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Baricity, Needle Direction, and Intrathecal Sufentanil Labor Analgesia

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Background: **Intrathecal sufentanil relieves labor pain but centrally mediated side effects are common. Preventing rostral spread of intrathecal sufentanil should limit these side effects. Both direction of the lateral opening of a pencil-point needle and drug baricity modify the spread of intrathecal local anesthetics. This randomized, prospective, double-blind study examines the effects of these variables on intrathecal sufentanil labor analgesia.**

Methods: **Forty laboring, full-term parturients, whose cervixes were dilated less than 5 cm and who requested analgesia for labor were enrolled. Combined spinal epidural analgesia was induced in patients in the sitting position. They were allocated to receive 10 μg intrathecal sufentanil diluted with either normal saline or dextrose with the aperture of the pencil-point needle directed cephalad or caudad during drug injection. Thus there were four groups of ten patients: dextrose up, dextrose down, saline up, and saline down. Sufentanil was diluted with normal saline to a concentration of 10 μg/ml. The study drug was made by mixing 1 ml sufentanil solution with either 1 ml 10% dextrose or 1 ml normal saline. Visual analog scores for pain, pruritus, nausea, and pain relief were recorded before and 5, 10, 15, and 30 min after drug injection.**

Results: **Baricity, but not needle orientation, influenced pain relief and pruritus. Sufentanil in dextrose produced less itching but also less analgesia. Nine of 20 women in the dextrose groups compared with 1 of 20 in the saline groups requested additional analgesia by 30 min.**

Conclusions: **Little or no labor analgesia developed for patients receiving sufentanil with dextrose. A supraspinal action may contribute to intrathecal sufentanil's analgesic efficacy. (Key words: Analgesia: spinal. Analgesics: sufentanil. Anesthesia: mechanisms; obstetric.)**

INTRATHECAL sufentanil rapidly provides profound analgesia for labor. Associated side effects such as pruritus, nausea, dysphagia, and respiratory depression arise with varying frequency.[1,2] These side effects may occur through actions at supraspinal sites; their rapid onset suggests that sufentanil reaches the brain quickly after intrathecal injection. Therefore, if we can limit cephalad spread of intrathecal sufentanil, we may be able to limit the frequency and intensity of associated side effects.

Previous studies have shown that aperture orientation of the pencil-point needle and baricity alter the cephalad distribution of intrathecally injected drugs.[3,4] Here, using a randomized, prospective, double-blind design, we examined the effects of these two variables on the analgesia and side effects produced by intrathecal sufentanil in laboring women.

Materials and Methods

The Jefferson Medical College Institutional Review Board approved the protocol for this prospective, randomized double-blind study. Written, informed consent was obtained from 40 healthy, laboring full-term parturients whose cervixes were dilated less than 5 cm. Each had a single fetus with a vertex presentation. Exclusion criteria included American Society of Anesthesiologists

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Table 1. Demographics

Group	Age (yr)	Height (cm)	Weight (kg)	Parity	Cervical Dilation (cm)
Dextrose up	29 ± 8	163 ± 11	70 ± 14	1 (0–3)	3.5 (1–4)
Dextrose down	30 ± 8	164 ± 7	76 ± 15	0 (0–3)	3 (1–4)
Saline up	30 ± 6	161 ± 7	80 ± 16	1 (0–3)	3 (1–4)
Saline down	27 ± 7	167 ± 5	80 ± 10	0.5 (0–1)	3 (1–4)

Values are mean ± SD or median (range).

physical status 3 or 4, prematurity or fetal complications, history of opioid or alcohol abuse, and previous parenteral opioid administration.

When a patient requested analgesia, she was assigned to one of four groups with differing injectate baricity and spinal needle aperture direction. Group assignment was performed by entering the participant's name in the next available slot on a previously generated randomization list. Women received sufentanil mixed with either normal saline or dextrose with the pencil-point spinal needle orifice facing either cephalad or caudad. Thus there were four groups of ten women each: dextrose up, dextrose down, saline up, and saline down.

