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The Dose–Response of Intrathecal Sufentanil Added to Bupivacaine for Labor Analgesia

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Background: **Regional analgesia for labor often is initiated with an intrathecal injection of a local anesthetic and opioid. The purpose of this prospective, randomized, blinded study was to determine the optimal dose of intrathecal sufentanil when combined with 2.5 mg bupivacaine for labor analgesia.**

Methods: **One hundred seventy parous parturients with cervical dilation between 3–5 cm were randomized to receive intrathecal 0 (control), 2.5, 5.0, 7.5, or 10.0 μg sufentanil combined with 2.5 mg bupivacaine, followed by a lidocaine epidural test dose, for initiation of analgesia (34 patients in each group). Visual analog scores and the presence of nausea, vomiting, and pruritus were determined every 15 min until the patient requested additional analgesia. Fetal heart rate tracings were compared between groups.**

Results: **Groups were similar for age, height, weight, oxytocin dose, duration of labor, and baseline visual analog scores. Duration of action was significantly shorter for control patients (39 ± 25 min [mean ± SD]) compared with those administered sufentanil, all doses (93 ± 32, 93 ± 47, 94 ± 33, 97 ± 39 min), but was not different among groups administered 2.5, 5.0, 7.5, or 10.0 μg sufentanil. More patients who received 10 μg sufentanil reported nausea and vomiting than did control patients. The severity of pruritus increased with administration of 7.5 and 10.0 μg sufentanil. There was no difference in fetal heart rate changes among groups.**

Conclusions: **Intrathecal bupivacaine (2.5 mg) without sufentanil did not provide satisfactory analgesia for parous patients. However, bupivacaine combined with 2.5 μg sufentanil provided analgesia comparable to higher doses, with a lower incidence of nausea and vomiting and less severe pruritus. (Key words: Intrathecal analgesia; intrathecal opioids; obstetric anesthesia.)**

REGIONAL analgesia for labor is often initiated with an intrathecal injection of a local anesthetic and opioid. This provides excellent labor analgesia with minimal motor block. Adding bupivacaine to intrathecal sufentanil prolongs labor analgesia without increasing side effects.[1] Several investigators have reported the dose-response relation for intrathecal sufentanil alone.[2,3] However, the dose-response of sufentanil combined with bupivacaine has not been determined. We hypothesized that, when combined with bupivacaine, a lower dose of sufentanil would provide satisfactory analgesia with a lower incidence of side effects.

The purpose of this study was to determine the dose-response relation and incidence of side effects (nausea, vomiting, pruritus, and fetal bradycardia) for intrathecal sufentanil when added to 2.5 mg bupivacaine to initiate labor analgesia.

Materials and Methods

Parous parturients scheduled for the induction of labor were asked to participate in this prospective, randomized, double-blind study approved by the Institutional Review Board. Patients were not eligible to participate if they had not undergone previous vaginal delivery or if they had coexistent maternal disease (*e.g.*, preeclampsia). After written, informed consent was obtained, patients were randomized (by a computer-generated random-number table) to one of five groups: sufentanil: 0, 2.5, 5.0, 7.5, or 10.0 μg (groups 0, 2.5, 5, 7.5, and 10, respectively). Patients were excluded if they requested regional labor analgesia at less than 3-cm or greater than 5-cm cervical dilation, or if they received systemic analgesia before the initiation of regional labor analgesia.

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For each patient, the study solution was prepared by an anesthesiologist not involved in the patient's care. Twice the assigned sufentanil study dose (sufentanil; Abbott Laboratories, North Chicago, IL; 50 μg/ml) was drawn up into a 1-ml tuberculin syringe. The needle was removed and the remainder of the syringe filled to 1 ml with preservative-free normal saline. The study solution (0.5 ml) was mixed with 2.5 mg bupivacaine (Sensorcaine-MPF; Astra Pharmaceutical Products, Inc., Westborough, MA; 0.5%, 0.5 ml) for a total volume of 1 ml.

Regional analgesia was initiated by an anesthesiologist blinded to patient group after a 500-ml crystalloid fluid bolus, with the patient in the sitting position using the "needle through needle" technique, at L3–L4 or L2–L3. The intrathecal dose was injected through a 27-gauge Whitacre needle (Becton Dickinson & Co., Franklin Lakes, NJ) after ascertaining free flow of cerebral spinal fluid. The epidural catheter was inserted and tested for intrathecal or intravascular placement with 1.5% lidocaine with epinephrine, 1:200,000, 3 ml (Astra USA, Inc., Westborough, MA). Patients were placed in the lateral position after the epidural catheter was secured.

