Postoperative Analgesia by Intra-articular Neostigmine in Patients Undergoing Knee Arthroscopy

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Background: Recently, the spinal administration of neostigmine was shown to produce a dose-dependent analgesia. However, this analgesia is limited by adverse effects. The purpose of this study was to examine the analgesic action of peripheral muscarinic receptors by administering intra-articular neostigmine after operation in patients undergoing knee arthroscopy.

Methods: Sixty patients (classified as American Society of Anesthesiologists status I or II) having arthroscopic meniscus repair during general anesthesia were randomized to receive, in a double-blind manner, after operation 125, 250, or 500 µg intra-articular neostigmine; 2 mg intra-articular morphine; or as control groups intra-articular saline or 500 µg neostigmine subcutaneously (SC). Visual analog pain scores (VAS), duration of analgesia as defined by first demand for patient-controlled analgesia by morphine, and subsequent 48 h consumption of morphine were evaluated.

Results: Intra-articular (500 µg) neostigmine resulted in significant VAS reduction 1 h after injection compared with patients given intra-articular saline and with those given intra-articular morphine. Analgesia lasted longer after 500 µg intra-articular neostigmine (350 ± 120 min) compared with intra-articular morphine (196 ± 138 min; P < 0.05) or with the control groups (intra-articular saline, 51 ± 11 min; SC neostigmine, 46 ± 8 min; P < 0.05). The need for supplementary analgesia was significantly higher in control groups than for patients given intra-articular morphine or 500 µg intra-articular neostigmine. No significant analgesic effects were observed for the two lower doses of intra-articular neostigmine. Among all study groups, no adverse effects were observed.

Conclusions: Intra-articular injection of the acetylcholinesterase inhibitor neostigmine produced a moderate but significant analgesic effect. Several mechanisms such as the hyperpolarization of neurons, reduction in the release of pronociceptive neurotransmitters, or activation of the nitric oxide–cyclic guanosine monophosphate pathway might mediate this peripheral cholinergic antinociception by elevating endogenous acetylcholine.

Key words: Cholinesterase inhibitor; muscarinic; neostigmine; peripheral.

IN preclinical and clinical trials, the spinal or epidural administration of the acetylcholine esterase-inhibitor neostigmine results in a dose-dependent analgesia. Muscarinic receptors, located in the substantia gelatosa of the spinal cord, are believed to be involved in this analgesic property, which is not due to stimulation of nicotinic or opioid receptors. However, this central delivery of neostigmine is limited by dose-related side effects such as nausea, vomiting, and pruritus, caused by cephalad spread of neostigmine in the cerebrospinal fluid. Recently for opioid and α2-adrenergic receptors, a peripheral analgesia was demonstrated. Because of the similarities in the different pain-modulating systems (opioid, α2-adrenergic, and cholinergic) and of the preclinical data suggesting peripheral antinociceptive effects of acetylcholine, we assumed a similar involvement of muscarinic receptors in peripheral pain mechanisms in humans. In addition, by choosing a different route of analgesic drug administration, specific side effects of central neostigmine should be reduced. Thus we tried to assess any peripheral analgesic activity of neostigmine in a defined clinical model of peripheral drug action, the intra-articular delivery of analgesics, and performed a double-blinded, randomized study in patients undergoing therapeutic knee arthroscopy and evaluated postoperative analgesia by intra-articular neostigmine.
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Table 1. Demographic Data of Patients Scheduled for Arthroscopic Meniscus Repair

<table>
<thead>
<tr>
<th></th>
<th>Gender (male/female)</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Anesthesia (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (IA saline)</td>
<td>6/4</td>
<td>37 ± 8</td>
<td>60 ± 11</td>
<td>145 ± 46</td>
</tr>
<tr>
<td>Group 2 (IA neostigmine 125 μg)</td>
<td>4/6</td>
<td>41 ± 7</td>
<td>56 ± 7</td>
<td>122 ± 32</td>
</tr>
<tr>
<td>Group 3 (IA neostigmine 250 μg)</td>
<td>8/2</td>
<td>43 ± 10</td>
<td>57 ± 12</td>
<td>117 ± 61</td>
</tr>
<tr>
<td>Group 4 (IA neostigmine 500 μg)</td>
<td>5/5</td>
<td>44 ± 9</td>
<td>62 ± 8</td>
<td>128 ± 24</td>
</tr>
<tr>
<td>Group 5 (IA morphine 2 mg)</td>
<td>3/7</td>
<td>38 ± 13</td>
<td>63 ± 8</td>
<td>151 ± 49</td>
</tr>
<tr>
<td>Group 6 (SC neostigmine 500 μg)</td>
<td>6/4</td>
<td>39 ± 11</td>
<td>59 ± 10</td>
<td>167 ± 73</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
IA = intraarticular; SC = subcutaneous.

Methods

After institutional review board approval and informed patient consent were obtained, 60 patients, classified as American Society of Anesthesiologists physical status 1 or 2 and scheduled for arthroscopic meniscus repair, were enrolled in this study. Exclusion criteria were age younger than 18 yr or older than 60 yr, use of analgesics within the last 24 h before the study, or previous allergic reactions to neostigmine or morphine.

Patients were prospectively studied and assigned in a randomized, double-blinded manner to one of six treatment groups (table 1) using a placebo-controlled design to evaluate analgesia and adverse effects.

Group 1: Intra-articular injection of 30 ml physiologic saline plus subcutaneous injection of 2 ml physiologic saline;

Group 2: Intra-articular injection of 125 μg neostigmine in 30 ml physiologic saline plus 2 ml physiologic saline given subcutaneously;

Group 3: Intra-articular injection of 250 μg neostigmine in 30 ml physiologic saline plus 2 ml physiologic saline given subcutaneously;

Group 4: Intra-articular injection of 500 μg neostigmine in 30 ml physiologic saline plus 2 ml physiologic saline given subcutaneously;

Group 5: Intra-articular injection of 2 mg morphine in 30 ml physiologic saline plus 2 ml physiologic saline given subcutaneously;

Group 6: Subcutaneous injection of 500 μg neostigmine in 2 ml physiologic saline.

All solutions were prepared free of preservatives by the hospital’s pharmacist using physiologic saline, neostigmine (Sintong Pharma, Taiwan), and morphine (Taiwan Narcotic Control Board), supplied as coded ampules in identical case packs. The day before surgery, the study patients were introduced to the visual analog scale (VAS) and the use of a postoperative patient-controlled intravenous analgesia pump system (PCA; Lifecare 4200; Abbott Laboratories, North Chicago, IL). For the VAS, the 100-mm scale included 0 as an indication of “no pain at all” and 100 as an indication of “the worst possible pain.” The test was subsequently performed by a single interviewer, who was not aware of the study medication given. Analgesic rescue medication consisted of a 1-mg bolus dose of morphine with a 10-min lockout interval provided by the PCA pump.

Evaluation of adverse effects included assessment of the occurrence of postoperative emesis and nausea (yes or no), pruritus, bradycardia (heart rate per min < 50), and urinary retention (voiding possible < 8 h after operation) by interviewing the patients 48 h after operation.

General anesthesia was scheduled for all surgeries. No premedication was given. Standard monitoring (continuous heart rate measurement with electrocardiogram and noninvasive blood pressure assessed every 5 min, continuous capnography and puls oxymetry) was used during operation. Anesthesia was induced with 5 mg/kg thiopental given intravenously and 2 μg/kg fentanyl given intravenously, and tracheal intubation was facilitated with 1 mg/kg succinylcholine given intravenously. Controlled ventilation was maintained in a semiclosed valvular system using 66% nitrous oxide and 34% oxygen. Anesthesia was achieved by the coadministration of 1 - 2% of the minimum alveolar concentration of inspired isoflurane and maintained until the end of the surgery. Before the arthroscope was removed, the drug was given intra-articularly or subcutaneously. No intra-articular drainage was used for any patient. Arrival at the postanesthetic care unit was recorded as time zero. The VASs were assessed at 1, 4, 8, 24, and 48 h after operation after the patients were instructed to bend
the operated knee to a 90° angle. Duration of effective analgesia was measured from time 0 until first use of the PCA and was recorded in minutes. The total amount of analgesic rescue medication was assessed over 48 h and recorded by the PCA device in total of milligrams of morphine (PCA was started immediately after arrival in the postanesthesia care unit).

