

Antinociceptive Effect of Low-Dose Intrathecal Neostigmine Combined with Intrathecal Morphine following Gynecologic Surgery

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Background: The purpose of this study was to determine whether combination of 1–5 μ g intrathecal neostigmine would enhance analgesia from a fixed intrathecal dose of morphine.

Methods: A total of 60 patients undergoing gynecologic surgery were randomized to one of five groups. Patients received 15 mg bupivacaine plus 2 ml of the test drug intrathecally (saline, 100 μ g morphine, or 1–5 μ g neostigmine). The control group received spinal saline as the test drug. The morphine group received spinal morphine as test drug. The morphine + 1 μ g neostigmine group received spinal morphine and 1 μ g neostigmine. The morphine + 2.5 μ g neostigmine group received spinal morphine and 2.5 μ g neostigmine. Finally, the morphine + 5 μ g neostigmine group received spinal morphine and 5 μ g neostigmine.

Results: The groups were demographically similar. The time to first rescue analgesic (minutes) was longer for all patients who received intrathecal morphine combined with 1–5 μ g neostigmine (median, 6 h) compared with the control group (median, 3 h) ($P < 0.02$). The morphine group ($P < 0.05$) and the groups that received the combination of 100 μ g intrathecal morphine combined with neostigmine ($P < 0.005$) required less rescue analgesics in 24 h compared with the control group. The incidence of perioperative adverse effects was similar among groups ($P > 0.05$).

Conclusions: The addition of 1–5 μ g spinal neostigmine to 100 μ g morphine doubled the duration to first rescue analgesic in the population studied and decreased the analgesic consumption in 24 h, without increasing the incidence of adverse effects. The data suggest that low-dose spinal neostigmine may improve morphine analgesia.

INTRATHECAL neostigmine has been shown to potentiate morphine analgesia^{1–4} while reducing undesirable side effects such as somnolence and respiratory depression.^{5,6} Although these promising data exist in animals, different studies conducted to evaluate the analgesic action of spinal neostigmine as part of a multimodal pain therapy approach in patients, including spinal neostigmine and spinal opioids, described an analgesic effect associated with nausea and vomiting, the most troublesome with the intrathecal anesthetic technique.^{7–13} What all clinical studies had in common was the evaluation of intrathecal neostigmine doses higher than 10 μ g (ranging from 10 to 200 μ g, depending on the study).

However, the benefits of adding lower intrathecal neostigmine doses to potentiate morphine analgesia has not been evaluated to date.

The purpose of this study was to determine whether combination of low-dose (1–5 μ g) intrathecal neostigmine would enhance analgesia from a fixed intrathecal dose of morphine, in patients undergoing gynecologic surgery with spinal anesthesia.

Methods

The Ethical Committee of the University of São Paulo's Teaching Hospital, Ribeirão Preto, approved the study protocol. After giving informed consent, 60 patient with American Society of Anesthesiologists status I and II who were scheduled for gynecologic abdominal surgery were randomized by computer to one of five groups ($n = 12$) and prospectively studied using a placebo-controlled, double-blind design to examine analgesia and adverse effects. The concept of visual analog scale (VAS), which consisted of a 10-cm line with 0 equaling "no nausea" (VAS N) or "no pain at all" and 10 equaling "worst possible nausea" or "the worst possible pain" was introduced before surgery.

Patients were premedicated with 0.05–0.1 mg/kg intravenous midazolam in the holding room. Hydration consisted of 10 ml/kg lactate solution preoperatively and 10 ml \cdot kg⁻¹ \cdot h⁻¹ after spinal anesthesia. Spinal anesthesia was performed in the operating room at the L3–L4 interspace with the patient in the sitting position. A total volume of 5 ml was injected at 1 ml per 7 s through a 25-gauge spinal needle. The intrathecal drugs were 15 mg hyperbaric bupivacaine (3 ml) plus the test drug (2 ml). Patients were placed in the supine position immediately after spinal injection. One anesthesiologist prepared the intrathecal drugs. A second anesthesiologist who was blind to the drug selection stayed during the intraoperative period and checked the postoperative period. The groups are described in table 1. Groups containing only low-dose neostigmine as test drug were not included in the study design as a dose such as 5 μ g has been previously demonstrated to not result in analgesia by itself.¹⁴

Intraoperative sensory loss assessment included the pinprick test 10 min after the spinal injection. Blood pressure was monitored noninvasively every 5 min throughout surgery, and heart rate and oxyhemoglobin saturation were continuously monitored throughout surgery. A decrease in mean arterial pressure greater than 15% below the preanesthetic baseline value was treated by incremental doses of 4 mg intravenous ephedrine.

