Midazolam versus Neostigmine Adding to Lidocaine in Post Operation Pain in Colporrhaphy Surgery in Spinal Anesthesia

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Received October 2011, Revised and accepted in January 2012

Abstract
Objective: To compare the effect of intrathecal midazolam versus neostigmine added to lidocaine on the duration of sensory block and the duration of postoperative pain relief in women undergoing colporrhaphy in spinal anesthesia.

Materials and methods: In this double blind clinical trial we evaluated 60 women (ASA I, II) that were candidate to elective colporrhaphy. The patients were randomly divided in three groups, first group (midazolam group) received hyperbaric lidocaine and 1 mg midazolam (0.5 cc), second group (neostigmine group) received hyperbaric lidocaine and 50 µg midazolam (0.5 cc) and third group were considered as control and received hyperbaric lidocaine plus normal saline (0.5 cc). VAS pain score 4, 12 and 24 hours after surgery and duration of analgesia in three groups were compared.

Results: The duration of sensory block in the midazolam group was 98.4 ± 18.2 minutes, 74.5 ± 32.6 in neostigmine and 64.5 ± 9.9 in control group and difference between three groups was significant (P = 0.001). Postoperative pain scores in midazolam group was 1.5 ± 1.3, in neostigmine group was 2.4 ± 1.6 and in control group was 3.5 ± 2.7 and difference between three groups was significant (P = 0.009).

Conclusion: Midazolam & neostigmine added to lidocaine 5% prolonged postoperative analgesia in colporrhaphy surgery in spinal anesthesia but midazolam was more effective than neostigmine.

Keywords: midazolam & neostigmine, Spinal anesthesia, analgesia, colporrhaphy

Introduction
Spinal anesthesia using local anesthetics has been broadly applied in lower limbs and lower abdominal operations. Postoperative pain is the most important cause of unintended hospital admissions following spinal anesthesia and a major source of dissatisfaction with perioperative outcome (1-2). A diver's class of intrathecal agents such as ketamine, clonidine, opioids and neostigmine are often added to enhance the duration of spinal anesthesia and reduce pain after surgeries. However, applying these agents are limited owing to adverse effects such as respiratory depression, hemodynamic instability, pruritis, urinary retention, nystagmus, and severe nausea and vomiting (3-6). It is well known that intrathecal midazolam create antinociception and potentiate the effect of local anesthetic without having remarkable side effects.

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effects (7). Moreover, other studies showed intrathecal midazolam is safe (8) and when combined with other intrathecal agents, improves postoperative recovery and increased painless period in patients under surgery (9). On the other hand some studies divulged that intrathecal neostigmine is adjunctive spinal analgesic in very small doses (10).

Hence we conducted this study to compare the intrathecal midazolam plus lidocaine with neostigmine added to lidocaine and their effect on the duration of sensory block and the duration of postoperative pain relief in patients undergoing colporrhaphy surgery.

Materials and methods

In this double blind clinical trial we evaluated 60 women aged 30-50, class American Society of Anesthesiologists (ASA) I, II that were candidate to elective colporrhaphy. The study protocol was approved by ethical committee of Arak university of medical sciences. Furthermore study protocol was explained for patients and informed written consent was taken from the patients. Patients with contraindications to regional anesthesia or sensitivity to study drugs and who were on chronic analgesic therapy were excluded from the study. Patients Were received with oral diazepam (0.3 mg/kg)1 and ranitidine (ampoule, sina pharmacy Co., Tehran, Iran 3 mg/kg) two the night before surgery. In the operating room, standard monitors (electrocardiogram, non-invasive blood pressure and pulse oximeter) was attached to the patient, and baseline vitals were recorded. An 18G intravenous line was secured and preloaded with Ringer’s lactate 10 mL/kg. The patients were randomly divided in three groups as follow: first group: received hyperbaric lidocaine (ampoule, Abureyhan pharmacy Co., Tehran – Iran) and 1mg midazolam (ampoule, Abureyhan pharmacy Co., Tehran – Iran); second group received hyperbaric lidocaine and 50µg neostigmine (ampoule, Tamin pharmacy Co., Rasht – Iran) and third group were considered as control and received hyperbaric lidocaine plus normal saline (0.5cc).

