Prophylactic Intravenous Ondansetron and Nalbuphine for Reduction of Subarachnoid Fentanyl-Induced Pruritus in Patients Undergoing Elective Cesarean Delivery

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Abstract

Background: Addition of fentanyl to spinal anaesthesia with bupivacaine improves the quality and success of anaesthesia. However, it has a frequent incidence of pruritus and a substantial incidence of nausea and vomiting. In this placebo controlled study, we compared the prophylactic efficacy of ondansetron and nalbuphine for the prevention of intrathecal fentanyl-induced pruritus after cesarean delivery.

Methods: Ninety elective parturients were assigned to one of the groups: Group O [Ondansetron 8mg IV n=30], Group N [Nalbuphine 4mg IV n=30] and Group S [Saline 0.9% IV n=30] as placebo. The study drugs were administered immediately after the umbilical cord was clamped. The occurrence of pruritus, nausea, pain and adverse reactions from ondansetron and nalbuphine was evaluated by pruritus score, 4-point rating score and visual analog scale respectively, at 15 minutes in the first hour after the injection of the study drugs. Afterward, evaluations were performed at 1, 2, 3 and 4 hours after the administration of study drugs.

Results: The overall incidence of pruritus, it was significantly more frequent in Group S (62%) compared with both Group O (43%) and Group N (42.5%). The incidence of pruritus during the different study intervals showed significant increase in Group S compared with the other groups mainly at 45min and 1 hour. The pruritus score was significantly different between Group O and Group S and between Group N and Group S (p<0.05) respectively, it was mostly mild in Group O and Group N and mostly moderate in Group S. Treatment for pruritus was requested by patients in 10%, 11% and 29% of patients in the Group O, Group N and Group S, respectively. There was no significant difference in the overall incidence and the severity of pruritus in the Group O and Group N and Group S respectively. No significant adverse reactions related to the study drugs reported during the different study intervals.

Conclusion: Although IV ondansetron and nalbuphine significantly decreased the incidence of fentanyl-induced pruritus more than placebo after cesarean delivery, further studies are recommended to show the other possible mechanisms, might be involved in the pathogenesis of fentanyl-induced pruritus.

Key Words: Prophylactic intravenous ondansetron – Nalbuphine – Addition of fentanyl – Induced pruritus – Elective cesarean delivery.

Introduction

PRURITUS or itch is a subjective, unpleasant and irritating sensation arising from the superficial layers of the skin that provoke an urge to scratch. It occurs frequently following opioid use, particularly after neuraxial administration. Stimulation of micro-opioid, serotonin [5-hydroxytryptamine 3] and dopamine 2 receptors mainly in the dorsal horn and medulla, prostaglandins and spinal inhibitory pathways may be involved in the genesis of pruritus [1-4].

The addition of small dose of intrathecal fentanyl [10-25 µg] to local anaesthetics during spinal anaesthesia enhances and increases the duration of sensory analgesia without intensifying the motor block or prolonging recovery [5-7]. This small dose of intrathecal fentanyl allows the use of less local anaesthetics, however, pruritus is reported in 60%-100% of patients [5,8].

Several pharmacological agents have been used both for the treatment of established pruritus and in its prevention. These agents include mixed opioid receptor agonists/antagonists, 5-hydroxytryptamine 3 [5-HT3] receptors antagonists, propofol, nonsteroidal anti-inflammatory drugs and dopamine 2 receptors antagonists [2].

Ondansetron, a 5-HT type 3 receptor antagonists is administered prophylactically in an attempt to reduce the frequency of subarachnoid morphine-induced pruritus in patients undergoing cesarean
delivery under spinal anesthesia [3]. It is often used for nausea and vomiting in patients undergoing chemotherapy or general anesthesia [9]. The role of 5-HT3 antagonists in the prevention of pruritus has not been clearly established [10].

Nalbuphine is a µ-receptor mixed agonist / antagonist, is effective in treating pruritus after intrathecal or epidural morphine and it accomplishes this with no increase in postoperative pain or other side effects. Although some reports suggest that nalbuphine has a similar beneficial effect on the associated nausea, other reports indicate only a modest benefit at best [11]. This study compares prophylactic intravenous [IV] administration of ondansetron with prophylactic IV administration of nalbuphine for parturients having spinal anesthesia for elective cesarean delivery.

Patients and Methods

After obtaining approval from the Local Ethics Committee and written informed consent, 90 elective parturients ASA I-II were enrolled in placebo-controlled study between May 2008 and January 2009. Exclusion criteria included preeclampsia, eclampsia, major systemic disease, current nausea or known allergy to any of the medications used in the study. Parturients were assigned to one of the groups: Group O [Ondansetron 8mg IV n=30], Group N [Nalbuphine 4mg IV n=30] and Group S [Saline 0.9% IV n=30] as a placebo. Their monitoring included electrocardiogram, pulse oximetry and non invasive arterial blood pressure. After rehydration with one liter of lactated ringer solution, the parturients received a subarachnoid injection of 10mg of preservative-free bupivacaine 0.5% and 25 µg of preservative-free fentanyl, both to increase the quality of anaesthesia and to provide postoperative analgesia. The spinal anaesthesia was performed with the patients in the sitting position at the L2-3 or L 3-4 interspace with a 25-gauge pencil point needle. They have been positioned supinely with a billow under their heads and the operating table was tilted at least 20° to the left, a urinary catheter was inserted. Oxygen 4ml/min was administered through a nasal catheter until delivery. Intravenous boluses of 5-10mg ephedrine and additional IV fluids were administered to treat hypotension, which was defined as decrease in systolic pressure more than 20% from the base value. The study drugs were diluted up to 5ml in volume, then were administered immediately after the umbilical cord was clamped. The occurrence of pruritus, nausea, pain and adverse reactions from ondansetron and nalbuphine including headache, cardiac dysrhythmia, extrapyramidal signs [twitching, dystonia, akathisia or rigor], respiratory depression, sedation and urinary retention was evaluated at 15 minutes in the first hour after the injection of the study drugs. Afterward, evaluations were performed at 1, 2, 3 and 4 hours after the administration of study drugs. The location and incidence were evaluated. The degree of pruritus was classified as 1=no pruritus, 2=mild pruritus, 3=moderate pruritus, 4=severe pruritus. Nausea severity was graded according to a 4- point rating score with 1=no nausea or vomiting, 2=queasy, 3=severe nausea, 4=vomiting and also its incidence was evaluated. Pain was assessed using visual analog scale with 0=no pain and 10=worst pain imaginable. At patients request, pruritus was treated with diphenhydramine 12.5mg IV, nausea and/or vomiting were treated with metoclopramide 10mg and pain was managed by diclofenac suppository and/or paracetamol 1 g IV. The presence of cardiac dysrhythmia was evaluated with patient complaint of palpitation. Twelve-lead electrocardiograms were performed for verification.

Statistical analysis:

Continuous data are reported as means ± standard deviation and were analyzed using ANOVA. Categorical data are reported as numbers and percentages and were analyzed using X² or Fisher’s exact test as appropriate. Nonparametric data such as scores are reported as medians and ranges and were analyzed using Mann-Whitney U test. A p value <0.05 was considered significant.

Results

Demographic and operative data were comparable between the three study groups (Table 1). The sites of pruritus were mainly at the face, neck and trunk. Regarding the overall incidence of pruritus, it was significantly more frequent in Group S [Saline] (62%) compared with both Group O [Ondansetron 8mg] (43%) and Group N [Nalbuphine 4mg] (42.5%) (p<0.05), but there was no significant difference between both Group O and Group N (p>0.05) (Table 2). The incidence of pruritus during the different study intervals showed significant increase in Group S compared with the other groups mainly at 45min and 1 hour (p<0.05) (Fig. 1). The pruritus score was significantly different between Group O and Group S and between Group N and Group S (p<0.05) respectively, it ranged between 1-2 in Group O and Group N, and between 3-4 in Group S. (Table 2, Fig. 2). Treatment for pruritus was requested by patients in, 10%, 11% and 29% of patients in the Group O, Group N and Group S, respectively (p<0.05) (Table 2). Time to pruritus was similar in the different study
groups (Group O 52±32min, Group N 53±31min and Group S 55±33min). There was no significant difference in the overall incidence and the severity of nausea and/or vomiting at different time study intervals (p>0.05). However, the number of patients requesting treatment for nausea and/or vomiting was significantly less in Group O and Group N when compared with Group S (p<0.05) (Table 3). As regard the visual analog scale, there was no significant difference in pain score between the different study groups (p>0.05) (Table 3). No significant adverse reactions related to the study drugs reported during the different study intervals.

Table (1): Demographic and operative data at study three groups.

<table>
<thead>
<tr>
<th></th>
<th>Group O</th>
<th>Group N</th>
<th>Group S</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=30)</td>
<td>(n=30)</td>
<td>(n=30)</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>32.5±4.6</td>
<td>30.7±6.7</td>
<td>32.6±4.5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161±5.1</td>
<td>162.4±7.1</td>
<td>160.1±14.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.7±9.5</td>
<td>79.4±10.8</td>
<td>67.7±8.8</td>
</tr>
<tr>
<td>Gestational age (week)</td>
<td>37.7±1.1</td>
<td>37.8±1.6</td>
<td>37.6±1.7</td>
</tr>
<tr>
<td>Surgery duration (min)</td>
<td>62.3±15.6</td>
<td>59.7±9.5</td>
<td>61.4±12.7</td>
</tr>
</tbody>
</table>

Data are represented as mean ± SD. No statistical significance was found among the three groups (p>0.05). Group O = Ondansetron group. Group N = Nalbuphine group. Group S = Saline group.

Table (2): Evaluation of pruritus at study three groups.

<table>
<thead>
<tr>
<th></th>
<th>Group O (n=30)</th>
<th>Group N (n=30)</th>
<th>Group S (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of pruritus</td>
<td>43% (13)#</td>
<td>42.5% (12)*</td>
<td>62% (19)</td>
</tr>
<tr>
<td>Pruritus score (1/2/3/4)</td>
<td>17/10/2/1</td>
<td>18/9/2/1*</td>
<td>11/3/9/7</td>
</tr>
<tr>
<td>Requested treatment for pruritus (%)</td>
<td>10 (3/30)#</td>
<td>11 (3/30)*</td>
<td>29 (9/30)</td>
</tr>
</tbody>
</table>

Pruritus score: 1 = None, 2 = Mild, 3 = Moderate, 4 = Severe.

#p<0.05 between Group O and Group S.

*p<0.05 between Group N and Group S.

Table (3): Evaluation of nausea and/or vomiting and pain scores at study three groups.

<table>
<thead>
<tr>
<th></th>
<th>Group O (n=30)</th>
<th>Group N (n=30)</th>
<th>Group S (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of nausea and/or vomiting</td>
<td>23.3% (7)</td>
<td>26.6% (8)</td>
<td>23.3% (7)</td>
</tr>
<tr>
<td>Nausea score (1/2/3/4)</td>
<td>23/3/3/1</td>
<td>22/3/4/1</td>
<td>23/0/0/7</td>
</tr>
<tr>
<td>Requested treatment for nausea (%)</td>
<td>3.3 (1/30)#</td>
<td>3.3 (1/30)*</td>
<td>23.3 (7/30)</td>
</tr>
<tr>
<td>Pain score (visual analog scale)</td>
<td>4.3±2.76</td>
<td>3.35±2.7</td>
<td>4.4±2.8</td>
</tr>
</tbody>
</table>

Nausea score: 1 = No nausea or vomiting, 2 = Queasy, 3 = Severe nausea, 4 = Vomiting. As regard the requested treatment for nausea.

#p<0.05 between Group O and Group S.

*p<0.05 between Group N and Group S.

Discussion

In the obstetric population, pruritus is very common after neuraxial opioids, possibly related to the interaction of estrogen with opioid receptors in the spinal cord and the increased cephalad spread of spinally administered drugs [12]. The present study showed that the overall incidence of pruritus was 48.9% in all parturients after intrathecal fentanyl administration (25 µg) combined with 10mg bupivacaine in spinal anaesthesia for cesarean delivery. A study about the intrathecal fentanyl on analgesia, pruritus and ventilation during labor found that there was a dose-response relationship between the dose of fentanyl and the incidence of pruritus. The overall incidence of pruritus was 65.6% in patients receiving intrathecal fentanyl 5, 7.5, 10, 15, 20 and 25 µg combined with 10mg bupivacaine in spinal anaesthesia for cesarean delivery. The precise mechanism of pruritus after intrathecal opioid is not completely clear. Borgeat and Stirnemann [14] reported that ondansetron was effective for the treatment of spinal or epidural morphine-induced pruritus. Serotonin type 3 receptors are abundant...
in the dorsal horn area of the spinal cord and in the spinal tract of the trigeminal nerve in the medulla [15,16]. Fan [17] reported that the morphine can activate serotonin type 3 receptors by a mechanism independent of opioid receptors. These observations suggest that the serotonin type 3 receptor is to certain degree implicated in the development of the pruritus associated with the application of neuroaxial opioids. Although ondansetron and nalbuphine in the present study significantly decreases the incidence of fentanyl-induced pruritus more than placebo, this complication still occurs in 43% and 42.5% of both group’s patients respectively. However, this study showed that there is no significant difference among groups in four rating score for nausea and vomiting. My results were coincided with Yavuz et al. [18] who demonstrated that ondansetron prophylaxis significantly reduced the incidence of intrathecal-fentanyl induced pruritus up to 39% in patients undergoing surgery under bupivacaine spinal anaesthesia. Also it was comparable with Charuluxanananan et al. [19] results which revealed that nalbuphine (4mg) and ondansetron (4mg and 8mg) are more effective than placebo for the prevention of intrathecal morphine-induced pruritus after cesarean delivery, but there are no differences among groups in nausea /vomiting score. Also some authors [10,20] reported that prophylactic use of ondansetron help to reduce incidence and severity of intrathecal opioid-induced pruritus, nausea and vomiting after cesarean delivery. These results were agreed with mine regarding to pruritus, but not to nausea and vomiting. In contrast with the present study, Wells et al. [21] demonstrated that prophylactic ondansetron 4mg or 8mg intravenously was ineffective in reducing the incidence or severity of intrathecal fentanyl-induced pruritus during labour. Some author’s results [3,22] were not with mine, which revealed that the prophylactic administration of 8mg ondansetron did not reduce the incidence of pruritus. However, it resulted in a significant decrease in the number of patients requesting rescue antiemetics, which was in agree with the present study.

In conclusion, although IV ondansetron and nalbuphine significantly decreased the incidence of fentanyl-induced pruritus more than placebo, it still occurred in 43% and 42.5% of patients respectively. So further studies are recommended to show the other possible mechanisms, might be involved in the pathogenesis of fentanyl-induced pruritus.

References


14- BORGEAT A. and STRINEMANN H.R.: Ondansetron is effective to treat spinal or epidural morphine induced pruritus. Anesthesiology, 90: 432-6, 1999.


