Anesthesiology
1999; 91:1293-8

Intrathecal Neostigmine and Sufentanil for Early Labor Analgesia

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Background: **Recent efforts to improve the combined spinal epidural (CSE) technique have focused on adding opioids to other classes of analgesics. In this study, the authors used intrathecal neostigmine in combination with intrathecal sufentanil to investigate the usefulness of neostigmine for reducing side effects and prolonging the duration of sufentanil.**

Methods: **One hundred six healthy pregnant women in labor were enrolled in this study, which was divided into four phases. In all phases, patients received a CSE anesthetic while in the lateral position. In phase I, three groups of six women each received intrathecal neostigmine, 5, 10, or 20 μg, in an open-label, dose-escalating safety assessment. In phase II, 24 women received intrathecal sufentanil alone to establish an ED_{50} (dose that produces > 60 min of labor analgesia in 50% of patients). In phase III, an ED_{50} was established for sufentanil combined with a fixed dose of neostigmine (10 μg). In phase IV, 40 women received either twice the ED_{50} of sufentanil alone or twice the ED_{50} of sufentanil plus neostigmine, 10 μg.**

Results: **Neostigmine alone had no adverse effects on maternal vital signs, fetal heart rate, or Apgar scores. Neostigmine, 20 μg, produced analgesia in one patient and severe nausea and vomiting in another. The ED_{50} for intrathecal sufentanil alone was 4.1 ± 0.31 μg, and the ED_{50} for intrathecal sufentanil combined with neostigmine, 10 μg, was 3.0 ± 0.28 μg. The duration of analgesia and side effects from double these ED_{50}s (sufentanil, 9 μg, or sufentanil, 6 μg, plus neostigmine, 10 μg) were similar between groups.**

Conclusions: **The 10-μg intrathecal neostigmine dose alone produced no analgesia or side effects, but reduced the ED_{50} of intrathecal sufentanil by approximately 25%. Additionally, doses approximately double these ED_{50}s each produced a similar duration of analgesia and side effects, indicating intrathecal neostigmine shifts the dose–response curve for intrathecal sufentanil to the left. (Key words: Acetylcholinesterase; combined spinal epidural analgesia; opioid; spinal; up–down method.)**

ALTHOUGH use of the combined spinal epidural (CSE) technique to produce labor analgesia has increased steadily during the past decade, relatively few dose-response studies have been performed to guide such therapy. Despite a faster onset and improved reliability of spinal over epidural analgesia, the usefulness of CSE is limited by the relatively short duration of analgesia and side effects of opioids used in the spinal portion of the technique.[1-3] One method to increase duration and reduce side effects is to administer combinations of lower doses of opioids with other classes of analgesics. One such class is cholinergic, because acetylcholine produces analgesia by a spinal mechanism.[4,5] After preclinical toxicity screening, human trials of intrathecal injection of the cholinesterase inhibitor neostigmine were initiated 5 yr ago.[6] Intrathecal neostigmine produces some analgesia alone, but with a long delay and accompanied by nausea and vomiting.[6] For these reasons, neostigmine is most commonly combined with other agents. Although intrathecal neostigmine has been shown to prolong analgesia from intrathecal sufentanil administered to women undergoing cesarean section and gynecologic surgery,[7,8] the effects of intrathecal sufentanil in combination with intrathecal neostigmine during labor are unknown.

The purpose of the current study was to systematically evaluate the utility of intrathecal neostigmine as an adjunct to intrathecal sufentanil for labor analgesia.

Materials and Methods

After approval by the Clinical Research Practice Committee and written informed consent, 106 healthy, preg-

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Received from the Department of Anesthesiology, Section on Obstetric Anesthesia, Wake Forest University School of Medicine, Winston-Salem, North Carolina. Submitted for publication March 17, 1999. Accepted for publication June 22, 1999. Supported in part by the 1997 Braun Fellowship Grant from the Society for Obstetric Anesthesia and Perinatology, Richmond, Virginia; and grant no. R01-GM48085 from the National Institutes of Health, Bethesda, Maryland.

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nant women were enrolled in this four-phase study. All patients were nulliparous, American Society of Anesthesiologists (ASA) physical status I or II, at term gestation, in active labor, and with a cervical dilation of 3–5 cm when requesting labor analgesia. Women with contraindications to regional anesthesia, weighing > 250 pounds, or with allergies to any study drug were excluded.