The anesthetics were administered intrathecal in lateral position in L3–4 or L4–5 space with a 25-gauze spinal needle. The study solution, prepared by another researcher who was not involved in the patient’s care, was injected through the spinal needle over a period of ten seconds with no barbotage. After injecting the drug, the patient was turned to supine position, and the onset time (defined as the time interval between the completion of intrathecal drug injection to the onset of complete loss of pinprick sensation at T8), level of sensory block (defined as the highest dermatomal level of sensory blockade by pinprick testing), time to achieve maximum sensory block level, duration of sensory block (defined as the time interval from completion of intrathecal drug injection and 2-segment regression of sensory block by pinprick method), duration of motor block (defined as the time taken from onset of complete motor block, score 3 to complete recovery of motor block, score 0) and time for rescue analgesia (defined as the time interval between administration of intrathecal drug to the time of administration of first rescue analgesia) were noted. Pain was weighed using the Visual Analogue Score (VAS) (0: no pain, 10: maximum pain). Pulse rate and blood pressure were monitored every five minutes in intraoperative and every ten minutes subsequently till 2-segment regression of block. Hypotension (> 20% decrease in systolic blood pressure from baseline) was managed with intravenous fluid (20 mL/kg).

Intraoperative rescue analgesia was administered with fentanyl (1 µg/kg, intravenously) (ampoule, Abureyhan pharmacy Co., Tehran – Iran), when required. If the pain was not relieved, the patient was given general anesthesia and excluded from the study. Postoperatively, rescue analgesic medication with diclofenac sodium suppository (1.5 mg/kg) (Dr Aabidi pharmacy Co., Tehran – Iran) was administered, if VAS was found to be ≥ 4. The level of sensory anesthesia was recorded at two-minute intervals for 15 minutes after completion of intrathecal injection, and every ten minutes thereafter. Motor block was assessed by the Bromage score (0: no motor loss, 1: inability to flex the hip, 2: inability to flex the knee joint, 3: inability to flex the ankle) at one-minute intervals until complete motor blockade occurred. Onset of motor block was defined as time taken from injection of drug to development of complete motor block (Bromage score 3). The level of sedation of the patients was assessed by the Ramsay sedation score (1: anxious, agitated and restlessness, 2: oriented and cooperative, 3: responds to command only, 4: brisk response to loud voice and light glabellas tap, 5: sluggish to no response to light glabellas tap or loud auditory stimulus, 6: no response even to pain). All patients were followed up after surgery for up to 24 hours (4h, 12h, 24h) for any behavioral side effects as confusion, dizziness,
nystagmus, nausea, vomiting or any neurological complications like pain or numbness in the leg.

Data were analyzed using the SPSS version 16.00. Student’s t-test was used for comparing the three groups, while the chi-square test was used to analyze categorical data. P-value < 0.05 was considered to be statistically significant.

**Results**

We evaluated 60 patients mean age 46.5±8.51 (three groups, 20 patients /group). Patients before study were properly matched and difference between groups regarding age was not significant. All patients had successful spinal anesthesia, and none required general anesthesia.

The duration of sensory blockade is illustrated in table 1. As assessed by kruskal-wallis test the duration was 98.4±18.2 minutes in the midazolam group, 74.5±26.6 in neostigmine and 64.5±9.9 in control group and difference between three groups was significant (P=0.001). The Mean number of diclofenac sodium suppository consumption in 24h post operation was 2.05±0.94 in neostigmine group, 1.6±0.68 in midazolam group and 4.4±1.4 in control group and difference between three groups was not significant (P=0.06). Mean arterial pressure before anesthesia in all patients was 80.90±5.0 and difference between three groups was not significant (P=0.06). Postoperative pain scores in midazolam group was 1.5±1.3, in neostigmine group was 2.4±1.6 and in control group was 3.5±2.7 and difference between three groups was significant as shown in table 2 (P=0.009). Pain scores 4 and 12 hours after operation in 3 studied groups are illustrated in table 3 and 4 respectively.

