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Preemptive Antiemesis using Intravenous Ondansetron to Control Intrathecal Morphine Induced Nausea and Vomiting

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Abstract

Background: Morphine is an opioid and its intrathecal use for postoperative pain relief is well documented. Nausea and vomiting are the common adverse effects with intrathecal morphine and might be distressing in patients undergoing abdominal surgeries limiting its usage. Ondansetron is helpful in treating of nausea and vomiting but would be of greater help when administered pre-emptively. *Aims and Objectives:* Primary aim of study was to study the effect of pre-emptive ondansetron in controlling intrathecal morphine induced nausea and vomiting. Secondary aims was to assess its effectiveness in controlling pruritus. *Methods and Materials:* In this prospective, randomized study ninety patients undergoing abdominal hysterectomy were categorized into 3 equal groups receiving 15mg hyperbaric Inj.bupivacaine, in addition 0.5ml saline in Group-I, and 100µg and 200µg of intrathecal morphine diluted to 0.5ml respectively in Group-II and Group-III. All patients received 4mg of Inj.ondansetron intravenously 10 minutes before administering spinal drug preparation. Patients were assessed for duration of analgesia, nausea, vomiting, pruritus and other adverse effects of intrathecal morphine. *Results:* There was statistical significant difference with respect to age, body mass index and duration of surgery between three groups. Intrathecal morphine resulted in significantly longer duration of analgesia in patients receiving intrathecal morphine ($p<0.001$). Pre-emptive ondansetron effectively controlled intrathecal morphine induced nausea ($p=0.809$) and vomiting ($p=0.199$) and it was statistically insignificant when compared to control group, but did not decrease incidence of pruritus ($p=0.027$). *Conclusion:* Pre-emptive intravenous Inj.ondansetron (4mg) effectively controls intrathecal morphine induced nausea and vomiting but not pruritus.

Keywords: Preemptive; Ondansetron; Intrathecal Morphine; Nausea; Vomiting; Pruritus.

Introduction

Postoperative pain is one of the unpleasant experience a patient would experience during hospital stay and many treatment modalities have been employed since decades and individual treatment option has its own advantages and disadvantages.

Intrathecal morphine is one of the efficient and effective treatment modality for postoperative pain, has the advantage of longer duration of analgesia but its common adverse effects e.g. nausea, vomiting, pruritus are undesirable, limiting its usage [1,2]. Antiemetics when used preemptively, reduce the incidence of postoperativenausea and vomiting (PONV) [3,5] andwhen used for patients receiving intrathecal morphine would havethe advantage of its longer action while reducing the incidence of PONV [3].

Few studies have been done using prophylactic antiemetic to control PONV in patients receiving intrathecal morphine, but they showed conflicting results [3-5]. This study was undertaken to assess preemptive antiemeticaction of ondansetron in decreasing incidence of PONV in patients receiving intrathecal morphine for abdominal hysterectomy.

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Methods

This was a prospective, randomized, controlled study with double blinding of the patientsand procedure undertaken. After institutional ethics committee approval, written and informed consent were obtained and 90 patients of ASA l and ll who were scheduled for elective abdominal hysterectomy were included in the study. Primary aim of the study was to assess the effectiveness of preemptive use of Inj.ondansetron 4 mg i.v. in decreasing the incidence of nausea and vomiting in patients receiving intrathecal morphine. Secondary aim of the study was to assess the effectiveness in decreasing the incidence of pruritus.

Patients with history of respiratory disease e.g. bronchial asthma, chronic obstructive pulmonary disease, history of gastro-esophageal reflux disease, sleep apneapsychiatric illness, body mass index of more than 25kg/m^2, patients on opioid medications, known allergy to morphine or any other opioid medication were all excluded from the study.

