No Enhancement of Sensory and Motor Blockade by Neostigmine Added to Mepivacaine Axillary Plexus Block

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Background: Intrathecal neostigmine induces analgesia but also several side effects. Recently, 500 μg neostigmine administered intraarticularly was shown to produce postoperative analgesia without side effects. The authors' goal was to determine whether 500 μg neostigmine added to mepivacaine in axillary plexus block prolongs postoperative analgesia. In addition, they wanted to determine the incidence of side effects in patients undergoing hand surgery.

Methods: Sixty-nine outpatients scheduled for carpal tunnel syndrome repair with axillary plexus block were randomly assigned to one of three groups that received saline solution in the axillary plexus and subcutaneously (group 1), 500 μg neostigmine in the axillary plexus and saline solution subcutaneously (group 2), or saline solution in the axillary plexus and 500 μg neostigmine subcutaneously (group 3). Sensory and motor block in the four hand nerve distributions were assessed every 5 min for 30 min. The duration of the sensory and motor blocks were assessed after operation. Side effects were also recorded.

Results: Neostigmine had no effect on sensory and motor block in any of the four nerve distributions, nor did it increase the median duration of sensory block (215 min; range, 120-330 min) compared with group 1 (247 min; range, 190-287 min) or group 3 (236 min; range, 160-280 min). Motor block was slightly shorter (P = 0.045) in group 3 (190 min; range, 135-285 min) compared with group 1 (218 min; range, 145-257 min) and group 2 (215 min; range, 105-343 min). Gastrointestinal side effects occurred in 30% of patients in both neostigmine groups but not in group 1 (P < 0.05).

Conclusions: This study suggests that 500 μg neostigmine added to mepivacaine in axillary plexus block does not prolong postoperative sensory block, but it does cause a relatively high incidence of side effects. These two findings raise doubts about the use of neostigmine associated with local anesthetics for plexus neural block. (Key words: Axillary plexus block; mepivacaine; neostigmine; sensory and motor blockade.)

INTRATECHAL neostigmine causes a dose-dependent analgesic effect in humans by inhibiting the breakdown of acetylcholine in the dorsal horn of the spinal cord.1-4 Furthermore, Pan et al.5,6 demonstrated a potentiation and prolongation of spinal bupivacaine block with neostigmine. However, its clinical use is limited by side effects (mainly nausea and vomiting) likely due to the rostral migration of the drug in the cerebrospinal fluid.1 Studies also support the hypothesis of a peripheral antinociceptive effect of acetylcholine.7,8 Recently, research showed that 500 μg neostigmine administered intraarticularly in patients undergoing arthroscopic meniscus repair produced a peripheral analgesic effect.9 This dose induced better analgesia than 2 mg morphine injected via the same route without evidence of side effects. These observations suggest peripheral mechanisms of cholinergic antinociception and therefore open a wide field of clinical investigation. Based on data having shown that the peripheral nerve contains elements needed for muscarinic receptor-mediated signal transduction,10 we hypothesized that a 500-μg dose of neostigmine added to mepivacaine during axillary plexus block (APB) would increase the duration of postoperative analgesia, alter the extension of the block, or both. Therefore, we tested this hypothesis in a prospective, randomized, double-blinded study.

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Methods

After our institutional review board gave their approval and patients gave written informed consent, we randomly assigned 69 outpatients undergoing surgery for carpal tunnel syndrome with APB to one of the following three groups, according to the drug and route of administration used. In the placebo group (group 1; n = 23), 1 ml saline solution was added in the APB, and 1 ml saline solution was administered subcutaneously; in the neostigmine group (group 2; n = 23), 500 µg neostigmine (Roche Laboratory, Neuilly-sur-Seine, France) in 1 ml was added in the APB, and 1 ml saline solution was administered subcutaneously; in the control group (group 3; n = 23), 1 ml saline solution was added in the APB, and 500 µg neostigmine in 1 ml saline solution was administered subcutaneously. Patients received no sedation before the brachial plexus block was induced. All blocks were performed at the axillary crease using a single injection once a motor response corresponding to the stimulation of the median nerve had been obtained. A 22-gauge insulated needle connected to a peripheral nerve stimulator (Stimuplex Dig; Braun, Melsungen, Germany) was used to locate the median nerve according to the specific motor-evoked activity as follows: wrist and second and third finger flexion and pronation. Once the needle was placed subcutaneously, the peripheral nerve stimulator was activated using a frequency and intensity of 2 Hz and 1.5 mA, respectively. Evoked motor activity of the median nerve at ≤0.5 mA was required before the local anesthetic solution was injected. In the three groups, the local anesthetic used was 40 ml 1.5% mepipavacaine. In all groups, 5 ml plain 2% lidocaine was injected subcutaneously on both sides of the brachial artery to anesthetize the intercostobrachial and median (brachial and antebrachial) cutaneous nerves. All blocks were performed by an anesthesiologist experienced in this technique. The anesthesiologist who evaluated the sensory and motor block was blinded to the drug used.