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Table 1. Study Groups

Group	Intrathecal Supplement (2 ml) Added to 15 mg Hyperbaric Bupivacaine
Control	2 ml saline
Morphine	100 μ g morphine (1 ml) + 1 ml saline
Morphine + 1 μ g neostigmine	100 μ g morphine (1 ml) + 1 μ g neostigmine (1 ml)
Morphine + 2.5 μ g neostigmine	100 μ g morphine (1 ml) + 2.5 μ g neostigmine (1 ml)
Morphine + 5 μ g neostigmine	100 μ g morphine (1 ml) + 5 μ g neostigmine (1 ml)

Decreases in heart rate below 50 beats/min were treated with incremental doses of 0.25 mg intravenous atropine. Intraoperative nausea was scored by the patient using the 10-cm VAS N. The number of patients having nausea (of any degree) or vomiting at any point intraoperatively was noted. Nausea scoring greater than 2 on the scale of 0 to 10 at any time or vomiting during the study were treated initially with 10 mg intravenous metoclopramide followed by 4 mg intravenous ondansetron, if necessary. For patients experiencing more than one episode of nausea, the VAS scores were averaged.

Postoperative assessment included pain scores, adverse effects, and the duration of motor block, measured from anesthetic injection until the time to reach Bromage 2 score.¹⁵ Patients were free to take rescue analgesics, and there was always someone from the staff present to administer the analgesic at the time requested. Intravenous ketoprofen (100 mg) was available at 6-h intervals. The second rescue analgesic drug was the nonsteroidal dipyrone (1 g), administered intravenously 1 h after the ketoprofen, if necessary. Pain was assessed at the time of first rescue analgesic and 24 h after the spinal puncture by the anesthesiologist who was blind to the treatment, during abdominal effort (e.g., crouching). Nausea and occurrence of vomiting were assessed intraoperatively and 24 h after the spinal puncture by the same anesthesiologist who was blind to the treatment. Duration of effective analgesia was measured as time from the intrathecal drug administration to the patient's first request for analgesic administration either in the recovery room or infirmary, recorded in minutes. The VAS at the time of first rescue analgesic medication was measured using the 10-cm VAS. The 24-h VAS pain score and VAS N reflected the patient's overall impression of the 24 h following spinal injection.

Statistical Analysis

The number of subjects was based on preliminary experimental data. We hypothesized that intrathecal morphine would increase the time to first rescue analgesic only by 20% compared with the control group in the population studied, because of the intensity of the surgical stimuli, and that the association of spinal neostigmine would increase the time to first rescue analgesic by 100% when compared with the control group. If we estimated an SD for this prospective power analysis of 40% and an α value of 0.05, these assumptions would

require at least five patients in each group to see a 100% increase in the time the first rescue analgesic.

The normality of the distributions was assessed using the Shapiro-Wilk test. Groups were compared for demographic data (age, weight, height) and duration of surgery by one-way analysis of variance. Incidence of adverse events, gender, American Society of Anesthesiologists status, and adjuvant drug use were compared among groups by chi-square test corrected for multiple comparisons. $P < 0.01$ was considered significant (0.05 divided by the number of groups). Blood pressure, heart rate, level of anesthesia (pinprick), and VAS scores were compared among groups by two-way analysis of variance for repeated measures. Tukey analysis was applied to decrease the probability of type I error. The time to first rescue analgesic and the number of rescue analgesics in 24-h were compared using the Kruskal-Wallis test, applied along with a nonparametric multiple comparison procedure, the Wilcoxon rank sum test. $P < 0.05$ was considered significant. Data are expressed as mean \pm SD unless otherwise stated.

