\frac{1}{2}''$ 17-G Weiss needle was inserted into the epidural space at either the L_{2-3} or L_{3-4} interspace using the loss-of-resistance-to-air technique. A $4\frac{11}{16}''$ 25-G Whitacre spinal needle (Becton-Dickenson, Rutherford, NJ) was passed *via* the epidural

Table 1. Maternal Demographic Characteristics

Characteristic	Sufentanil (n = 20)	Sufentanil–Epinephrine (n = 20)
Age	28 ± 5	29 ± 5
Height (cm)	170 ± 4	173 ± 4
Weight (kg)	75 ± 9	76 ± 7
Parity		
0	13	10
≥1	7	10
Birth weight (kg)	3.4 ± .3	3.5 ± .3
Cervical dilation at time of study drug (cm)	4.0 ± 1	4.0 ± 2

Data expressed as mean ± SD. No significant differences between groups.

needle into the subarachnoid space until clear cerebrospinal fluid was obtained. All patients received, in a double-blind fashion, 10 μg sufentanil either with (SUF–EPI, n = 20) or without (SUF, n = 20) 0.2 mg epinephrine. The study drug was diluted in a total volume of 2 ml preservative-free normal saline. Following intrathecal injection of the study drug, the spinal needle was removed and an epidural catheter placed 2 cm into the epidural space, but no local anesthetics were injected. All study solutions were prepared by an anesthesiologist not involved in subsequent data collection, and randomized according to a random number scheme with instructions contained in sequentially numbered, sealed opaque envelopes.

Analgesia was assessed using a 10-cm linear visual analogue scale (VAS) at the time of study drug injection and 5, 10, 20, 30, 40, 60, 90, 120, and 180 min thereafter. Maternal blood pressure was measured at the same intervals. Patients could request additional analgesia (0.25% bupivacaine *via* the epidural catheter) if pain relief was unsatisfactory by 15 min after injection of study drug. When additional analgesia was requested, the study protocol and data collection were terminated. Patients were then given epidural bupivacaine as per usual clinical routine for the remainder of their labor. The time from study drug administration until request for additional analgesia was noted. Side effects (pruritus, nausea, and somnolence) were assessed at each observation point using a four-point ordinal scale in which 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Motor blockade was assessed by asking the patients to flex their hip, knee, and ankle at each observation point. Continuous electronic fetal heart rate (FHR) monitoring was employed on all patients throughout labor.

Continuous data are expressed as both median (range) and mean (SD) and analyzed using the Mann-Whitney test. Categorical data are analyzed using chi-square analysis with Yates continuity correction or Fisher's exact test as appropriate. A value of $P \leq 0.05$ was considered to indicate statistical significance.

Results

Demographic characteristics did not differ among groups (table 1). The median (range) and mean (SD), respectively, duration of analgesia (time until first request for epidural bupivacaine) was 90 (40–310), 109 (56) min in the SUF group and 90 (45–230), 95 (45) min in the SUF–EPI group (P = NS). Visual analogue scale scores did not differ among groups at any observation point (table 2). The mean and median VAS scores significantly decreased within 5 min after drug injection, and most patients (16 in each group) achieved complete pain relief (VAS of zero) at some point during

Table 2. Visual Analog Scale (VAS) Data

	Time (min)								
Group	0	5	10	20	30	40	60	90	120
Sufentanil									
Median (range)	8 (4–10)	4 (0–9)	2 (0–8)	0 (0–7)	0 (0–7)	0 (0–7)	0 (0–4)	4 (0–8)	3 (0–6)
Mean (SD)	8 (1.7)	4.1 (2.8)	2.5 (2.6)	1.1 (2)	0.8 (1.8)	1 (2)	1.4 (1.9)	2.7 (2.6)	3.1 (2.5)
n	20	20	20	20	20	20	18	15	7
Sufentanil–epinephrine									
Median (range)	8 (6–10)	2 (0–8)	0 (0–8)	0 (0–8)	0 (0–8)	0 (0–7)	0 (0–7)	1.5 (0–6)	1 (0–4)
Mean (SD)	8.3 (1.3)	2.5 (2.6)	2 (1.8)	1.4 (2.4)	1.0 (2.1)	0.9 (2)	0.7 (1.3)	2.7 (2.6)	1.8 (1.8)
n	20	20	20	20	20	18	16	13	6

No significant difference between groups at any observation point. All VAS scores at all points from 5 min and thereafter are significantly less ($P < 0.01$) than baseline VAS score.

n = number of patients remaining in study at indicated observation point.

the study interval. There were two patients (one in each group) who failed to achieve profound analgesia and persistently reported VAS scores of 7 throughout the study period. These two patients both reported predrug scores of 10, and, therefore, did experience some degree of pain relief on a relative basis.

