Epidural Neostigmine *versus* Fentanyl to Decrease Bupivacaine Use in Patient-controlled Epidural Analgesia during Labor

A Randomized, Double-blind, Controlled Study

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ABSTRACT

Background: The addition of opioids to epidural local anesthetic reduces local anesthetic consumption by 20% but at the expense of side effects and time spent for regulatory compliance paperwork. Epidural neostigmine also reduces local anesthetic use. The authors hypothesized that epidural bupivacaine with neostigmine would decrease total hourly bupivacaine use compared with epidural bupivacaine with fentanyl for patient-controlled epidural analgesia.

Methods: A total of 215 American Society of Anesthesiologists physical status II, laboring parturients requesting labor epidural analgesia consented to the study and were randomized to receive 0.125% bupivacaine with the addition of either fentanyl (2 μg/ml) or neostigmine (2, 4, or 8 μg/ml). The primary outcome was total hourly local anesthetic consumption, defined as total patient-controlled epidural analgesia use and top-ups (expressed as milliliters of 0.125% bupivacaine) divided by the infusion duration. *A priori* analysis determined a group size of 35 was needed to have 80% power at α = 0.05 to detect a 20% difference in the primary outcome.

Results: Of 215 subjects consented, 151 patients were evaluable. Demographics, maternal and fetal outcomes, and labor characteristics were similar among groups. Total hourly local anesthetic consumption did not differ among groups (*P* = 0.55). The total median hourly bupivacaine consumption in the fentanyl group was 16.0 ml/h compared with 15.3, 14.6, and 16.2 ml/h in the 2, 4, and 8 μg/ml neostigmine groups, respectively (*P* = 0.55).

Conclusions: The data do not support any difference in bupivacaine requirements for labor patient-controlled epidural analgesia whether patients receive epidural bupivacaine with 2 to 8 μg/ml neostigmine or epidural bupivacaine with 2 μg/ml fentanyl. (ANESTHESIOLOGY 2017; 127:50-57)

TRADITIONALLY epidural infusions for labor analgesia have consisted of a combination of local anesthetic plus an adjuvant opioid. The addition of an opioid to epidural local anesthetic reduces the dose of local anesthetic needed for analgesia, thereby minimizing side effects from local anesthetic blockade, especially maternal motor block and, potentially, hypotension. However, these epidurally administered opioids can produce side effects themselves, including pruritus and decreased fetal heart rate variability.[1] For these reasons, there has been interest in nonopioid adjuvants to reduce epidural local anesthetic dose. The cholinesterase inhibitor, neostigmine, produces analgesia when given intrathecally or epidurally, *via* increased acetylcholine stimulation of spinal muscarinic and possibly nicotinic receptors.[2]

Studies of intrathecal neostigmine in the mid to late 1990s demonstrated analgesic efficacy and lack of neurologic injury but also dose-dependent, severe nausea and vomiting, and further clinical development was abandoned.[3,4] In

What We Already Know about This Topic

- Single- and intermittent-dose epidural neostigmine reduces local anesthetic requirement for labor analgesia
- Effects of adding neostigmine to epidural local anesthetic infusion on local anesthetic consumption for labor analgesia are unknown

What This Article Tells Us That Is New

- Adding neostigmine (2, 4, or 8 μg/ml) to bupivacaine for patient-controlled epidural analgesia during labor did not reduce bupivacaine requirement compared with bupivacaine plus fentanyl

contrast, epidural administration of neostigmine has been shown in both adults and children to reduce local anesthetic requirements in the postoperative setting without nausea and vomiting.[5–9] Epidural neostigmine also has been shown in small, single-dose studies to reduce epidural local

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anesthetic requirement for labor analgesia to a degree similar to that of opioids, including a study in which epidural analgesia was titrated *via* patient-controlled epidural analgesia (PCEA).[10–12] In contrast to opioids, there are no large randomized controlled studies evaluating the effects of epidural neostigmine as an adjunct to local anesthetics in the obstetric population for continuous PCEA during labor. The purpose of the current study was to compare the effects of epidural neostigmine, 2, 4, or 8 μg/ml, with that of a commonly used concentration of fentanyl (2 μg/ml) when added to 0.125% bupivacaine *via* PCEA during labor. We hypothesized that epidural bupivacaine with neostigmine would reduce total hourly bupivacaine use compared with epidural bupivacaine with fentanyl for labor analgesia. A secondary analysis was intended to evaluate the clinical dose response of 2 to 8 μg/ml of epidural neostigmine on local anesthetic consumption for labor analgesia compared with 2 μg/ml of fentanyl if significant clinical differences were detected for all doses of neostigmine studied.