Results

All patients underwent intraabdominal gynecologic surgery. In the control group and in the morphine + 2.5 μ g neostigmine group, eight patients underwent abdominal hysterectomy, and four patients underwent Burch surgery. In the morphine group, the morphine + 1 μ g neostigmine group, and the morphine + 5 μ g neostigmine group, nine patients underwent abdominal hysterectomy, and three patients underwent Burch surgery ($P > 0.05$). The five groups showed no differences with regard to American Society of Anesthesiologists status, age, weight, and height ($P > 0.05$; table 2). The sensory level to pinprick at 5 and 10 min, surgical and anesthetic time, and intraoperative ephedrine consumption were similar among groups (table 3).

The postoperative data are shown in table 4. The pain VAS score at the time of first rescue analgesic medication was similar among the five groups ($P > 0.05$). The time to first rescue analgesic medication (minutes) was longer for all patients who received the combination of both 100 μ g morphine and 1–5 μ g neostigmine compared with the control group ($P < 0.02$). The control group was not different from the morphine group ($P > 0.05$). The intravenous administration of ketoprofen during the first 24 h postoperatively was less in the morphine group

Table 2. Demographic Data

	ASA Physical Status (I/II), n	Age, yr	Weight, kg	Height, cm
Control group	7/5	44 ± 9	65 ± 12	157 ± 7
Morphine group	8/4	45 ± 11	70 ± 13	157 ± 4
Morphine + 1 µg neostigmine group	7/5	47 ± 11	66 ± 10	154 ± 5
Morphine + 2.5 µg neostigmine group	7/5	44 ± 11	71 ± 16	156 ± 5
Morphine + 5 µg neostigmine group	7/5	42 ± 7	67 ± 13	155 ± 5
P	0.9666	0.7675	0.7712	0.6126

Data are expressed as mean ± SD.

($P < 0.05$) and for all patients who received the combination of both 100 µg morphine and 1–5 µg neostigmine ($P < 0.005$) compared with the control group.

There were no differences regarding the incidence of perioperative adverse effects ($P > 0.05$). Intraoperatively, none of the patients complained of nausea or vomiting. Postoperatively, one patient from the control group complained of bowel constipation and another of back pain (VAS, 4 cm). One patient from the morphine group had vomited once, and another two patients experienced flatulence. One patient from the morphine + 1 µg neostigmine group had one episode of diarrhea. Two patients from the morphine + 2.5 µg neostigmine group experienced flatulence, one had vomited once, and another had diarrhea. Finally, two patients from the morphine + 5 µg neostigmine group had vomited once after dinner; one patient complained of pruritus, and another patient complained of transitory dizziness after standing to walk in the infirmary. The mean overall 24-h nausea VAS score was similar among groups ($P > 0.05$).

Discussion

The results of this study report an enhancement of the analgesic action of 100 µg intrathecal morphine for postoperative pain relief following intraabdominal gynecologic surgery by 1, 2.5, and 5 µg intrathecal neostigmine. Median duration to rescue medication use (intravenous ketoprofen) in patients receiving only spinal 100 µg morphine was 3 h; the addition of a low dose of neostigmine doubled the time to first rescue analgesic without increasing the incidence of adverse effects. In addition, all patients who received intrathecal morphine

combined with neostigmine used less rescue intravenous ketoprofen injections in 24 h.

In the population studied, the dose of 100 µg intrathecal morphine did not delay the time to first use of rescue analgesics, probably because of the strong pain intensity present in this type of procedure, albeit this group used less rescue analgesics in 24 h compared with the control group. In addition, the spinal doses of neostigmine selected were also not expected to produce analgesia by themselves, as 100 µg intrathecal neostigmine has been previously demonstrated to be ineffective in a similar circumstance.¹⁶ The fact that intrathecal neostigmine would enhance the analgesic action of an opioid has been demonstrated before by different groups of researchers.^{7,8,11} However, the interesting data from this study were that doses such as 1 µg could double the analgesic profile of 100 µg intrathecal morphine.

A possible explanation includes the advantage of the combination of a specific class of drug, such as cholinergic, which is physiologically involved in the mechanism of action of morphine. The prolongation of the analgesic action of morphine in our study could reflect an activation of descending pain inhibitory systems, which rely on a cholinergic link,¹⁷ which would be exacerbated in patients under noxious stimuli, such as surgery.¹⁸ The analgesic effect from intrathecal neostigmine results from increase in the concentration of the neurotransmitter acetylcholine and consequent action at muscarinic M1 and M3^{19,20} and presynaptic nicotinic receptors,²¹ present in the cholinergic interneurons at the laminae II and V of the dorsal horn.²² An action at nicotinic receptors at the dorsal root ganglion²³ and at the spinal meninges²⁴ has also been suggested.

