

Epidural Neostigmine Produces Analgesia but Also Sedation in Women after Cesarean Delivery

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Background: **Intrathecal neostigmine produces analgesia but also nausea, limiting its utility. In contrast, epidural administration of neostigmine has been suggested to produce postoperative analgesia without nausea in nonpregnant patients. The purpose of this study was to examine the dose range for efficacy and side effects of epidural neostigmine in women at cesarean delivery receiving combined spinal–epidural anesthesia.**

Methods: **After institutional approval and informed consent, 80 patients for elective cesarean delivery were given combined spinal–epidural anesthesia with 8 mg hyperbaric bupivacaine plus 10 μg fentanyl. Patients were randomized to receive either saline or 75, 150, or 300 μg neostigmine (n = 20 per group) in 10 ml saline after cord clamping. Pain, morphine consumption, and side effects were monitored for 24 h.**

Results: **Global pain assessment for the first 24 h was reduced from 5.4 ± 0.2 in the saline group to 3.0–3.5 ± 0.3 in the neostigmine groups, dose independently. Correspondingly, global satisfaction with neostigmine was also improved ($P < 0.05$). Nausea and morphine consumption were similar among groups. Intraoperative shivering and sedation were increased in the 300-μg neostigmine group only ($P < 0.05$), and postoperative sedation was increased by neostigmine in a dose-independent fashion ($P < 0.05$).**

Conclusions: **Epidural neostigmine produced modest analgesia in women after cesarean delivery. In contrast with previous reports, which focused primarily on nausea, these data suggest that epidural neostigmine can also produce mild sedation for several hours. These data suggest a limited role for single bolus-administration epidural neostigmine for analgesia after cesarean delivery. They also support future study of epidural neostigmine for obstetric analgesia.**

MUSCARINIC receptors are present in the dorsal horn of the spinal cord of humans and rats,[1] and intrathecal injection of muscarinic receptor agonists produces antinociception in rats, which is reversed by intrathecal atropine.[2] Although muscarinic agonists have not been injected intrathecally in humans, physostigmine, a cholinesterase inhibitor that crosses the blood–brain barrier, has been administered systemically and produces postoperative analgesia in humans.[3] After preclinical toxicity screening,[4] the polar cholinesterase inhibitor, neostigmine, was introduced into clinical trials in 1995 for intrathecal injection.[5] Intrathecal neostigmine produces analgesia to experimental pain stimuli in normal volunteers,[5] as well as in patients with chronic pain[6] and after surgery.[7] These studies indicate that spinal cholinergic receptor stimulation produces analgesia in humans as well as animals, most probably by an interaction with muscarinic receptors.

Intrathecal neostigmine also produces dose-dependent and severe nausea and has been practically abandoned for clinical use. More recently, epidural administration of neostigmine has been suggested to produce analgesia without nausea in patients with chronic pain[8] and after surgery.[9–13] There is a discrepancy among these studies in the effective dose of epidural neostigmine, which may partly be explained by the level of surgical intervention. After knee arthroscopy or minor knee surgery, for example, epidural neostigmine produces up to 8 h of analgesia from doses of less than 100 μg,[11] whereas after abdominal hysterectomy, 250 μg epidural neostigmine is ineffective, and 480 μg produces less than 4 h of analgesia.[12] In addition, although nausea has not been reported in these studies, other side effects, which were present in initial studies of intrathecal neostigmine, including sedation,[5] and those from peripheral muscarinic receptor stimulation, including salivation and sweating, were not systematically assessed. One purpose of the current study was to determine whether epidural neostigmine produces these central or peripheral effects in patients after surgery.

Epidural neostigmine has not previously been examined in women after cesarean delivery, a group that commonly receives spinal or epidural anesthesia and is sensitive to low doses of intrathecal analgesics, such as morphine, but also exhibits a high incidence of side effects, especially nausea. Epidural neostigmine could represent a new nonopioid adjunct for labor analgesia. To introduce epidural neostigmine into obstetric analgesia, it is important to begin with an assessment of tolerability in the mother immediately after delivery of the baby.

