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ORIGINAL ARTICLE

COMPARATIVE STUDY OF PROPHYLACTIC METOCLOPRAMIDE VERSUS ONDANSETRON FOR CONTROL OF POSTOPERATIVE NAUSEA AND VOMITING (PONV) ASSOCIATED WITH IV TRAMADOL

Anjali P. Savargaonkar[1], Kavitha Chendhilkumar[2], Rajesh V. Nagmothe[3]

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ABSTRACT: AIMS AND OBJECTIVE: This prospective double blind randomized study was conducted to compare: 1. The efficacy and safety of prophylactic administration of Metoclopramide versus Ondansetron in the control of postoperative nausea and vomiting in patients receiving intravenous Tramadol as postoperative analgesic. 2. To study the incidence of postoperative nausea and vomiting with IV bolus Tramadol. **METHODS:** 90 patients ASA grade I and II, age 18-60 years, posted for hernia, hydrocele and other peripheral lower limb surgeries under subarachnoid block were selected. Patients were randomly allocated into three groups of thirty each. All surgeries were performed under subarachnoid block and received IV Tramadol 100 mg 8 hourly for 24 hours as post-operative analgesic. Group N received no prophylactic antiemetic. Group M received 10 mg Metoclopramide 12 hourly. Group O received 4 mg Ondansetron 12 hourly. Vital signs, nausea, vomiting, pain, sedation, need for rescue antiemetic, rescue analgesic and adverse effects were recorded for 24 hours. **RESULTS:** Ondansetron group (Group O) significantly reduced the incidence of PONV as compared to Metoclopramide (Group M) and no antiemetic group (Group N).But Metoclopramide was found to be not significantly effective in controlling PONV in patients receiving Tramadol as analgesic. None of the patients in Group O required rescue antiemetic as compared to 13.3% patients in Group M and 26.7% patients in Group N. There was statistically no significant difference between the 3 groups with respect to requirement of rescue analgesic. No major adverse effects were observed which can be attributed to either Metoclopramide or Ondansetron. **CONCLUSION:** Ondansetron was more effective than Metoclopramide in controlling PONV, in patients receiving IV Tramadol as post-operative analgesia.

KEYWORDS: Metoclopramide, Ondansetron, Tramadol, Prophylactic antiemetic, Rescue antiemetic, Rescue analgesic.

INTRODUCTION: The most common and distressing symptoms, which follow general, regional and local anaesthesia and surgery, are pain and emesis. The incidence of PONV constituted more than 50% of the minor complications reported and there is growing concern about reducing the incidence and severity of PONV. The syndrome of nausea, retching and vomiting is known as "sickness" and each part of it can be distinguished as a separate entity.[1] PONV along with pain is often listed by the patient as their most important peri-operative concerns.[2] In addition, PONV may occasionally lead to electrolyte imbalance, dehydration and aspiration of vomitus leading to major complication. Surgical complications such as abdominal wound dehiscence, bleeding

beneath skin flaps and loss of vitreous fluid following intraocular surgery may follow severe PONV.[3]

There are number of factors influencing the occurrence of PONV which includes patient factors (age, gender, obesity, anxiety, history of motion sickness or previous PONV and gastro paresis), operative procedures, anaesthetic techniques (drugs for general anaesthesia, regional anaesthesia and monitored anaesthesia care) and post-operative factors (pain, dizziness, ambulation, oral in-take and opioids). A thorough understanding of these factors, with physiology related to PONV and neuro-pharmacology of multiple emetic receptors is necessary to most effectively manage PONV.

Several drugs have been used for preventing PONV. Most of them act as antagonist at the receptors which are involved in emesis. The traditional anti emetics include antihistamines, anticholinergics and dopamine-receptor antagonists[4]. Newer class of drugs, such as the Serotonin Receptor Antagonists (SRA) provides better efficacy and safety as compared to the traditional drugs. Ondansetron, a prototype of this group is widely used drug in our country.[2,5,6]