Side Effects (table 3)

No patient in the SUF group complained of nausea, while seven (35%) of those in the SUF–EPI group experienced nausea after drug injection ($P = 0.004$). Sixteen patients (80%) in the SUF group experienced pruritus, *versus* nine (45%) in the SUF–EPI group ($P = 0.05$). Moreover, the pruritus was more profound in the SUF group, as four patients in the SUF group *versus* none in the SUF–EPI group complained of severe pruritus ($P = 0.05$). No patient complained of dysphoria or excessive sedation or demonstrated abnormalities of FHR tracing. No patient developed hypotension (systolic blood pressure less than 100 mmHg), nor did any patient have detectable motor blockade. All patients had satisfactory analgesia after initiation of epidural bupivacaine administration. No patient had evidence of subarachnoid migration of the catheter, as evidenced by appropriate response to subsequent epidural bupivacaine. No patient developed postdural puncture headache during the duration of their hospital stay. Fifteen patients in the SUF group had spontaneous vaginal delivery, *versus* 19 in the SUF–EPI group (P = NS).

Table 3. Side Effects

	Sufentanil	Sufentanil–Epinephrine
Pruritus (incidence)	16*	9
Scores = 0, 1, 2, 3, respectively	4, 7, 5, 4*	11, 7, 2, 0
Nausea (incidence)	0*	7
Scores = 0, 1, 2, 3, respectively	20, 0, 0, 0	13, 3, 3, 1

* $P \leq 0.05$ compared to other group.

Discussion

Our results show that 10 μg intrathecal sufentanil provides rapid onset and profound analgesia, although of relatively short duration (median 90 min), during labor. The addition of epinephrine does not appear to change the analgesic profile of intrathecal sufentanil. However, the incidence of side effects is altered. Epinephrine significantly decreased the incidence and severity of pruritus following intrathecal sufentanil, while the incidence of nausea was increased.

The use of intrathecal and epidural opioids has become widespread in recent years. Many investigators have examined the effect of epinephrine on epidural opioid analgesia in various clinical settings. In general, epinephrine appears to enhance the analgesic effects of epidural opioids, although side effects (nausea, pruritus) are often increased.[5–11] Studies in animal models confirm that epinephrine (and other α-adrenergic receptor agonists, such as clonidine) enhance the analgesic effects of intrathecally administered opioids.[12] Kitahata postulates that this apparent synergism may be caused by coactivation of both opioid and adrenergic receptors, rather than an alteration in opioid clearance owing to spinal vasoconstriction.[13] In contrast, Zakowski *et al.* (in humans following cesarean section) found that epinephrine added to spinal morphine has inconsequential effects on both plasma morphine pharmacokinetics and analgesic duration. Side effects were not described.[14] However, these conclusions are based on data using the slowly cleared opioid morphine. The clearance of sufentanil from cerebrospinal fluid is rapid; thus, the local effects of epinephrine on sufentanil pharmacokinetics in CSF may potentially differ from results obtained with morphine.[15] Such data are lacking at present.

Several investigators have examined the effects of epinephrine on epidural sufentanil analgesia. McMorland *et al.* used 30 μg epidural sufentanil following cesarean delivery.[11] Satisfactory analgesia of 4–5 h was obtained, and epinephrine had no effect on duration of analgesia or incidence of side effects. Both Verborgh *et al.*,[9] using 75 μg epidural sufentanil following abdominal surgery, and Klepper *et al.*,[10] using 50 μg in volunteers, found that analgesia was prolonged by the addition of epinephrine. Both studies found a high incidence of somnolence, probably because of the high dose of sufentanil used. None of these three studies noted any effect on pruritus or nausea when epinephrine was added to epidural sufentanil. Differences in dose of opioid, patient population, or route of administration may contribute to differences in side-effect profile between these and our study.