Patients were asked to be nil oral eight hours before surgery. None of the patients in either groups received preoperative sedative, so as to have accurate assessment of intrathecal morphine induced sedation and respiratory depression and also to have frequent communication with patients. All patients were counselled and reassured preoperatively about the intraoperative events so as not to be apprehensive as they did not receive preoperative sedation. All patients received Inj.pantoprazole 40mg i.v. 1 hour before surgical procedure.

Patients were randomly allocated by envelope method into following three groups.All patients received 3ml of 0.5% hyperbaric bupivacaine in 8% dextrose and inaddition 0.5ml of the following: Group-l 0.9% normal saline, Group-ll 100 µg of morphine and Group-lll200 µg of morphine diluted to 0.5ml. Total volume of drug was made to 3.5ml. An anesthesiologist not involved in the study prepared the drug preparation. A 18.G. i.v. cannula was secured in holding room and patients were preloaded using 10ml/kg of Ringer's lactate. All patients received 4mg of Inj.ondansetron intravenously 10 minutes before injection of the spinal drug preparation.

Intraoperative monitoring included 5-lead electrocardiography (ECG), noninvasive blood pressure (NIBP) and plethysmography SpO_2. Under strict aseptic precautions in left lateral position, drug preparation was injected intrathecally using 27.G. Quinke's needle. To ensure safety of patients with regard to respiratory depression, oxygen by face mask 5 liters/min was administered for the first 24 hours irrespective of their SpO_2 reading.

Patients were observed and monitored for pain relief, nausea, vomiting, pruritus, bradycardia, hypotension, sedation, respiratory depressionin the first 24 hours-both intraoperatively and postoperatively. Respiratory depression was defined as rate < 10/min, bradycardia as heart rate < 50/min, hypotension as reduction of mean arterial pressure 20% from the baseline.Hypotension was treated using i.v. fluids and Inj.ephedrine, bradycardia using Inj.atropine, respiratory depression according to the severity. I.V. fluids and blood transfusion were undertaken on individual patient basis. All patients were catheterized for bladder because of surgical necessity (abdominal hysterectomy) and hence they were not monitored for urinary retention.

Patients who vomited more than once or havingunbearable nausea even after preemptive Inj.ondansetron received Inj.metaclopramide 10mg i.v. Pain was assessed using Visual Analogue Score (VAS), and a score more than 3 was treated using Inj.tramadol 2mg/kg as a rescue analgesic and pruritus was treated using Inj.pheniramine10 mg i.v. Postoperative monitoring of patients included ECG, NIBP and SpO_2. In addition patients were assessed for pain relief by time of rescue analgesic administered for a VAS >3, nausea, vomiting, pruritus, sedation, bradycardia, hypotension. As patients were catheterized urinary retention was not assessed.

After administration of spinal anesthesia all patients were assessed for level of sensory blockade using acold swab and the highest level achieved varied from T_4-T_8 level. There was no sparing action or incidence of failed spinal anesthesia in either of the groups. All patients were preloaded and received i.v. fluids according to the blood loss and hypotension. Two patients in Group-II and one patient in Group-I developed bradycardia and were treated using 0.6 mg Inj.atropine intravenously. Surgery was completed with spinal anesthesia technique alone and none of the patients, intraoperatively received any adjuvant medications for pain. Duration of surgery did not vary significantly between the three groups. Patients were reassured for intraoperative anxiety.

Statistical analysis was done using SPSS 17.0.2. Descriptive and inferential statistical analysis has been used in our study. Results on continuous measurements are presented on Mean±SD

(Minimum-Maximum) and results on categorical measurements are presented in percentage numbers (%). 'p' value of less than 0.05 was considered to be significant. The following assumptions on data were made - dependent variables were normally distributed, random sampling from the population was ensured and the cases of the samples were independent.

Student t test (two tailed, independent) and Chi-square/ Fisher Exact test were used to assess the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters and categorical scale between two or more groups respectively. Leven1s test for homogeneity of variance has been performed to assess the homogeneity of variance and $p \leq 0.01$ was considered to be strongly significant.