Statistics

Unless otherwise indicated, data are represented as means ± SD. Statistical analysis of the data included the Kolmogorov-Smirnov test for all data. A repeated analysis of variance followed by post hoc analysis (Scheffe’s test) was performed for VAS over time, total morphine consumption, and time to first use of PCA. In all tests, \( P < 0.05 \) was considered significant.

Results

All 60 patients completed the study. As shown in table 1, there were no significant intergroup differences with regard to sex distribution, age, weight, or duration of anesthesia. In addition, no difference in the normal distribution of the values for VAS, morphine consumption, and time to first PCA use were observed (tested by Kolmogorov-Smirnov test).

In all groups, no adverse effects (nausea, vomiting, pruritus) were observed.

Postoperative intra-articular delivery of neostigmine produced a significant reduction in the VAS scoring 1 h after operation compared with intra-articular morphine or saline (\( P < 0.05 \)). However, there was no significant difference between the VAS between 500 \( \mu \)g neostigmine given intra-articularly or subcutaneously. For the two lower doses of intra-articular neostigmine, no significant VAS reduction compared with saline-treated patients was observed (low doses of intra-articular neostigmine are not shown in figure 1).

The total amount of rescue morphine recorded with the PCA system appeared to be lower with increasing doses of intra-articular neostigmine, but there was no significant difference between saline, 125 or 250 \( \mu \)g neostigmine given intra-articularly, or 500 \( \mu \)g neostigmine given subcutaneously. However, compared with intra-articular saline and subcutaneous neostigmine, patients who received the highest applied dose of intra-articular neostigmine (500 \( \mu \)g) showed a significant decrease in the need for supplementary analgesia. Intra-articular delivery of morphine, as assessed by the total consumption of morphine with the PCA over 48 h, resulted in a significant decrease in the need for rescue analgesics compared with patients given intra-articular saline (\( P < 0.05 \)). However, there was no significant discrepancy between intra-articular morphine and 500 \( \mu \)g intra-articular neostigmine with regard to total morphine consumption (\( P > 0.1 \), fig. 2).

Intra-articular administration of 500 \( \mu \)g neostigmine provided longer-lasting analgesia as defined by the first-time use of PCA compared with the intra-articular morphine (\( P < 0.05 \)) or intra-articular saline groups. This was also true compared with 500 \( \mu \)g neostigmine given subcutaneously. There was no difference noted for all other groups regarding the time of first use of intravenous rescue medication (fig. 3).

Discussion

Recently new interest has focused on cholinergic systems that modulate pain perception and transmission. It was shown that the intrathecal or epidural administration of cholinesterase inhibitors such as edrophonium or neostigmine produce a dose-dependent analgesia and display a synergistic or additive analgesia by coadministration of \( \alpha_2 \)-agonists or opioids in animal or human studies, respectively.\(^5,6,17\) The analgesic effects of neostigmine are more likely to be related to muscarinic than to nicotinic receptor stimulation. However, the subarachnoid administration of neostigmine, which counteracts the hypotension of spinal anesthetics or \( \alpha_2 \)-agonists is limited by its own characteristic adverse effects, such as vomiting, nausea, headache, bradycardia, hypotension, or pruritus.\(^1,5,15,18\) For other pain-modulating systems, such as the \( \alpha_2 \)-adrenoceptors or opioid receptors, a peripheral route of drug delivery resulted in peripheral analgesia in preclinical and clinical studies.\(^9,10,19\) In addition, specific centrally mediated adverse effects appeared to be reduced by the peripheral delivery of these compounds.

