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A Multi-center Study of Intrathecal Neostigmine for Analgesia following Vaginal Hysterectomy

Gabriela R. Lauretti, M.D., M.Sc., Ph.D.,* David D. Hood, M.D.,† James C. Eisenach, M.D.,‡ Ben L. Pfeifer, M.D., Ph.D.§

Background: Intrathecal neostigmine injection produces analgesia in volunteers and reduces hypotension from intrathecal bupivacaine in animals. Initial clinical trials with neostigmine studied doses of more than 100 μg , but animal studies suggest that smaller doses may be effective. In addition, all controlled clinical trials of neostigmine have come from one Brazilian university. This multicenter, placebo-controlled trial investigated the effects of 25–75 μg intrathecal neostigmine on analgesia and blood pressure in women undergoing vaginal hysterectomy.

Methods: After institutional review board approval was obtained at the three university centers, and after patients gave informed consent, 92 women scheduled for vaginal hysterectomy were randomized to receive an intrathecal injection of 2 ml bupivacaine, 0.75%, in dextrose plus either 1 ml saline or 25, 50, or 75 μg neostigmine. Blood pressure, heart rate, pain and nausea (both assessed by visual analog scale), and intravenous morphine use were recorded during surgery and at specified intervals afterward.

Results: Morphine use was reduced similarly by all doses of neostigmine. Only the 75- μg dose of neostigmine increased the nausea score in the recovery room. The incidence of treatment for nausea was greater in patients receiving neostigmine (61%) than in those receiving saline placebo (29%) and was unaffected

by neostigmine dose. Neostigmine did not reduce the incidence of hypotension from bupivacaine.

Conclusion: These data in patients after vaginal hysterectomy suggest that analgesia from intrathecal neostigmine may occur at doses less than 50 μg . In these doses, neostigmine does not reduce spinal bupivacaine-induced hypotension but may increase the need for treatment of nausea. (Key words: Acetylcholine; cholinergic; pain relief; spinal injection.)

INTRATHECAL injection of neostigmine produces analgesia in animals,¹ human volunteers,² and patients with acute postoperative³ and chronic⁴ pain. Human volunteers achieve dose-dependent analgesia from doses more than 100 μg .² Intrathecal neostigmine probably produces analgesia by inhibiting the breakdown of spinally released acetylcholine, and spinal acetylcholine release is increased in the presence of pain.⁵ As a result, it might be expected that the potency of intrathecal neostigmine will increase in the postoperative period, and this was observed in animals.⁶

Few dose-response data exist for intrathecal neostigmine for postoperative analgesia. Intrathecal neostigmine, at a dose of 50 μg , produced no postoperative analgesia compared with placebo in women undergoing vaginoplasty in one study,⁷ whereas 100 μg was more effective than placebo in another study.⁸ A dose-response study in women undergoing vaginoplasty showed prolongation of time-to-first-rescue medication after 200 μg , but not after 100 or 50 μg neostigmine.³ That study, however, included only six patients per group, and the resultant low statistical power may explain the lack of a statistically significant effect of 100 and 50 μg neostigmine, despite the two- and fivefold increases in the mean time-to-first-rescue medication observed. A larger study with 15 patients per group showed a dose-independent reduction in morphine use after administration of 25, 50, and 100 μg intrathecal neostigmine compared with a control after lower-extremity orthopedic surgery.⁹ The primary purpose of the current study was to determine, using a multiple-institution study design with more than 20 patients per group,

* Assistant Professor, Discipline of Anesthesiology, Department of Surgery, Orthopedics and Traumatology, Faculty of Medicine of Ribeirão Preto, University of São Paulo, São Paulo, Brazil.

† Associate Professor, Department of Anesthesiology, Wake Forest University School of Medicine.

‡ Professor and Francis M. James, III, Chair for Anesthesiology Research, Wake Forest University School of Medicine and Bowman Gray School of Medicine.

§ Director of Clinical Research, Department of Anesthesiology, University of Kentucky.