Finally, none of the previous studies examined epidural neostigmine using the current needle-through-needle approach to combined spinal–epidural anesthesia but rather examined a pure epidural technique or an epidural with a spinal needle inserted at a different interspace. The primary purpose of this study was to test whether epidural neostigmine would yield efficacy without side effects when using a standard combined spinal–epidural technique.

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Materials and Methods

After institutional approval and informed consent, 80 patients at Uludag University (Bursa, Turkey) who were scheduled to undergo elective cesarean delivery were randomly allocated into four groups of 20 patients each to receive epidural saline or neostigmine, 75, 150, or 300 μg in a total volume of 10 ml, after spinal anesthesia. Exclusion criteria included weight greater than 110 kg, age less than 18 yr, American Society of Anesthesiologists physical status greater than I, and allergy or intolerance to neostigmine or bupivacaine.

The study was randomized and double blind. After a 500-ml intravenous infusion of balanced salt solution, combined spinal–epidural anesthesia was performed with the patient in the sitting position at the L2–L3 or L3–L4 interspace. The epidural space was located with an 18-gauge, 8.89-cm Perican needle (B. Braun, Melsungen, Germany) using loss of resistance to air. A 27-gauge, 12.7-cm Spinocan needle (B. Braun) was inserted through the epidural needle. After free flow of clear cerebrospinal fluid was obtained, 8 mg hyperbaric (0.5%) bupivacaine plus 10 μg fentanyl were injected. Then, the spinal needle was removed, and a 20-gauge multiport Perifix catheter (B. Braun) was inserted 3 cm cephalad within the epidural space and secured. Patients were then immediately turned supine with left uterine displacement. No test dose was administered through the catheter, but aspiration through the catheter was negative in each case for blood or clear fluid. Immediately after delivery and cord clamping, the study solution (saline or neostigmine, 75, 150, or 300 μg in 10 ml saline; n = 20/group) was injected over 1 min. The duration of surgery and spinal anesthesia was recorded, and the epidural catheter was withdrawn at the end of surgery.

Postoperative analgesia was provided by intravenous patient-controlled analgesia (PCA) using morphine. The PCA device was set to deliver a bolus of 1 ml (1 mg morphine), a lockout interval of 5 min, and no basal infusion. PCA was continued for 24 h. The numbers of demand–delivery in PCA and morphine consumption were recorded at 8, 16, and 24 h.

Pain Assessment

The severity of intraoperative and postoperative pain was scored using a 10-cm visual analog scale (VAS). Postoperative pain assessments were made at rest by a research pain nurse blinded to the treatment group. Acute pain scores were recorded at the time of first pain report, the time of first analgesic administration, and at fixed intervals after surgery (0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 11, 12, and 24 h). A 24-h global VAS pain score was obtained to reflect the patient's overall impression of pain in the 24 h after surgery. The time of first ambulation was at the discretion of the obstetrician and according to when the patient felt well enough to walk.

Hemodynamic and Side Effect Measurements

Blood pressure, heart rate, and oxyhemoglobin saturation were continuously monitored during surgery and at intervals for 24 h. A decrease in mean arterial pressure greater than 20% below preanesthetic baseline was treated with intravenous fluid or incremental doses of ephedrine, 5–10 mg. A decrease in heart rate less than 50 beats/min was treated with 0.5 mg intravenous atropine. Sedation, shivering, sweating, dizziness, and respiratory depression were graded during surgery and for 24 h thereafter as absent, mild, moderate, or severe. For sedation, the clinical description associated with the scoring was as follows: absent = awake; mild = drowsy but arouses to verbal stimulus; moderate = arouses to light touch; severe = arouses to firm touch. The number of patients with intraoperative and postoperative nausea and vomiting was recorded, and if necessary, patients were treated with 10 mg metoclopramide. In addition, postoperative nausea VAS scores were obtained by the research nurse at the same time intervals as for acute pain, as well as 24-h VAS scores for nausea and overall patient satisfaction.