Metoclopramide, a prokinetic benzamide, act through both dopaminergic (D2) and serotonergic receptor. It has antiemetic properties and is widely used for the prevention and treatment of PONV. It is generally well tolerated but extra pyramidal reactions, abdominal cramping, sedation, dizziness and cardiac arrhythmias are the side effects reported with this drug. It is popular drug used for postoperative, drug induced and disease associated nausea and vomiting.[7] However Ondansetron is the 5-HT3 receptor antagonist and its antiemetic efficacy is well established.[8] Ondansetron is generally used as prophylactic antiemetic to patients receiving Tramadol, but Ondansetron is more expensive than Metoclopramide and its efficacy for Tramadol induced postoperative nausea and vomiting is ambiguous.[9,10,11,12,13,14]

Tramadol is a centrally acting analgesic of moderate potency with opioid and non- opioid modes of action. It acts by different mechanisms and in combination with NSAID; Tramadol is expected to produce better pain relief than either drug alone. Its lack of sedative action is of particular value to day care surgery but that is potentially limited by its high incidence of PONV. The incidence of nausea and vomiting quoted in literature varies from 24-40% and 9-20% respectively; also varying according to the route of administration of Tramadol.[9] Keeping this in mind, this study was conducted to find the efficacy and safety of prophylactic administration of Metoclopramide versus Ondansetron in the control of postoperative nausea and vomiting in patients receiving intravenous bolus Tramadol as a postoperative analgesic and to study the incidence of post-operative nausea and vomiting in patients receiving IV bolus Tramadol as post-operative analgesia.

MATERIALS AND METHODS: After obtaining the Institution ethical committee approval and written consent from all the patients, study was conducted in 90 patients, belonging to ASA grade I and II with the age and weight between 18-60 years and 40 to 70 kg respectively, posted for surgery with low emetogenic potential like hernia, hydrocele and lower limb surgeries to be performed under subarachnoid block. This prospective, double blind randomized controlled study was carried out at Tertiary Care Hospital in the Department of Anaesthesiology. Patients with past history of postoperative nausea and vomiting, history of acid peptic diseases, epilepsy, motion

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sickness, vestibular disturbances and extra pyramidal symptoms, patients with gastrointestinal distension and abdominal surgery, patients on concurrent medication with emetic or antiemetic effects like monoamine oxidase inhibitors, phenothiazines, butyrophenones, patients with uncontrolled systemic diseases like hypertension, ischemic heart diseases, diabetes mellitus and CNS disorders were excluded from study. Ninety selected patients were divided into three equal Groups of 30 patients by random selection of sealed envelopes. Group N received 100 mg IV. Tramadol over 2mins, 8 hourly for 24hrs and no prophylactic antiemetic. Group M received 100 mg IV. Tramadol over 2mins, 8 hourly for 24hrs and 10 mg IV Metoclopramide 12 hourly. Group O received 100 mg IV. Tramadol over 2mins, 8 hourly for 24hrs and 4 mg IV Ondansetron 12 hourly. The medication was prepared by third party (anesthesiologist) so that both patients and investigator were blinded.

A detailed preoperative evaluation including medical history, physical examination, vital signs, laboratory tests and concurrent medical assessment was done for all the patients. All patients received diazepam 10 mg orally on the night prior to surgery. Routine preoperative fasting guidelines were followed in all the patients. Patients were evaluated again in the morning in Operation Theater. In the operation theatre standard Multipara monitor with electrocardiogram, NIBP and pulse-oximeter was applied to the patient for recording of SPO2, ECG and NIBP. After securing IV access, all patients received IV Ranitidine 50 mg. All patients were preloaded with IV Ringer Lactate 5 to 6 ml/kg over 10 minutes. Under strict aseptic precautions in lateral decubitus position, lumbar puncture was done with spinal needle 23G and 0.5% Bupivacaine (heavy) were injected with the dose depending upon the height of patient. Maximum sensory level was noted with pinprick method at 20 min. and 30 min after injection of Bupivacaine. After giving subarachnoid block all patients were given IM Diclofenac 75 mg before start of surgery. Intraoperative heart rate, blood pressure, SPO2 and ECG was monitored. Patients who needed intraoperative supplementation of opioids, general anaesthesia or patient who had persistent hypotension (>30% fall from preoperative systolic BP) for more than 5 minutes requiring continuous vasopressor support were excluded from further study analysis. Patients in all three groups received IV bolus Tramadol 100 mg slowly over 2 min and 8 hourly for 24 hours as postoperative analgesia. First dose of Tramadol was administered in the operation theatre at the end of surgery during skin closure. The patients from Group N received no prophylactic antiemetic. Patients in the Group M received first dose of Metoclopramide 10 mg, 10 minutes prior to administration of Tramadol and Group O patients received first dose of Ondansetron 4 mg, 10 minutes prior to administration of Tramadol. Patients in all the groups received IV Ranitidine 50 mg 12 hourly for 24 hrs.