Materials and Methods

The study was registered before recruitment of the first subject (http://www.clinicaltrials.gov; NCT00779467), was performed under Investigational New Drug (No. 42281) oversight by the U.S. Food and Drug Administration, and was reviewed on an ongoing basis by a data safety monitoring board. After approval from the institutional review board (Wake Forest School of Medicine, Winston-Salem, South Carolina; No. 5917), written informed consent for study participation was obtained before a patient's request for labor epidural analgesia. Parturients were eligible to participate if they were American Society of Anesthesiologists physical status II, spoke English, weighed less than 115 kg, were in active labor with a single fetus, had cervical dilation 5 cm or less, and had not received IV analgesics within 60 min before epidural administration. Patients with allergies to local anesthetics, fentanyl, or neostigmine also were excluded. The institutional review board initially approved the enrollment of 200 patients for a goal of 160 evaluable patients, but an amendment to increase the number of enrolled patients to 220 was approved in April 2013 due to the need to replace excluded or ineligible patients. Based on updated data used in our power analysis, our goal of 40 evaluable patients per group also was revised at that time to a minimum of 35 patients per group for the final analysis (fig. 1).

Patients were randomized in a balanced manner to one of four study groups *via* a computer-generated number allotment that was concealed in a sealed envelope. At the time of epidural labor analgesia request, an anesthesiologist not involved in the patient's care or data collection prepared the epidural study solution. All members of the patient's care team were blinded to the assignment and study drug. A lumbar epidural catheter was inserted after the administration of a combined subarachnoid and intravenous test dose with 45 mg lidocaine and 15 μg epinephrine. Patients were randomized to receive 15 ml bupivacaine, 1.25 mg/ml, mixed
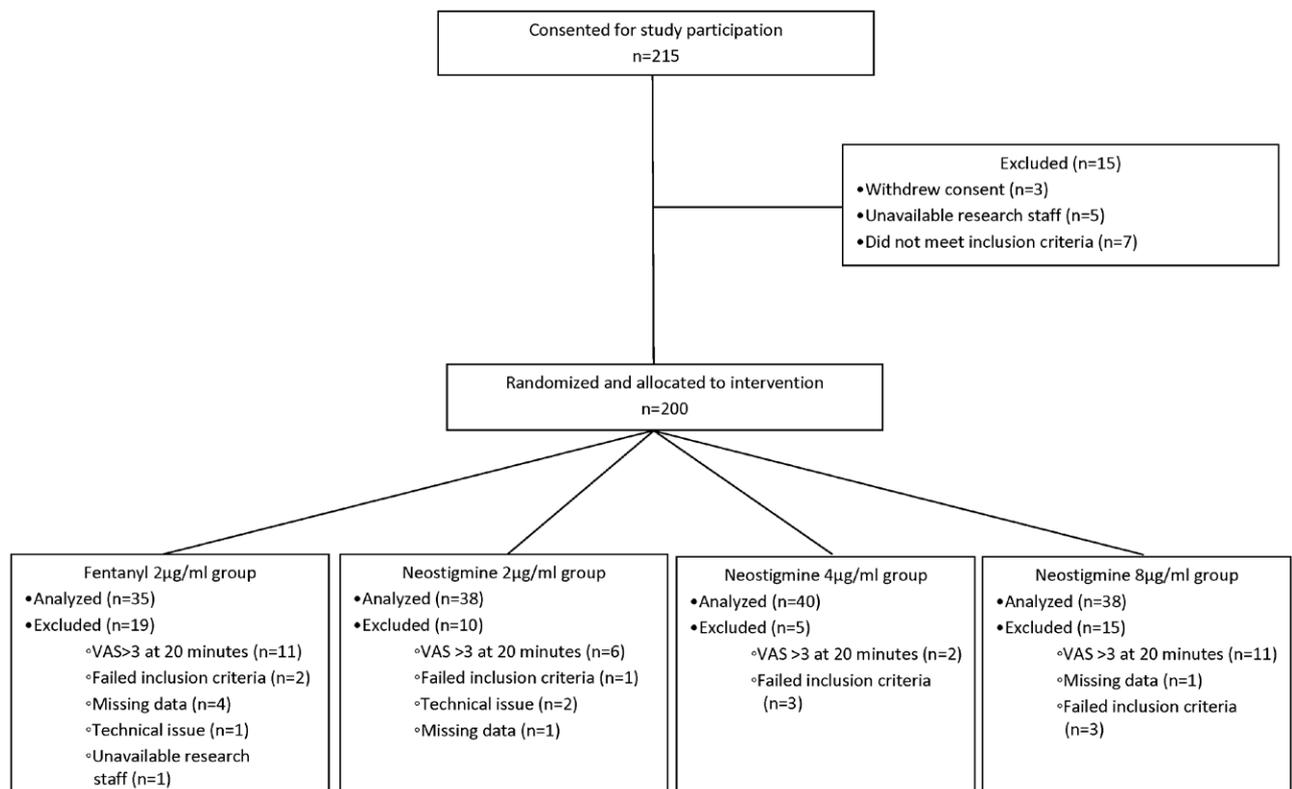