Labor pain was assessed using a 100-mm visual analog scale (VAS) immediately before the initiation of analgesia (baseline) and at 15-min intervals after the intrathecal injection until the patient requested additional analgesia. VAS scores were obtained by an anesthesia research nurse blinded to patient group. If the patient had incomplete analgesia 10 min after the intrathecal injection and had a VAS score of more than 20 mm, the patient was administered a rescue dose of epidural 0.125% bupivacaine with 100 μg fentanyl. The study ended when the rescue dose was given or when the patient requested additional analgesia. The VAS score at this point was recorded as the VAS score for every subsequent time interval for purposes of data analysis.

The anesthesia nurse also asked the patients whether nausea, vomiting, or itching was present at each 15-min interval. Vomiting was recorded as present if it was witnessed or if the patient stated she vomited in response to questioning. Nausea and pruritus were graded as mild, moderate, or severe. Additional data recorded included time in the sitting position after the intrathecal injection, time of request for additional analgesia, time of complete cervical dilation, maximum oxytocin dose, and time of delivery. Duration of action was defined as the time from intrathecal injection until request for additional analgesia, or time to delivery, whichever occurred sooner.

Continuous fetal heart rate (FHR) tracings were analyzed by a perinatologist, blinded to patient group, at the end of the study. Fifteen minutes of tracing immediately before initiation of analgesia and the first 30 min of tracing after initiation were analyzed initially. Variability was graded as absent (< 2 beats/min), decreased (> 2, < 6 beats/min), normal (> 6 beats/min), or increased (> 25 beats/min). The presence of prolonged decelerations (< 100 beats/min for > 60 s) was noted. Persistent variable decelerations (> 50% of contractions) were graded as none, mild (< 15 beats/min), moderate (> 15 beats/min, < 60 beats/min), or severe (> 60 beats/min). Late decelerations were graded as present or absent. Overall, the before and after tracings were assessed as reassuring or not reassuring. Any change in the tracing after initiation of analgesia and any obstetric interventions were noted. The perinatologist evaluated the entire tracing if a nonreassuring pattern was identified.

Statistical Analysis

During the design phase of the study a power analysis was performed using control data from a previous study (effective labor analgesia with intrathecal bupivacaine

Table 1. Demographic Data

Group	0 (n = 34)	2.5 (n = 34)	5 (n = 34)	7.5 (n = 34)	10 (n = 34)
Age (yr)	33 ± 5	35 ± 5	33 ± 4	33 ± 4	34 ± 4
Height (cm)	164 ± 6	166 ± 6	166 ± 6	164 ± 8	165 ± 6
Weight (kg)	78 ± 12	80 ± 13	75 ± 11	75 ± 9	74 ± 13
Time sitting (min)	5 ± 2	6 ± 1	6 ± 2	6 ± 2	6 ± 2
Maximum oxytocin dose (mU/min)	19 ± 10	16 ± 8	16 ± 9	16 ± 7	18 ± 9
Time to complete cervical dilation (min)	151 ± 94	132 ± 88	145 ± 101	124 ± 64	136 ± 53
Time to delivery (min)	184 ± 90	168 ± 107	182 ± 107	154 ± 65	171 ± 71
Baseline VAS (mm)	59 ± 18	55 ± 20	60 ± 23	56 ± 19	60 ± 18

Data are mean ± SD. All times are time from intrathecal injection. There are no differences among groups for any variable.

VAS = visual analog scale.

Table 2. Outcome Data

Group	0 (n = 34)	2.5 (n = 34)	5 (n = 34)	7.5 (n = 34)	10 (n = 34)
Duration of action (min)	39 ± 25	93 ± 32*	93 ± 47*	94 ± 33*	97 ± 39*
Epidural bolus at ≤15 min (n)	12	2†	3†	0†	3†
Delivery before epidural bolus (n)	0	6‡	8‡	4‡	6‡

Duration of action is mean ± SD.

* Significantly different from Group 0, $P < 0.001$.

† Combined Groups 2.5, 5, 7.5, and 10 significantly different from Group 0, $P < 0.001$. See text.

‡ Combined Groups 2.5, 5, 7.5, and 10 significantly different from Group 0, $P < 0.05$. See text.

lasted 70 ± 35 min[1]). To detect a 30-min difference in effective analgesia from the control group (bupivacaine only), assuming $\alpha = 0.05$ and a power of 0.8, a group size of 34 patients is needed.