Results and Observation

The three groups did not vary significantly with respect to age, body mass index and duration of surgery (Table 1). Spinal anesthesia was successful in all patients and there was no incidence of failed spinal anesthesia. The mean duration of analgesia in Group-I, Group-II and Group-III were respectively 3.4 hours, 16.15 hours and 24.9 hours (Table 2) and the difference was statistically significant when compared to control group ($p<0.001$). The duration of analgesia was dose dependent and it was higher in Group-III when compared to Group-II.

The three groups did not vary significantly with respect to incidence of nausea ($p=0.809$, Table 3) and vomiting ($p=0.199$, Table 3). The incidence of PONV

Table 1: Patient characteristics among the three groups. Data are mean (range) or Mean ± SD*

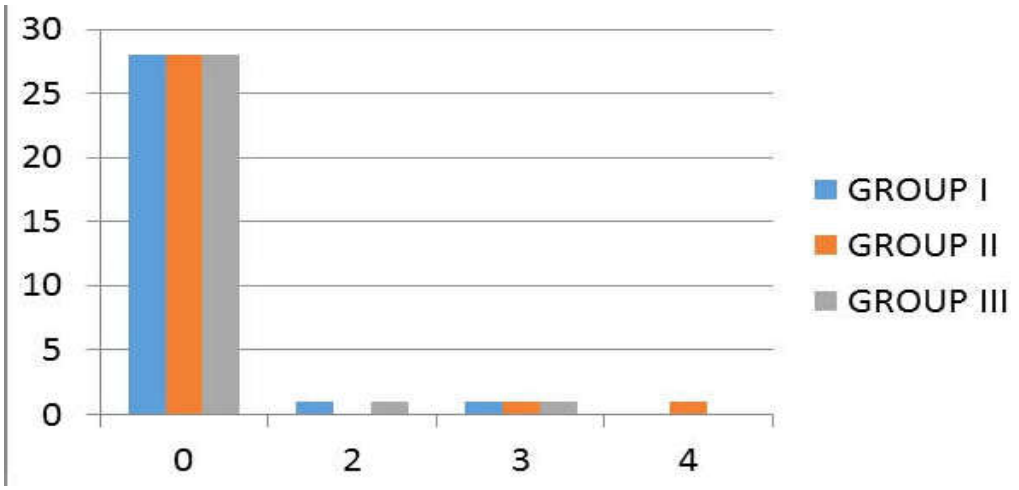
	Group I (n=30)	Group II (n=30)	Group III (n=30)	p-value
Age (years)	48.50 ± 2.17	49.40 ± 3.22	48.73 ± 2.18	0.377 (ns)
Body Mass Index (kg/m²)	21.72 ± 2.43	22.33 ± 1.89	22.26 ± 1.57	0.781 (ns)
Mean duration of surgery (in minutes)	97.50 ± 3.20	95.10 ± 3.03	94.86 ± 3.08	0.814 (ns)

Abbreviations: ð SD = standard deviation, $p<0.05$ significant, ns= statistically not significant

Table 2: Comparison of Duration of Analgesia (hours) among the three groups

	Sample number (n)	Duration of Analgesia (hours)	p-value
Group I	30	3.43 ± 0.40	
Group II	30	16.15 ± 2.26	<0.001 (hs)
Group III	30	24.90 ± 2.26	