Table 3. Intraoperative Data

	Pinprick		Duration of Surgery, min	Anesthetic Time, min	Ephedrine, mg
	5 min*	10 min*			
Control group	9 (6–12)	6 (6–10)	111 ± 46	182 ± 40	8 ± 15
Morphine group	9 (7–10)	6 (6–8)	124 ± 44	190 ± 52	12 ± 13
Morphine + 1 µg neostigmine group	7 (6–9)	6 (6–8)	108 ± 43	203 ± 35	7 ± 8
Morphine + 2.5 µg neostigmine group	7 (6–8)	6 (6–6)	113 ± 36	183 ± 32	8 ± 16
Morphine + 5 µg neostigmine group	6 (6–8)	6 (6–6)	110 ± 48	182 ± 20	3 ± 8
P	0.1384	0.2932	0.9040	0.5728	0.5591

Pinprick refers to dermatome anesthesia to a pinprick on the skin. Anesthetic time refers to the amount of time to reach Bromage 2.

*Median (25–75% percentile confidence). Other data are expressed as mean ± SD.

Table 4. Postoperative Data

	Control Group	Morphine Group	Morphine + 1 μ g Neostigmine Group	Morphine + 2.5 μ g Neostigmine Group	Morphine + 5 μ g Neostigmine Group	P
Time to first rescue analgesic, min*	180 (165–253)	235 (180–330)	385 (240–600)	330 (230–570)	345 (240–585)	†
VAS at first rescue analgesic	7 \pm 2	7 \pm 2	6 \pm 2	7 \pm 2	7 \pm 3	0.8083
Number of IV ketoprofen injections in 24 h*	3 (3–5)	2 (2–3)	2 (1–3)	2 (1–3)	2 (1–3)	‡
Overall 24-h VAS pain	4 \pm 1.7	4 \pm 2.1	2.3 \pm 2.5	3 \pm 2.9	3.6 \pm 2.7	0.2863
Overall 24-h VAS nausea	2 \pm 3	2 \pm 3	2 \pm 3.3	3.6 \pm 2.7	2.7 \pm 3.3	0.9078

* Median (25–75% percentile confidence); other data are expressed as mean \pm SD. †Morphine and neostigmine groups were different from control group ($P < 0.02$); other groups were similar. ‡Morphine and neostigmine groups were different from control group ($P < 0.005$); morphine group was different from the control group ($P < 0.05$); other groups were similar.

VAS = visual analog scale.

In addition to the apparent synergistic interaction between neostigmine and morphine observed in this study, a synergistic interaction between the nonsteroidal anti-inflammatory drug ketoprofen has been described as synergistic to spinal neostigmine in mice.²⁵ Because ketoprofen was used as rescue analgesic as part of the protocol, an interaction among the three different drugs cannot be ruled out. This would indirectly reflect an interaction between spinal morphine, spinal neostigmine, and intravenous ketoprofen.²⁵

There was no difference regarding the incidence of emesis, although there was a trend toward more nausea with doses higher than 1 μ g, probably not evidenced because of the number of patients evaluated. Our results did not demonstrate an exacerbation of the motor block, as described by other investigators^{12,26}; however, there was a faster, but not significant, tendency to reach the maximal level of sensory block when neostigmine was added to the spinal drugs. Although a pilot study has mentioned intrathecal doses of neostigmine resulting in involuntary defecation,¹¹ the incidence of adverse effects was not different among groups. One patient who received spinal neostigmine and morphine experienced diarrhea, while one patient from the control group complained of constipation.

In conclusion, the combination of low-dose intrathecal neostigmine (1–5 μ g) to 100 μ g intrathecal morphine doubled the duration to first use of rescue analgesic in the population studied and decreased the analgesic consumption in 24 h, without increasing the incidence of adverse effects. The data suggest that low-dose spinal neostigmine may improve morphine analgesia.

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