

Comparison of Ondansetron with Gabapentin for prevention of intrathecal morphine induced pruritus

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ABSTRACT

Background:

Ondansetron has been used successfully for prophylaxis and treatment of intrathecal morphine induced pruritus. Gabapentin has anxiolytic, antiemetic, antipruritic effects and has also been shown to potentiate the analgesic effect of intrathecally or epidurally administered opioids.

Materials and method: We compared the effectiveness of oral gabapentin with intravenous ondansetron to prevent incidence of intrathecal morphine induced pruritus. In a prospective, double-blind study, sixty patients aged 18-65 years with ASA physical status I and II undergoing surgery under subarachnoid block were randomized to receive placebo tablets (ondansetron group) or gabapentin 1200 mg (gabapentin group) 2 hours before surgery. Patients receiving placebo tablets received 8 mg of intravenous ondansetron and those receiving gabapentin received 4 ml of intravenous normal saline just prior to subarachnoid block with 3 ml of 0.5% hyperbaric bupivacaine plus 0.2 mg morphine. The incidence, onset, severity, location of pruritus and incidence of side effects were studied for next 24 hours. **Results** The overall incidence of pruritus was 48.3%. The incidence, severity, location of pruritus was comparable between the two groups. There was significant difference between the onset of pruritus between groups ($p=0.009$). The incidence and grade of nausea vomiting, requirement of intraoperative sedation was comparable between groups. The incidence of urinary retention was significantly high in gabapentin group ($p=0.020$). Respiratory depression was observed in one patient. **Conclusion** A single dose of 1200 mg oral gabapentin 2 hours before, is as effective as prophylactic intravenous ondansetron 8 mg for prevention of intrathecal morphine induced pruritus.

Keywords

Gabapentin; Ondansetron; Intrathecal morphine; Pruritus

INTRODUCTION

In anesthetic practice, opioids have been used intrathecally and epidurally as a sole agent or in conjunction with local anesthetics to improve the quality and duration of analgesia. A single dose of intrathecal morphine provides excellent postoperative analgesia for up to 18–24 hours after administration.¹ Pruritus is one of the most common side effect of intrathecal morphine, with incidence being 30-100%.^{2,3} The incidence of intrathecal morphine induced pruritus is between 30% and 60% following major orthopedic surgery.^{2,3} Parturient are more susceptible with incidence between 60% and 100%.⁴⁻⁶ Ondansetron has been used for prophylaxis and treatment of intrathecal morphine induced pruritus.⁷⁻¹¹ Gabapentin has been shown to be effective in pruritus of different origin.¹²⁻¹⁶ Prophylactic gabapentin has also been seen to decrease postoperative pain and nausea vomiting due to various cause.¹⁷⁻²⁰ We compared the effectiveness of oral gabapentin with intravenous ondansetron for prevention of intrathecal morphine induced pruritus.

MATERIALS AND METHOD

This prospective randomized double blind, comparative study was performed during the period of four months at Tribhuvan University Teaching Hospital after ethical clearance from institutional review board.

Sixty patients with ASA physical status I and II, aged 18 to 65yrs undergoing surgery under subarachnoid block were included after informed written consent. Patients with known hypersensitivity or contraindication to study drugs, complain of pruritus before surgery, morbid obesity, seizure disorder, mental illness, headache, neuropathic pain, liver disease, use of antipsychotic, anticonvulsants and antidepressants were excluded from the study.

All patients were evaluated preoperatively and were premedicated with diazepam 0.2 mg/kg the night before and fasted for at least six hours. The patients were counselled about the possible occurrence of pruritus, dizziness, sedation, nausea, vomiting and to communicate with nursing staffs and doctor. They were randomly assigned to one of the two study group using sealed envelope technique. Each group had sample size of thirty. Group G received gabapentin tablets 1200 mg

two hours before surgery plus 4 ml intravenous normal saline just prior to subarachnoid block. Group O received placebo tablets two hours before surgery plus 4 ml (8 mg) intravenous ondansetron just prior to subarachnoid block.

In the preparation room baseline systolic, diastolic, mean arterial pressure, pulse rate, respiratory rate and peripheral oxygen saturation were measured. Intravenous access was made with 18G IV cannula and all patients were preloaded with Ringers lactate 5 to 10 ml/kg body weight.

