Prophylactic Intravenous Ondansetron for Intrathecal Morphine Induced Pruritus

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ABSTRACT

INTRODUCTION: Intrathecal morphine has an important role in increasing the duration of analgesia without prolongation of motor recovery. However, it is not free of side effects like pruritus, nausea, vomiting, respiratory depression and urinary retention. Among all these, pruritus is an important side effect as it is very much distressing to the patient. Hence, this is an important concern to anesthesiologist. Studies had been done on different drugs like Ondansetron, Propofol, Gabapentin, Pentazocine for solution of this problem. This is a prospective, randomized single blinded study to find out whether prophylactic administration of intravenous ondansetron is effective or not in reducing intrathecal morphine induced pruritus.

METHODS: Fifty patients were randomized into two groups. One group (n=25) received intravenous 8mg(4ml) ondansetron and the other group(n=25) received 4ml normal saline before administration of spinal anesthesia with 12.5mg Bupivacaine and 250µg morphine. Both the groups were assessed for pruritus in different time interval after anesthesia at 15min, 30 min, 1hr, 2hr, 4hr, 6hr and 24 hrs. The severity and sites of pruritus were also observed. The severity of pruritus was graded into four as no pruritus, mild pruritus, moderate pruritus requiring treatment and severe pruritus.

RESULTS: The episodes of pruritus was more than two times in placebo group compared to ondansetron group (20% versus 8.6%). One patient (4%) from each group required treatment for pruritus. Inj Pheneramine maleate was sufficient for the rescue treatment.

CONCLUSION: Prophylactic intravenous ondansetron helps to reduce the episodes of intrathecal morphine induced pruritus.

KEY WORDS: Intrathecal morphine, ondansetron, pruritus

INTRODUCTION

Spinal anesthesia is a type of neuroaxial block which can provide intraoperative and postoperative analgesia. It can avoid the complications of general anesthesia. Adding adjuncts with intrathecal local anesthetic helps to prolong the duration of analgesia and reduce the dose of local anesthetics without prolongation of motor recovery. Different adjuncts like ketamine, clonidine, midazolam and opioids can be used. Among all, opioids have been recognized as among the most effective treatment for pain management. Adding an opioid like morphine, fentanyl or sufentanil along with the local anaesthetic can enhance the analgesic effect of local anaesthetic, prolong the duration of action and speed the onset of action. Thus, they have important role in increasing and enhancing the duration of analgesia intraoperatively and post operatively.1 However they have side effects like pruritus, nausea, vomiting, urinary retention, respiratory depression and sedation. Among all, pruritus is an important side effect of intrathecal opioid, which is very distressing to the patient.2,3

Pruritus4 is a subjective feeling as an unpleasant and irritating sensation on the skin. Scratching (itching)
is the response (or action). The incidence of pruritus after intrathecal opioid varies from 30% to 100%. It is an important concern to anesthesiologists because pruritus is very unpleasant and distressing to patient leading to patient discomfort and dissatisfaction. The exact mechanism of neuroaxial opioid induced pruritus is very complex.

Both systemic and neuroaxial opioids can cause pruritus by their action on centrally located receptors. Those receptors are present in both superficial and deep dorsal horn neurons which may be involved in signaling the sensation of itch. The central mechanism of intrathecal and epidural opioid-induced pruritus may be related to cephalic spread of the drug in the cerebrospinal fluid and its action on the medullary dorsal horn and a trigeminal nucleus in the medulla. Neuroaxial opioid induced itching may be related to opioids acting as antagonists to inhibitory central neurotransmitters (gamma amino butyric acid and glycine). Neuroaxial opioids can also cause itching by acting on 5HT3 (5Hydroxytryptamine3) receptors present in the dorsal horn of spinal cord and the trigeminal nucleus of the medulla. Because of this 5HT3 antagonists have been tried in some studies for prevention of neuroaxial opioid induced pruritus.

Based on the studies regarding the mechanism of neuroaxial morphine induced pruritus, different studies have been done using different drugs for prevention and treatment of intrathecal morphine induced pruritus. The drugs used in different studies are 5HT3 receptor antagonists like ondansetron, dolansetron, opioid antagonist like naloxone, opioid agonist antagonist like nalbuphine, intravenous anaesthetic agent like propofol, Gabapentin and steroids like dexamethasone.

In studies with ondansetron, prophylactic single dose was sufficient to reduce the intrathecal morphine induced pruritus with additional antiemetic property. Besides, it has no sedative effect as of propofol, does not reverse analgesia like naloxone and is better tolerated by patients. Hence, this study was conducted with the hypothesis that prophylactic administration of intravenous ondansetron reduces intrathecal morphine induced pruritus.