Postoperatively, all the patients were under observation for 24 hrs and observed for the time of occurrence of nausea, vomiting and any other significant complaint. The incidence of nausea, vomiting, pain, sedation, adverse effects and need for rescue medications was noted.

The scoring system used for grading of nausea and vomiting, pain and sedation.

1. **Nausea score:** 0: No nausea, 1: Mild nausea, not requesting pharmacological rescue, 2: Nausea requesting pharmacological rescue, 3: Nausea resistant to pharmacological rescue.

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2. **Vomiting score:** 0: No vomiting, 1: Vomiting once not followed by nausea and not requiring treatment, 2: Vomiting more than once, or vomiting once followed by nausea requiring treatment, 3: Intractable vomiting not responding to treatment.
3. **Sedation Score:** 0: alert, 1: Drowsy, 2: asleep but arousable, 3: asleep but difficult to arouse, 4: sedated.
4. **Pain score:** Using Visual Analogue scale, 0-No pain, 10-Worst conceivable pain.

Rescue Medication: Rescue antiemetic was given when nausea score =2 or >2 and when vomiting score = 2 or >2. In the Group N, IV Metoclopramide 10 mg was given as an initial rescue antiemetic and if vomiting or nausea persisted for more than 15 minutes after Metoclopramide given, then IV Ondansetron 4 mg was administered. In Group M another dose of IV Metoclopramide 10 mg was given as a rescue antiemetic. In Group O another dose of IV Ondansetron 4 mg was given as a rescue antiemetic.

In the case of no response to rescue antiemetic, the next dose of IV Tramadol to be given was omitted and IM Diclofenac was given for analgesia. In patient with VAS score > 6 thirty minutes after administration of IV bolus Tramadol, IM Diclofenac 75 mg was given as rescue analgesia.

STATISTICAL ANALYSIS: Data was analyzed on SPSS 7.0. The mean and standard deviation were used to describe continuous variables. Chi square test was used to determine the statistical significance between Groups. ANOVA and t test was applied to measure the variation between the three Groups. P value <0.05 was considered as significant.

OBSERVATIONS AND RESULTS: We found no statistically significant difference in all three groups in terms of demographic profiles of the patients and duration of surgery (Table 1). Also all the groups were comparable with respect to types of surgeries performed (Table 2). Since maximum surgeries were hernia and hydrocele, female population in our study was only 3.3% and included predominately male patients in all three groups (Table-1), hence results of this study would be generally applicable to male population.

Incidence of nausea and vomiting was 40% each at the end of 24 hours in patients belonging to Group N who received IV Tramadol as postoperative analgesic but no prophylactic antiemetic. At the end of 24 hours the incidence of nausea and vomiting in Group M was 36.7% and 26.7% respectively and in Group O, 10% and 6.6% respectively (Table 4 and Graph 3). We found statistically significant difference with respect to nausea and vomiting when Group O was compared with Group M and Group N, while the difference in incidence of nausea and vomiting was not found to be statistically significant when Group M was compared with Group N. Thus Ondansetron significantly reduced the incidence of PONV when compared to Metoclopramide but Metoclopramide was found to be not significantly effective in controlling PONV in patients receiving Tramadol as analgesic. Graph 1 and 2 shows that more number of patients in each group had nausea and vomiting during 8-16 hours as compared to 0-8 hours and 16-24 hours.

None of the patients in Group O required rescue antiemetic compared to 13.3% patients in Group M and 26.7% patients in Group N. The difference between Group O and Group N was

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statistically significant(p=0.007) although less number of patients in Group M required rescue antiemetic as against Group N, difference was not statistically significant. The difference between Group O and Group M as regards to antiemetic requirement was also statistically not significant.