Standard monitor was applied to the patient and after giving the assigned study drug, subarachnoid block was performed in sitting position, midline approach with 25G Quincke needle in L3-L4 intervertebral space. 15 mg (3 ml) of 0.5% hyperbaric bupivacaine plus 0.2 mg (0.2 ml) of preservative free morphine was injected with total volume 3.2 ml. Patients were kept supine immediately and blood pressure, heart rate, peripheral oxygen saturation was recorded continuously. Sensory level and the grade of motor blockade was noted at the beginning of surgery. Injection midazolam 0.04 mg/kg was given intravenously as required.

Pruritus was defined as the sensation that provoked desire to scratch. Pruritus was evaluated by inquiring at 3,6,9,12,24 hrs or noted whenever the patient complained so after the administration of intrathecal morphine. Patients were questioned about the presence, onset, location and degree of pruritus. Patients requiring rescue treatment were recorded.

Degree of severity of pruritus was classified as

Grade 1: no pruritus

Grade 2: pruritus with mild itching (treatment not necessary)

Grade 3: pruritus with moderate itching (treatment desirable)

Grade 4: severe pruritus with itching and scratching (treatment necessary)

Treatment of pruritus

Intravenous Pheniramine maleate 45.5 mg slowly was used as first line and intravenous naloxone 40 mcg repeated every 3 mins as required was used as second line treatment.

Nausea and vomiting was assessed using the scale

Grade 1: none

Grade 2: nausea

Grade 3: nausea and vomiting

Patients with score 2 or 3 received 10 mg of intravenous metoclopramide. Naloxone 40 mcg repeated every 3 mins as required was reserved for those not improving with first line treatment.

Respiratory depression was defined as reduced respiratory rate less than 10 breaths per minute. Severity was graded as:

Grade 1: none

Grade 2: Mild: Sp_o₂ 90-94% in room air (no treatment, only observation)

Grade 3: Moderate: Sp_o₂ 85-89% in room air (treat with O₂ via facemask)

Grade 4: Severe: Sp_o₂ ≤ 85% in room air (O₂ via facemask and naloxone 40 mcg) if no improvement. Bag and mask ventilation, intubation and mechanical ventilation as required.

Any other side effects were noted and managed accordingly.

For postoperative pain: Intramuscular diclofenac sodium was given as rescue analgesic.

Data were entered in Microsoft excel and analyzed using (SPSS) software, version 12.0. Demographic data were compared by using chi-square test, unpaired t-test.

Categorical data were presented as frequency. Incidence of pruritus between two groups were compared with chi-square test. Location of pruritus between two groups was compared with Fisher’s exact test. P value <0.05 was considered to be statistically significant.

RESULTS

Demographic parameters, baseline hemodynamic parameters and duration of surgery were comparable between two groups (Table 1).

Overall incidence of pruritus was 48.3%. The incidence of pruritus between the groups was comparable (p=0.301). The onset of pruritus was early in group O with significant difference between groups (p=0.009) (Table 2).

Table 1: Comparison of demographic parameters, baseline hemodynamic parameters and duration of surgery

Parameter	Group G (n=30)	Group O (n=30)	p value
Mean age(years)	37.3	39.53	0.571
Mean weight (kg)	59.23	59.27	0.988
Male	19	13	0.195
Female	11	17	
Mean SBP (mm Hg)	122.73	120.7	0.442
Mean DBP (mm Hg)	78.7	75.7	0.216
Mean SPO ₂ (%)	96.37	96.4	0.929
Duration of surgery (mins) ±SD	103.33±49.902	85.5±37.905	

Table 2: Incidence and onset of pruritus

Primary outcome		Group G (n=30)	Group O (n=30)	p value
Incidence of pruritus		17(56.7%)	12(40%)	0.301
Onset of pruritus	<6hrs	9(52.9%)	12(100%)	0.009
	>6hrs	8(47.1%)	0	

The severity and location of pruritus was comparable between the groups with p value >0.05(Figure1) (Figure2).