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Address reprint requests to Dr. Lauretti: rua Mantiqueira, 460, Ribeirão Preto, São Paulo, Brazil 14025/600. Address electronic mail to: dhoo@bgsm.edu.

whether small doses of intrathecal neostigmine (25, 50, and 75 μ g) produce dose-dependent analgesia in patients after surgery.

Methods

The study protocol was approved by the human investigation committees of Wake Forest University School of Medicine (Coordinating Center), the University of São Paulo, and the University of Kentucky. After giving informed consent, 92 women classified as physical status 1 or 2 by the American Society of Anesthesiologists who were scheduled for total vaginal hysterectomy during spinal anesthesia were studied at the three university centers. Women older than 70 yr; those with known hypersensitivity to bupivacaine, neostigmine, propofol, or morphine; those with bradyarrhythmia; and those unable to understand the consent process or the use of the patient-controlled analgesia device were excluded.

The study was performed in a prospective, randomized, double-blind, placebo-controlled manner. Investigators at the coordinating center prospectively assigned neostigmine group quotas based on a computer-generated randomized balanced design and the anticipated availability of potential study patients. The number of patients observed was determined previously to be adequate to show a 25% linear dose-dependent reduction in morphine use (highest dose compared with placebo), an increase in the percentage incidence of nausea after surgery from 10% for placebo to 40% at the highest dose, a reduction in visual analog pain score (VAS) of 1.8 cm, and an increase in the VAS nausea score by 2 cm.

No premedication was administered on the night before surgery, although benzodiazepine was not discontinued in any patients who were routinely receiving it at

night. The concept of a VAS, which consisted of a 10-cm line, with 0 signifying "no nausea" or "no pain at all" and 10 representing "the worst possible nausea or vomiting" or "the worst possible pain," was introduced the day before surgery. On the day of surgery, an intravenous catheter was inserted, and midazolam, up to 4 mg in 0.5-mg increments, was administered intravenously in the holding room as needed for anxiolytic purposes. Lactated Ringer's solution, 15 ml/kg, was infused over 30–60 min before intrathecal drug injection. Lumbar puncture was performed in the operating room with the patient in the lateral decubitus position, using either a 25- or 27-gauge Whitacre needle at the L3–L4 or L4–L5 interspace. After free flow of clear cerebrospinal fluid was obtained, the study solution was injected, with the needle orifice facing the ceiling. The final volume of 3 ml was injected at 1 ml per 10 s. Patients received 2 ml bupivacaine, 0.75%, in dextrose plus either 1 ml saline or an equal volume of saline containing 25, 50, or 75 μ g neostigmine. The neostigmine study solution was prepared immediately before lumbar puncture by a local anesthesiologist who was not involved in the study, and the investigator (blinded to the study solution content) added this 1 ml of solution to the bupivacaine solution. All centers used the same preparation of neostigmine (IMS Ltd, El Monte, CA). Patients were positioned supine immediately after injection and in the lithotomy position within 15 min of spinal injection. After adequate sensory blockade from spinal bupivacaine was established, all patients received propofol by constant intravenous infusion that was titrated to deep sedation during surgery.

Sensory level to pinprick was assessed every 5 min for 15 min after spinal injection, when patients arrived in the recovery room, and every 30 min until discharge. At these times in the recovery room, motor strength in the

Table 1. Demographic and Intraoperative Characteristics

Variable	Neostigmine Dose			
	0 μ g (n = 24)	25 μ g (n = 22)	50 μ g (n = 23)	75 μ g (n = 23)
Age	53 \pm 13	51 \pm 13	56 \pm 13	52 \pm 11
Height (cm)	157 \pm 9	156 \pm 7	157 \pm 9	156 \pm 7
Weight (kg)	59 \pm 11	66 \pm 11	67 \pm 14	69 \pm 16
Surgery time (min)	124 \pm 44	143 \pm 53	112 \pm 40	112 \pm 43
Recovery room time (min)	150 \pm 74	128 \pm 51	155 \pm 33	165 \pm 98
Propofol infused (mg)	341 \pm 208	447 \pm 282	327 \pm 207	365 \pm 258
IV fluid administered (ml)	1,716 \pm 360	1,684 \pm 483	1,695 \pm 495	1,590 \pm 408
Midazolam (mg)	2 \pm 2	2 \pm 1	2 \pm 1	3 \pm 2
Fentanyl (μ g)	23 \pm 60	26 \pm 70	26 \pm 82	22 \pm 72