All patients had a CSE anesthetic administered while in the lateral decubitus position. A 17-gauge Weiss epidural needle, a 27-gauge Whitacre 4 1/16-inch spinal needle, and an 18-gauge closed-end triple-port epidural catheter were used for each patient (Becton Dickenson, Franklin Lakes, NJ). All intrathecal injections were administered in a 1.5-ml volume containing study drug in normal saline with 5% dextrose (D_5NS). Study solutions were prepared using 1-ml TB syringes. Detailed written instructions were attached to the randomization list, and the same three anesthesiologists not participating in patient care prepared study solutions in attempt to minimize mixing errors. In all four phases, the epidural catheters remained untested until the patients requested additional analgesia but no sooner than 20 min after intrathecal injection.

The study was performed in four phases. First, because intrathecal neostigmine had not previously been administered in an obstetric setting, we performed a small, open-label, dose-ranging study to evaluate unexpected adverse effects. Second, we determined the potency of intrathecal sufentanil by defining the dose that produced at least 60 min of analgesia in 50% of parturients (ED_{50}). Third, we determined this ED_{50} of sufentanil in the presence of a fixed dose of intrathecal neostigmine. Finally, in a randomized blinded study, we compared analgesia and side effects from approximately twice the ED_{50} of intrathecal sufentanil alone and with neostigmine.

In phase I, 18 women (3 groups of 6 each) were administered intrathecal neostigmine, 5, 10, or 20 μg, after an open-label, dose-escalating design.

In phase II, 24 women were administered intrathecal sufentanil alone to establish an ED_{50} for intrathecal sufentanil, which was the dose that produced 60 min of labor analgesia in 50% of patients. The ED_{50} was established using an up-down sequential allocation design wherein each patient's dose was determined by the previous patient's response. Sixty minutes was arbitrarily chosen as a clinically significant duration of labor analgesia. Starting with an initial dose of intrathecal sufentanil, 5 μg, patient responses were categorized as a success, a failure, or a rejection. Patients who experienced > 60 min of analgesia (4–5 pain relief on a 0–5 pain scale, 0 = no pain relief and 5 = complete pain relief) were categorized as a success. We chose to use pain relief scores rather than a specific "target" reduction in VAS score because the latter can be affected by the initial VAS score whereas the former is not. When successful analgesia occurred, the subsequent patient's dose of intrathecal sufentanil was decreased by 1 μg. When a failure occurred (pain relief < 4 on a 0–5 scale or complete pain relief lasting < 60 min), the subsequent patient's dose of intrathecal sufentanil was increased by 1 μg. Any patient experiencing cervical dilation of 8 cm or greater within 60 min of spinal injection was rejected from analysis to preserve homogeneity between groups because intrathecal opioids produce less effective analgesia for second-stage labor. When this occurred, the same dose was repeated for the next patient.

In phase III, an ED_{50} was established for the sufentanil-neostigmine combination, which produced 60 min of labor analgesia using the same up-down sequential allocation design as described for phase II. Twenty-four women were administered various doses of sufentanil plus a fixed 10-μg dose of intrathecal neostigmine.

The analgesic duration and side effects of each solution were compared in phase IV using a dose approximately double the ED_{50}s estimated in phases II and III. In phase IV, 40 women were randomized, using a double-blind design, to receive either intrathecal sufentanil, 9 μg, or intrathecal sufentanil, 6 μg, plus neostigmine, 10 μg.

In all four phases, maternal blood pressure and heart rate, fetal heart rate, and tocodynamometry were recorded throughout the study. Pain relief scores (1 = no relief, 2 = a little relief, 3 = half gone, 4 = almost gone, 5 = complete pain relief), cutaneous sensory levels to pinprick, 0–10 visual analog scores (VAS) for pain, and side effects including dizziness, pruritus, subjective leg weakness, nausea, and sedation were recorded at baseline, 5, 10, 15, and 20 min after injection, and at 30-min increments thereafter until the patient requested additional analgesia. All observations were assessed by an anesthesiologist or obstetric anesthesia fellow blinded to the treatment administered. Apgar scores were recorded after delivery.