Fig. 1. Enrollment diagram. VAS = visual analog scale.

with one of four adjuvant medications: 2 μg/ml fentanyl or 2, 4, or 8 μg/ml phenol-free neostigmine methylsulfate (1 mg/ml, American Regent, USA; 10-ml multidose vial but discarded after single use). If the patient reported a verbal pain score greater than 3 on a 0 to 10 scale at 20 min after epidural injection, she was excluded from the study and the epidural catheter was replaced or managed by the anesthesiologist at his or her discretion.

After the initial dosing of the epidural catheter with the study solution to establish labor analgesia, a PCEA infusion pump was programmed and initiated with the assigned solution for maintenance analgesia with the following parameters: basal rate of 6 ml/h; PCEA bolus of 5 ml with a 10-min lockout interval; maximum dose of 30 ml/h. Patients with breakthrough pain were treated with a 5- to 10-ml bupivacaine, 2.5-mg/ml bolus, at the discretion of the anesthesiologist to achieve adequate labor analgesia. Patients reporting inadequate labor analgesia after receiving a bupivacaine bolus or patients requiring more than one bolus dose per hour were excluded from the study.

Pain was assessed on a 0 to 10 verbal scale at the following time points: before epidural catheter placement, immediately after combined subarachnoid/intravenous test dose, every 5 min for 20 min after initial epidural bolus of the study solution, and then every 2 h until delivery. In addition, the following parameters were recorded every 2 h until delivery: dermatomal level of sensory blockade to pinprick testing, degree of motor block according to a 0 to 3 scale described by Bromage,[13] maternal self-report of sedation (0 to 10), intensity of nausea (0 to 10), pruritus (0 to 10), and sleepiness (0 to 10), an observer's assessment of maternal alertness[14] (1 to 5), and presence of shivering. Maternal hypotension (20% change or greater from baseline and/or requiring treatment), maternal bradycardia (maternal heart rate less than 60 beats/min or greater than 20% decrease from the patient's baseline heart rate), fetal heart rate abnormalities, mode of delivery, and 1- and 5-min Apgar scores also were recorded. The total volume of study solution administered, the number of PCEA demand boluses, and the number and volume of anesthesiologist-administered bupivacaine 2.5-mg/ml bolus doses were recorded after termination of the PCEA infusion. After delivery, patients also were asked to rate their overall degree of epidural labor analgesia using a 1 to 5 verbal score (1 = not satisfied at all, 5 = extremely satisfied).

Written informed consent for study participation initially was obtained from 160 patients. The initial goal of 40 evaluable patients per group was based on preliminary data from a previous study evaluating epidural bupivacaine use with and without the addition of epidural neostigmine.[12] An estimated mean bupivacaine use of 11.0 ± 3.2 ml/h was used to detect a 20% difference between any groups with an effect size of 0.8, power 0.8, and alpha 0.05. Replacement of unevaluable patients was based sequentially on the randomization assignment of the previously excluded patients after enrollment of the initial 160 patients was completed.

