THE EFFECTS OF INTRATHECAL NEOSTIGMINE ADDED TO BUPIVACAINE ON POSTOPERATIVE ANALGESIC REQUIREMENT IN PATIENTS UNDERGOING LOWER LIMB ORTHOPEDIC SURGERY

HAMID KAYALHA*, ZINAT SADAT MOUSAVI**, AMENEH BARIKANI***, SIAMAK YAGHOOBI**** AND MARZIEH BEIGOM KHEZRI*****

Abstract

Background: Several additives have been suggested to enhance analgesic effect of local anesthetic agents to decrease the adverse effects of them and increase the degree of satisfaction. We designed this randomized double-blind controlled study to evaluate the analgesic efficacy of the neostigmine added to bupivacaine using spinal anesthesia in patients undergoing lower limb orthopedic surgery.

Methods: Sixty patients 18-80 yr old American Society of Anesthesiologists (ASA) physical status I or II, scheduled for femur surgery under spinal anesthesia, were recruited in a prospective, double-blinded, randomized way. The patients were randomly allocated to one of two groups of 30 each. The neostigmine group (group N) received bupivacaine 20 mg combined with 25 µg neostigmine, and the placebo group (group C) received bupivacaine 20 mg combined with 0.5ml distilled water (intrathecally) 5 minutes prior to surgery. The time to the first analgesic request, analgesic requirement in the first 12 hours after surgery, the duration of sensory and motor blockade, the incidence of adverse effects such as nausea, vomiting, hypotension, ephedrine requirements, bradycardia, and hypoxemia were recorded.

Results: Patients receiving neostigmine had a significantly prolonged duration of motor block (95%CI 30.27 to 87.65; P <0.001) and sensory block (95%CI 101.04 to 224.64; P <0.001) compared to the control group. The difference of the mean time to the first analgesic request was also significantly longer in neostigmine group (95%CI 83.139 to 208.526; P <0.001). The total analgesic consumption during the first 12 hours after surgery was devoid of any significant difference between groups N and C (p = 0.41). The two groups were not significantly different in terms of intraoperative and postoperative side effects.

Conclusion: Intrathecal neostigmine 25 µg with bupivacaine caused a prolonged time to the first analgesic request and its use was not associated with any side effects.

Keywords: Spinal anesthesia, bupivacaine, neostigmine, sensory block, motor block, pain.

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Introduction

Postoperative pain is associated with catecholamine release, and the central sensitization is supposed to be among the mechanisms concerned with the persistence of postoperative pain\(^1\).

Neuraxial blocks have been introduced to produce superior analgesia and decrease the blood loss and the incidence of deep venous thrombosis (DVT), pulmonary embolism, and to minimize the adverse effects of general anesthesia and improve the patients outcomes\(^2\).

There are many additives to be used to enhance analgesic effect of neuraxial blocks such as clonidine, magnesium, ketamine, opioids, vasoconstrictor agents and steroids, and neostigmine\(^3-5\).

It is reported that the inhibition of spinal cholinesterase by neostigmine produces great enhancement of endogenous acetylcholine, which is most likely released from intrinsic cholinergic neurons within the dorsal horn of the spinal cord\(^6\). An action at nicotinic receptors at the dorsal horn ganglion\(^7\) and at the spinal meninges\(^8\) has also been demonstrated\(^9\). Muscarinic receptor antagonists have been shown to reverse the analgesic effects of intrathecal neostigmine\(^10\).

We hypothesized that neostigmine may provide a better pain relief after orthopedic surgery under spinal anesthesia compared to conventional agents. In addition, unlike opioids, neostigmine does not produce pruritus, respiratory depression or hyperalgesia. To test our hypothesis, we designed this randomized-double-blind, placebo-controlled study to evaluate the postoperative analgesic effect of intrathecal neostigmine added to bupivacaine in patients undergoing lower limb surgery.