Data from phase I were analyzed by analysis of variance (ANOVA). Data from phases II and III were analyzed by the Dixon and Massey method to derive median effective doses (ED_{50}) with 95% confidence intervals. These data were also subjected to probit regression

Table 1. Phase II and III Demographics

	Phase II		Phase III	
	Success (n = 10)	Failure (n = 10)	Success (n = 12)	Failure (n = 8)
Age (yr)	26 ± 5	27 ± 6	25 ± 5	22 ± 3
Height (cm)	164 ± 5	161 ± 6	166 ± 4	168 ± 7
Weight (kg)	77 ± 8	83 ± 14	80 ± 12	78 ± 15

Data are mean ± SD. No differences exist between groups.

analysis as a back-up sensitivity test. The estimated ED_{50}s from phases II and III were compared using a standard z test. Data from phase IV and side effects were analyzed by χ^2, Fisher exact test, and ANOVA as appropriate. Differences in fetal heart rate variability were analyzed using a standardized institutional variability scoring system previously described.[9] $P <$ than 0.05 was considered significant. The sample size for the open-label phase I safety study was somewhat arbitrary and was similar to those typical for these types of studies.[6,10] Sample size estimations for phases II and III were based on an unpublished pilot study of 40 patients (multiparous and nulliparous women) administered various doses of intrathecal sufentanil by up-down sequential allocation. From this data it was estimated that a minimum of 20 women would be required per group to achieve adequate power to determine the ED_{50} with a coefficient of variation of < 20%. Sample size for phase IV was estimated by power analysis to detect a 30-min difference in duration of analgesia between groups.

Results

Phase I

All women enrolled in phase I completed the study. Intrathecal neostigmine had no effect on maternal blood pressure, heart rate, or fetal heart rate. Apgar scores were similar among all three neostigmine dose levels, with no infant having a score < 8. The only side effect produced was protracted nausea, which occurred in one patient administered neostigmine, 20 μg. Likewise, only one patient, administered neostigmine, 20 μg, reported any pain relief, which lasted 60 min. All other patients received rescue analgesia *via* the epidural catheter 20 min after intrathecal neostigmine injection.

Phases II and III

Demographic variables were similar in patients experiencing successful and unsuccessful analgesia in phases II and III (table 1). The ED_{50} for intrathecal sufentanil alone was 4.1 ± 0.31 μg by the Dixon method and 4.1 ± 0.37 μg by probit analysis (fig. 1). In phase II (sufentanil alone), sufentanil, 3 μg, never produced 60 min of analgesia, whereas sufentanil, 6 μg, always produced > 60 min of analgesia. The ED_{50} of intrathecal sufentanil in combination with neostigmine, 10 μg, was 3.0 ± 0.28 μg by the Dixon method and probit analysis (fig. 2). In phase III sufentanil, 2 μg, never produced 60 min of analgesia, whereas sufentanil, 5 μg, always produced > 60 min of analgesia. The reduction in ED_{50} of intrathecal sufentanil from 4.1 ± 0.31 μg alone or 3.0 ± 0.28 μg when combined with intrathecal neostigmine was statistically significant ($P = 0.008$).

Phase IV

Demographic variables and labor characteristics (oxytocin use, mode of delivery, sensory levels, and VAS scores) were similar between groups in phase IV (table 2). Likewise, the incidence of side effects (pruritus, subjective leg weakness, hypotension, and light-headedness) was similar between groups (table 3). The duration of analgesia was similar for patients administered sufentanil, 9 μg, alone or sufentanil, 6 μg, plus neostigmine, 10 μg (fig. 3).