$p<0.05$ is significant, Abbreviations: hs= highly significant



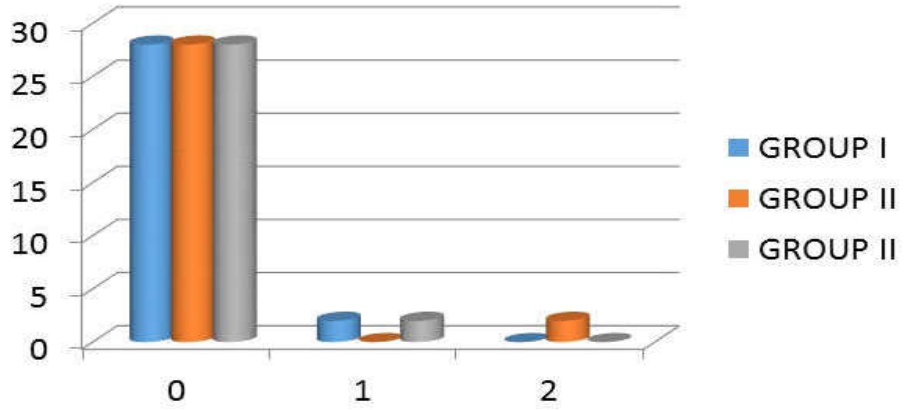
x-axis= number of episodes, y-axis= number of patients

Fig. 1: Comparison of incidence of Nausea among the three groups

Table 3: Comparison of adverse effects among the three groups

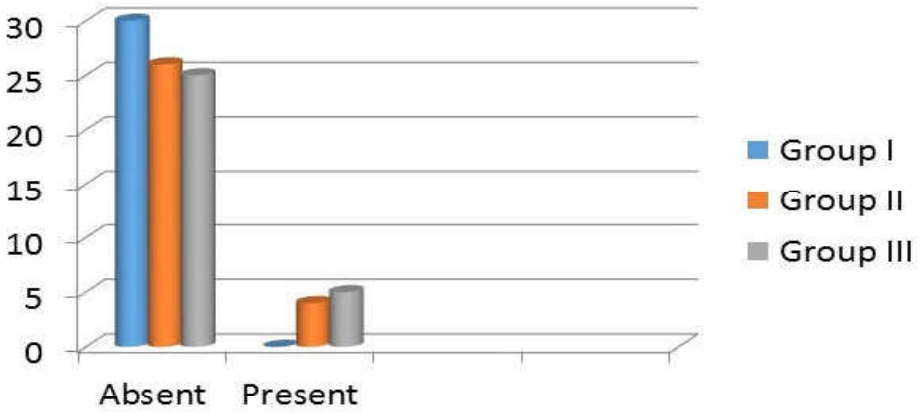
Adverse Effects		Group I (n=30)	Group II (n=30)	Group III (n=30)	p-value
Nausea	2*	1	0	1	0.809 (ns)
(number of episodes)	3*	1	1	1	
	4*	0	1	0	
Vomiting	1*	2	0	2	0.199 (ns)
(number of episodes)	2*	0	2	0	
Pruritus		0	5	5	0.027 (ns)
Sedation		0	3	2	0.227(ns)
Bradycardia		0	2	1	0.725 (ns)

Abbreviations: ð number of episodes complained by the patient, $p < 0.05$ is significant, ns= statistically not significant



x-axis= number of episodes, y-axis= number of patients

Fig. 2: Comparison of incidence of Vomiting among the three groups



x-axis= pruritus present (or) absent, y-axis= number of patients

Fig. 3: Comparison of incidence of Pruritus among the three groups

was not related to the dose of intrathecal morphine received.Incidence of pruritus was significant in Group II and Group III when compared to Group I (p=0.027) (Table 3).

Sedation scores were similar between Group-II and Group-III and it was statistically insignificant (p=0.227, Table 3).

Discussion

Postoperative nausea and vomiting (PONV) is one of the common symptoms patients would experience in perioperative period. This may be related to patients own risk factors, drug induced or the surgical procedure patient has undergone.

Irrespective of the cause, PONV delays recovery and prolongs the duration of stay in postoperative anesthesia care unit (PACU) and at times it would be very distressing for the patient [6].

Intrathecal morphine provides good pain relief having the advantage of longer duration of action. However, PONV is a common adverse effect noted after the use of intrathecal morphine for perioperative pain relief [2]. PONV reduces the quality of recovery and increases the duration of stay in PACU [6]. Higher incidence of PONV with the use of intrathecal morphine, prolonging PACU stay and decreasing the quality of recovery is the main drawback of its use, especially when used for intraabdominal surgeries.