Sufentanil, supplied in a 50 μg/ml ampule, was diluted with preservative-free normal saline to a concentration of 10 μg/ml . Study drug was made by adding either 1 ml 10% dextrose to 1 ml sufentanil solution (density at 37°C: 1.01265 g/ml [M. Richardson, M.D., written communication, July 17, 1996]) or 1 ml normal saline to 1 ml sufentanil solution (density at 37°C: 0.99893 ± 0.00004 g/ml).[5]

Each parturient received combined spinal epidural labor analgesia. With the patient sitting, we identified the epidural space at the L2–3 or L3–4 interspace using the loss-of-resistance technique with a 90-mm, 18-gauge Hustead needle (B. Braun Medical, Bethlehem, PA). A 120-mm, 24-gauge Sprotte needle (Pajunk, Germany) was passed through the epidural needle into the subarachnoid space. After seeing freely flowing cerebral spinal fluid (CSF), we injected 10 μg sufentanil within 10 s. The spinal needle was removed and a polyamide catheter inserted 5 cm into the epidural space and secured. The patient was positioned either on her side or supine with left uterine displacement and the head of the bed elevated between 10° and 30°.

Patients and the data collector were blinded to group assignment. Before and 5, 10, 15, and 30 min after intrathecal drug injection, patients reported their pain (no pain to worst pain), nausea, pruritus, and pain relief (no relief to complete relief) on 10 cm, unmarked, horizontal visual analog scales. We also recorded maternal blood pressure at these times. At 30 min we looked for sensory changes using an alcohol swab. The patient could request additional analgesia after 30 min. The time from opioid injection to request for additional analgesia was noted. At request for additional analgesia, patients received an epidural injection of 10 ml 0.125% bupivacaine with 5 μg/ml fentanyl.

Continuous data (age, height, weight, duration of pain relief) were compared by analysis of variance. Comparisons of serial measurements (hemodynamics, pain, nausea, pruritus, and pain relief visual analog scores) were performed with repeated measures analysis of variance. Fisher's protected least significant difference test was used for intergroup comparisons when appropriate. Ranked data were analyzed with the Kruskal-Wallis and Mann-Whitney U tests when appropriate. Categorical data were examined by chi-squared analysis. Probability values less than 0.05 were considered significant.

Results

There were no significant differences in age, height, weight, parity, or cervical dilation among the groups (table 1). Aperture orientation had no effect on the onset or intensity of analgesia. Baricity significantly altered the analgesic efficacy of intrathecal sufentanil. Although pain scores did not differ significantly among the groups, patients in the dextrose groups had significantly lower pain relief scores after intrathecal injection compared with those in the saline groups (table 2, fig. 1). Nine of the 20 women in the dextrose groups compared with 1 of 20 in the saline groups requested additional analgesia by 30 min ($P = 0.01$). There was no difference in the duration of pain relief among the women who remained in the study beyond 30 min (table 3).

Table 2. Post Hoc Comparisons among Groups (Fisher's Protected Least Significant Difference Test)

Comparison	Pain Relief (*P*)	Pruritus (*P*)
Dextrose up *vs.* dextrose down	0.99	0.54
Dextrose up *vs.* saline up	0.03*	0.0006*
Dextrose up *vs.* saline down	0.02*	0.01*
Dextrose down *vs.* saline up	0.03*	0.003*
Dextrose down *vs.* saline down	0.02*	0.05*
Saline up *vs.* saline down	0.88	0.28

Initial repeated measures analysis of variance revealed a significant group effect.

* Significant differences.

Aperture orientation also lacked effect on the frequency or intensity of itching. However, women in the saline groups reported significantly greater visual analog scores for itching after drug injection (table 2, fig. 2). Quality of pain relief influenced the amount of itching reported. Women requesting additional analgesia at 30 min had significantly ($P < 0.0001$) lower itching visual analog scores than did women reporting adequate pain relief. Baricity had no effect on itching visual analog scores within the group of women who reported acceptable analgesia.

Nausea was minimal in all groups. No patient vomited during the study.

Nine patients had detectable sensory changes: three in the saline down group and two in each of the other groups. Levels ranged from L3 to T6. Eight of the nine patients with a sensory level were comfortable at 30 min. There was no statistically significant correlation between the presence of a sensory level and adequate pain relief.

Table 3. Duration of Pain Relief

Group	No. of Women Comfortable at 30 min	Mean Duration of Pain Relief* (min)	Range* (min)
Dextrose up	7/10	126.1	56–266
Dextrose down	4/10	79.3	54–121
Saline up	10/10	105.1	45–177
Saline down	9/10	161.6	73–523

* Values are only for those women remaining in the study after 30 min.