Time 0 (TO) was defined as the time corresponding to the end of the regional anesthesia procedure (i.e., removal of the insulated needle from the skin). Sensory and motor block were assessed every 5 min for 30 min. Peripheral sensory distribution of each of the four major nerves of the hand and the forearm was assessed using light touch, on a three-point scale (0 = normal sensation; 1 = blunted sensation; 2 = no perception). The motor block of each of the four major nerves of the hand and forearm was also assessed (radial nerve, extension of the elbow; median nerve, flexion of the wrist; ulnar nerve, opposition of the thumb; and was defined as complete (100%) when no movement against gravity was detected; otherwise, it was considered incomplete. The duration of the sensory block was defined as the time from a complete block to restoration of sensation at the surgical site. The duration of the motor block was the time from the occurrence of a complete motor block to restoration of global mobility in the hand and the wrist. Hemodynamic variables, including mean arterial blood pressure and heart rate, were recorded before induction of the APB and then every 5 min for 15 min and at 30 and 60 min after administration of the study drug, and then at the end of surgery and at discharge from the hospital. Each side effect was recorded at the same intervals. Furthermore, a telephone follow-up interview was performed the day after hospital discharge and again 6 months later.

We hypothesized that the results of group 3 would be comparable to those of group 1 and that these results would be significantly different from those of group 2. In their study, Yang et al. found in the 500 µg neostigmine group a prolongation of postoperative analgesia of about 300 min compared with placebo, with a standard deviation of 400 min. Thus, the calculated number of patients required was 23 in each group, using a one-sided test, to detect a similar difference of duration of postoperative analgesia, with α = 0.05 and β = 0.10. Mean arterial pressure and heart rate are expressed as the mean ± SD and compared using analysis of variance for repeated measures. Age, weight, and height were compared among the groups using a Kruskall-Wallis test because they were not normally distributed. The onset times of anesthesia and of motor block in the different nerve distributions also were not normally distributed and were expressed as medians and ranges and were compared using a Kruskall-Wallis test. The durations of sensory and motor blocks were analyzed using Kaplan-Meier estimates and the log-rank test. Discrete variables (sex ratio, American Society of Anesthesiologists physical status, and side effects) were compared using chi-squared analysis. P < 0.05 was considered significant.

**Results**

Sixty-nine patients were included in the study. Because a rescue technique was required, three patients in group 1, two patients in group 2, and three patients in group 3 were excluded from the study (P > 0.05). As shown in
Table 1. Demographic Data of Patients Scheduled for Carpal Tunnel Syndrome

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>ASA (1/2)</th>
<th>Gender (female/male)</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Intensity of Stimulation (mA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>18/5</td>
<td>15/8</td>
<td>50 (31–72)</td>
<td>75 (53–117)</td>
<td>164 (155–183)</td>
<td>0.30 (0.14–0.40)</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>17/6</td>
<td>17/6</td>
<td>43 (28–78)</td>
<td>70 (50–120)</td>
<td>167 (152–194)</td>
<td>0.34 (0.14–0.50)</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>16/7</td>
<td>14/9</td>
<td>51 (25–82)</td>
<td>76 (57–100)</td>
<td>168 (147–185)</td>
<td>0.27 (0.14–0.39)</td>
</tr>
</tbody>
</table>

Values are median (range). Group 1 received 1 ml saline in the APB and 1 ml saline subcutaneously; group 2 received 500 μg neostigmine in 1 ml in the APB and 1 ml saline subcutaneously; group 3 received 1 ml saline in the APB and 500 μg neostigmine in 1 ml subcutaneously.

Table 1, there was no significant intergroup difference with regard to American Society of Anesthesiologists physical status, sex, age, weight, height, or intensity of nerve stimulation. Onset times for complete sensory and motor block in the different nerve distributions (i.e., median, ulnar, radial, and musculocutaneous) were not significantly different among the three groups (table 2).

The duration of sensory block (fig. 1A) was 247 min (range, 190–287 min) in group 1, 215 min (range, 120–330 min) in group 2, and 236 min (range, 160–280 min) in group 3 (P = 0.5). In groups 1 and 2, the median duration of motor block was 218 min (range, 145–257 min) and 215 min (range, 105–343 min), respectively, whereas in group 3, the duration of motor block was significantly shorter (190 min; range, 135–285 min; P = 0.045; fig. 1B). Hemodynamic parameters (heart rate and mean arterial blood pressure), listed in figure 2, were not significantly different among the three groups. Side effects occurred in six and five patients in groups 2 and 3 respectively, but in no patients in group 1 (P < 0.05).

These side effects, presented in table 3, were mainly of gastrointestinal origin. They were also transient, of short duration (maximal duration was 2 h in one patient in group 3), and did not require any therapeutic intervention.