Data are mean \pm SD. There were no differences among groups in any variable.

SPINAL NEOSTIGMINE DOSE RESPONSE

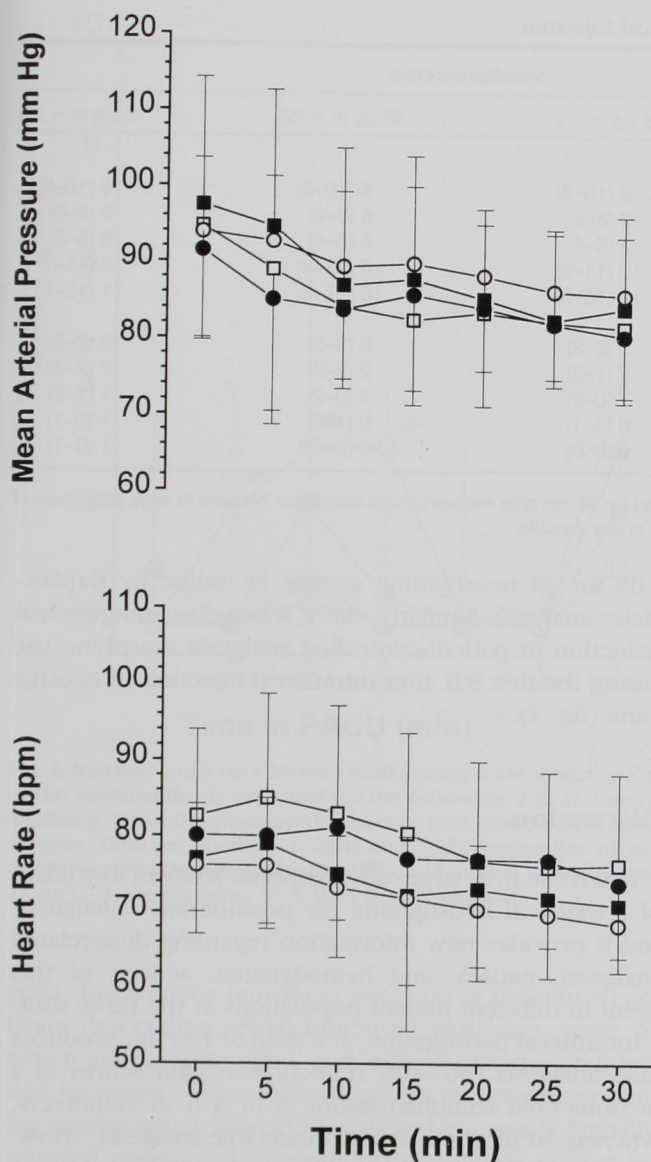


Fig. 1. Mean arterial blood pressure (upper) and heart rate (lower) after injection at time 0 of intrathecal bupivacaine; 15 mg with 1 ml saline (■); or 25 μ g (□), 50 μ g (●), or 75 μ g (○) neostigmine. Data are mean \pm SD of 22 to 24 patients. The groups did not differ.

lower extremities were assessed by a four-point scale (0 = able to move normally, 1 = subjective weakness, 2 = able to move feet but not flex knees, 3 = unable to move lower extremities). Blood pressure was monitored noninvasively every 5 min during surgery, and heart rate and oxyhemoglobin saturation were continuously monitored throughout surgery. Blood pressure and heart rate were recorded before drug injection, at 5-min intervals during surgery, at 15-min intervals after surgery until 3 h

from the time of intrathecal injection, hourly until recovery room discharge, then every 6 h until 24 h after injection. A decrease in mean arterial pressure of more than 20% below preanesthetic baseline level was treated by 5-mg intravenous increments of ephedrine and by intravenous fluid administration. Decreases in heart rate of less than 50 beats/min were treated with 0.25-mg increments of atropine administered intravenously. Nausea at any time during the study was treated with either 2–4 mg ondansetron or 20 mg metoclopramide administered intravenously.