Intrathecal sufentanil (3–10 μg) has been found to provide effective, albeit short-duration, analgesia during labor.[1–4] Intrathecal sufentanil also appears to be most effective during the early stages of labor.[2] The effects of sufentanil are significantly improved when administered intrathecally, rather than epidurally or systemically.[1] Low doses (5–10 μg) of epidural sufen-

tanil may provide effective analgesia, but only when combined with small doses of local anesthetic supplementation,[16] indicating some degree of either an additive or synergistic effect between the opioid and local anesthetics. Epidural sufentanil alone appears to provide insufficient analgesia during labor.[17] The intrathecal administration of a small dose of sufentanil (or other lipid-soluble opioids, such as fentanyl) using a combined spinal–epidural technique may thus be considered as an alternative to systemic opioid use during early labor and an adjuvant to subsequent epidural analgesia.[18] The absence of motor blockade or hypotension are characteristics that may render this technique useful for obstetric analgesia.

We performed the current study to determine if the duration of intrathecal sufentanil analgesia could be prolonged by the addition of epinephrine. Our results suggest that epinephrine does not provide prolongation of analgesia in this setting. Using standard formulae,[19] our sample size was adequate to detect a 30-min difference in duration of analgesia (with $\alpha = 0.05$ and $\beta = 0.20$). The majority of studies using either spinal or epidural opioids, with the exception of Zakowski *et al.*[14] and McMorland *et al.*,[11] have found that analgesic quality and duration is enhanced with the addition of epinephrine. These studies used either postoperative pain or volunteers as study models, thus providing a relatively stable level of painful stimuli. In contrast, labor is a dynamic process, with markedly increasing nociceptive input as progression of cervical dilation and fetal descent occurs. This phenomenon may contribute to the lack of benefit from epinephrine in this setting.

Alternatively, the lack of observed effect of epinephrine could be caused by the single dose of sufentanil used (10 μg) in our study. However, the available data to date indicates that a dose-response effect does not seem to be apparent with smaller doses of sufentanil. Naulty, using 3 μg, found a mean duration of analgesia of 3.3 h,[3] and Honet, using 5 μg, found a mean duration of 104 min.[4] Other studies using 10 μg sufentanil have found values similar to that reported in this study.[1,4] This apparent lack of dose-response effect in the commonly used dose range for plain intrathecal sufentanil, and our results of lack of benefit of epinephrine on 10 μg sufentanil, implies that a clinically useful, dose-sparing effect of epinephrine on lower doses of sufentanil is unlikely. Even if a dose-sparing effect with epinephrine did occur, this dose range of sufentanil is sufficiently small that reduction of major adverse effects (such as respiratory depression) would be unlikely to occur. Moreover, the requirement for opening and mixing of additional drug ampules introduces the possibility of dosing errors with epinephrine and adverse effects thereof.[20] We, therefore, believe that further studies of epinephrine on the dose-response curve of small doses of intrathecal sufentanil during labor are unlikely to provide clinically useful results. Thus, we chose to study a single dose, rather than multiple doses, of sufentanil. We chose 10 μg, because this appears to be the most commonly used dose of sufentanil for intrathecal analgesia during labor (Multiple personal communications).

In contrast to the analgesic effect, we did find significant influence on side effects. Nausea was increased from 0 to 35% with added epinephrine, a finding also noted by others when using neuroaxial epinephrine.[5,9] Pruritus was decreased from 80 to 45% and the intensity was also significantly decreased as quantitated on a four-point ordinal scale. Malinow, using intrathecal fentanyl following postpartum tubal ligation, also found that the addition of epinephrine significantly decreased the incidence of pruritus.[6] Other investigators have found that epinephrine increases the incidence and severity of pruritus when spinal morphine is used.[5] The mechanism of pruritus as a result of intrathecal opioid administration is unknown; however, differences in lipophilicity, patient populations, effects of labor, and/or pregnancy itself may contribute to the development of pruritus when intrathecal opioids are used.

In conclusion, we found that the addition of 0.2 mg epinephrine did not prolong the duration or quality of analgesia from 10 μg intrathecal sufentanil during labor. Nausea was increased, yet pruritus was decreased, by the addition of epinephrine. Although the decrease in pruritus was beneficial, the lack of effect on analgesia, increased incidence of nausea, and requirement for opening and mixing additional drug ampules precludes recommendation of added epinephrine in this setting. Perhaps other opioids, in other clinical settings, may have different analgesic and side-effect profiles when epinephrine is included.

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