Total number of patients requiring rescue analgesic over 24 hours were 1(3.3%) patient in Group N, 3(10%) patient in Group M and 3(10%) patients in Group O, there was statistically no significant difference between the three groups. The number of patients requiring rescue antiemetic and rescue analgesic during 0-8 hrs, 8-16 hrs, 16-24 hrs and 0 -24 hrs is shown in table 5. There was no statistically significant difference between the groups in terms of mean sedation score and mean pain scores. The adverse effects observed like headache, sedation, and tachycardia did not differ significantly in three groups included in the study [Table 6].

Variable	Group- N (n=30)	Group- M (n=30)	Group- O (n=30)
Age(yrs) mean(±SD) Range	42.00±(15.72) (18-60)	43.87±(14.68) (18-60)	41.80±(13.51) (24-60)
Weight(kgs) mean(±SD) Range	50.8±(6.59) (40-65)	54.93±(4.53) (48-62)	53.23 ±(6.66) (40-65)
Duration of surgery(min) mean(±SD) Range	73.17±(28.69) (40-120)	84.37±(35.25) (45-150)	86.17±(28.23) (40-180)
Sex % Male Female	28(93.3%) 2(6.6%)	29(96.7%) 1(3.3%)	30(100%) 0

Table 1: Demographic data and duration of surgery

ANOVA, f = 0.18126, p = 0.8345(Not Significant).

Surgery	Group- N (n=30) n (%)	Group- M (n=30) n (%)	Group- O (n=30) n (%)
Hernia	13(43.3%)	18(60.0%)	10(50.0%)
Hydrocele	15(50.0%)	6(20.0%)	10(33.3%)
Other	2(6.6%)	6(20.0%)	5(16.7%)

Table 2: Type of surgery performed

	Group- N (n=30) n(%)	Group- M (n=30) n(%)	Group- O (n=30) n(%)
0-8Hrs			
Nausea	5(16.7%)	5(16.7%)	1(3.3%)
Vomiting	7(23.3%)	3(10.0%)	1(3.3%)
8-16Hrs			
Nausea	9(30.0%)	8(26.7%)	2(6.6%)
Vomiting	8(26.7%)	7(23.3%)	1(3.3%)

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16-24Hrs			
Nausea	6(20.0%)	5(16.7%)	1(3.3%)
Vomiting	5(16.7%)	4(13.3%)	1(3.3%)

Table 3: Number of patient with nausea and vomiting during 0-8hrs,8-16hrs, 16-24hrs

Chi square test.
For vomiting during 0-8hrs Gr. N Vs Gr.O, p=0.049(significant).
For nausea during 8-16hrs Gr. N Vs Gr. O, p= 0.0453(significant) and Gr. M. Vs Gr. O, p = 0.038 (significant).
For vomiting during 8- 16 hrs Gr. N Vs Gr. O, p = 0.011(significant) and Gr. M Vs Gr. O, p = 0.023 (significant).

	Group- N (n=30) n(%)	**Group- M (n=30) n(%)**	**Group- O (n=30) n(%)**
Nausea	12(40.0%)	11(36.7%)	3(10.0%)
Vomiting	12(40.0%)	8(26.7%)	2(6.6%)

Table 4:- Total number of patients with nausea and vomiting over 24 hrs

Chi square test.
For nausea Gr N Vs Gr O, p = 0.0072(significant) and Gr M Vs Gr O, p =0.015 (significant).
For Vomiting Gr N Vs Gr O, p = 0.0022(significant) and Gr M Vs Gr O, p =0.038 (significant).

	Group- N (n=30) n (%)	**Group- M (n=30) n (%)**	**Group- O (n=30) n (%)**
0-8 Hrs			
Rescue Antiemetic	6(20.0%)	2(6.6%)	0
Rescue Analgesic	0	0	1(3.3%)
8-16 Hrs			
Rescue Antiemetic	4(13.3%)	2(6.6%)	0
Rescue Analgesic	0	3(10.%)	1(3.3%)
16-24 Hrs			
Rescue Antiemetic	0	0	0
Rescue Analgesic	1(3.3%)	0	1(3.3%)
0-24 Hrs			
Rescue Antiemetic	8(26.7%)	4(13.3%)	0
Rescue Analgesic	1(3.3%)	3(10.0%)	3(10.0%)

Table 5: Number of patients requiring rescue antiemetic and rescue analgesic during 0-8hrs, 8-16hrs and 16-24hrs

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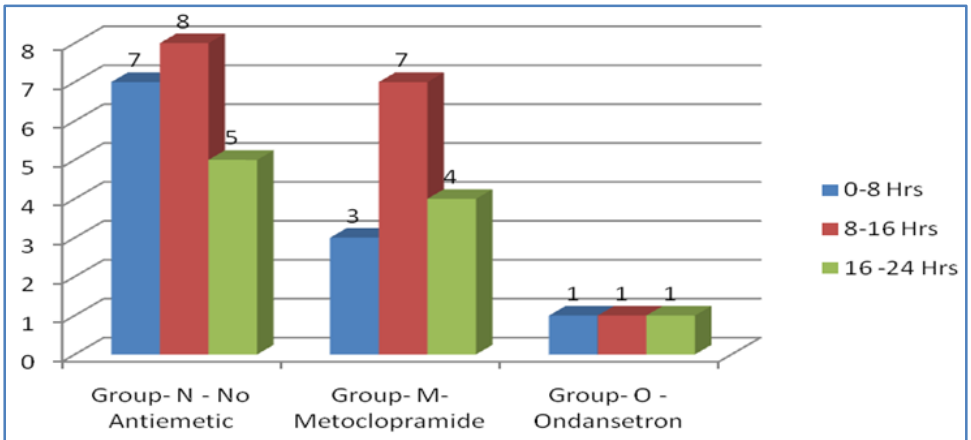
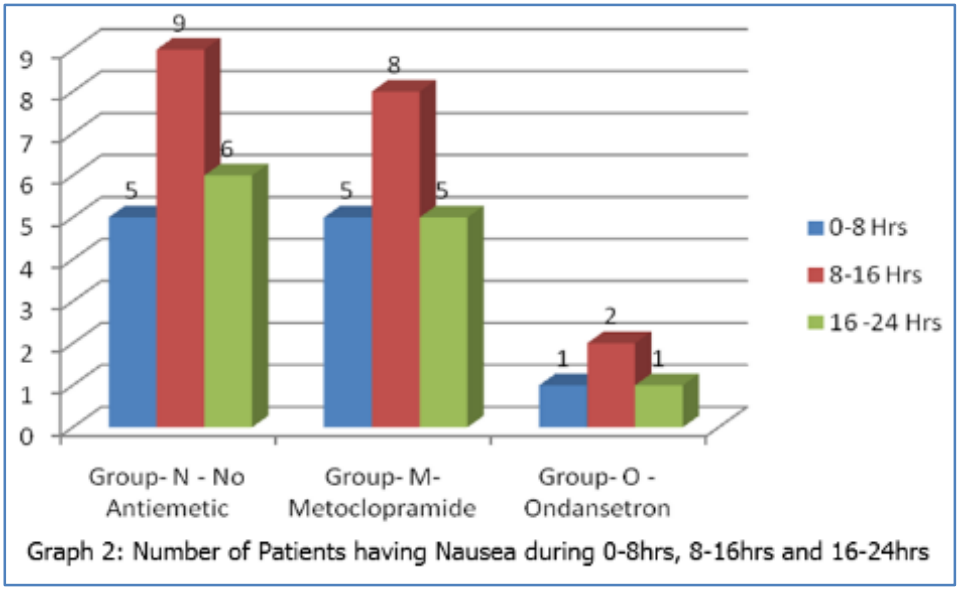
Adverse Effect	Group- N (n=30) n (%)	Group- M (n=30) n (%)	Group- O (n=30) n (%)
Haedache	1(3.3%)	0	2(6.6%)
Tachycardia	2(6.6%)	0	0
Hypotension	0	0	0
Sedation	0	0	0
Extra pyramidal symptoms	0	0	0