Any intraoperative pain was treated with intravenous fentanyl in 25- μ g increments. Pain was assessed by the 10-cm VAS at arrival in the recovery room and every 30 min until discharge and was treated with intravenous patient-controlled morphine, with initial settings of a 2-mg dose, 10-min lockout, and an hourly limit of 12 mg. The VAS was also recorded at discharge from the recovery room and 24 h after the study solution was injected. At these same times, patients rated their nausea on a 10-cm VAS scale.

Data are presented as mean \pm SD or median and quartiles, as appropriate. Groups were compared for demographic data, and the duration of surgery and time in the recovery room were determined by one-way analysis of variance. The time-to-first-patient-controlled analgesia use was compared among groups using the Kaplan-Meier analysis and the Wilcoxon's rank sum. The incidence of adverse events and adjuvant drug use were compared among the groups by chi-squared analysis. Blood pressure, heart rate, and VAS scores were compared among the groups by two-way analysis of variance for subsequent measures. Categorical scale data and cumulative morphine use for 8 h after intrathecal injection (the expected duration of drug action) were compared among the groups using the Kruskal-Wallis test followed by the Wilcoxon's rank sum test. *P* values were corrected by *post hoc* tests, and a level of 0.05 was considered significant.

Results

Sixty patients were observed at the University of São Paulo, 23 were observed at Wake Forest University School of Medicine, and 9 were observed at the University of Kentucky. Demographic characteristics, duration of surgery, duration of stay in the recovery room, or intraoperative fluid or drug administration did not differ in the neostigmine-dose groups (table 1). Blood pressure

Table 2. Sensory Block to Pinprick and Motor Blockade after Intrathecal Injection

Variable	Neostigmine Dose			
	0 µg (n = 24)	25 µg (n = 22)	50 µg (n = 22)	75 µg (n = 22)
Thoracic dermatome of blockade				
5 min after injection	9 (10-8)	9 (10-8)	8 (10-8)	10 (10-8)
10 min after injection	6 (6-6)	6 (8-5)	6 (8-6)	8 (8-6)
15 min after injection	6 (7-4)	7 (8-4)	5 (8-4)	6 (8-5)
Recovery room admission	10 (10-8)	10 (11-9)	10 (11-9)	10 (11-7)
30 min later	12 (12-9)	12 (12-8)	10 (12-8)	11 (12-7)
Motor blockade				
Recovery room admission	3 (3-3)	3 (2-3)	3 (3-3)	3 (2-3)
30 min later	2 (1-3)	2 (1-3)	2 (2-3)	2 (2-3)
60 min later	1 (1-2)	1 (0-2)	1 (0-2)	1 (1-2)
90 min later	1 (0-1)	0 (0-1)	0 (1-0)	1 (0-1)
Recovery room discharge	0 (0-0)	0 (0-0)	0 (0-1)	1 (0-1)

Data are median (25th and 75th percentiles). Sensory dermatomal levels only provided for 30 min after recovery room admission because of large proportion of patients thereafter without sensory block. There were no differences among groups in any variable.

or heart rate before intrathecal injection or after bupivacaine injection did not differ in the groups (fig. 1). Similarly, blood pressure or heart rate in the recovery room or for the subsequent 24 h (data not shown) did not differ. The incidence of treatment with ephedrine for hypotension did not differ between saline control treatment (25%) and neostigmine treatment (25%), and it did not differ with neostigmine dose (25% after placebo, 36% after 25 µg, 27% after 50 µg, 13% after 75 µg; *P* = 0.18 by chi-squared analysis). The incidence of treatment for bradycardia did not differ between saline control treatment (0%) and neostigmine treatment (9%), and it did not differ with neostigmine dose (5% after 25 µg, 14% after 50 µg, and 9% after 75 µg). Neostigmine did not affect the onset of sensory blockade from intrathecal bupivacaine (table 2).