METHODS

After obtaining approval from institutional review board for research, this single blinded randomized prospective study was carried out in total 50 patients undergoing elective surgeries under spinal anesthesia after obtaining their consent. The study was conducted in 3-months duration in Bir Hospital. A power analysis showed that 23.55 patients per group would provide 80% power to detect 50% decrease in incidence of pruritus from 80% in placebo group to 40% in Ondansetron group within confidence limit of 95%. We included 25 patients in each group.

Patients aged between 16 to 75 years, both male and female, ASA physical status I and II, weight between 40 to 80 kg, scheduled for elective Urological, Orthopedics, General surgery, vascular surgery and other surgeries below umbilicus were included in the study. The exclusion criteria were patient’s refusal, contraindication to spinal anesthesia, known allergy to anyone of the drugs used in the study, history of any disease associated with pruritus, patients on antihistaminics and abnormal liver function test.

All the patients undergoing elective surgery were admitted at least one day before surgery. Preanesthetic checkup was done. Counselling regarding the anesthetic procedure and the study were done in patients under inclusion criteria. Patients were also taught to notice the time and site whenever they had pruritus. None of the patients was premedicated. Patients were kept nil per orally. 50 patients were randomly divided into two groups using sealed envelopes, which contained codes P for placebo and O for Ondansetron group. Any one envelope was randomly selected by anesthesia nurse for the study. The placebo group (P) received 4ml of normal saline and the study group (O) received 8mg (4ml) Ondansetron (Ondem 2mg/ml) intravenously just before spinal anesthesia.

Intravenous line was opened with wide bore cannula in the operation theatre. Patients were prehydrated with Ringer’s Lactate or Normal saline 20ml/kg before spinal anesthesia. The monitors used were: ECG, noninvasive blood pressure and pulse oximeter. Base line blood pressure, heart rate and Oxygen Saturation were noted. Spinal anesthesia was given in sitting or lateral position under all aseptic precautions. 2.5ml of 0.5% hyperbaric bupivacaine (Sensorcaine heavy) was injected along with preservative free morphine 250µg in L3-4 or L4-5 lumbar space with 25 gauge spinal Quincke needle. Morphine (15mg/ml) was diluted in
9ml of NS so that each ml contained 1.5mg(1500µg). This 1ml was again diluted in 2ml of NS so that each ml of total volume 3ml contained 500µg. So 0.5ml of this solution contained 250µg of morphine. This 0.5ml was added to the bupivacaine which was to be injected intrathecally. Thus the total volume to be injected became 3ml. A resident anesthetist helped to prepare this drug. Hypotension was defined as 20% decrease in base line blood pressure and bradycardia was defined as heart rate <60bpm. Hypotension was treated with intravenous fluid bolus and mephentermine 6mg IV. Bradycardia was treated with atropine 0.6mg IV. Each patients were assessed for pruritus after anesthesia at the interval of 15min, 30min, 1hr, 2hr, 4hr, 6hr and 24 hr. So the patients were assessed inside the operation theatre and in post anesthetic care unit. Since each patient was assessed for 7 times, the total number of assessment would be 175 in each group. They were assessed for the severity and site of pruritus. The patients were directly interviewed for the assessments.

The severity of pruritus was classified as 17

1=no pruritus
2=mild pruritus
3=moderate pruritus requiring treatment
4=severe pruritus

The side effects of ondansetron like arrythmias, dizziness, extra pyramidal effects, hallucination if present were also observed. Cardiac arrhythmias were to be evaluated with cardiac auscultation after any patient complaining of palpitation and verified by 12 leads ECG.

The first rescue treatment for pruritus was Inj Pheneramine maleate i.e, Inj Avil 2ml (22.75mg/ml) IV. If the pruritus still persist, then Inj naloxone 0.1µg/kg IV was scheduled.

Data were analyzed with the help of SPSS software 11.5 version. Chi square test was applied for the categorical data and student’s t test applied for the quantitative data.

RESULTS

Table 1. Demographic variables

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ondansetron</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(Year)</td>
<td>45.8±15.036</td>
<td>39.8±15.77</td>
<td>0.17</td>
</tr>
<tr>
<td>Male</td>
<td>20(80%)</td>
<td>19(76%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Female</td>
<td>5(20%)</td>
<td>6(24%)</td>
<td></td>
</tr>
<tr>
<td>Weight(Kg)</td>
<td>56.16±5.4</td>
<td>55.8±9.2</td>
<td>0.69</td>
</tr>
<tr>
<td>ASA I</td>
<td>20(80%)</td>
<td>23(92%)</td>
<td>0.41</td>
</tr>
<tr>
<td>ASA II</td>
<td>5(20%)</td>
<td>2(8%)</td>
<td></td>
</tr>
</tbody>
</table>

n=25, values are in mean±SD and percentage.