Table 6: Adverse Effects Observed



Graph 1: Number of Patients having Vomiting during 0-8hrs, 8-16hrs and 16-24hrs



Graph 2: Number of Patients having Nausea during 0-8hrs, 8-16hrs and 16-24hrs

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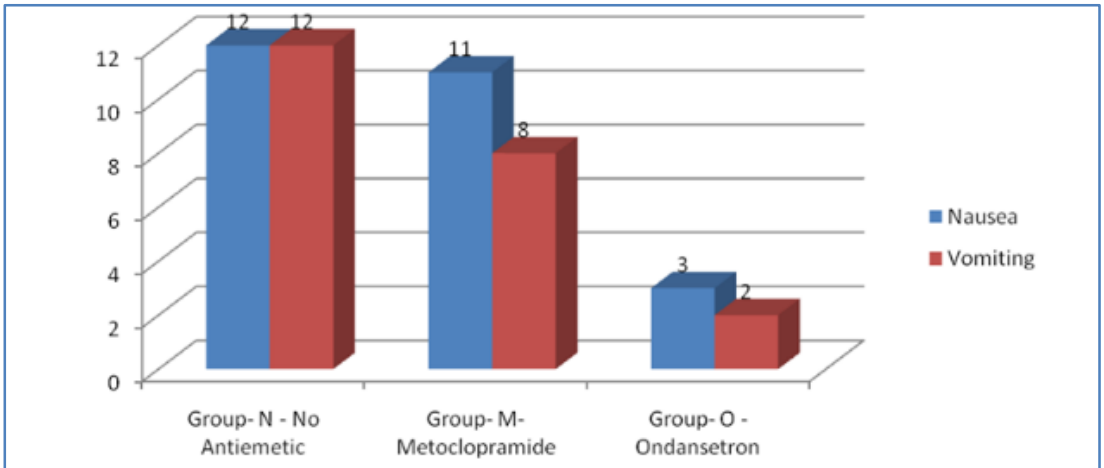

Graph 3: Number of patients having Nausea and Vomiting in Three Groups at the End of 24hrs

DISCUSSION: Opioids are commonly prescribed for post-operative pain but post-operative nausea and vomiting is common with opioids, in fact effective control of pain can be limited by PONV associated with opioids.[15] For the relief of mild to moderate pain, the opioid commonly used is Tramadol because of having less chances of respiratory depression and providing good pain relief but its use is restricted because of nausea and vomiting associated with it. The incidence of PONV varies with different routes of administration of Tramadol with IV (20%), IM (7%) and overall (9-20%).[16]

According to various authors **(**Pang et al,[17] Kelly et al[16] and Carilo and Cordova[18]) the onset of action for analgesia is faster with intravenous route; therefore, we decided to give Tramadol as IV bolus slowly for the relief of control of postoperative pain in our study. Since the analgesic effect of Tramadol is mediated by reduced uptake of $5HT_3$ in descending pathway of spinal cord leading to raised $5HT_3$ level which contribute to its emetic effect. $5HT_3$ antagonist such as Ondansetron might be of particular value in reducing the PONV associated with Tramadol whereas Metoclopramide, a dopamine receptor antagonist is a commonly used antiemetic since a long time. There are very few comparative studies of Ondansetron and Metoclopramide as antiemetic against Tramadol induced PONV. Considering the cost difference between these two drugs, Ondansetron being costly, we decided to compare the efficacy and safety of using Metoclopramide versus Ondansetron as an antiemetic for Tramadol induced PONV.

We selected 4 mg IV dose of Ondansetron, 12 hourly based on the study conducted by Mc Kenzle et al[19] and Rung et al.[20] Henzi et al[21] in systematically searched review of antiemetic efficacy of Metoclopramide has mentioned the best documented regime of Metoclopramide in adult as IV 10 mg. Hence, we used Metoclopramide 10 mg IV, 12 hourly.

Surgeries with mild to moderate postoperative pain were selected for the study to minimize the effect of postoperative pain on PONV. Hence, surgeries chosen for our study were peripheral and superficial, with mild to moderate postoperative pain, performed under standardized spinal anaesthetic technique. Surgeries and anaesthesia technique chosen had low emetogenic potential so that other factor affecting the incidence of PONV would be minimized.

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In the present study the incidence of nausea and vomiting in Group N is 40% each and this reflects the incidence of nausea and vomiting in patients receiving IV Tramadol as postoperative analgesic without any prophylactic antiemetic. Our finding correlates with the finding of Kelly et al.[16] In our study at the end of 24 hours the overall incidence of nausea in no antiemetic group was 40% as against 36.7% in Metoclopramide group and 10% in Ondansetron group. The difference between Ondansetron and No antiemetic group (p=0.0072) and Ondansetron versus Metoclopramide group (p = 0.015) was statistically significant. Although Metoclopramide group had less number of patients with nausea compared to No antiemetic group, the difference between them was not statistically significant.