Only the 75-µg dose of neostigmine increased the nausea score in the recovery room (fig. 2). Similarly, the incidence of treatment for nausea was greater in patients who received neostigmine (61%) than in those who did not (29%). However, the incidence of nausea treatment was unrelated to neostigmine dose (the incidence of nausea treatment was 54% after 25 µg, 64% after 50 µg, and 64% after 75 µg).

The analgesic effect of intrathecal neostigmine was dose independent. All doses of neostigmine reduced VAS pain scores in the recovery room to a similar degree (fig. 3). All doses of neostigmine prolonged the time-until-first-morphine-dose by a similar amount. The time-to-first-morphine-dose (median, 25th to 75th percentiles) was 3 h (3 to 4 h) after saline administration, 4 h (4 to 6.5 h) after 25 µg neostigmine administration, 4 h (3 to 5.5 h) after 50 µg, and 6 h (4 to 8.5 h) after 75 µg (*P* <

0.05 for all neostigmine groups *vs.* saline by Kaplan-Meier analysis). Similarly, there was a dose-independent reduction in patient-controlled analgesia morphine use during the first 8 h after intrathecal injection of neostigmine (fig. 4).

Discussion

This is the first, large, dose-response study of low doses of intrathecal neostigmine for postoperative analgesia, and it provides new information regarding dose-related analgesia, nausea, and hemodynamic actions of this agent in different patient populations at the three sites.

Intrathecal neostigmine, at a dose of 100 µg, produces mild analgesia (30–40% reduction in pain scores to a noxious cold stimulus) lasting 3 or 4 h in volunteers, whereas 50 µg produces no detectable analgesia.² However, a painful stimulus, such as occurs after surgery, might increase the apparent potency of neostigmine. This is confirmed by studies with sheep that showed an increase in acetylcholine concentrations in lumbar cerebrospinal fluid during painful electrical stimulation.⁵ In addition, the antinociceptive effect of intrathecal neostigmine is enhanced in the first 2 days after lumbar laminectomy surgery in sheep.⁶ The current study showed significant analgesia, as defined by a reduction in morphine use, with administration of 25–50 µg intrathecal neostigmine in women after surgery, suggesting that a similar phenomenon may occur in humans.

An alternative explanation to the effect of small doses of neostigmine in the current study relates to the mechanisms of action of systemic opioids in producing anal-