5-HT_3 antagonists have been used frequently to decrease the incidence of nausea and vomiting, and ondansetron is one of the common medication used in this class of drugs [7]. Dolasetron, ramosetron and palanosetron are other medications of the same class which are used more recently [3,8-10].

Morphine is a hydrophilic opioid and hence its action with regard to pain relief and adverse effects are delayed in onset when compared to other lipophilic opioids [11,12]. Hence, intrathecal morphine induced nausea and vomiting occur more frequently in postoperative than intraoperative period. 5-HT_3 antagonists like ondansetron have been used to treat intrathecal morphine induced PONV. Ondansetron when administered pre-emptively, would reduce the incidence of intrathecal morphine induced nausea and vomiting [3,13,14]. This would improve the quality of recovery and decrease the stay in postoperative unit.

Ondansetron when usedpre-emptively has been shown to reduce nausea and vomiting in patients receiving intrathecal morphine [2,14]. In our study, all patients received 4 mg of intravenous ondansetron, 10 minutes before injection of spinal drug preparation. Patients were monitored and treated for nausea and vomiting intraoperatively and postoperatively. We observed statistically insignificant difference in incidence of nausea ($p=0.809$) and vomiting ($p=0.199$) in patients receiving intrathecal morphine when compared to control group (Table 3). Incidence and frequency of nausea and vomiting were not related to the dose of intrathecal morphine used.

There are many risk factors for patients to develop perioperative nausea and vomiting e.g.- GERD, peptic ulcers, obesity, gastropathy, NSAIDs, opioids, abdominal surgeries etc. and different treatment medications have been used. Each factor would contribute collectively to cause PONV. In our study we excluded patients who had risk factors to develop PONV so as to avoid bias on the results with the use of intrathecal morphine. We maintained the uniformity of the patients chosen and limited our study for abdominal hysterectomy patients.We did not notice any significant difference between control group and intrathecal morphine group. In addition, PONV was not related to dose intrathecal morphine used (100 µg versus 200 µg) and correlates with the study conducted by other authors [2,14].

Pre-emptive use of ondansetron to reduce incidence of pruritus have been studied by various authors and have been observed to be effective [3,5,15,16] by few authors while others have found it to be ineffective [4,14]. In our study incidence of pruritus was statistically significant ($p=0.027$) in Group II and Group III when compared to Group I. None of the patients in control group developed pruritus, whereas 5 patients each in Group-II and Group-III developed pruritus (Table 3).

Sedation as an adverse effect with the use of intrathecal morphine was statistically insignificant ($p=0.227$) and it was mild (Table 3). Respiratory depression associated with the use of intrathecal morphine is dose dependent and higher incidence was observed when dose exceeded 300 µg and safe when used less than 300 µg [2]. We used 100 µg and 200 µg in Group-II and Group-III respectively and hence did not observe respiratory depression.

Bradycardia and hypotension are observed less frequently with the use of intrathecal morphine.[2]In our study we noted bradycardia in two patients in Group-II and one patient in Group-III which responded to 0.6mg Inj.atropine i.v. (Table 3). Incidence of bradycardia in our study was more likely because of dilution of the spinal drug preparation using normal saline, reducing the baricity of the drug preparation resulting in higher level of blockade than expected. It was unlikely to the doses of intrathecal morphine used.

Conclusion

Preemptive antiemesis with ondansetron 4 mg administered intravenously 10 minutes before injection of intrathecal morphine, reduces the incidence of intraoperative and postoperative nausea and vomiting. Duration of analgesia was significant and dose dependent in patients receiving intrathecal morphine, and better tolerated because of lesser incidence of PONV. Pruritus was higher in patients receiving intrathecal morphine and did not decrease with the use of preemptive ondansetron.

Conflicts of Interest

Nil

Acknowledgement

Nil

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