The results of phases II–IV demonstrate that a fixed

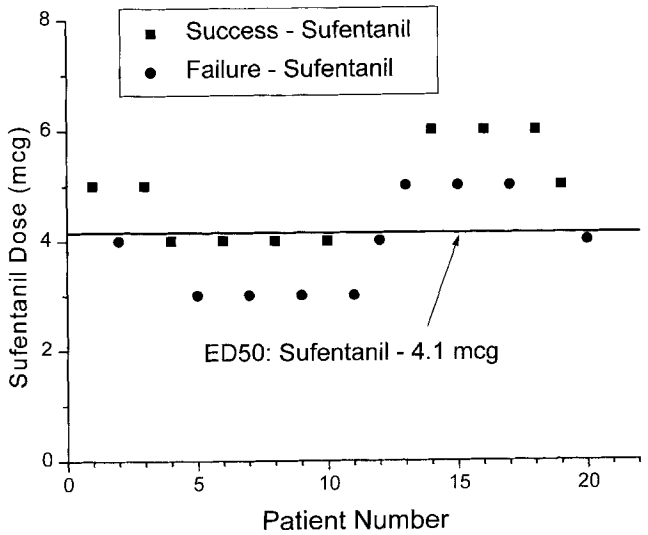

Fig. 1. The ED_{50} of intrathecal sufentanil as determined by up–down sequential allocation in phase II of the study. Black squares represent at least 60 min of labor analgesia. When this occurred, the next patient's dose of intrathecal sufentanil was then reduced by 1 μg. Black circles indicate < 60 min of analgesia. When this occurred, the next patient's dose was then increased by 1 μg. The ED_{50} for intrathecal sufentanil that produces 60 min of labor analgesia is 4.1 μg.

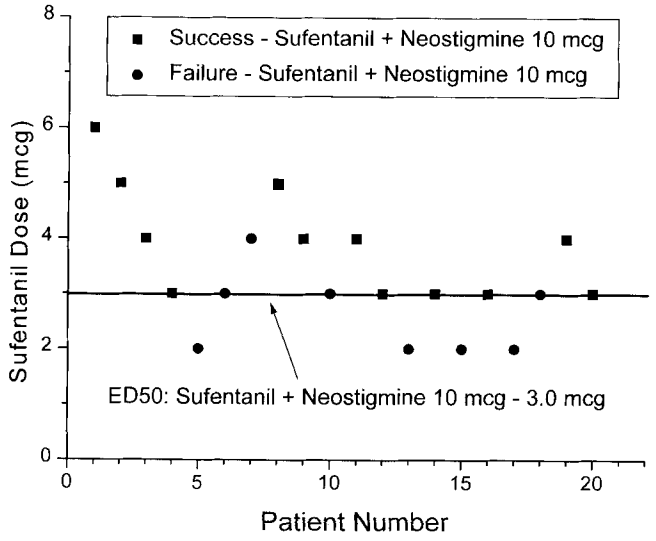

Fig. 2. The ED_{50} of intrathecal sufentanil as determined by up–down sequential allocation in phase III of the study when neostigmine, 10 μg, was added to each dose. Black squares represent at least 60 min of labor analgesia. When this occurred, the next patient's dose of intrathecal sufentanil was reduced by 1 μg. Black circles indicate < 60 min of analgesia. When this occurred, the next patient's dose was then increased by 1 μg. The ED_{50} for intrathecal sufentanil with neostigmine, 10 μg, that produces 60 min of labor analgesia is 2.99 μg.

dose of intrathecal neostigmine shifts the dose–response curve of intrathecal sufentanil to the left (fig. 4).

Discussion

This is the first report of intrathecal neostigmine use in laboring women, and we therefore began with a safety study. Previous to this study, intrathecal neostigmine had been administered to more than 100 patients, and side effects included nausea and vomiting, subjective leg weakness, spontaneous micturition and defecation, spontaneous ejaculation in men, sensations of vaginal contractions in women, hallucinations, and increased blood pressure and heart rate.[6] These side effects are dose-dependent, with nausea and vomiting and leg weakness occurring at doses > 50 μg, and ejaculation, vaginal contractions, hallucinations, and increased blood pressure and heart rate at doses > 200 μg.[6] We therefore chose a dose range of 5–20 μg because these doses would be unlikely to cause side effects and have produced evidence of analgesia in clinical trials. Theoretically, large doses of neostigmine could reduce uteroplacental blood flow by activating systemic nervous system activity and by causing uterine contractions by a direct effect. However, fetal heart rate patterns and maternal

Table 2. Phase IV Demographics and Labor Characteristics

	Sufentanil (n = 20)	Sufentanil + Neostigmine (n = 20)
Age (yr)	28 ± 6	26 ± 6
Height (cm)	165 ± 8	165 ± 7
Weight (kg)	75 ± 9	79 ± 11
Pitocin use (%)	40	55
Mode of delivery (%)		
Vaginal, spontaneous	60	65
Vaginal, assisted	30	20
Cesarean section	10	15
Sensory levels to pinprick at 20 min*	T5 (T4,T8)	T4 (T3,T6)
VAS scores		
Prior to spinal injection	9 ± 1	8 ± 2
10 min postinjection	1 ± 2	2 ± 2

Unless indicated, data are mean ± SD. No differences exist between groups.