We obtained permission from the institutional review board to increase the number of enrolled patients because we did not have enough evaluable patients after 200 patients consented initially. Study enrollment occurred over a 5-yr period (October 2008 to November 2013), with intermittent pauses in enrollment due to neostigmine shortages, researcher availability for enrollment, and technical issues. Final analysis of the previous neostigmine study by Ross *et al.*[12] revealed a mean bupivacaine use of 11.9 ± 3.0 ml/h. With these new data, a sample size of 35 evaluable patients per group, instead of 40 patients, would be adequate to detect a 20% difference between any groups. Due to the prolonged enrollment of the study and intermittent difficulties obtaining neostigmine, the study was terminated in November 2013 when a minimum of 35 evaluable patients per group were enrolled and completed the study.

Data Analysis

Data are presented as mean ± SD or median with quartiles as appropriate. The primary outcome was defined as hourly bupivacaine use during labor. A sample size of 35 patients per group was chosen to detect a clinically meaningful difference of 20% in hourly bupivacaine use among groups ($\alpha = 0.05$; $1 - \beta = 0.20$). Groups were compared for the primary outcome by one-way ANOVA. Pain scores and maternal side effects were intended to be analyzed by repeated-measure ANOVA methods, but assumptions of ANOVA were violated and were therefore analyzed with linear mixed effect modeling. Other variables were compared with the Student's *t* test, chi-square analysis, Mann–Whitney U rank sum test, or Fisher exact test as appropriate. $P < 0.05$ was considered significant.

Statistical analyses were conducted with SigmaStat version 3.0 for Windows (SPSS Inc., USA, and then acquired by IBM [USA] in 2009). Descriptive statistics were calculated for all variables and compared among groups, such that mean ± SD was used for normally distributed variables; median [interquartile range] for data that were not normally distributed or for data with outliers or ordinal data; and number (percentage) for categorical data. Kolmogorov–Smirnov (with Lilliefors correction) test was used to test for normality of data distribution of each variable.

Results

Written informed consent for study participation was obtained from a total of 215 patients before their request for labor epidural analgesia. Data from 151 evaluable patients were included in the final analysis with a minimum of 35 patients per group (fig. 1). The most common reason for patient exclusion was visual analog scale pain score greater than 3 at 20 min after epidural placement.

Demographic information, labor characteristics, or neonatal outcomes did not differ among the 151 evaluable patients in the four study groups (table 1). There was no difference in median hourly bupivacaine use in PCEA, supplemental boluses, or their combination (fig. 2). The

Table 1. Demographics, Labor Characteristics, and Neonatal Outcomes of Laboring Patients

	Fentanyl, 2 µg/ml	Neostigmine, 2 µg/ml	Neostigmine, 4 µg/ml	Neostigmine, 8 µg/ml	P Value
Sample size, n	35	38	40	38	
Age, yr	27 ± 6	28 ± 6	27 ± 6	28 ± 5	0.68
BMI, kg/m^2	31 ± 5	31 ± 5	30 ± 5	30 ± 4	0.89
Parity	1 [0–1]	0 [0–1]	0 [0–1]	0.5 [0–1]	0.89
Estimated gestational age, wk	40 ± 1	40 ± 1	40 ± 1	40 ± 1	0.99
Cervical dilation at epidural placement, cm	3.8 [2.3–4.0]	3.0 [2.1–3.9]	3.0 [2.0–3.8]	3.0 [2.0–3.5]	0.82
Epidural placement to cervix complete, min	235 [192–373]	268 [167–452]	330 [221–517]	258 [154–366]	0.26
Epidural placement to delivery, min	322 [242–484]	415 [202–579]	396 [286–703]	303 [193–520]	0.29
Total study analgesia duration, min	410 ± 309	424 ± 290	480 ± 295	406 ± 322	0.69
Percent requiring cesarean delivery, %	14 (5/35)	24 (9/38)	15 (6/40)	21 (8/38)	0.67
Percent requiring bupivacaine bolus for labor analgesia, %	57 (20/35)	53 (20/38)	60 (24/40)	55 (21/38)	0.93
Patient satisfaction score, 1–5	4 [3–5]	4 [3–5]	4 [4–5]	5 [3–5]	0.82
Neonatal weight, g	3,424 ± 383	3,437 ± 485	3,403 ± 449	3,448 ± 430	0.97
1-min Apgar score	7 ± 2	8 ± 2	8 ± 2	8 ± 2	0.93
5-min Apgar score	9 ± 0	9 ± 1	9 ± 1	9 ± 0	0.83

