The Optimal Dose Range of Epidural Naloxone to Minimize Nausea during Continuous Epidural Infusion of Morphine

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Background: This study was designed to determine the optimal dose range of epidural naloxone that can preserve analgesia while minimizing nausea, one of the most common side effects caused by epidural morphine.

Methods: Seventy-four patients undergoing combined epidural and general anesthesia for hysterectomy were randomly assigned to one of three groups. All received 2 mg epidural morphine bolus just before closing abdominal cavity and a continuous epidural infusion was started containing 4 mg morphine in 100 ml bupivacaine 0.125% with either no naloxone (Group 1, n = 24), 0.167 mg/kg/hr of naloxone (Group 2, n = 19) or 0.412 mg/kg/hr of naloxone (Group 3, n = 31) for postoperative pain control. Analgesia and nausea were evaluated by blinded observers.

Results: The combination of epidural morphine and bupivacaine provided good analgesia. Pain scores in group 3 were lower than in group 1 after surgery, but there were no significant statistical differences except at 16 hr. Group 2 showed the lowest pain scores at 8, 16 and 24 hr (P < 0.05). Nausea scores were lower in group 2 and 3 than in group 1 at 16 and 24 hr (P < 0.05).

Conclusions: Epidural administration of naloxone below 0.412 mg/kg/hr was optimal and safe dose range that maintained the analgesic effects of morphine while minimizing nausea. (Korean J Anesthesiol 2005; 48: S38-41)

Key Words: analgesia, bupivacaine, epidural morphine, epidural naloxone, nausea, postoperative pain control.

INTRODUCTION

Epidural morphine and local anesthetics have been used as one of the most common agents for postoperative pain control.1-3 But epidural morphine has several adverse effects including respiratory depression, vomiting and nausea. This has led to attempt to combine epidural morphine administration with butorphanol or droperidol in the hope of minimizing side effects.4-6 Intravenous administration of small dose naloxone reduces epidural morphine induced side effects effectively without reversing analgesia.7 Choi et al.8 reported that epidural coadministration of morphine and naloxone reduced morphine induced side effects in dose dependent fashion without reversal of the analgesic effect. And they concluded that epidural administration of naloxone 0.167 mg/kg/hr or less could preserve analgesia while minimizing adverse effects of epidural morphine. Little is known about the optimal dose range of naloxone in the view of dose response relationship when administered into the epidural space in human subjects. We started our research to determine the optimal epidural naloxone dose range that would minimize nausea, one of the most common side effects of epidural morphine, without reversing epidural morphine induced analgesia.

MATERIALS AND METHODS

The protocol of this study was approved by the Human Subjects Review Board of Catholic Medical Center’s Kangnam St. Mary Hospital, and informed consent was obtained from all patients. Seventy-four ASA grade I and II who were scheduled to undergo hysterectomy were studied. Patients weighed 50-60 kg and had a height of 150-160 cm.
After identification of the epidural space using the loss of resistance technique, a 20 gauge epidural catheter was inserted at the L3-4 interspace and fixed 3 cm cephalad into the epidural space. An initial dose of 10 ml bupivacaine 0.33% was then injected via the epidural catheter. Next, general anesthesia was induced with 4 mg/kg thiopental and 1 mg/kg succinylcholine, and maintained with etomidate (< 0.5 vol%, end-tidal), N₂O (60% in oxygen) and 0.08 mg/kg vecuronium. Five minutes after induction, 5 ml bupivacaine 0.33% were administered again via the epidural catheter. Patients then received 1/3 of the initial dose (15 ml) at an hour interval until the end of the surgery.

As the surgeons started to close the abdominal cavity, each patient was given 2 mg morphine into the epidural catheter. A continuous epidural infusion was then initiated by two-day infusion devices (Accufuser PLUS, Korea), containing 4 mg morphine in 100 ml bupivacaine 0.125%. Patients were randomly allocated into three groups, each of which received a different medication mixture via the two-day infusion device. Group 1 received 80 mg morphine in 2 ml bupivacaine 0.125% per hour. Group 2 received the same mixture, but with the addition of 0.167 mg/kg/hr of naloxone. Group 3 was identical to Group 2 except that the naloxone infusion rate was 0.412 mg/kg/hr.

Visual analogue scale (VAS) for assessing pain was employed postoperative period at 2, 8, 16, 24 and 48 hours. Nausea was assessed using nausea five point scale (1 = no nausea, 2 = mild nausea, treatment is not necessary, 3 = moderate nausea, treatment may be desirable, but patient can be tolerable, 4 = severe nausea, treatment is necessary, 5 = intractable nausea, complain with even treatment). The assessment was carried out by anaesthesiologists who had not been involved in care of the patients and were blinded to the group assignment. The effects of the treatments were evaluated at each point using the Kruskal-Wallis statistic to determine whether significant differences existed among groups and specific inter-group differences were identified using the Mann-Whitney U test.

**RESULTS**

There were no differences among groups in age, height and weight (Table 1).

All three groups experienced good pain control after 2 hr. Group 3 had lower VAS scores than group 1 but showed no significant difference except at 16 hr. Group 2 had the lowest VAS scores at 8, 16 and 24 hr compared to group 1 (P < 0.05).

Group 2 and 3 showed significant lower nausea score than group 1 at 16 and 24 hr (P < 0.05). Also the nausea scores were lower in group 2 and 3 at 2, 8, and 48 hr than in group 1, but there were no statistical differences among the groups (Table 2).

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**Table 1. Patients’ Characteristics**

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (± SD)</th>
<th>Weight (± SD)</th>
<th>Height (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46.2 ± 7.7</td>
<td>56.4 ± 5.8</td>
<td>155.2 ± 5.2</td>
</tr>
<tr>
<td>2</td>
<td>46.4 ± 5.1</td>
<td>53.5 ± 8.2</td>
<td>157.7 ± 4.1</td>
</tr>
<tr>
<td>3</td>
<td>42.8 ± 8.5</td>
<td>54.5 ± 7.3</td>
<td>157.3 ± 4.6</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

**Table 2. The Outcome of Data Analyses**

<table>
<thead>
<tr>
<th></th>
<th>2 hr</th>
<th>8 hr</th>
<th>16 hr</th>
<th>24 hr</th>
<th>48 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAPS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>2.5 ± 1.6</td>
<td>2.4 ± 1.5</td>
<td>2.2 ± 1.4*</td>
<td>1.8 ± 1.2*</td>
<td>1.3 ± 0.8*</td>
</tr>
<tr>
<td>Group 2</td>
<td>2.4 ± 1.7</td>
<td>1.2 ± 0.4*</td>
<td>1.1 ± 0.3*</td>
<td>1.0 ± 0.2*</td>
<td>1.1 ± 0.4*</td>
</tr>
<tr>
<td>Group 3</td>
<td>2.2 ± 1.5</td>
<td>1.9 ± 1.3</td>
<td>1.5 ± 0.9*</td>
<td>1.4 ± 0.8*</td>
<td>1.2 ± 0.4*</td>
</tr>
<tr>
<td>NFPS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>2.4 ± 1.7</td>
<td>2.4 ± 1.5</td>
<td>2.0 ± 1.2*</td>
<td>1.8 ± 1.2*</td>
<td>1.4 ± 0.9*</td>
</tr>
<tr>
<td>Group 2</td>
<td>1.8 ± 1.1</td>
<td>1.5 ± 1.0</td>
<td>1.2 ± 0.4*</td>
<td>1.1 ± 0.3*</td>
<td>1.0 ± 0.2*</td>
</tr>
<tr>
<td>Group 3</td>
<td>1.8 ± 1.3</td>
<td>1.8 ± 1.1</td>
<td>1.4 ± 0.7*</td>
<td>1.2 ± 0.6*</td>
<td>1.0 ± 0.1*</td>
</tr>
</tbody>
</table>

Values are mean ± SD. VAPS: visual analogue pain score on a 10 cm scale, NFPS: nausea five point scale (1 = no nausea, 2 = mild nausea, treatment is not necessary, 3 = moderate nausea, treatment may be desirable, but patient can be tolerable, 4 = severe nausea, treatment is necessary, 5 = intractable nausea, complain with even treatment). *: P < 0.05 vs Group 1; **: P < 0.05 vs postoperative 2 hr.
DISCUSSION

Choi et al.\(^1\) reported that epidural naloxone co-administration with morphine reduced nausea, vomiting and itching while not reversing analgesia and that, at certain doses, naloxone improved the analgesic effect in human subjects. The efficacy of intravenous administration of naloxone in reducing nausea and vomiting while preserving the analgesic effects of epidural morphine is well documented.\(^9\) However titration of the dose of administered naloxone is critical since excessive naloxone may reverse analgesic effect of morphine and is capable of inducing hyperalgesia. Levine et al.\(^10,11\) found that naloxone initially produces analgesia in dose dependent manner and then postoperative hyperalgesia occurs. In a rat model, Woolf\(^12\) noted that small doses of naloxone produced paradoxical analgesia, whereas larger doses resulted in hyperalgesia. The exact mechanism by which low-dose naloxone induces analgesia is not yet defined. However, there are several possible explanations. Naloxone in low doses has been shown to release endorphins, or perhaps displaces endorphins from receptor sites not relevant to analgesia, whereas at higher doses it blocks the action of the released or displaced endorphin at the postsynaptic receptor for analgesia.\(^13\) It is also possible that the low dose of naloxone would bind to highly sensitive presynaptic receptors, responsible for an inhibitory control of endogenous opioid release,\(^14\) as confirmed by biochemical studies;\(^15\) on the other hand, the high dose would interact with less sensitive post-synaptic receptors to induce its antagonistic effects. Gan et al.\(^1\) found that small doses of naloxone infused at 0.25 or 1 mg/kg/hr are equally effective in reducing opioid-related side effects during patient-controlled analgesia. They also showed that naloxone at 0.25 mg/kg/hr has the additional advantage of providing opioid-sparing effects. In spite of our two previous epidural naloxone study,\(^1,16\) the exact dose range inducing hyperalgesia with epidural naloxone has not been established in human subjects. Main purpose of our study was to find optimal safe dose range of epidural naloxone that preserves analgesia while minimizing nausea, one of the most common side effects induced by epidural morphine.

The important finding of our study is that group 2 showed more effective pain control than group 1 at 8, 16 and 24 hours after surgery. But group 3, despite larger dose of epidural naloxone, showed statistically significant difference compared to group 1 only at 16 hours. In spite of statistical difference among 3 groups, VAS score of all groups showed effective pain control state clinically. Less nausea was produced in group 2 and group 3 compared to group 1 at 16 and 24 hours postoperatively, and the degree of reducing the severity of nausea was the same in both group.

Even though we could not ascertain the exact mechanism how epidural naloxone exerts a biphasic dose-dependent effect in our study, we can surmise that epidural naloxone shows different action regarding postoperative pain and nausea at different doses.

According to our study, we concluded as below. First, epidural administration of naloxone 0.167 mg/kg/hr was the most effective analgesic dose while minimizing nausea. Second, in the point of statistical dose/effect ratio, epidural administration of naloxone above 0.412 mg/kg/hr might be less advantageous for maintaining analgesia in spite of larger dose.

REFERENCES

9. Vedrenne JB, Esteve M, Guillaume A: Preventing the adverse