Data Analysis

Data are presented as mean ± SE or, in the case of incidence data, as median. Groups were compared for continuous variables, including VAS, by two repeated-measures analysis of variance. Incidence data were compared among groups by Fisher exact test or by nonparametric repeated-measures analysis of variance. $P < 0.05$ was considered significant. The primary outcome variable for analgesia was VAS pain report over the first 4 h after injection, the time of anticipated drug action. Assuming a 30 ± 30-min increase in analgesia with each greater neostigmine dose, as observed in a previous study,[14] a sample size of 20 was powered to observe, with a β error of 0.80, an increase in analgesia from epidural neostigmine.

Results

Patient groups did not differ in demographic, surgical, or anesthetic variables (table 1). Epidural neostigmine produced analgesia, although this was not dose dependent in the dose range studied. For example, VAS pain scores were reduced by neostigmine in the first 4 h after epidural injection, but there was no dose dependency (fig. 1). Similarly, 24-h overall assessment of pain by VAS was greater in the control group than in the neostigmine groups in a dose-independent fashion (table 2). The time to first pain and to first PCA morphine use was prolonged by neostigmine, but this was significant in *post*

Table 1. Patients' Demographic, Surgical, and Anesthetic Characteristics

		Neostigmine		
	Saline	75 μg	150 μg	300 μg
Age	30 ± 1.1	30 ± 1.5	31 ± 1.2	31 ± 1.2
Height, cm	161 ± 1.5	160 ± 0.9	161 ± 1.1	157 ± 5.2
Weight, kg	74 ± 1.9	76 ± 2.0	77 ± 2.1	82 ± 1.9
Surgical time, min	57 ± 2.5	56 ± 3.7	55 ± 2.6	62 ± 4.9
Anesthesia time, min*	111 ± 7.1	107 ± 5.9	118 ± 8.3	120 ± 8.5

Data are expressed as mean ± SE of 20 individuals.

* Time until patients were able to move their ankles.

hoc testing only for the 150-μg group, and total morphine use over 24 h (or, in separate analysis, for each 8-h block in the first 24 h) was not affected by neostigmine in any dose (table 2). Time to ambulation was shorter and overall satisfaction was improved in women receiving neostigmine compared with control, in a dose-independent fashion (table 2).

Intraoperatively, there was a high incidence of hypotension, which was similar among groups (13, 14, 11, and 15 of 20 women receiving 0, 75, 150, and 300 μg neostigmine, respectively), and the dose of ephedrine administered to treat hypotension did not differ among groups (median doses of 10, 10, 5, and 13 mg in women receiving 0, 75, 150, and 300 μg neostigmine, respectively). Bradycardia was uncommon and not related to neostigmine administration, occurring in 0, 0, 2, and 1 women receiving 0, 75, 150, and 300 μg neostigmine, respectively. Intraoperative shivering and sedation were more common in women receiving 300 μg neostigmine than in the controls, whereas the incidence of nausea or vomiting did not differ with neostigmine treatment (table 3). Postoperative sweating and sedation were more common in women receiving neostigmine, the latter being dose independent, whereas the incidence of dizziness and nausea did not differ with neostigmine treatment (table 3). One patient in the 300-μg neostigmine group had increased salivation during and after surgery. No patient experienced respiratory depression. The incidence of nausea in the first 4 h after surgery was similar among groups (fig. 2). Up to 35% of patients receiving 300 μg neostigmine had nausea 2–3 h after administration, but this did not differ from the control group ($P = 0.18$). In addition, the intensity of nausea, as measured by VAS at hourly intervals or at 24-h global assessment, did not differ among groups ($P > 0.50$), nor did the incidence of treatment with metoclopramide (table 3).

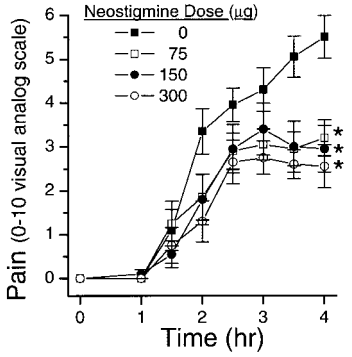

Fig. 1. Visual analog scale pain in the first 4 h after epidural injection of saline control or neostigmine (75, 150, or 300 μg). Data are expressed as mean ± SE. All neostigmine groups differ from control beyond 3 h (* $P < 0.05$).

Discussion

Clinical trials with neostigmine have convincingly shown the relevance of spinal cholinergic receptor activation to treat pain in humans, but the practical application of this drug remains unclear. Certainly, it is difficult to imagine a common use for intrathecal neostigmine, given the high incidence of distressing nausea and vomiting produced by analgesic doses by this route of administration. The current study confirms previous reports in nonpregnant patients after surgery[9–13] showing that epidural neostigmine does not cause nausea. In addition, this study provides several unique observations regarding central and peripheral side effects from epidural neostigmine and paves the way for future assessment of this therapy in obstetrics.

Cesarean Delivery Analgesia

Analgesic interventions intended for use in labor are often introduced first in the cesarean delivery patient population because this allows for determination of short-term effects in the pregnant patient and on the fetus. For example, intrathecal neostigmine was first examined in this group before trials in laboring women.[15] There were no unusual or severe maternal side effects in the current study that would preclude future investigation of epidural neostigmine in obstetrics. Epidural neostigmine was administered after cord clamping, a time when oxytocin is infused, and therefore, potential increased myometrial tone or uterine contractions from peripheral muscarinic receptor stimulation[16] could not be assessed. A logical next step would be to administer epidural neostigmine in women before elective cesarean delivery to determine effects on uterine activity and potential fetal bradycardia, which has been reported after large intravenous doses of neostigmine.[17]

Table 2. Pain during the First 24 h after Cesarean Delivery

		Neostigmine		
	Saline	75 μg	150 μg	300 μg
Time to first pain, min	107 ± 4.3	126 ± 6.6	135 ± 8.3*	129 ± 8.4
Time to first morphine use, min	123 ± 5.2	136 ± 6.3	176 ± 10.8*	145 ± 10
24-h morphine use, mg	55 ± 5.7	51 ± 4.7	40 ± 5.6	48 ± 4.7
Time to first ambulation, h	17 ± 0.5	15 ± 0.4*	14 ± 0.5*	14 ± 0.3*
24-h global pain	5.4 ± 0.2	3.2 ± 0.3*	3.5 ± 0.3*	3.0 ± 0.3*
24-h global satisfaction	7.5 ± 0.2	8.4 ± 0.2*	8.6 ± 0.2*	8.7 ± 0.2*

Data are expressed as mean ± SE.

* $P < 0.05$ compared with 0 neostigmine.

In addition, the cesarean delivery patient population offers several advantages for the study of a novel analgesic intervention: residual effects of general anesthesia are not present; sedatives are generally avoided; the surgical procedure is uniform; pain is severe for 12–24 h, typically necessitating 40–60 mg morphine for treatment; and pain consists of visceral and somatic components. Furthermore, neostigmine may produce analgesia more potently in women than in men.[18] The current study suggests that epidural neostigmine in this patient group produces short-lived and modest analgesia, prolonging the time to rescue medication by less than 1 h and having no effect on the total dose of morphine administered over 24 h. This is in contrast to neostigmine administered by the intrathecal route, which significantly reduces pain and 24-h morphine consumption in this patient group, although it is accompanied by a high incidence of nausea.[15] Interestingly, there was an effect on 24-h global assessment of pain by neostigmine as well as on pain reported during the initial period of time of presumed drug action. This has been observed in previous studies of epidural neostigmine.[10,11]

Epidural neostigmine produced evidence of benefit, as measured by reduced pain reports in the initial few hours after administration, as well as reduced global pain and increased satisfaction scores and earlier time of mobilization in this patient group. Earlier ambulation may be particularly important in these women who are highly motivated to recover early to normal activity. However, these effects were small and not clearly related to a dose over the 75- to 300-μg range studied. Only two previous studies have examined a range of epidural neostigmine doses. One, in minor orthopedic procedures on the knee,[11] showed a lack of dose dependency over a 65- to 265-μg dose range, with all doses producing more than 8 h of analgesia. Most likely, the shorter duration of effect observed in the current study reflects a more painful surgical procedure, although it is conceivable that the difference reflects the combination of neostigmine in the previous study with lidocaine or a difference due to pregnancy. The other study[12] observed a lack of analgesia from 250 μg epidural neostigmine but a 2-h prolongation of analgesia from 480 μg after abdominal hysterectomy, a surgery more similar in characteristics to cesarean delivery. Therefore, the analgesic potency and efficacy of epidural neostigmine after cesarean delivery seems less than that for minor orthopedic procedures on the knee but greater than that for abdominal hysterectomy.