Descriptive statistics were calculated for all variables such that mean ± SD was used for normally distributed variables; median [interquartile range] for data that were not normally distributed or for data with outliers or ordinal data; and number or percentage for categorical data. ANOVA, chi-square analysis, Mann–Whitney U rank sum test, and Fisher exact test were applied as appropriate. For all analyses, P was set at 0.05 for statistical significance.
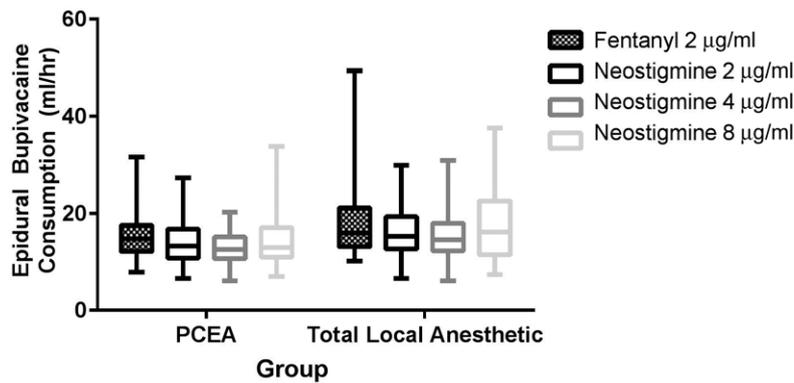
BMI = body mass index.

Fig. 2. Median local anesthetic consumption between groups. Median hourly bupivacaine consumption of parturients with an epidural for labor analgesia. *Box* indicates 25th and 75th percentile; *bars* indicate minimum and maximum values; and *middle line* in box indicates median consumption (ml/h). PCEA = patient-controlled epidural analgesia.

median hourly total bupivacaine consumption of patients in the fentanyl group was 16 ml/h, and in neostigmine 2, 4, and 8 µg/ml groups was 15.3, 14.6, and 16.2 ml/h, respectively (P = 0.55). The median hourly bupivacaine consumption of patients from only the PCEA pump was 14.8 ml/h in the fentanyl group and 13.3, 12.6, and 13.0 ml/h in the 2, 4, and 8 µg/ml epidural neostigmine groups, respectively (P = 0.25). The duration of total study epidural labor analgesia was nonsignificant among groups (P = 0.69). In addition, there was no difference among groups in number of patients requiring additional bupivacaine boluses for improved labor analgesia (P = 0.93).

Mean pain scores during labor did not differ between the groups over time (P = 0.36; fig. 3). Pain scores improved in all four groups after epidural placement. Overall patient satisfaction with labor analgesia did not differ among
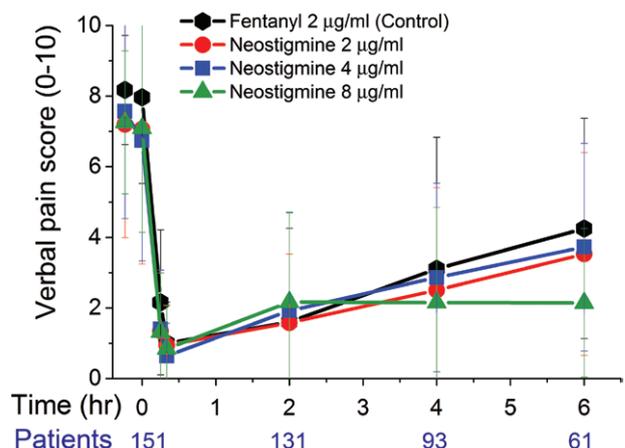

Fig. 3. Mean verbal pain scores (0 to 10) ± SD over time during labor.

groups (P = 0.82). The overall median satisfaction score was 4.0 (very satisfied) with a 1 to 5 scale. Patients in the epidural fentanyl group had a median satisfaction score of 4.0, whereas patients in the 2, 4, and 8 µg/ml epidural neostigmine groups had median satisfaction scores of 4.0, 4.0, and 4.5, respectively.