Blood pressure changed little during the study period. There were no statistically significant decreases in systolic blood pressure. There was a slight but statistically significant decrease in diastolic blood pressure over time. Neither aperture orientation nor baricity influenced these blood pressure changes. Adequacy of analgesia did not have a statistically significant effect on blood pressure changes. No patient required treatment for a hemodynamic event. There were no adverse fetal events during the study period.

Discussion

We studied the influence of two factors, aperture orientation and baricity on the efficacy and side effects of

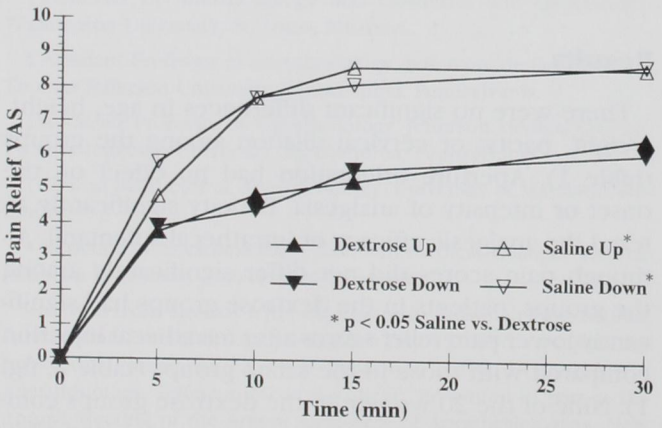

Fig. 1. Pain relief visual analog scores after intrathecal injection of 10 μg sufentanil mixed with either dextrose or saline *via* a 24-gauge Sprotte needle with the aperture facing either cephalad (up) or caudad (down). Patients in the dextrose groups had significantly less pain relief than did those in the saline groups (see table 2).

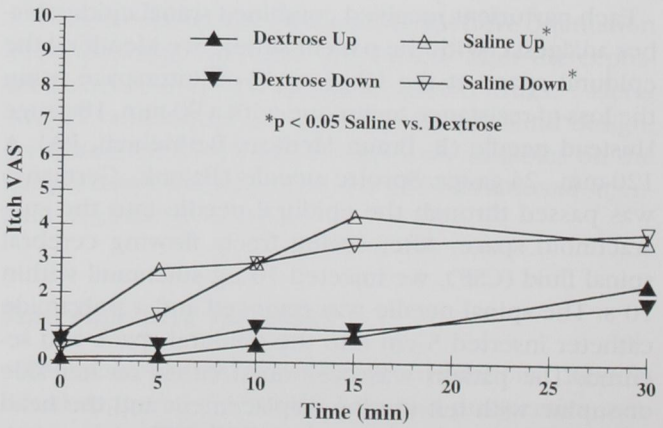

Fig. 2. Pruritus visual analog scores after intrathecal injection of 10 μg sufentanil mixed with either dextrose or saline *via* a 24-gauge Sprotte needle with the aperture facing either cephalad (up) or caudad (down). Patients in the saline groups had significantly more itching than did those in the dextrose groups (see table 2).

intrathecal sufentanil. In other settings, these variables have influenced the cephalad spread of intrathecal drug.

Pencil-point needles produce directional flow of injected drug. Using isobaric local anesthetic, others have found higher and more rapid spread of block after cephalad compared with caudad injection using either Sprotte[3] or Whitacre[6] point needles. In contrast, we found no effect of aperture orientation on the analgesia and side effects associated with intrathecal sufentanil. Sufentanil spreads rapidly and extensively within the cerebrospinal fluid after neuraxial injection.[7] This propensity to widespread distribution seems to outweigh any small effect on drug distribution produced by differences in aperture orientation.

Baricity influences the action of various intrathecal drugs. For example, hyperbaric and isobaric local anesthetics produce different patterns of sensory blockade.[4] Cephalad spread of neostigmine with saline produces severe, protracted nausea and vomiting. In contrast, the incidence and severity of nausea are markedly diminished by using neostigmine with dextrose.[8] Finally, another group also reported decreased analgesic efficacy of fentanyl with dextrose compared with fentanyl with saline in laboring women who sat while anesthesia was induced.[9]