Data were analyzed using chi-square analysis or the Fisher exact test (need for epidural bolus at ≤ 15 min, delivery before epidural bolus, incidence of nausea and vomiting, FHR tracing changes), and analysis of variance, followed by a two-tailed, unpaired *t* test (age, height, weight, oxytocin dose, duration of labor, and duration of action), and Kruskal–Wallis test (VAS, pruritus). Bonferroni correction or the Dunn test for multiple comparisons were applied when appropriate. Kaplan–Meier survival curves (percentage of patients in each group with continuing effective analgesia at each time interval) were compared using the log-rank test. $P < 0.05$ was considered to be significant.

Results

One hundred seventy patients were randomized to five groups. One patient in group 10 received the incorrect dose of sufentanil (0 μg instead of 10.0 μg). Data were analyzed by intention to treat.

Groups were not different for mean age, height, weight, time spent sitting after the intrathecal injection, maximum oxytocin dose, time to complete cervical dilation, time to delivery, or baseline VAS (table 1). All patients but one received oxytocin before the initiation of analgesia.

The duration of action of the initial intrathecal injection was significantly shorter in group 0 patients compared with all other groups (table 2). Figure 1 shows the percentage of patients in each group with continuing analgesia as a function of time. By log-rank tests between curves, group 0 was significantly different from groups 2.5, 5, 7.5, or 10 ($P < 0.001$), but groups 2.5, 5, 7.5, and 10 were not different from each other. Significantly more patients in group 0 required an epidural bolus at 15 min or less, compared with all other groups (table 2).# Significantly more patients in combined groups 2.5, 5, 7.5, and 10 were delivered before epidural bolus administration, compared with group 0 (table 2).#

Visual analog scale scores are shown in figure 2. Control group VAS scores are significantly higher than in groups 2.5, 5, 7.5, and 10 at 15 min through 120 min; higher than in groups 5.0, 7.5, and 10 through 165 min; and higher than in groups 5 and 7.5 for the remainder of the study.

Nausea was analyzed as present or absent because most nausea was rated as mild. Significantly more patients in group 10 had nausea compared with group 0 (fig. 3) and with combined groups 2.5, 5, and 7.5. Groups 2.5, 5, 7.5, and 10 were not different from each other. Significantly more patients in group 10 vomited compared with group 0 (fig. 3).

Pruritus was not present in any group 0 patient but was present in all but four patients who received sufentanil (fig. 4). After correction for multiple comparisons the degree of pruritus was not different among sufentanil groups. However, the degree of pruritus was significantly greater in combined groups 7.5 and 10 compared with combined groups 2.5 and 5 (fig. 4).

One hundred sixty-seven FHR tracings were available for analysis. All tracings were reassuring before the initiation of analgesia. Twenty-eight tracings had decelerations within 30 min of analgesia initiation. Seven of these tracings had variable decelerations immediately before initiation of analgesia that were either unchanged or

Data were initially analyzed by a 5 × 2 chi-square contingency table ($P < 0.001$). However, by a 2 × 2 Fisher exact test contingency table comparing each group to group 0, group 5 (epidural bolus at ≤ 15 min), or group 7.5 (delivery before epidural bolus) does not differ from group 0 when corrected for multiple comparisons. As suggested by Glantz,[14] groups 2.5, 5, 7.5, and 10 did not differ from one another (4 × 2 contingency table). Therefore, these groups were combined and compared with group 0 (chi-square 2 × 2, corrected for multiple comparisons).

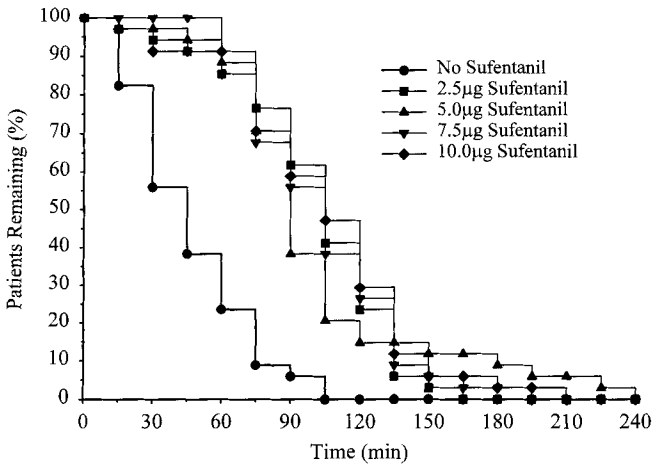

Fig. 1. The percentage of patients in each group with continuing pain relief as a function of time. Group 0 (no sufentanil) is significantly different from groups 2.5–10 ($P < 0.001$). Groups 2.5–10 are not different among each other.

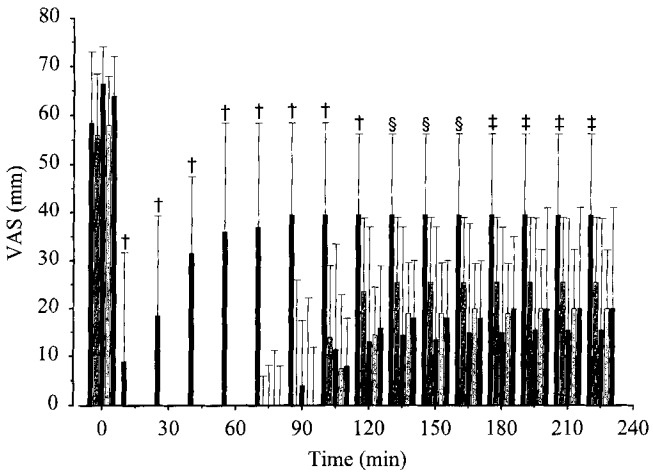

Fig. 2. Visual analog scale (VAS) scores as a function of time: median (bar) and seventy-fifth percentile are indicated. Time 0 = baseline VAS. The first bar in each group (black) is group 0, followed by groups 2.5, 5, 7.5, and 10, respectively. The VAS scores at the time patients requested supplemental epidural analgesia are recorded as the VAS scores for every subsequent time interval. †Indicates that group 0 is different from groups 2.5, 5, 7.5, and 10. §Indicates group 0 is different from groups 5, 7.5, and 10. ‡Indicates group 0 is different from groups 5 and 7.5.

resolved afterward. Thirteen tracings showed development of variable decelerations of no clinical significance. Eight FHR tracings showed development of late decelerations, none of which were associated with hypotension. There were no differences among groups in the incidence of either variable or late decelerations. In six of eight patients with late decelerations, no obstetric intervention was deemed necessary and the decelerations resolved spontaneously within 10–60 min. In the remaining two patients, one with a prolonged deceleration (90 s), the oxytocin infusion was discontinued. All eight patients with late decelerations experienced normal, spontaneous vaginal deliveries, except one patient who underwent a low forceps delivery. Umbilical artery pH values ranged from 7.19 to 7.42 among these eight patients.

Discussion

Initial studies of combined spinal–epidural labor analgesia describe the use of intrathecal sufentanil, 10 μg, without local anesthetic, for initiation of analgesia.[4,5] Several years later Campbell *et al.*[1] demonstrated superior analgesia of longer duration after the intrathecal injection of 10 μg sufentanil combined with 2.5 mg bupivacaine, compared with sufentanil or bupivacaine alone. Two groups of investigators have sought to determine the median and 95% effective doses (ED_{50} and ED_{95}, respectively) of intrathecal sufentanil injected alone.[2,3] The calculated ED_{95} of sufentanil was 8.9 μg (7.5–11.5 μg, 95% confidence interval).[2] However, the optimal dose of intrathecal sufentanil in combination with bupivacaine has not been previously determined.

The results of this study support our hypothesis that when intrathecal sufentanil is combined with bupivacaine (in the presence of an epidural lidocaine test dose), a sufentanil dose significantly lower than the ED_{50} of sufentanil alone provided excellent analgesia in most patients. The lowest sufentanil dose tested, 2.5 μg, provided analgesia comparable to higher doses. Lower doses of sufentanil were associated with a lower incidence of nausea, vomiting, and severity of pruritus.

We elected to study parous parturients scheduled for induction of labor because they represent a homogenous population. Because the progress of labor in nulliparous parturients is slower than in parous parturients, we assumed that the optimal dose for parous parturients would also provide satisfactory analgesia for nulliparous parturients.

There are several limitations to our conclusion that 2.5 μg sufentanil is the optimal dose. We studied patients with cervical dilation between 3 and 5 cm at initiation of analgesia. It is possible that 2.5 μg sufentanil may not provide satisfactory analgesia for patients in more advanced labor or that the duration of action would be shorter.[6,7] However, many of the patients in this study had satisfactory analgesia and delivered before an epi-

dural bolus was necessary. In addition, mean duration of labor (from time of analgesia initiation) was less than 3 h, suggesting that this low dose of sufentanil would also be satisfactory in patients in more advanced labor.

Another limitation is that a test dose of local anesthetic was administered through the epidural catheter immediately after insertion to test for intrathecal or intravascular placement. This is the standard procedure at Northwestern University Medical School. It is our opinion that an epidural test dose immediately after initiation of combined spinal-epidural remains a clinically useful practice. It is safer for the patient, more convenient for the anesthetist, and more satisfactory for the patient to replace a catheter while the patient is prepared and draped for the initial insertion. However, the epidural test dose may have contributed to analgesia and a higher intrathecal dose might be necessary if no epidural test dose was used.

In contrast to other studies, we found a lower incidence of nausea, vomiting, and severity of pruritus in patients who received lower doses of sufentanil.[2,3,8] However, this study was designed to detect a difference in the primary outcome variable: duration of action. It was sufficiently powered to detect differences in side effects (secondary outcome variables) between the control and sufentanil groups, and these differences were detected. However, a limitation of this (and other studies) is that the study was underpowered to detect differences between sufentanil doses for secondary outcome variables. For example, when analyzed in isolation, patients who received the lowest sufentanil dose had less severe pruritus compared with those who received the highest dose. However, within the context of the current experimental design, after making corrections for multiple applications of *post hoc* tests to the same data, the current study was underpowered to detect differences between sufentanil groups. As an example, for this difference in degree of pruritus to be detected with the current study design, we would have needed 57 subjects per group, or a total of 285 subjects.

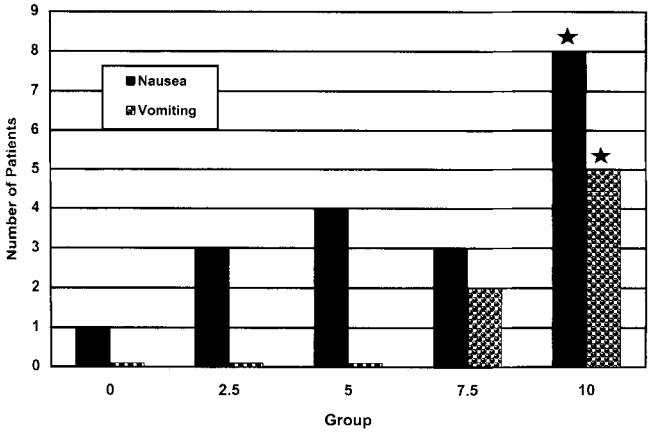

Fig. 3. Number of patients in each group with nausea and vomiting. *Indicates incidence different from group 0 ($P < 0.05$).

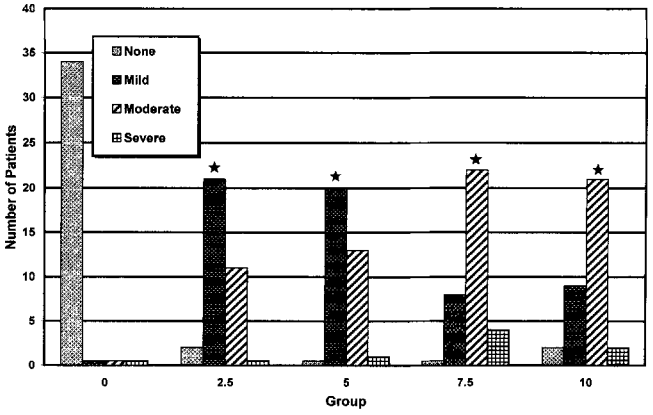

Fig. 4. Number of patients each group with no, mild, moderate, or severe pruritus. *Indicates incidence and severity different from group 0 ($P < 0.05$).

The duration of action of intrathecal bupivacaine alone (group 0)[1] and bupivacaine plus 10 μg sufentanil (group 10)[1,7,9] were shorter than previously reported. The likely explanation for the former is that the investigators studied nulliparous patients and excluded patients who did not obtain pain relief with bupivacaine.[1] The likely explanation for the latter is that other studies included patients of mixed parity[7,9] or with cervical dilation less than 3 cm.[1,9]

Fetal heart rate changes not associated with hypotension have been described after regional labor analgesia.[10,11] Only one patient in our study had a prolonged deceleration within 30 min of analgesia initiation. The presence of a nonreassuring FHR tracing after initiation of analgesia was not related to sufentanil dose.

Respiratory depression after administration of neuraxial opioids can be life threatening.[12] We did not study the respiratory depressant effect of different doses of sufentanil. However, Herman *et al.*[13] demonstrated a dose-dependent change in ventilation after intrathecal fentanyl for labor analgesia. It is likely that lower doses of sufentanil are associated with less respiratory depression. Therefore, the finding that lower doses of sufentanil provide satisfactory analgesia may make the combined spinal-epidural analgesia technique safer.

In conclusion, this study has shown that 2.5 μg sufen-

tanil combined with 2.5 mg bupivacaine provides satisfactory labor analgesia in parous patients who underwent induced labor and is associated with a lower incidence of nausea and vomiting and less severe pruritus than is 7.5 or 10.0 μg. Sufentanil doses higher than 2.5 μg provide no added benefit.

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