There is evidence for the presence of choline acetyltransferase in primary afferents and for the existence of cholinergic receptors at the central nerve endings of small afferent fibers.\(^9,26\) Duarte et al.\(^7\) showed that the intraplantar injection of acetylcholine will result in antinociceptive effects in animals. Putative mechanisms of a peripheral cholinergic-mediated antinociception at the peripheral nerve ending are the hyperpolarization of neurons,\(^21\) the reduction of pronociceptive neurotransmitters, and the activation of the nitrous oxide-cyclic
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Fig. 1. Visual analog scale scores expressed in millimeters in groups of intra-articular saline, neostigmine (125, 250, and 500 µg), morphine (2 mg), or subcutaneous neostigmine (500 µg) given over 48 h. Data are presented as means ± SD of 10 patients per group. The asterisk indicates a significant difference in VAS reduction 1 h after operation of 500 µg intra-articular neostigmine compared with all other groups (P < 0.05), excluding subcutaneous neostigmine (P > 0.05).

Morphine Consumption with PCA

Fig. 2. Total intravenous morphine consumption in milligrams over 48 h as assessed by the use of the patient-controlled analgesia pump in patients (n = 10 for each group) given intra-articular saline, neostigmine (125, 250, or 500 µg), morphine (2 mg), or subcutaneous neostigmine (500 µg). Data are presented as means ± SD. A significant difference (P < 0.05) between groups and saline is marked by an asterisk and between groups and 500 µg neostigmine given subcutaneously is indicated by #.
guanosine monophosphate pathway, as it was shown for the central delivery of muscarinic agents.\textsuperscript{22,23}

In the present study, we tried to evaluate any analgesic activity of peripheral muscarinic receptors by administering after operation neostigmine intra-articularly in patients having arthroscopic meniscus repair. We found, with the suppression of postoperative pain scores and the decrease of postoperative pain medication, a peripheral analgesic effect by intra-articular injection of neostigmine. The reduction of pain scores observed by subcutaneous administration of neostigmine correspond with observations made by Pedigo,\textsuperscript{24} who described a systemic analgesic effect of cholinesterase inhibition. However, the concomitant use of a PCA device in our study might have affected the pain scores obtained. Thus the assessment of pain 1 h after operation probably reveals the only unmasked, true analgesic effect evaluated by VAS scoring considering the differences in the first use of the PCA between all groups. Administration of the enzyme inhibitor neostigmine might cause an analgesic effect by increasing endogenous acetylcholine levels at the peripheral nociceptor. Acetylcholine could act there as an analgesic agonist at similar receptor subtypes as in the spinal cord, muscarinic receptors type 1 or 2.\textsuperscript{25} In our study, a 10-fold higher dose of peripherally (intra-articularly) administered neostigmine than an analgesic effective dose of spinaly delivered neostigmine produced an analgesic effect.\textsuperscript{15} However, as noted before, even a small dose of 50 $\mu$g neostigmine given intrathecally might be associated with nausea or other adverse effects.\textsuperscript{26} This was not observed for intra-articular doses of 500 $\mu$g neostigmine, indicating that this route of neostigmine administration would be appropriate for further trials. Because of its chemical structure, neostigmine might display longer stability, thereby ensuring a longer analgesic effect. Thus it might enhance the availability of more acetylcholine at assumed peripherally distributed muscarinic receptors. Peripherally delivered neostigmine provided a longer lasting analgesic effect (approximately 5–6 h) than did intra-articular morphine, which by its peak effect of approximately 3 h produced a similarly long-lasting antinociceptive effect, as shown previously.\textsuperscript{10} Peripheral analgesic action of opioids was shown by intra-articular delivery of morphine in the same model of patients undergoing arthroscopic surgery.\textsuperscript{10} For peripheral opioid analgesia, the analgesic efficacy is enhanced by inflammatory processing. Hassan et al.\textsuperscript{27} found that inflammatory conditions induce a new synthesis and migration of opioid receptors from the dorsal root ganglion to the peripheral nerve ending. In addition, the breakdown of the perineurium by in-
flammation increases the accessibility of peripheral opioid receptors.\textsuperscript{28} It might be a reasonable assumption that the observed analgesic effect after intra-articular injection of neostigmine could be also enhanced in states of chronic inflammation, based on the observed similarities of the different receptor systems (opioid and cholinergic systems).\textsuperscript{20,29}

In conclusion, the results of this study suggest that neostigmine acts at peripheral sites, resulting in postoperative analgesia in humans with no side effects.

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