Labor progress did not differ among groups, nor did the cesarean delivery rate or neonatal outcomes (table 1). We also performed an intention-to-treat analysis of all patients, including those patients who were withdrawn from the study, for neonatal Apgar scores and mode of delivery. We found no significant difference in Apgar scores at 1 and 5 min (P = 0.84 and P = 0.39, respectively) or cesarean delivery rate (P = 0.84).

Epidural neostigmine at any of the doses studied did not cause greater intensity scores than epidural fentanyl of undesired side effects such as maternal nausea (P = 0.66), sedation (P = 0.64), shivering (P = 0.40), or degree of motor blockade (P = 0.33) (table 2). Average maximum pruritus scores of patients in the epidural fentanyl group were significantly greater than patients receiving epidural neostigmine (P = 0.001). We also examined whether the side effects of patients in the epidural fentanyl group (2 µg/ml) differed significantly from patients in the three epidural neostigmine groups (2, 4, and 8 µg/ml) at the time of epidural placement and over time. The four groups did not differ in the incidence of motor blockade, maternal self-assessment of nausea, maternal self-assessment of sleepiness, or pruritus over time (data not presented, fig. 4). Due to the significant decline in the number of patients in each group over time as patients underwent successful deliveries, the time scale for figure 4 has been limited to 6 h.

Discussion

Study solutions of epidural bupivacaine with varying doses of neostigmine (2 to 8 µg/ml) provide similar hourly epidural bupivacaine requirements to solutions of epidural bupivacaine with 2 µg/ml fentanyl in PCEA for labor. Within the definition of minimum clinically meaningful difference, epidural neostigmine was indistinguishable from epidural fentanyl as an analgesic adjunct to epidural bupivacaine.

Although a control group without epidural fentanyl was not included in this study, the use of epidural fentanyl at this concentration (2 µg/ml) is common and well documented to reduce local anesthetic use while still providing adequate labor analgesia.[15] The routine use of local anesthetic alone for epidural labor analgesia, without the addition of an adjuvant opioid, is uncommon in current practice in the United States.[16]

Because we found no significant difference in local anesthetic consumption for labor analgesia between neostigmine and fentanyl or among different doses of neostigmine, we were therefore unable to perform a subanalysis on the clinical dose response for epidural neostigmine. This is in contrast to the clear dose response seen for neostigmine to reverse neuromuscular blockade by its action on acetylcholinesterase. Neuraxial neostigmine may act in part by inhibiting meningeal acetylcholinesterase, thereby increasing the cerebrospinal fluid concentration of acetylcholine, resulting in increased bioavailability of acetylcholine in cholinergic spinal neurons.[17] However, the lack of dose response suggests a plateau effect on the blockade of meningeal acetylcholinesterase locally at the studied concentrations of epidural neostigmine, suggesting that neostigmine concentrations greater than 2 µg/ml under these infusion conditions are not needed and lower concentrations may be effective.

The study design also may have prohibited us from finding a significant difference in bupivacaine consumption between the three epidural neostigmine groups. The study was designed as a test of superiority, with the sample size deliberately constrained to ensure that the study only had 80% power to detect a difference in total bupivacaine consumption per hour between groups. Thus, we would not be able to detect a difference in bupivacaine consumption less than 20% between groups.

In addition, the concentration of bupivacaine (0.125%) used for labor PCEA in our study may have caused patients to reach the plateau phase of sensory blockade at the basal infusion rate. Thus, additional epidural adjuvants such as fentanyl or neostigmine may not have contributed to improving pain scores or reducing bupivacaine consumption.