Table 2. Onset Time (min) before Obtaining Surgical Anesthesia (SA) or a Complete Motor Blockade (CMB)

<table>
<thead>
<tr>
<th></th>
<th>SA</th>
<th>CMB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td>Median</td>
<td>15 ± 5</td>
<td>10 ± 5</td>
</tr>
<tr>
<td>Ulnar</td>
<td>10 ± 11.2</td>
<td>15 ± 10</td>
</tr>
<tr>
<td>Radial</td>
<td>17.5 ± 5</td>
<td>15 ± 12.5</td>
</tr>
<tr>
<td>Musculocutaneous</td>
<td>25 ± 7.5</td>
<td>20 ± 10</td>
</tr>
</tbody>
</table>

IQR = interquartile range.

Values are median ± IQR; group 1 (placebo, n = 20); group 2 (500 μg neostigmine in axillary block, n = 21); group 3 (500 μg neostigmine subcutaneously, n = 20). P > 0.05.

Discussion

The major finding of this study was a lack of effect of 500 μg neostigmine on the duration of sensory blockade after mepivacaine APB. We also found a high incidence of side effects in the two groups that received subcutaneous neostigmine (five patients) or APB-added neostigmine (six patients).

Neostigmine has been shown previously to produce analgesia in animals and humans by increasing the concentration of acetylcholine at central and peripheral sites of action.1–4,11,12 Previous laboratory investigations suggest a peripheral implication of acetylcholine at the central nerve endings of small afferent fibers and have shown that acetylcholine receptors exist at the peripheral nerve level.8,13 Two studies recently showed in rats a peripheral analgesic effect of neostigmine either intraarticularly or after subcutaneous administration.7,14 Furthermore, Yang et al.9 showed in humans that intraarticular administration of 500 μg neostigmine induced peripheral postoperative analgesia after arthroscopic meniscus repair. Nevertheless, despite the presence of muscarinic receptors on nerve axons, the current study


The telephone follow-up interview conducted at day 1 and 6 months after discharge revealed neither persistent nor recurrent side effects and no neurologic complications after APB among the three groups.
performed with the same dose of 500 μg neostigmine added to the APB showed no improvement in the duration of sensory block and was associated with a high rate of side effects. Because we assessed the onset of sensory block on each of four major nerves of the hand, we could not show a better spread of the APB with neostigmine compared with placebo. Our negative results are, however, in accordance with other recent data using a similar clinical model.\(^{15}\)

Several reasons may be proposed to explain why several studies found effective analgesia and others, including ours, did not show any clinical benefit. It is unlikely that the absence of significant change in the duration of analgesia comes from an error in the \textit{a priori} statistical
Side effects were less frequently observed in our study than after intrathecal neostigmine.\textsuperscript{1,11,18,19} Their frequency (approximately 30\% in both groups receiving neostigmine) is too high given the lack of postoperative analgesic benefit. Furthermore, their incidence was the same in group 2 (six patients) and in group 3 (five patients), suggesting that APB-added neostigmine and subcutaneous neostigmine have the same systemic parasympathetic effects. Yang \textit{et al.}\textsuperscript{9} did not observe any side effect with the same dose of intraarticular (500 \textmu g) neostigmine. This may reflect the fact that intraarticular administered neostigmine was less absorbed in the systemic circulation.

Large doses of intrathecal neostigmine (> 100 \textmu g) increase blood pressure and heart rate in sheep.\textsuperscript{20} This effect is related to the stimulation of preganglionic sympathetic neurons.\textsuperscript{21,22} In contrast, systemically administered neostigmine decreases heart rate. In the current study, with the dose of neostigmine used, we observed neither bradycardia nor mean arterial blood pressure alterations among the three groups.

Both motor weakness and reduction in deep tendon reflexes have been noted in volunteers who received neostigmine intrathecally at large doses.\textsuperscript{18} No such effects were found in our study, but surprisingly, a significantly shorter duration of motor block was seen in group 3. We do not have a clear explanation for this result.

Intrathecal neostigmine also produces sedation at large doses (100 and 200 \textmu g) in humans.\textsuperscript{2,17} In the current study, only one patient of group 3 had light sedation, which may be attributed not only to neostigmine but also to a systemic effect of mepivacaine. Nevertheless, the incidence of this effect, if related to neostigmine, remains less than after intrathecal administration.

In conclusion, the current study suggests that neostigmine does not act at the level of the axillary plexus nerve trunks and does not prolong postoperative analgesia after APB when combined with mepivacaine. In addition, the high incidence of neostigmine-related side effects is disturbing. These two findings raise doubts about the utility of neostigmine associated with local anesthetics for plexus neural block.

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2. Lauretti GR, Reis MP, Prado WA, Klamt JG: Dose-response study
of intrathecal morphine versus intrathecal neostigmine: Their combination or placebo for postoperative analgesia in patients undergoing anterior and posterior vaginoplasty. Anesth Analg 1996; 82:1182–7