The demographic variables in the both groups were comparable as shown in Table 1

Table 2. Overall episodes of pruritus

<table>
<thead>
<tr>
<th>Groups</th>
<th>Episodes of pruritus</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>35/175(20%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>15/175(8.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 shows the overall episodes of pruritus. Since each patient was observed seven times, the total number of observation would be 175 in each group. As shown in table 2 the episodes of pruritus was more than two times in placebo compared to ondansetron but not significant statistically (p>0.05).

Table 3. Severity and Incidence of pruritus at different time intervals

<table>
<thead>
<tr>
<th>Time</th>
<th>Mild pruritus</th>
<th>Moderate pruritus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Ondansetron</td>
<td>Placebo</td>
</tr>
<tr>
<td>15min</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30min</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1hr</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>2hr</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>4hr</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>6hr</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>24hr</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

n=25

When the patients were observed at different time intervals, number of the patients having pruritus were more in placebo group as shown in Table 3. But statistically significant result was in 4 hr time only where 12 patients had pruritus in placebo and 4 had pruritus in ondansetron. One patient in each group had pruritus requiring the rescue drug. In both the groups, the first line rescue treatment was sufficient.
Table 4: Sites of Pruritus

<table>
<thead>
<tr>
<th>Sites</th>
<th>Placebo</th>
<th>Ondansetron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>12(48%)</td>
<td>2(8%)</td>
</tr>
<tr>
<td>Nose</td>
<td>9(36%)</td>
<td>3(12%)</td>
</tr>
<tr>
<td>Thorax</td>
<td>2(8%)</td>
<td>2(8%)</td>
</tr>
<tr>
<td>Trunk</td>
<td>5(20%)</td>
<td>7(28%)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>5(20%)</td>
<td>7(28%)</td>
</tr>
</tbody>
</table>

Table 4 shows that the site of pruritus was more in face in placebo group (48%) compared to 8% in ondansetron group. The other sites were nose, thorax, trunk and abdomen. Same patient may have pruritus at different sites which made the disparity in number of patients between two groups.

The side effects of ondansetron were not observed in this study.

**DISCUSSION**

5HT3 receptors are abundant in dorsal horn of spinal cord and in medulla. The interaction of intrathecally administered opioid with 5HT3 receptor is one of the mechanisms for intrathecal morphine induced pruritus. As ondansetron, a 5HT3 receptor antagonist, has no sedative effect, does not reverse analgesia and is easy to administer, it has been used in different studies for prophylaxis of intrathecal morphine induced pruritus.

In our study, the episodes of pruritus were more in placebo group (20% versus 8.6%) compared to ondansetron group but not statistically not significant (p=0.26). George R B et al also found that there was no significant difference in the incidence of pruritus when ondansetron was used for prophylaxis of intrathecal morphine induced pruritus for patients undergoing cesarean delivery. The incidence of pruritus in ondansetron and placebo group were 89.6% and 81.2% respectively.

Yeh H M et al found that the incidence of pruritus was significantly lower in ondansetron group (25%) than placebo group (85%) (p<0.05). Pirat A et al also found significant difference in incidence of pruritus between placebo (86%) group and ondansetron i.v. group (66%) (p=0.017) and ODT group (56% p=0.001). They concluded that both the regimens were associated with less incidence of intrathecal morphine induced pruritus. Chritos A. et al found that prophylactic use of ondansetron helped to reduce the incidence and severity of intrathecal morphine induced pruritus in patients undergoing elective urologic, vascular or orthopedic surgery under spinal anaesthesia. They found that incidence of pruritus was significantly lesser in ondansetron group (12 out of 35;34%) (p<0.01) compared with placebo group (23 out of 35;66%). In comparison to these studies, the episodes of pruritus were lesser in this study. This difference could be because of difference in study population and different age group. The study by Yeh H M et al was conducted in obstetric patients but our study was conducted in nonobstetric patients. In the other study, larger sample size was taken and the dose of ondansetron was only 4mg which is lesser than this study (8mg). Ondansetron has dose related efficacy also.

The incidence of intrathecal opioid induced pruritus is more common in obstetric patients. This is due to the interaction of estrogen with opioid receptor. The increased cephalic spread of spinaly administered drugs in pregnant women at term as compared with general population may also play a role. So most of the previous studies were done in obstetric patients undergoing cesarean section under spinal anesthesia.

Regarding the severity of pruritus, Yeh H M et al found decrease in severity of pruritus in ondansetron group, compared to placebo group. 4 patients (sample size 20 in each group) in placebo group received treatment for pruritus compared to only 1 in ondansetron group. But in our study, one patient from both group received treatment for pruritus. This difference could be because obstetric population are more sensitive to morphine induced pruritus as discussed earlier.