Patients enrolled in either the epidural fentanyl or epidural neostigmine groups were very satisfied with their labor analgesia. This is likely because the protocol excluded poorly functioning epidurals with visual analog scale pain scores greater than 3 at 20 min after placement. Because labor pain relief was adequate and similar among all groups, satisfaction

Table 2. Side Effect Profile of Epidural Fentanyl *versus* Neostigmine

	Fentanyl, 2 µg/ml	Neostigmine, 2 µg/ml	Neostigmine, 4 µg/ml	Neostigmine, 8 µg/ml	*P* Value
Average maximum nausea score (0–10)	1 ± 2	2 ± 3	2 ± 3	1 ± 3	0.66
Average maximum sedation score (0–10)	4 ± 3	3 ± 3	3 ± 3	3 ± 3	0.64
Average maximum shivering score (0–10)	0 ± 0	0 ± 1	0 ± 0	0 ± 0	0.40
Average maximum pruritus score (0–10)	1 ± 2	0 ± 0	0 ± 0	0 ± 0	0.001*
Average maximum Bromage score (0–3)	1 ± 1	1 ± 1	1 ± 1	1 ± 1	0.33

All statistical variables are mean ± SD.

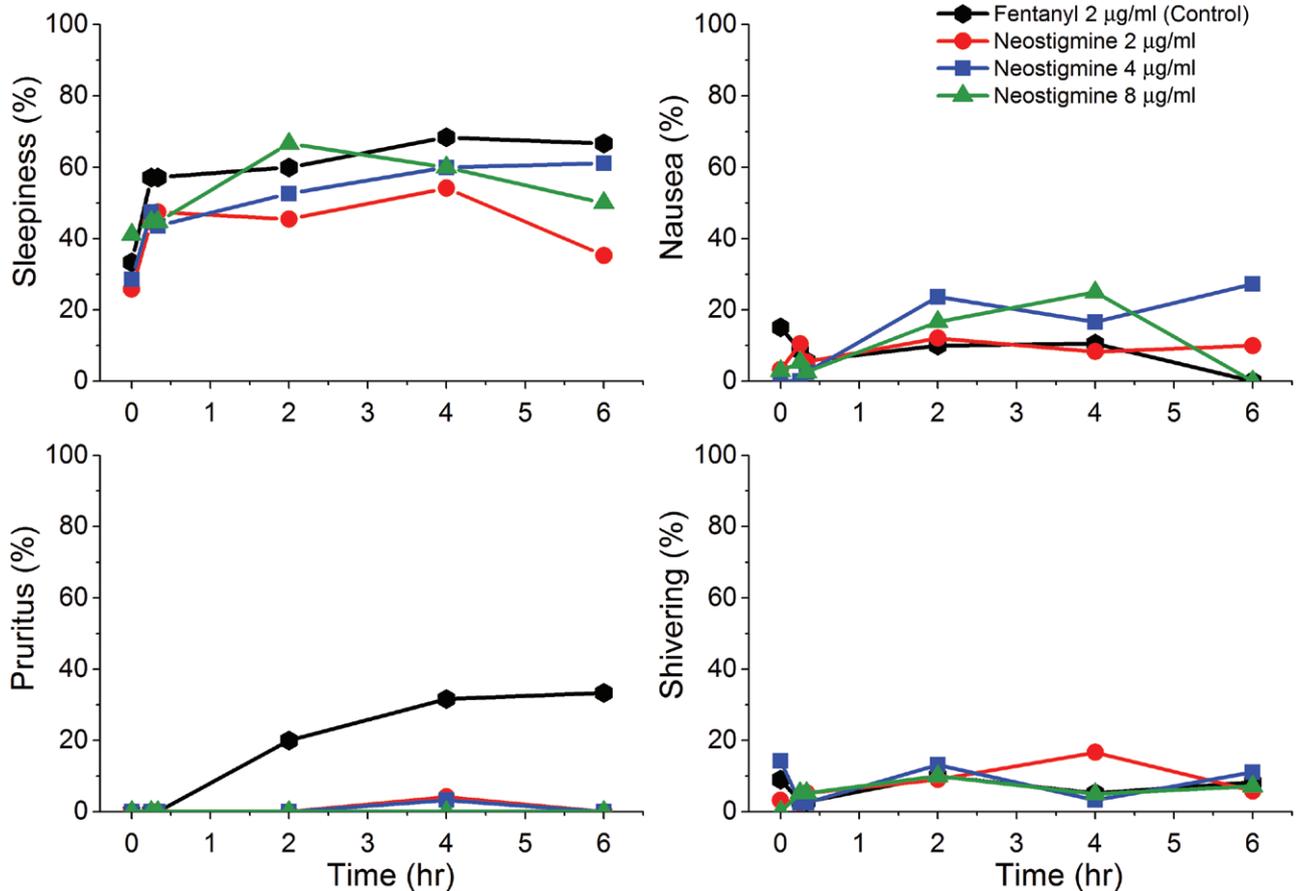*Statistically significant ($P < 0.05$).