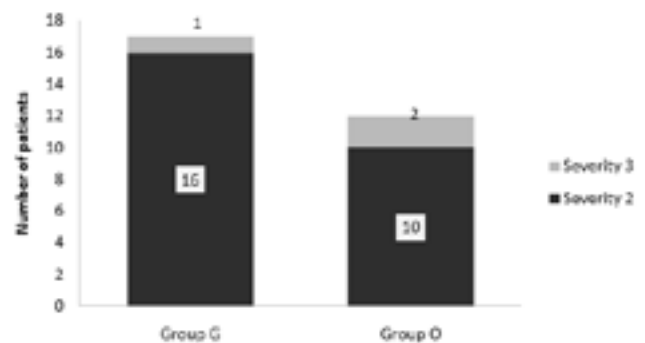


Figure:1 Severity of pruritus

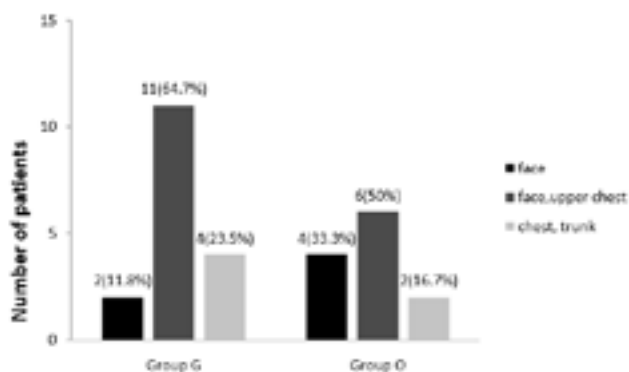


Figure:2 Location of pruritus

The overall incidence of nausea vomiting was 38.5% and incidence was comparable between groups (P=0.680). There was statistically significant difference in incidence of urinary retention between the group (P=0.020) with higher incidence in group O (Table 3).

Table 3: Incidence of side effects

Parameter	Group G (n=30)	Group O (n=30)	p value
Nausea vomiting	11(47.8%)	12(52.2%)	0.680
Urinary retention	21(70.0%)	28(93.3%)	0.020

Respiratory depression was observed in one patient which was moderate and required treatment in the form of oxygen supplementation via facemask.

DISCUSSION

Neuraxial injection of opioids provides effective analgesia in various types of surgery. Intrathecal opioids have significant role in surgical pain management and is utilized widely for different surgical procedures with multiple beneficial effects. It prolongs the duration of analgesia with less dose of neuraxial local anesthetics. It facilitates motor recovery and ambulation after surgery. However, spinal opioids are associated with a wide variety of side-effects such as nausea, vomiting, pruritus and respiratory depression.¹ The reported incidence of pruritus after neuraxial opioid administration varies from 30% to 100%.^{2,4,5} Pruritus is very unpleasant and distressing to the patient. Parturient appear to be more susceptible. The incidence of neuraxial opioid induced pruritus in parturient has been reported to be between 60% and 100% and appears to be dose dependent.^{4,5} The incidence of pruritus after intrathecal opioid following

major orthopedic surgery is between 30% and 60%.¹⁶ Efficacy of different drugs like propofol, ondansetron, dolasetron, gabapentin, pentazocine and naloxone has been studied for prevention and treatment of intrathecal opioids induced pruritus. As ondansetron does not have any sedative effect, does not reverse analgesia and is easy to administer, it has been used in different studies to prevent or treat intrathecal morphine induced pruritus.^{3,5-9} Gabapentin is an anticonvulsant, a structural analogue of gaba-aminobutyric acid. Several studies have shown gabapentin to be effective in the case of brachioradial pruritus¹², uremic pruritus^{13,14} and pruritus of unknown origin.¹⁵ Antipruritic effect of gabapentin in prevention of neuraxial opioid induced pruritus has not been studied much. In one study gabapentin has been shown to prevent pruritus induced by intrathecal morphine in patients undergoing lower limb surgery with spinal anesthesia.¹⁶ Studies comparing the efficacy of ondansetron with gabapentin for prevention of intrathecal morphine induced pruritus has not been conducted in the past. In our study, we hypothesized that preoperative use of oral gabapentin is as effective as prophylactic intravenous ondansetron to prevent intrathecal morphine induced pruritus. We used either 1200 mg gabapentin tablets 2 hours before or 8 mg intravenous ondansetron just prior to subarachnoid block. We assessed incidence, onset, severity and location of pruritus as well as any side effects between the groups. In our study, the overall incidence of pruritus was 48.3%. There was no significant difference in incidence, severity, location of pruritus between group G and O. Though, there was significant difference between onset of pruritus and incidence of urinary retention between groups. The demographic characteristics in both group were comparable. There was no significant difference in patient distribution in terms of age, weight, sex, baseline hemodynamic parameters and duration of surgery. Therefore, further analysis of findings in terms of incidence, onset, severity, location and the incidence of side effects can be compared between the study groups. There was no significant difference between overall incidence of pruritus between the groups. The incidence of pruritus in gabapentin group was 56.7% and ondansetron group was 40% respectively. In a study by Sheen et al¹⁶ the incidence of pruritus in gabapentin group was found to be 47.5% as compared to the placebo group

77.5%. Similarly, in study performed by Iatrou et al³ regarding use of prophylactic ondansetron for prevention of intrathecal opioid induced pruritus, the incidence of pruritus was 34% which is similar to our results. There was significant difference between the onset of pruritus between groups. The average onset time in intrathecal morphine induced pruritus in ondansetron group was 2-3 hours after intrathecal injection. Our data was comparable to study done by Yeh et al⁵ and Charuluxananan et al.⁶ All the patients in the ondansetron group had onset of pruritus within 6 hours but patients in the gabapentin group had onset as late as 9-12 hours. Similar delay in onset of pruritus by oral gabapentin was noticed in the study performed by Sheen et al,¹⁶ from 3.1 hours in the placebo group to 6.2 hours in the gabapentin group. This phenomenon can be explained as the delay of neuronal transmission during itch processing by gabapentin. The severity of pruritus was not statistically significant between the groups. Out of the 29 patients who developed pruritus, only two patients of the group ondansetron needed rescue treatment with pheniramine maleate. The severity of pruritus was also significantly reduced in gabapentin group compared to placebo group in study performed by Sheen et al.¹⁶ There were also significant difference in severity of pruritus between placebo group and ondansetron group in other studies comparing the efficacy of ondansetron on prevention and treatment of intrathecal morphine induced pruritus.^{3,9} In our study, though we did not have placebo group to compare, the severity of pruritus was comparable in both group which signifies that gabapentin is as effective as ondansetron in decreasing severity of pruritus. In our study, majority of patients in both the groups had pruritus in the face and upper chest region which is comparable. This finding is similar to that shown in other studies.^{3,6,10} Facial areas innervated by trigeminal nerve are predominantly affected. Such distribution is likely to be due to cephalad migration of opioids in CSF and subsequent interaction with trigeminal nucleus and nerve roots.²

The efficacy of 5HT₃ antagonists for the prophylaxis of PONV in patients receiving intrathecal morphine has been established by other studies as well as many systematic reviews.^{3,8,11} In a study done by Pandey et al,¹⁹ 250 patients undergoing elective laparoscopic cholecystectomy who received either a single dose of 600 mg gabapentin or

placebo two hour before the operation found that the patients receiving gabapentin had a significantly lower incidence of PONV. In our study incidence of nausea vomiting was comparable between the groups 36.7% in gabapentin group vs 40% in ondansetron group. However, our study was not designed to evaluate this phenomenon. A study oriented to PONV with appropriate size and exclusion criteria could more clearly define the impact of ondansetron versus gabapentin on PONV in patients with intrathecally administered morphine.

Our results showed significant difference in the incidence of urinary retention between gabapentin and ondansetron group (30% vs 6.7%) with p 0.02. This might be because of unequal surgical distribution of patients between the groups. 46% of patients in the ondansetron group underwent gynecological procedures whereas only fourteen percent of patients in gabapentin group. As all patients who underwent gynecological procedure were routinely catheterized postoperatively, difference in incidence of urinary retention in immediate postoperative period between the two groups were significant. However, similar patient group undergoing similar surgery is required to comment upon such difference. Our study had several limitations like absence of placebo group to compare the baseline difference, absence of monitoring system that records scratching and varied surgical population. Further studies comparing the effect of gabapentin with ondansetron or in combination for prevention of intrathecal morphine induced pruritus is recommended.

CONCLUSION

In conclusion, a single dose 1200 mg of oral gabapentin two hours before is as effective as prophylactic intravenous ondansetron 8 mg just prior to intrathecal morphine administration for prevention of intrathecal morphine induced pruritus.

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