* Data are median (25th percentile, 75th percentile).

Table 3. Phase IV Side Effects (%)

	Sufentanil (n = 20)	Sufentanil + Neostigmine (n = 20)
Pruritus	85	70
Subjective leg weakness	25	35
Hypotension (SBP decrease of 20% or more)	15	15
Subjective feeling of dizziness	0	5

No differences exist between groups.

SBP = systolic blood pressure.

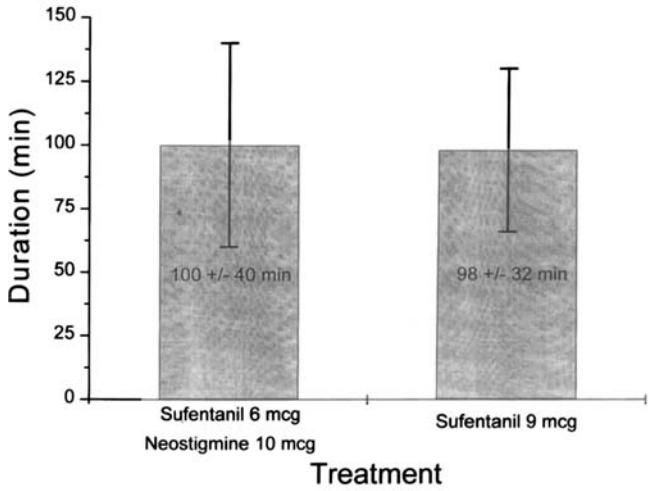

Fig. 3. The duration of analgesia from double the ED_{50} of sufentanil alone, compared with double the ED_{50} of sufentanil when combined with neostigmine, 10 μg, as described for phase IV of the study. There is no significant difference in duration between the two.

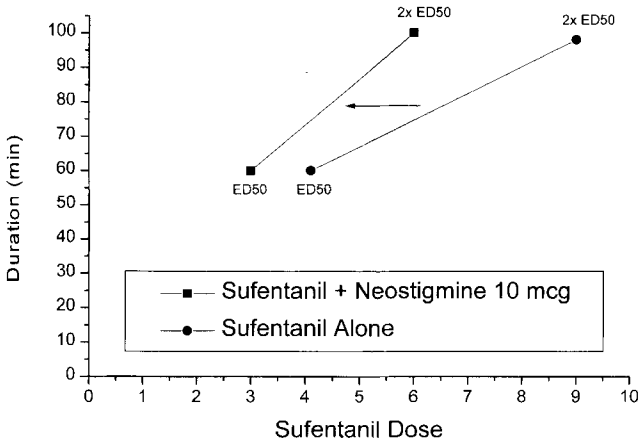

Fig. 4. The dose–response for duration of sufentanil with (*squares*) and without (*circles*) neostigmine, 10 μg. The addition of intrathecal neostigmine to intrathecal sufentanil shifts the sufentanil dose–response curve for labor analgesia to the left.

hemodynamic variables were unaffected by intrathecal neostigmine administered to women before cesarean section[7] and during labor (this study). Although small phase I trials do not define safety, the current phase I trial provided no evidence of worrisome side effects of intrathecal neostigmine in this dose range in labor. The one case of severe nausea and vomiting after administration of intrathecal neostigmine, 20 μg, caused us to use the next lower dose (10 μg) for subsequent studies. Of course, one cannot predict the incidence of nausea from neostigmine from these pilot data. Likewise, conclusions about the analgesic effects of intrathecal neostigmine cannot be drawn from the one patient who reported analgesia.

Lack of analgesia within 20 min of intrathecal neostigmine injection in phase I is not surprising. In human volunteers, the smallest dose of intrathecal neostigmine that produces analgesia alone is 100 μg.[6] In contrast, animal studies demonstrate that spinal acetylcholine release is increased in the presence of pain,[11,12] which would increase the potency of neostigmine. This may explain the analgesic effect observed after administration of intrathecal neostigmine, 10 μg, in women after cesarean section.[7] In volunteers and patients, intrathecal neostigmine exhibits a time to peak analgesia of 30–60 min,[6,13] in keeping with its poor lipid solubility. We believed it was unethical to withhold rescue pain medication for this long in women with an epidural catheter in place, and we may have missed the analgesic effect of intrathecal neostigmine alone as a result.

Only recently have dose–response studies of intrathecal analgesics for labor been reported. The discrepancy between the ED_{50} for 60 min of labor analgesia with intrathecal sufentanil alone that we observed (4.1 ± 0.31 μg) and those obtained in two recent studies (1.8 μg and 2.6 μg)[14,15] most likely represents differences in study design. The previous studies determined the ED_{50} of intrathecal sufentanil that produced 30 min of labor analgesia using a standard dose–response study design, whereas we estimated the ED_{50} of intrathecal sufentanil that produced 60 min of labor analgesia using an up-down sequential allocation design.

The current study observed a reduction in the ED_{50} of intrathecal sufentanil for labor analgesia of approximately 25% (from 4.1 to 3.0 μg) when intrathecal neostigmine was added. In animals there is a synergistic interaction between intrathecal neostigmine and morphine for antinociception to an acute heat stimulus.[16] This finding is expected because there is a synergistic interaction between spinal α_2-adrenergic agonists and opioids and because spinal α_2-adrenergic agonists act to produce analgesia in part *via* spinal acetylcholine release. Others have observed potentiation of spinal analgesia from opioids by intrathecal neostigmine in other patient populations[17] and in volunteers,[18] but this is the first study to test this interaction for labor analgesia. The study was not designed to determine the nature of the interaction (synergy *vs.* additivity) because we did not test the analgesic effect of intrathecal neostigmine alone. In phase IV we compared the duration of analgesia and the side effects from approximately double the ED_{50} of sufentanil alone and for the sufentanil–neostigmine combination established in phases II and III. We chose to double the ED_{50}s as an approximation of the ED_{95} because a major limitation of the up–down sequential allocation design is that the data can only be used to reliably estimate the ED_{50}, not the ED_{95}. In addition, doubling the ED_{50} of intrathecal sufentanil alone to 9 μg closely agreed with our clinical experience that this dose would produce analgesia in approximately 95% of patients. A dose of intrathecal sufentanil 9 μg was chosen, rather than 8 μg, because preliminary results indicated the ED_{50} to be 4.6 μg, rather than the final 4.1 μg. Because evidence suggests the upper end of the sufentanil dose–response curve is flat with estimations of the ED_{95} ranging between 8.9–15.3 μg,[14,15] 8 and 9 μg intrathecal sufentanil would be expected to be nearly clinically indistinguishable.

Intrathecal neostigmine, 10 μg, shifted the dose–response curve of intrathecal sufentanil to the left, thus less sufentanil was required to produce similar labor

analgesia. Although a left-shift in the dose-response curve would be expected to result in less side effects, side effects were similar between groups in this study (table 3). It is possible that a "side effect threshold" exists, above which narcotic side effects will occur, and that even sufentanil, 6 μg, exceeds this threshold. It is also possible that our study lacked the power to detect minor differences in side effects, although no serious adverse events were noted.

Although these results are encouraging, we do not recommend the routine use of intrathecal neostigmine in laboring patients because the incidence of side effects was not reduced in this study. However, additional studies of intrathecal neostigmine are warranted. The addition of other adjuncts, such as clonidine, to sufentanil and neostigmine may enhance analgesia and reduce side effects. Intrathecal neostigmine interacts synergistically with μ- and α_2- receptor agonists in rats[16] and inhibits clonidine-induced hypotension in sheep.[19] These interactions may also occur in laboring patients. The ultimate goal of these studies is to prolong spinal analgesia while minimizing side effects so that we may rely less on epidural analgesia, which is labor intensive and often produces inadequate labor analgesia.

We conclude that intrathecal neostigmine, 10 μg, reduces the ED_{50} of intrathecal sufentanil by approximately 25%, from 4.1 ± 0.31 μg to 3.0 ± 0.28 μg. In addition, doses approximately double these ED_{50}s produce a similar duration of labor analgesia and similar side effects, indicating intrathecal neostigmine shifts the dose-response curve for intrathecal sufentanil to the left.

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