Fig. 4. Percent incidence of nonzero verbal scores of maternal sleepiness, nausea, pruritus, and shivering after initiation of patient-controlled epidural analgesia for labor.

scores were high. Pain scores increased overall in all four groups over time, likely related to labor advancement, epidural migration, and/or greater incidence of dysfunctional labor as time progressed. Overall labor satisfaction scores also may be influenced by concurrent delivery outcomes other than pain scores such as neonatal outcomes, duration of pushing, or need for forceps or vacuum delivery.

The maternal and neonatal outcomes in our study are consistent with previous smaller studies in obstetric patients,[18] showing no adverse effects on neonatal Apgar scores, maternal heart rate or blood pressure, or mode of delivery. Pruritus scores were significantly greater in the epidural fentanyl group, although the clinical importance of pruritus on a subjective basis is questionable due to the low mean reported scores. Other maternal side effects, such as motor block, nausea, and sedation, also were not significant among groups, suggesting that epidural neostigmine at these doses is well tolerated. Our study did not specifically examine fetal heart rate variability as a labor outcome, as this was felt to be logistically difficult due to the long duration of the infusion for labor analgesia and the potential for intermittent changes in the fetal heart rate tracing related to labor progression. We did record the fetal heart rate before and after epidural analgesia and every 2 h subsequently until

delivery similar to the Ross *et al.* study,[12] and we found no significant difference between groups (data not shown). In addition, when performing an intention-to-treat analysis that included patients who were withdrawn from the study, we found no difference in neonatal Apgar scores or mode of delivery. The data from our study suggest that epidural neostigmine does not provide any clinical advantages or disadvantages over epidural fentanyl in terms of the overall side effect profile for labor analgesia.

Although neostigmine may be a more expensive alternative to fentanyl for epidural local anesthetic infusions, epidural neostigmine may be useful in a small number of clinical scenarios. Neostigmine may be a useful alternative in patients with extreme sensitivity (pruritus or vomiting) to opioids such as fentanyl. Neostigmine also can be used as a nonopioid adjunct alternative in women with a history of addiction or those who wish to avoid any opioid use for psychologic reasons. Neostigmine also may be used as an adjuvant for women who take buprenorphine or those with chronic opioid exposure secondary to chronic pain or addiction with potential significant dysregulation of opioid and pain receptors.

Major disadvantages of neostigmine include the fact that it remains an investigational drug by the U.S. Food

and Drug Administration for epidural use, the relatively small number of obstetric patients in the literature exposed to neuraxial neostigmine,[4,10,12,18–30] and the lack of clinical effect as measured by local anesthetic consumption in this study. Epidural neostigmine has not been shown to have adverse effects on maternal vital signs, maternal sedation, Apgar scores, or fetal heart rate tracings in this and previous studies, but there may be unrecognized or unusual side effects, given the overall small sample size in the literature to date.

In conclusion, we found that laboring parturients receiving epidural neostigmine in differing concentrations (2, 4, and 8 µg/ml) had similar hourly bupivacaine consumption and mean pain scores during labor compared with parturients receiving epidural fentanyl (2 µg/ml). Also, patients receiving either epidural fentanyl or epidural neostigmine combined with bupivacaine for epidural labor analgesia were satisfied equally at delivery. Although previous studies have demonstrated an improvement in postoperative analgesia in both adults and children with epidural neostigmine compared with epidural local anesthetic alone,[31,32] we were unable to show a clinical difference with epidural neostigmine compared with epidural fentanyl when combined with bupivacaine for labor analgesia. Although future studies are needed to further evaluate the clinical safety of neostigmine as well as the clinical effect of lower doses of epidural neostigmine on labor analgesia, the likelihood of futures studies are lessened by the intermittent inability to obtain neostigmine from the manufacturer due to production shortages, the cost of neostigmine, and lack of evidence showing a significant clinical effect compared with epidural fentanyl.

Research Support

Competing Interests

Reproducible Science

Correspondence

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