**Table 1: Duration of sensory blockade after operation and the number of diclofenac suppositories used in three studied groups**

<table>
<thead>
<tr>
<th>Duration of anesthesia (minutes)</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>20</td>
<td>98.4500</td>
<td>18.25398</td>
</tr>
<tr>
<td>Neostigmin</td>
<td>20</td>
<td>74.5500</td>
<td>32.62785</td>
</tr>
<tr>
<td>Control</td>
<td>20</td>
<td>64.5500</td>
<td>9.96560</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>79.1833</td>
<td>26.22619</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Diclofenac suppositories used (n)</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20</td>
<td>1.6000</td>
<td>0.68056</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>2.0500</td>
<td>0.94451</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>4.4000</td>
<td>1.46539</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>2.6833</td>
<td>1.63118</td>
</tr>
</tbody>
</table>

**Table 2: Pain score in recovery ward**

<table>
<thead>
<tr>
<th></th>
<th>Mean± SD</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>1.5±1.3</td>
<td>P=0.009</td>
</tr>
<tr>
<td>Neostigmin</td>
<td>2.4±1.6</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3.5±2.7</td>
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</table>

* by Kruskal- Wallis test

**Table 3: Pain score 4 hours after operation**

<table>
<thead>
<tr>
<th></th>
<th>Mean± SD</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>5.8±1.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Neostigmin</td>
<td>6.7±1.4</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>6.1±2.3</td>
<td></td>
</tr>
</tbody>
</table>

* by ANOVA

**Table 4: Pain score 12 hours after operation**

<table>
<thead>
<tr>
<th></th>
<th>Mean± SD</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>2.3±1.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Neostigmin</td>
<td>3.1±1.1</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4.05±1.6</td>
<td></td>
</tr>
</tbody>
</table>

* by ANOVA

**Discussion**

Several studies have revealed intrathecal midazolam have analgesic properties and when adding to intrathecal local anesthetics, potentiates the effects of these agents (11-14). Some of these studies indicated that intrathecal midazolam released an endogenous opioid acting at spinal delta receptors(15). Therefore, adding intrathecal midazolam may potentiate the antinociceptive effect of morphine-like agents(12). In a comparative study Shadangi et al used 2 mg midazolam as an additive to bupivacaine for intrathecal administration and reported that addition of preservative-free midazolam to bupivacaine intrathecally prolonged the postoperative analgesia without increasing motor block(16). Furthermore Son et al in a study on 40 women (ASA I,II) under cesarean surgery showed intrathecal midazolam added to lidocaine 0.05% is more effective in post operation pain control than lidocaine 0.05% alone(17).

In this trial we divulged the duration of sensory blockade in the midazolam group significantly was more than neostigmine and control groups'. Moreover post operation analgesic consumption in midazolam group significantly was lower than control and neostigmine groups. Furthermore we did not detect any adverse effect in our patients in 24 h postoperation in three groups. Previous studies agree that 1–2 mg intrathecal midazolam is safe and effective (12-15) and one study on patients under cesarean section exposed intrathecal midazolam 2 mg
moderately prolonged postoperative analgesia as compared to 1 mg when used as an adjunct to bupivacaine(18).

We designated postoperative pain scores were lower in patients who received intrathecal midazolam in addition to lidocaine than patients received neostigmine and control group. In line with our results, Bharti et al. reported the postoperative pain scores were lower in patients who received intrathecal midazolam (1 mg) with bupivacaine(19). Moreover, in agreement to our results, Prakash et al. administered intrathecal bupivacaine along with midazolam in either 1-mg or 2-mg doses and specified the duration of postoperative analgesia was significantly prolonged with the addition of intrathecal midazolam and that the effect was dose-dependent (18).

We did not observe any complication in postoperative period, in line with our study; Tucker et al. evaluated and followed up a large group of patients (574 cases) for one month for a wide range of symptoms related to neurotoxicity who received intrathecal midazolam. They revealed occurrence of neurological symptoms did not increase when they administered up to 2 mg intrathecal midazolam (7). However, in contrast to our results two studies indicated the duration of motor blockade was more prolong in the midazolam group compared with the control group (14, 19).

Our study encountered some limitations. Firstly, our study was not sufficiently powered to remark conclusively on the adverse effects in the three groups. Secondly, the relatively small sample size in this review limits the ability to generalize the result of our survey. Therefore, a larger study is necessary that is adequately powered to study the side effect profile of intrathecal midazolam.

In conclusion, the addition of midazolam & neostigmineto lidocaine 5% prolonged postoperative analgesia in colporrhaphy surgery in spinal anesthesia but midazolam was more effective than neostigmine.

References
17. Sen A, Rudra A, Sarkar SK, Biswas B. Intrathecal
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