Cholinergic Side Effects

After neuraxial administration, neostigmine could move cephalad, leading to inhibition of cholinesterase in the supraspinal central nervous system and inducing

Table 3. Side Effects

		Neostigmine		
	Saline	75 μg	150 μg	300 μg
Intraoperative				
Shivering	1	3	0	8*
Sedation†	0/0/0	5/0/1	5/1/0	9/3/0*
Nausea	6	10	6	10
Postoperative				
Sweating	2	4	2	9*
Sedation†	1/0/0	6/1/0*	5/0/1*	8/0/0*
Dizziness	2	3	2	6
Nausea	7	9	5	10
Metoclopramide treatment	5	6	3	8
24-h global nausea	0.85 ± 0.34	0.95 ± 0.34	0.55 ± 0.20	1.00 ± 0.29

Data are expressed as number of individuals per group, with 20 in each group, or mean ± SE.

* $P < 0.05$ compared with 0 neostigmine. † For sedation, numbers represent the individuals per group with mild/moderate/severe sedation.

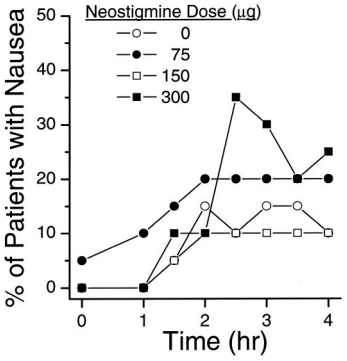

Fig. 2. Incidence of nausea in the first 4 h after epidural injection of saline control or neostigmine (75, 15, or 300 μg). Groups do not differ.

central cholinergic side effects. Alternatively, the larger doses of neostigmine administered epidurally rather than intrathecally could result in adverse effects from systemic absorption. Perhaps not surprisingly, previous studies of epidural neostigmine have focused on the side effect of nausea, which is prominent after intrathecal administration. However, sedation, which was noted in early studies of large doses of intrathecal neostigmine[5] and which could reflect increased central cholinergic receptor stimulation, was only specifically examined in one previous study, in patients after abdominal surgery,[9] in which it was not observed. Sedation was associated with neostigmine administration in the current study, although it was mild in nearly all cases and did not adversely affect satisfaction. Future studies of epidural neostigmine should include specific measurements of this side effect, certainly in the pregnant patient. Sweating was noted with increased incidence in women receiving the highest neostigmine dose, 300 μg, in the current study, and one patient receiving this dose noted increased salivation, potentially reflecting peripheral cholinergic activation. However, other signs of such peripheral activation, especially abdominal cramping, were not observed, and previous studies have not shown such peripheral effects from neostigmine doses of less than 500 μg.

Future Clinical Development

Perhaps epidural neostigmine alone provides a useful tool for treatment of pain after procedures producing mild to moderate pain and in which epidural or spinal anesthesia is commonly used, such as outpatient arthroscopy. However, the current study is in accordance with previous studies in abdominal surgery in nonpregnant patients to indicate that this therapy alone adds some benefit but not complete and sustained analgesia. It further suggests that doses greater than 75 μg in this patient population are not necessary, and 300 μg is associated with mild sedation. Neostigmine may considerably prolong analgesia from small doses of epidural morphine,[13] and future studies are warranted to investigate the use of combinations of neostigmine and morphine in this patient group.

In summary, epidural neostigmine, 75–300 μg as a single bolus, reduces global assessment of pain and improves satisfaction in the first 24 h after cesarean delivery, without causing maternal nausea. Epidural neostigmine, as in previous experience with intrathecal administration, results in mild sedation that extends into the postoperative period. These results suggest that epidural neostigmine alone produces modest analgesia in this patient population at doses of 75–300 μg, without creating common and acute serious adverse effects in the mother. Although these results are encouraging for the use of epidural neostigmine for obstetric analgesia, future studies should include assessment of potential adverse effects of epidural neostigmine on uterine tone and activity and on fetal heart rate.

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