Method

This study was a placebo-controlled, randomized, double-blind clinical trial in which the patients, investigators and anesthesiologists were blinded to the given treatment. Patients were fully informed about the study protocol and provided written informed consent. The study was approved by the institutional ethics committee and performed during July 2011 to February 2012. Exclusion criteria included significant coexisting complications such as hepatorenal and cardiovascular diseases, any contraindication to regional anesthesia such as local infection or bleeding disorders, allergy to neostigmine, long-term opioid use, or a history of chronic pain, pregnancy and menstruation, digestive problems with nausea or vomiting, and asthma. Using a computer-generated randomization schedule, sixty patients 18-80 yr old ASA physical status I or II, scheduled for lower limb orthopedic surgery under spinal anesthesia, were randomly allocated to one of the two groups of 30 members each. The Consolidated Standards of Reporting Trials (CONSORT) recommendations for reporting randomized, controlled clinical trials were followed (Fig. 1)\(^{11}\). Blinding was achieved through the use of equal amounts of drugs (4.5 ml) while the syringes used were labeled as A and B according to their content. Identical coded syringe prepared by the operating room personnel, not involved in the study, were randomly handed to the anesthetist, who was unaware of the identities of the drugs. The neostigmine group (group N) received bupivacaine 20 mg combined with 25 µg neostigmin (Trittau, Germany), and the control group (group C) received bupivacaine (Mylan S.A.S France) 20 mg combined with 0.5ml distilled water intrathecally. All patients received an intravenous preload of 5-7 ml/kg lactated Ringer’s solution before a subarachnoid block. After, using an aseptic technique, a 25-gauge Quincke needle was inserted intrathecally via a midline approach into the L4-5 interspaces by the anesthetist who was unaware of patient assignment while the patient in sitting position. Following a successful dural puncture, the anesthetic solution was injected. The primary outcomes were to evaluate the time to the first requirement of analgesic supplement and the total analgesic consumption in the first 12h postoperative. In this study, postoperative analgesia was defined as the time to the first requirement of analgesic supplement from the time of the intrathecal anesthetic solution injection. No additional analgesic was administered unless requested by the patient. Patients were elucidated preoperatively for the use of the verbal rating scale (VRS) from 0 to 10 (0 no pain, 10 maximum imaginable pain) for pain assessment. If the VRS exceeded four and the patient requested a supplement analgesic, pethidine 25 mg IV was
given. The secondary outcome of this study included the assessment of sensory and motor duration of blockade, the incidence of hypotension, ephedrine requirements, bradycardia, hypoxemia (Saturation of peripheral oxygen (SpO2)<90), pruritus, nausea and vomiting. Sensory block was assessed by a pinprick test. The duration of sensory block was defined as the time between the end of injection of the intrathecal anesthetic and the appearance of pain at the T10 dermatome. Motor block was assessed by the modified Bromage score (0, no motor loss; 1, inability to flex the hip; 2, inability to flex the knee; and 3, inability to flex the ankle); whereas the duration of motor block was assumed as the time between the end of injection of the intrathecal anesthetic when the modified Bromage score was zero. Continuous mean arterial pressure (MAP) and heart rate (HR) were measured by an observer blinded to the patient group assignment. If the systolic blood pressure (SBP) decreased to 20% below the baseline or less than 90 mmHg, ephedrine 5 mg was administered intravenously. Also, if HR was less than 50 beats/min, atropine sulfate 0.5 mg was administered intravenously. A follow-up telephone call was made 24h after the surgery and again 1 and 6 months later during which the patients were asked about side effects, and dysesthesia of the lower limbs or buttocks. The study data were collected and analyzed by a member of statistics department who was not involved in the study. To calculate the sample size, data from previous similar studies were taken into consideration. Sample size analysis assumed that a total of 25 patients (n = 25) per group was required to detect a 20 min difference in the mean duration of analgesia between the groups with a power of 0.9 and an α equal to 0.05. We included 30 patients in each group to allow for dropouts and protocol violations. Data were analyzed using SPSS (SPSS 15.0, SPSS Inc, Chicago, II, USA). Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Parametric data were expressed as mean and standard deviation (SD) and analyzed using the independent T test. The χ² test was used to analyze

Fig. 1
Consort flow diagram of the trial

- Assessed for eligibility (n=75)
  - Randomized (n=60)
    - Excluded (n=15)
      - Not meeting inclusion criteria (n=10)
      - Refused to participate (n=5)
    - Allocated to intervention (n=30)
      - Received allocated intervention (n=30)
      - Did not receive allocated intervention (n=0)
    - Lost to followup (n=0)
  - Analyzed (n=30)
- Allocated to intervention (n=30)
  - Received allocated intervention (n=30)
  - Did not receive allocated intervention (n=0)
  - Lost to followup (n=0)
  - Analyzed (n=30)
the incidence of adverse events. A P value <0.05 was considered statistically significant.

**Results**

Among 75 patients initially enrolled in this study, 15 patients had to be excluded because of logistical reasons or violations of the study protocol. Sixty patients were included and randomly assigned to the treatment groups (Fig. 1).

There were no significant differences in sex, age among the two groups. The duration of surgery was also similar (Table 1).

**Table 1**

Demographic data for two study groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group N (n = 30)</th>
<th>Group C (n = 30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.8 ± 14.6</td>
<td>61.2 ± 17.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Sex(M/F)</td>
<td>8/22</td>
<td>9/21</td>
<td>0.6</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>109.1 ± 9.5</td>
<td>111.2 ± 7.5</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number of patients. C = control, N = neostigmine.

There is a statistically significant difference in duration of sensory block between the N and C groups (Table 2). Also, there is a statistically significant difference in mean duration of motor blockade time between groups N and C (Table 2).