Although dextrose-free solutions of local anesthetics and opioids are usually called "isobaric," they are actually hypobaric. The density of CSF from parturients is 1.00030 ± 0.00004 g/ml at 37°C.[10] Solutions with densities less than 1.00018 g/ml at 37°C (mean − 3 SD CSF density) are hypobaric.[10,11] The densities of "plain" 0.25–0.5% bupivacaine, fentanyl 0.005%, sufentanil 0.005%, saline, and mixtures of these solutions are all less than 1.00000 g/ml at 37°C.[5] Thus sufentanil in normal saline is hypobaric. This hypobaricity may help explain some of the effects produced by intrathecal sufentanil. In contrast, sufentanil in 5% dextrose has a density of 1.01265 g/ml 37°C. This value is well above the upper range of CSF density (1.00042 g/ml in parturients or 1.00124 g/ml in patients who are not pregnant[10]).

Why doesn't intrathecal sufentanil in dextrose provide adequate labor analgesia? One possible explanation is that dextrose inactivates sufentanil. This is unlikely because dextrose is compatible with most commonly used intrathecal drugs. In addition, intrathecal sufentanil with dextrose effectively provides labor analgesia when injected in patients lying on their sides.** Alternatively, dextrose might increase spinal cord blood flow and hasten the uptake of intrathecal sufentanil. In dogs, however, 5% and 7.5% dextrose have no effect on spinal cord blood flow.[12] A more likely explanation of our results is that dextrose limits sufentanil's access to its site of action.

Perhaps hyperbaric sufentanil pools in the sacral regions of the spinal canal and does not reach the T10 to L2 dermatomes in adequate concentrations to produce labor analgesia. But hyperbaric local anesthetics spread to the mid-thorax even when injected into patients in the sitting position.[13] Hyperbaric neostigmine ascends high enough to produce upper extremity analgesia when given to patients who sit for injection and then lie with their heads elevated 30° during testing.[8] Our patients received a combined spinal epidural anesthetic. Perhaps the additional time spent sitting while the epidural catheter was inserted allowed the hyperbaric sufentanil to pool in the most caudal CSF. However, sitting for as long as 25 min after intrathecal injection of hyperbaric bupivacaine does not limit the ultimate spread of sensory blockade.[13] All of our patients were lying supine with left uterine displacement within 10 min. Thus hyperbaric sufentanil should spread at least to T10. One patient in the dextrose down group did develop sensory changes in the T12 to L1 dermatomes. Still she did not obtain acceptable pain relief. In this patient, at least, hyperbaric sufentanil did reach the lower thoracic spinal cord but did not produce adequate labor analgesia. If intrathecal sufentanil has a strictly spinal site of action, patients in the dextrose groups should have developed adequate analgesia.

Although strong evidence of a segmental spinal site of action exists for local anesthetics, morphine, clonidine, and neostigmine,[4,8,14,15] there is little evidence in humans of a strictly spinal site of action of intrathecal sufentanil. The former drugs produce analgesia or anesthesia in lower extremities with little or no effect in the upper extremities. The only human study suggesting a spinal site of action for intrathecal sufentanil did not compare upper and lower extremity analgesia.[16] Camann *et al.*[16] compared the analgesic efficacy of 10 μg intrathecal *versus* epidural *versus* intravenous sufentanil in laboring women. Only intrathecal injection provided adequate labor analgesia. Although this indirect evidence is compatible with a spinal site of action, these data could merely indicate that intrathecal injection is an effective way to deliver sufentanil to its site or sites of action.

** Gage JC, D'Angelo R, Miller R, Eisenach JC: Does dextrose affect analgesia or side effects of intrathecal sufentanil? (abstract). Society for Obstetric Anesthesia and Perinatology 1996; 155

Perhaps intrathecal sufentanil produces labor analgesia by acting at both spinal and supraspinal sites. Various direct and indirect evidence supports this theory. Many studies show that phenylpiperidines quickly reach the brain after neuraxial injection. In dogs, sufentanil appears rapidly in the cisternal CSF after lumbar epidural injection.[7] In humans, fentanyl appears in cervical CSF within 10 min of lumbar epidural injection.[17] Clinical evidence also suggests that sufentanil ascends rapidly to the brain stem after lumbar intrathecal injection. It is generally accepted that rapid cephalad spread and supraspinal actions produce many of the side effects associated with intrathecal sufentanil.[1,2] It also is plausible that a supraspinal action contributes to the analgesia produced by intrathecal sufentanil.