SPINAL NEOSTIGMINE DOSE RESPONSE

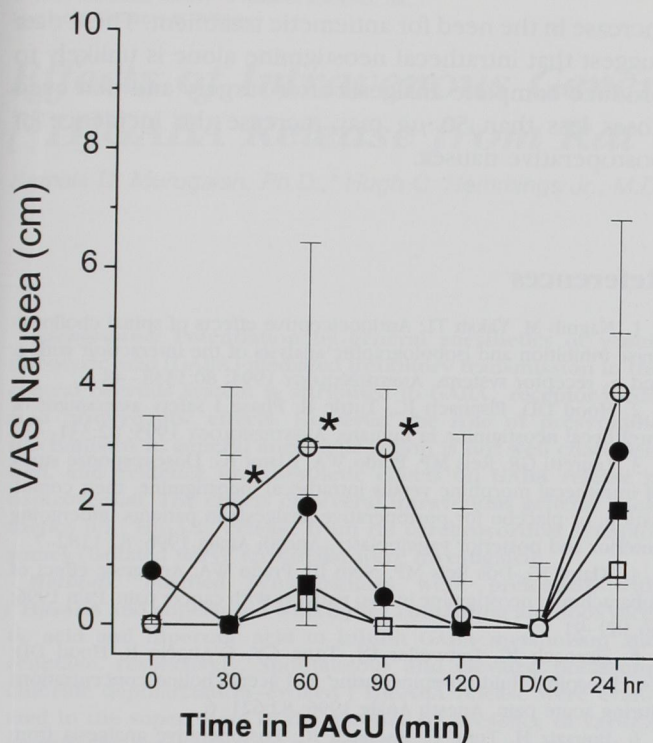


Fig. 2. Nausea scores on a 10-cm visual analog scale at admission to the postanesthesia care unit for the following 2 h, at time of discharge from the postanesthesia care unit, and at 24 h after surgery. Data are median \pm 25th and 75th percentiles of patients receiving intrathecal saline (■) or 25 μ g (□), 50 μ g (●), or 75 μ g (○) neostigmine. * $P < 0.05$ versus control.

gesia. Intravenous morphine injection is thought to activate descending spinal inhibitory pathways, some of which are noradrenergic, and, as such, morphine injection increases concentrations of norepinephrine in lumbar cerebrospinal fluid in animals and humans.¹⁰ Spinally released norepinephrine produces analgesia in part by activating spinal cholinergic neurons to release acetylcholine, and, as such, intravenous morphine increases cerebrospinal concentrations of acetylcholine.¹⁰ All patients in the current study received intravenous morphine by patient-controlled analgesia, and it is possible that smaller doses of intrathecal neostigmine were more effective in these patients than in others because the patients were receiving morphine, which stimulated acetylcholine release on which neostigmine could act.

Regardless of the mechanism, the current study suggests that doses of intrathecal neostigmine of less than 50 μ g reduce intravenous morphine requirements for 8 h after vaginal hysterectomy. Previous literature does not consistently report a dose-dependent analgesic effect

of neostigmine. As reviewed previously, large doses (200 μ g) uniformly produce analgesia, but also nausea. With one exception,³ 100 μ g neostigmine also produces analgesia, but in most cases it is associated with an increased incidence of nausea. The current study corresponds with previous data from open-label studies in women after cesarean section,¹¹ and in patients after orthopedic procedures,⁹ that doses of more than 100 μ g also may be effective. The clinical usefulness of this reduction in morphine use for 8 h may be limited. Preliminary data suggest that a much longer duration of analgesia can be obtained by coadministration of intrathecal neostigmine with morphine,³ reflecting the synergistic interaction between these agents by intrathecal administration.¹

Intrathecal neostigmine produces nausea in volunteers and patients at doses ≥ 100 μ g.² The current study suggests that doses as small as 25 μ g may increase the requirements for antiemetic treatment. It is conceivable that the use of propofol during surgery for sedation