In the other study orally disintegrating tablet (ODT) form of ondansetron was more successful than intravenous ondansetron compared to placebo group when patients were observed in PACU and at 2, 6 and 12 hours post operatively. 40% in placebo group received treatment for pruritus compared to 18% (p=0.013) in ODT group. 34% in intravenous ondansetron group received treatment for pruritus compared to placebo (p>0.05). Hence, ODT form of ondansetron had better result. In our study, clinically episodes of pruritus were reduced in ondansetron group when we compared the number of patient having pruritus at different time intervals. But the result was not statistically significant. One patient from each group required treatment.
for pruritus at different time intervals. This could be because of several reasons like different route of administration (oral versus intravenous), different preparation of ondansetron (ODT versus intravenous) and sample size (n = 50 versus 25).

Ondansetron has oral bioavailability of about 60% with therapeutic blood level appearing within 30-60 minutes after administration. When it is given intravenously, its peak effect occurs after 15 min of administration. The lipid solubility of morphine is lesser than other opioids like fentanyl and sufentanyl. So pruritus does not occur immediately after intrathecal morphine. The peak plasma concentration of orally administered ondansetron might be closer to the time of onset of pruritus resulting better action. But intravenous ondansetron peaked earlier than the time of onset of pruritus. This might be a reason for better result in ODT form of ondansetron in their study. In our study we used intravenous ondansetron.

Charuluxananan S et al also found significant reduction in the incidence of pruritus at 4 hour period in PACU. 48% in placebo group has pruritus compared to 16% in ondansetron group (p<0.03). 51% in ondansetron group and 72% in placebo group required treatment for pruritus. Inj propofol 20mg IV was sufficient for treatment. 3 patients in each group required further treatment with naloxone 0.1 to 0.2mg for pruritus. But in our study, only one patient (4%) in each group required treatment for the pruritus. Inj pheneramine maleate IV was given. None of the patient required naloxone. This disparity could be because our study was conducted in nonobstetric population.

Chritos A. et al they found that the severity of pruritus was lesser in 2hr, 4hr and 8hr post operatively in ondansetron group compared to placebo in their study. But in our study, in the same time intervals, the severity of pruritus was lesser in ondansetron group clinically only but statistically significant result was observed only in 4hr period (4/12;p=0.03). In their study, none of the patients in ondansetron group received treatment for pruritus but one in placebo group received treatment for pruritus. In our study, one patients from both groups received treatment for pruritus.

These differences could be because of the complex mechanism of action of intrathecal morphine induced pruritus. Interaction of 5HT3 receptor and intrathecal morphine is one of the postulated mechanisms. There are other mechanisms also for intrathecal morphine induced pruritus which could have contributed for pruritus in ondansetron group in our study. Hence there was not significant reduction in incidence and severity of pruritus in our study.

One of those mechanisms 4 is the interaction of opioid with mu (µ) opioid receptor in the dorsal horn of spinal cord and medulla. The other mechanism may be due to opioid acting as antagonist to inhibitory central neurotransmitters (Gamma amino butyric acid and glycine) 4. Hence a study was also done using gabapentin, an anticonvulsant and structural analogue of Gamma amino butyric acid for the prevention of intrathecal morphine induced pruritus after orthopedic surgery19.

Another mechanism 4 may be related to the substance P, which is an important central neurologic mediator that helps to modulate “itching” and pain despite being a peripheral histamine releaser. It is present in “C” fiber of the dorsal root ganglia, substantial gelatinous in spinal cord and brain (trigeminal nuclei, amygdaloid nuclei and preoptic nuclei). When intrathecal opioid was given, there was control over pain but “itching” mechanism might have activated. Because of these reasons, combined drug therapy, drugs acting via different mechanisms may be effective in preventing the incidence and severity of intrathecal morphine induced pruritus. Further studies have to be carried out for this in future.

In our study, both the groups of patients had pruritus in face, trunk, nose, abdomen thorax. This is also similar to other studies 13,14. This shows that intrathecal morphine induced pruritus occurs in the area supplied by trigeminal nerve. Since 5HT3 receptors are abundant in the dorsal horn of the spinal cord and the spinal tract of trigeminal nerve in medulla, this is also an evidence to support that the one of the mechanisms of intrathecal morphine induced pruritus can be interaction of opioids with 5HT3 receptors.

No adverse effects of 5HT3 receptor antagonists such as headache, cardiac arrhythmias or extrapyramidal signs were reported in other studies according to a quantitative systemic review by M P Bonnet et al. In our study also none of the patients had such side effects.
CONCLUSION
The mechanism of intrathecal morphine induced pruritus is complex and its incidence is more in obstetric population. However, it does occur even in nonobstetric population. Interaction with 5HT3 receptor is one of the mechanisms of the pruritus. This study conducted in nonobstetric population shows that episodes of pruritus in ondansetron group is more than two times lesser than placebo group. Hence, it could be concluded that prophylactic ondansetron also helps to reduce the occurrence of intrathecal morphine induced pruritus in nonobstetric population.

REFERENCES