Animal data suggest the potential magnitude of this contribution. For instance, morphine produces antinociception in rats by acting at either spinal or supraspinal sites. But simultaneous intrathecal and intracerebroventricular administration of morphine yields a profoundly multiplicative (synergistic) interaction.[18,19]

The nature of this interaction is very complex and may require stimulation of more than one receptor type or subtype. Although published reports agree the intrathecal and intracerebroventricular morphine (which acts at μ, Δ, and K receptors) interact synergistically, studies examining more receptor-specific agents conflict. Fentanyl, a selective mu agonist, has only an additive interaction when given by both intrathecal and intracerebroventricular injection.[20] In contrast, a synergistic interaction occurs with simultaneous intrathecal and intracerebroventricular injection of a different selective mu agonist, DAMPGO (Tyr-D-Ala^2-Gly-NMePhe^4-Gly-ol^5).[21,22] Other investigators report that Δ, α_2, or μ_2-opioid receptors are involved in this interaction between spinal and supraspinal sites.[23,24]

Differences in the lipid solubilities of various opioids may partially explain these conflicting results. It is possible to isolate the spinal and supraspinal actions of a poorly lipid-soluble drug such as morphine.[18] This task, however, is problematic when studying more lipophilic agents such as fentanyl and sufentanil. These drugs often produce supraspinal effects after intrathecal injection alone.[25–28] As a result, it is difficult, if not impossible, to attribute a given drug effect to a specific site of action. Thus although intrathecal morphine can produce analgesia by a local spinal effect, "it is likely that the antinociceptive effects of intrathecal fentanyl result from a dual activation of spinal as well as supraspinal sites."[28]

Unfortunately, our data offer little help in resolving these issues. Many investigators report sensory changes after intrathecal sufentanil.[29,30] The reported frequency and extent of the changes varies considerably. (Cohen *et al.*[29] recorded "decreased sensation to pinprick and cold," whereas we looked for inability to perceive cold. These methodologic differences may explain some of the variation in reported frequency of sensory changes.) The mechanism of these changes remains unclear. The published *in vitro* data concerning sufentanil-conduction blockade conflict.[31,32] In addition, opioid-induced conduction blockade is not naloxone reversible,[31,32] so it is unclear what, if any, correlation exists between sensory changes and analgesia. In our study, eight of nine patients with sensory changes reported adequate pain relief. Seven of these eight women had sensory change to at least the T12 level. However, two reported changes only in the L2 or L3 dermatomes. The one woman with detectable sensory changes but inadequate analgesia had sensory change to the T12 level. In this woman, sufentanil reached the lower thoracic spinal cord in a concentration sufficient to produce sensory changes but did not reach the site or sites that produce analgesia.

More than one half of the women in the dextrose groups obtained adequate analgesia. Thus, in these women, hyperbaric intrathecal sufentanil did reach its site or sites of action. A 10-μg dose of sufentanil may produce adequate analgesia in some women by a spinal mechanism alone. Or, in some patients, adequate concentrations of hyperbaric sufentanil may still reach supraspinal sites.

Lacking any other measure of supraspinal *versus* spinal action, this study cannot pinpoint intrathecal sufentanil's site of action. The incidence and severity of itching were higher in the women reporting adequate analgesia. In addition, baricity did not decrease the severity of itching in those women who did become comfortable. If pruritus were purely a supraspinal effect of intrathecal sufentanil, these observations would lend strength to our theory. Unfortunately, pruritus after intrathecal opioids stems from both segmental spinal and supraspinal actions.[33,34] In addition, there is no evidence to suggest that analgesia and pruritus result from action at the same site. Analgesia produced by an action at one site may unmask pruritus produced at a distant site.

In conclusion, when injected into patients in the sit-

ting position, intrathecal sufentanil with saline provides better labor analgesia than does intrathecal sufentanil with dextrose. A plausible explanation for this finding is that intrathecal sufentanil with saline ascends rapidly to the brain stem and produces profound analgesia by acting at both spinal and supraspinal sites. On the other hand, hyperbaric drug remains confined to the spinal cord and produces only limited labor analgesia. To paraphrase Yeung and Rudy[18] in their discussion of the actions of systemically administered drug, agonism at both spinal and supraspinal opioid-sensitive sites may be essential for the production of analgesia by spinally administered opioids, and neither site can logically be deemed the "primary" site of action. The dual sites of action of intrathecal sufentanil may make attempts to separate analgesia from side effects futile.

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