In our study at the end of 24 hours the overall incidence of vomiting in No antiemetic group was 40% as against 26.7% in Metoclopramide group and 6.6% in Ondansetron group. The difference between Ondansetron and No antiemetic group (p = 0.0022) and Ondansetron versus Metoclopramide group (p = 0.038) was statistically significant. Although Metoclopramide group had less number of patients with vomiting compared to no antiemetic group, the difference between them was not statistically significant.

Broome et al,[10] Robert et al[11] and Pang et al[12] in their study have quoted Ondansetron not to be effective against Tramadol. However other studies by Dev N Kumar et al.,[13] Eli Alon et al[9] and Joslyn et al[14] have shown that Ondansetron was a better antiemetic compared to Metoclopramide but in these studies Tramadol was not used. Our results have shown that Ondansetron was more effective than Metoclopramide when Tramadol was used as analgesic. However, the incidence of nausea and vomiting in all three groups in the present study was less compared to previous studies, the reasons being our study was conducted in low emetogenic surgeries under regional anaesthesia. Intra operatively other than Tramadol no other opioid was used and other confounding factors leading to nausea and vomiting were minimized.

In our study, we observed that in no antiemetic group the severity of vomiting was higher as compared to the Ondansetron group. Since the number of patients who had vomited twice, thrice and more than thrice in no antiemetic group was 16.7%, 13.3%, 3.3% respectively as compared to only 3.3% patients in Ondansetron group vomited more than twice. Although this difference was observed, it was not statistically significant.

The severity of nausea was observed to be less in Group O. None of the patients in Group O had nausea score of more than one during the 24hr observation period, as against 10% patients in Group N and 6.6% patients in Group M and nausea score of 2 i.e. severity of nausea was also more in Group N and Group M. Similarly, score of vomiting was also found to be less in Group O. No patients in Ondansetron Group had vomiting score of more than one during 24hrs observation period as against 20% and 6.6% patients had vomiting score of 2 in Group N and Group M respectively during initial 8hrs after surgery. And 6.6% patients each in Group N and Group M had vomiting score of 2 during 8-16hrs observation periods. This showed that Ondansetron is effective in reducing not only the incidence of nausea and vomiting seen with Tramadol but also the severity of nausea and vomiting. We were able to demonstrate that Ondansetron when given as prophylactic antiemetic along with IV bolus Tramadol resulted in significantly lower incidence of postoperative nausea and vomiting. While Metoclopramide was not found to be effective in controlling the postoperative nausea and vomiting associated with IV

bolus Tramadol. We also noted that the incidence of nausea and vomiting with IV bolus Tramadol is 40%.

The difference between the Group O and Group N was statistically significant while the difference between other groups were not statistically significant with respect to requirement of rescue antiemetic. We observed that 1(3.3%) patient in Group M and 2(6.6) patients in Group O had headache and this headache as quoted by Tramer et al[22] is dose dependent. No major adverse effects were observed which can be attributed to either Metoclopramide or ondansetron.

CONCLUSION: From the observations in the present study, it can be concluded that Ondansetron when given as prophylactic antiemetic along with Tramadol is effective and safe in controlling postoperative nausea and vomiting whereas Metoclopramide was not found to be effective in the doses used. Incidence of PONV in patients who received IV Tramadol as postoperative analgesic was significant, suggesting need for routine administration of prophylactic antiemetic. Our study predominantly included male patients hence these results may not be applicable to female population.

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AUTHORS:

1. Anjali P. Savargaonkar
2. Kavitha Chendhilkumar
3. Rajesh V. Nagmothe

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Anesthesia, Government Medical College, Nagpur, Maharashtra.
2. Ex Resident, Department of Anesthesia, Government Medical College, Nagpur, Maharashtra.
3. Associate Professor, Department of Anesthesia, Government Medical College & Super Speciality Hospital, Nagpur, Maharashtra.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Anjali P. Savargaonkar,
Sarang 801, Yashodham Enclave,
Prashant Nagar, Ajani,
Nagpur-440015, Maharashtra.
E-mail: anj123sg@yahoo.com

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