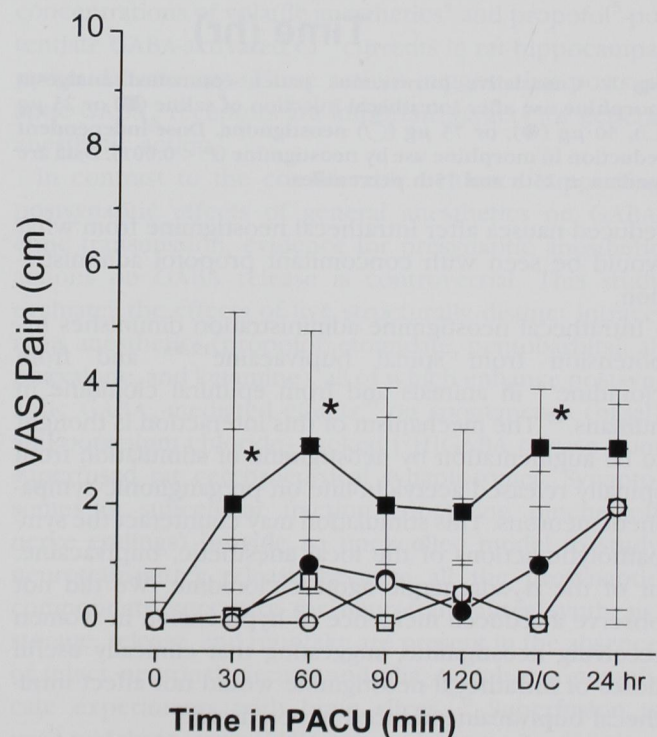


Fig. 3. Pain scores on a 10-cm visual analog scale at admission to the postanesthesia care unit, for the following 2 h, at time of discharge from the postanesthesia care unit, and at 24 h after surgery. Data are median \pm 25th and 75th percentiles of patients receiving intrathecal saline (■) or 25 μ g (□), 50 μ g (●), or 75 μ g (○) neostigmine. * $P < 0.05$ versus all neostigmine groups.

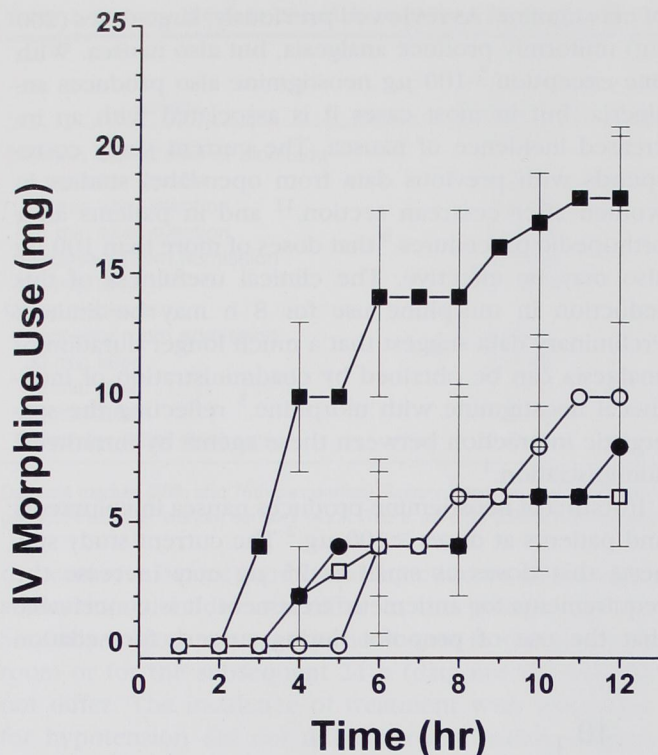


Fig. 4. Cumulative intravenous patient-controlled analgesia morphine use after intrathecal injection of saline (■) or 25 µg (□), 50 µg (●), or 75 µg (○) neostigmine. Dose-independent reduction in morphine use by neostigmine ($P < 0.001$). Data are median \pm 25th and 75th percentiles.

reduced nausea after intrathecal neostigmine from what would be seen with concomitant propofol administration.

Intrathecal neostigmine administration diminishes hypotension from spinal bupivacaine^{12,13} and from clonidine¹⁴ in animals and from epidural clonidine in humans.¹⁵ The mechanism of this interaction is thought to be augmentation by neostigmine of stimulation from spinally released acetylcholine on preganglionic sympathetic neurons. This stimulation may counteract the sympatholytic actions of the local anesthetic, bupivacaine, or of the α_2 -adrenergic agonist clonidine. We did not observe a reduced incidence of hypotension in women receiving neostigmine, suggesting that clinically useful doses of intrathecal neostigmine would not affect intrathecal bupivacaine-induced hypotension.

In conclusion, 25–75 µg intrathecal neostigmine produces a dose-independent reduction in morphine use for 8 h after vaginal hysterectomy and a dose-independent

increase in the need for antiemetic treatment. These data suggest that intrathecal neostigmine alone is unlikely to produce complete analgesia after surgery and that even doses less than 50 µg may increase the incidence of postoperative nausea.

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