Meanwhile, there was a significant difference in mean time to first analgesic request between groups N and C (Table 2). The total analgesic consumption during the first 12 hours after surgery did not show any significant difference between groups N and C (Table 2). Transient hypotension occurred at various times in groups N and C despite a pre-block volume loading. These patients were treated with 5-mg boluses of ephedrine IV to maintain their SBP within 20% of baseline values or 90 mmHg. There was no significant difference in incidence of hypotension episodes between groups N and C.

The overall difference in ephedrine requirement between the three groups was not statistically significant (Table 2).

**Table 2**

Characteristics of spinal anesthesia

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group N (n = 30)</th>
<th>Group C (n = 30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of sensory block (min)</td>
<td>318 ± 99</td>
<td>125 ± 55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of motor block (min)</td>
<td>221 ± 68</td>
<td>165 ± 40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to first request of analgesic (min)</td>
<td>435 ± 152</td>
<td>289 ± 78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total ephedrine requirement (mg)</td>
<td>1.61 ± 2.0</td>
<td>2.10 ± 2.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Total pethidine consumption in 12h (mg)</td>
<td>40.8 ± 21.25</td>
<td>45 ± 17.85</td>
<td>0.4</td>
</tr>
</tbody>
</table>

All data are presented as mean ± SD, C = control, N = neostigmine.

As shown in Table 3, there were no significant differences in terms of intraoperative and postoperative side effects.

**Table 3**

Side effects

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group N (n = 30)</th>
<th>Group C (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>1(3.33%)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>8(26.7%)</td>
<td>7(23.3%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>3(10%)</td>
<td>1(3.33%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1(3.33%)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Shivering</td>
<td>2(6.7%)</td>
<td>4(13.3%)</td>
</tr>
</tbody>
</table>

Values are the number of patients (%). C = control, N = neostigmine.

**Discussion**

Based on the data found in the present study, it could be concluded that the administration of intrathecal neostigmine 25 µg/kg with bupivacaine caused a prolonged duration of sensory, motor block and also time to the first analgesic request compared to the control group after lower limb surgery. These findings are consistent with some previous studies. Analgesic properties of neostigmine have been shown...
to depend on the release of NO in spinal cord and increasing acetylcholine in the spinal synapses which leads to the further stimulation of nicotinic and muscarinic receptors6-10,19. The selection dose of intrathecal neostigmine was based on the fact that several previous studies showed that the 25 µg/kg of neostigmine adding to bupivacaine could prolong the duration of spinal analgesia without additional side effects12-14,15.

The second observation which should be noted is that the transient hypotension episodes and ephedrine requirement between the two groups was statistically insignificant. The overall results of our study is in consistency with studies by Hye MA13, who declared that the use of intrathecal neostigmine was associated with minimal hemodynamic fluctuations. However in Gupta S study, hypotension in the group receiving neostigmine 75 µg was more than the other group receiving 50µg of neostigmine12. These apparently controversial results may be due to either different dosage of neostigmine or population variation.

The third finding which should be taken into account is that, the incidence of nausea and vomiting between the two groups was statistically insignificant. This finding is in contrast with the result obtained in the Klamt study16 in which a significant difference in nausea and vomiting episodes in patients who received 100µg of neostigmine and bupivacaine was reported. The authors of the present study speculate that the lower dose of neostigmine was not associated with high incidence of nausea vomiting. This idea is supported by the result of GuptaS12 and Lauretti18 studies in which observed that the incidence of nausea and vomiting increased with larger dose of neostigmine.

The another observation which should be emphasized is that neostigmine prolonged the time to first analgesic requirement but it failed to decreased total opioids consumption in the first 12 hours postoperatively as compared with the control group. The possible explanation for this finding is that the analgesic effect of neostigmine follows a dose-dependent manner. This result is harmony with the findings by Gupta S study12 who reported that total of analgesic consumption after surgery in the patients receiving 75 mg of neostigmine and bupivacaine was lower than the other patients receiving 50 mg neostigmine and bupivacaine; and both groups used less drugs comparing to the bupivacaine group.

We concluded that intrathecal neostigmine 25 µg with bupivacaine prolonged sensory, motor block and the time to first analgesic request compared to control group, and its use was not associated with any serious side effects. However, the total analgesic consumption in the first 12h postoperative was similar in bupivacaine and neostigmine groups following surgery. Further studies are needed to evaluate the analgesic efficacy of neostigmine with other neuraxial drug combinations such as epinephrine, ketamine, and magnesium to provide better analgesia and reduce the incidence and severity of side effects.
References


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- 97% of BRIDION patients recovered to a TOF ratio of 0.9 from 1 to 2 PTCs ³ within 5 minutes³

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- BRIDION rapidly reversed patients from 1 to 2 PTCs within 2.7 minutes³

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¹ Train-of-four
² Post-tetanic count
³ Second twitch

**REFERENCES:**

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Answer.

References: