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RESEARCH ARTICLE

A COMPARATIVE STUDY OF ONDANSETRON AND GRANISETRON IN COMBINATION WITH DEXAMETHASONE IN PREVENTION OF POST OPERATIVE NAUSEA AND VOMITING(PONV) IN TOTAL ABDOMINAL HYSTERECTOMY CASES PERFORMED UNDER GENERAL ANAESTHESIA

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ABSTRACT

Post operative nausea and vomiting (PONV) is a common problem and distressing symptom in surgical patient population. The incidence is about 72% in women undergoing general anesthesia for major gynecological surgery. General anaesthesia with inhalational agents is associated with an average PONV incidence of 20-30 % in surgical patients. Post operative vomiting will harm skin flaps, abdominal wall sutures, vascular anastomoses, and other areas recently operated on. It increases intra-ocular, intra-cranial pressure and may also cause tachycardia, electrolyte imbalance, wound dehiscence, oesophageal tears and aspiration pneumonitis.Granisetron and Ondansetron are among the commonly used 5HT3 antagonists and used in combination with dexamethasone for prophylaxis against PONV .This study was intended to compare combination of 5HT3 receptor antagonists-Granisetron and Ondansetron with Dexamethasone in prevention of PONV in females undergoing major gynecological surgery under general anesthesia. To study the incidence of PONV in females undergoing abdominal hysterectomy under general anaesthesia and also to compare the efficacy of combination of antiemetics – Granisetron 1mg+Dexamethasone 8mg and Ondansetron 4mg+Dexamethasone 8mg in prevention of post operative nausea and vomiting . After obtaining clearance from institutional ethics committee and Informed consent from all the patients, 75 patients of ASA 1&2 were randomly allocated to three groups – Group O+D (n=25) received Ondansetron 4mg + Dexamethasone 8mg; Group G+D (n=25) – received Granisetron 1mg+Dexamethasone 8mg; Group C- received saline. Standard General Anaesthesia protocol was followed. Study drugs were administered at the time of induction. Post operative nausea and vomiting was studied for period of 24 hrs. Severity was assessed using PONV Score[0=no nausea;1=nausea only;2=retching;3=vomiting]. The adverse effects were also studied.

The incidence of PONV was 60%, 12 % and 12% in placebo group, O+D group and G+D group respectively. The complete response after 24 hr period was 40% in control group, 88% in Group O+D, and 88% in group G+D. Rescue antiemetics were required only in control group. The incidence of PONV was highest in first 6 hours of post operative period and highest incidence was noted in placebo group. There was no statistical difference noted between G+D & O+D groups but there was clinical and statistical significance noted between groups which received prophylactic antiemetic combination and control. Adverse effects were not observed in any group.Granisetron 1mg and Ondansetron 4mg in combination with dexamethasone 8mg are equally effective and safe in decreasing the incidence of post operative nausea and vomiting in Total Abdominal Hysterectomy surgery.

Key words: PONV, ondansetron, granisetron, dexamethasone, ondansetron + dexamethasone, granisetron +dexamethasone, Total Abdominal Hysterectomy.

INTRODUCTION

Post operative nausea and vomiting (PONV) is the most common post operative complication and the most distressing symptom in surgical patient population. PONV has been characterized as 'the big little problem' [1] and has been a common complication for both in- patients and out-patients undergoing virtually all types of surgical procedures. The incidence of nausea and vomiting was 75-80% in 'ether era' [2] & the incidence of PONV is still as high as 70% to 80% among high-risk patients [3]. PONV occurs frequently in gynecological, obstetric, ocular, breast and middle ear surgeries. The incidence is about 72% in women undergoing general anesthesia for major gynecological surgery [3].General anesthesia with inhalational agents is associated with an average PONV incidence of 20-30 % in surgical patients[4] The consequences of PONV are physical, surgical and anaesthetic complications for patients, as well as financial implications for the hospitals or institutions [4, 5,6]

Many treatments are available for PONV, but none has been proved 100% effective[7]. Anti-emetics acting on dopamine, cholinergic, histamine, 5HT and NK1 receptors have been tried. Combinations of anti-emetic drugs with different mechanisms of action are being studied for the prophylaxis of PONV with variable results. There is increasing evidence that the multimodal approach may improve the outcome. Double and triple antiemetic combinations are recommended for patients at high risk for PONV. [3]

METHODS

This study was proposed to compare double anti emetic combination- 5HT3 receptor antagonists-Granisetron and Ondansetron in combination with Dexamethasone for prevention of PONV in abdominal hysterectomy cases performed under general anesthesia.

The proposed study was conducted at Cheluvamba hospital attached to Mysore Medical College and Research Institute, Mysore, after obtaining approval from the Institutional ethics committee. The study was conducted for a period of two years (2007-09). 75 female patients, of ASA I and II in the age group of 20-60 years, scheduled to undergo Elective Total Abdominal Hysterectomy under General Anaesthesia were selected for the study. Patients with known hypersensitivity or contra-indications to study drugs; History of nausea, vomiting or retching in 24 hours before anesthesia; patients who have received anti-emetic drugs or drugs with anti-emetic property during 24 hours before anesthesia; conditions requiring chronic opioids use; history of motion sickness and those suffering from gastrointestinal, liver and renal diseases were excluded.

The study was a prospective, randomized and double blind one. Pre anesthetic evaluation was done on the previous day and assessed for risk factors. Written informed consent was taken from all patients.

All patients were premedicated with Tab. Ranitidine hydrochloride 150mg and Tab. Diazepam 10mg on the night before surgery.

Patients were randomly allocated into the following three groups by a computer generated random numbers.

Group O+D [n=25] - received Ondansetron 4mg plus Dexamethasone 8mg I V (5ml)

Group G+D [n=25] – received Granisetron 1mg plus Dexamethasone 8mg IV (5ml)

Group C – control/placebo group received saline IV (5ml)

Ondansetron 4mg (2ml) and Dexamethasone 8mg (2ml) were diluted in normal saline (1ml) to achieve a total volume of 5 ml. Granisetron 1mg(1ml) and dexamethasone 8mg(2ml) were diluted with 2ml of normal saline to make the volume to 5 ml. Patients in control group received 5ml of normal saline.

[Granisetron (*granidem*, Aristo pharmaceuticals) 1mg; Ondansetron (*ondem*, Berger Health Care, A division of Alkem)]

The observer and the patient were blinded for the study drugs. The drugs were administered in 5 ml filled identical syringes by an anaesthetist who was not involved in the study. Standardized anaesthesia regimen was followed. Intravenous access was secured with 18 gauge intravenous canula. Monitors for NIBP, SPO_2 and ECG were connected and baseline values were recorded.

All patients were premedicated with Inj.Atropine (0.5 mg) Inj.Pentazocine (15mg) & Inj.Midazolam (1mg) I.V. Study drug was administered just before induction. General anesthesia was induced with Inj.Thiopentone sodium 5mg/kg I.V; Inj. Succinlycholine 1.5mg/kg I V was used to facilitate endotracheal intubation. Patients were intubated with 7.5 mm I D cuffed Endotracheal tube and anaesthesia was maintained on intermittent positive pressure ventilation with O2 (33%) + N_2O (66%) + 0.5% of Halothane and intermittent doses of Inj.Vecuronium bromide after a bolus of 4mg , for intraoperative muscle relaxation. Intra operative events were monitored using NIBP, SPO_2 and ECG.

Inj. Diclofenac sodium 75 mg was administered I.M 20 min before extubation. Surgical incision site was infiltrated with 0.25 % of Bupivacaine (20ml) by the surgeons for added post operative analgesia. Neuromuscular blockade was reversed with Inj. Neostigmine 0.05mg/kg and Inj.Atropine 0.02mg/kg and extubated. Post operatively Inj. Ketorolac 30mg I. M was administered to all patients only if they complained of pain.

The incidence of nausea, vomiting and retching was studied after extubation for a total period of 24 hrs post operatively. All patients were assessed every hourly for the first 6 hours, three hourly for next 6 hours and sixth hourly for subsequent 12 hours using the following PONV scoring system [8]

Score 0- no nausea,
Score 1- nausea only
Score 2- nausea with retching
Score 3- vomiting

Nausea[4] was defined as a subjectively unpleasant sensation associated with an urge to vomit. **Retching**[4] was defined as spasmodic, rhythmic contraction of respiratory muscles without expulsion of gastric contents

Vomiting[4] was defined as forceful expulsion of gastric contents.

Nausea and vomiting occurring within first 6 hrs was considered as early nausea and early vomiting[9].

Complete response was defined as absence of nausea, retching, vomiting and no requirement of rescue antiemetic.[9]

Vomiting and Retching episodes separated by less than 5min were taken as a single episode. All patients were given rescue anti-emetic Inj. Metoclopromide10mg I.V only if they complained of nausea and vomiting for more than two episodes[10] in 1hr period. Patients who received rescue antiemetics were excluded from the study.

Patients were also be monitored for adverse effects like headache, dizziness, drowsiness, flushing and sedation in 24 hr post operative period.

Statistical analysis

The data obtained was analyzed and subjected to statistical analysis. The Statistical software SPSS 11.5 version was used for the analysis of the data. Statistical differences between the three groups were tested using Chi-square test. Descriptive statistics and regression analysis were also used to compare the groups. P value <0.05 was considered significant. Microsoft word and Excel have been used to generate graphs, tables etc**.**

RESULTS

All patients were followed up for 24 hrs post operatively .Any episode of Nausea, Retching and Vomiting was recorded and assessed using PONV score[8]

The groups were comparable with respect to age, weight and body mass index. There was no statistical significance observed between groups. Hemodynamic parameters were also within normal limits and no statistical difference was observed among three groups.there was no difference observed in the duration of surgery(Table-1).

PONV scores were assessed and tabulated.(Table-2)(Fig-1). In the first 6 hrs, complete response(score-0) was 92%, 88%and 56% in group O+D, group G+D and group C respectively. The incidence of PONV(score-1,2,3) was 8 %, 12% and 44% group O+D, group G+D and group C. There were no adverse effects noted in any of the groups in first 6hrs. four patients received rescue antiemetics in group C and were excluded from further observation.Complete response (score 0) during 6-12 hour was 100%, 100%and 61.9%% in group O+D, group G+D and group C respectively. (Fig-2) The incidence of PONV(score-1,2,3) was 0 %, 0% and 28.1% group O+D, group G+D and group C. There was no statistical difference observed between group O+D and G+D till 12 hours but there was a significant difference between group O+D , G+D and control groups.

In 12-18 hour period, The complete response(score 0) was noted in 96%, 96% & 75% in Group O+D, Group G+D and Control group respectively. (Fig-3) The incidence of PONV was 4 %, 4% and 25% group O+D, group G+D and group C. In 18-24 hour,(fig-4) Complete response(score 0) was 96%, 100% and 85% in Groups O+D, Groups G+D and Group C respectively. There was no statistical significant difference between the groups but the clinical

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differece observed was significant. Adverse effects were absent in all the three groups. No patient required rescue antiemetic.(table-2)

Over a period of 24 hours, highest incidence of PONV was noted in first 6 hours and it was noted in the control group.

In 24 hour period, Group O+D,22 patients did not experience nausea, retching or vomiting and their scores were 0 throughout the study. Therefore, complete response was 88%. Three patients experienced nausea, retching or vomiting at different time interval during the study period. Therefore the incidence of PONV was 12% in Group O+D.(Table-3)

In 24 hour period, Group G+D. 22 patients did not experience nausea, retching or vomiting and their scores were 0 throughout the study. Therefore, complete response was 88%. Three patients experienced nausea, retching or vomiting at different time interval during the study period. Therefore the incidence of PONV was 12% in Group G+D.(Table-3)In the control group study period only 10 patients did not experience nausea, retching or vomiting and the PONV scores were 0 throughout the study period. Hence, the complete response in overall 24 hours was 40% and the incidence of PONV was 60%.In overall 24 hours, the complete response was 88% in Group O+D,88 % in Group G+D and 40% in Group C/placebo group. (Table-4)

TABLE-1

	Group O+D	**Group G+D**	**Group C**
Age(±SD)	40.4(7.15)	40.5(7.37)	41(6.6)
weight(±SD)	50(6.25)	50.44(6.47)	50.12
BMI(±SD)	21.66(3.16)	21.60(3.37)	21.21(1.54)
Duration of anaesthesia	104.08(20.82)	105.00(25.23)	103.84(15.89)

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TABLE-2 COMPARISON OF PONV SCORES AMONG GROUPS O+D, G+D AND C IN 24 HR PERIOD

	Group O+D	Group G+D	Group C	O+DVSG+D	O+D VS C	G+D VS C	
PONV SCORES IN 6 HOURS							
0	23(92%)	22(88%)	14(56%)	P=0.7	P<0.05	P<0.05	
1	1(4%)	2(8%)	6(24%)				
2	0(0%)	0(0%)	1(4%)				
3	1(4%)	1(4%)	4(16%)				
	n=25	n=25	n=25				
PONV SCORES IN 6-12 HOURS							
0	25(100%)	25(100%)	13(61.9%)	P=0.469	P<0.05	P<0.05	
1	0(0%)	0(0%)	5(23.8%)				
2	0(0%)	0(0%)	1(4.7%)				
3	0(0%)	0(0%)	2(9.5%)				
	n=25	n=25	n=21				
PONV SCORES IN 12-18 HOURS							
0	24(96%)	24(96%)	15(75%)	P=0.76	P=0.81	P=0.65	
1	1(4%)	1(4%)	4(20%)				
2	0(0%)	0(0%)	0(0%)				
3	0(0%)	0(0%)	1(5%)				
	n=25	n=25	n=20				
PONV SCORES IN 18-24 HOURS							
0	24(96%)	25(100%)	17(85%)	P=0.698	P=0.67	P=0.89	
1	1(4%)	0(0%)	3(15%)				
2	0(0%)	0(0%)	0(0%)				
3	0(0%)	0(0%)	0(0%)				
	n=25	n=25	n=20				

Four patients in group C received rescue antiemetics within 6 hrs and were excluded from the subsequent follow up for PONV. Two patients had vomiting and one patient required rescue antiemetics and this patient was excluded from the study.The other patient was followed up for remaining study period.

Table-3 INCIDENCE OF NAUSEA, RETCHING & VOMITING IN ALL THE GROUPS IN 24 HRS

GROUP	PERCENTAGE
O+D	12%
G+D	12%
C	60%

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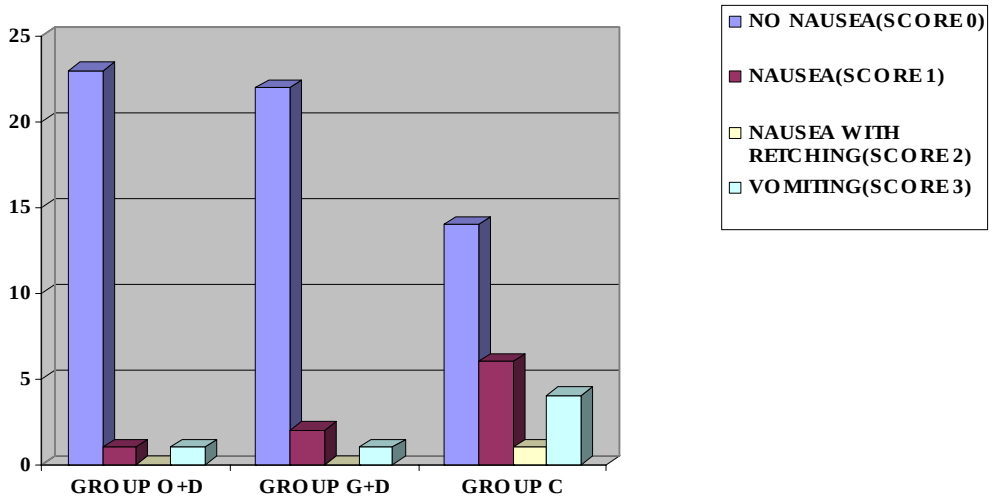
Table-4 COMPLETE RESPONSE IN ALL THE GROUPS IN 24 HOURS

GROUP	PERCENTAGE
O+D	88%
G+D	88%
C	40%

COMPARISON OFPONV SCORES IN FIRST 6 HOURS



COMPARISON OFPONV SCORES IN FIRST 6-12 HOURS

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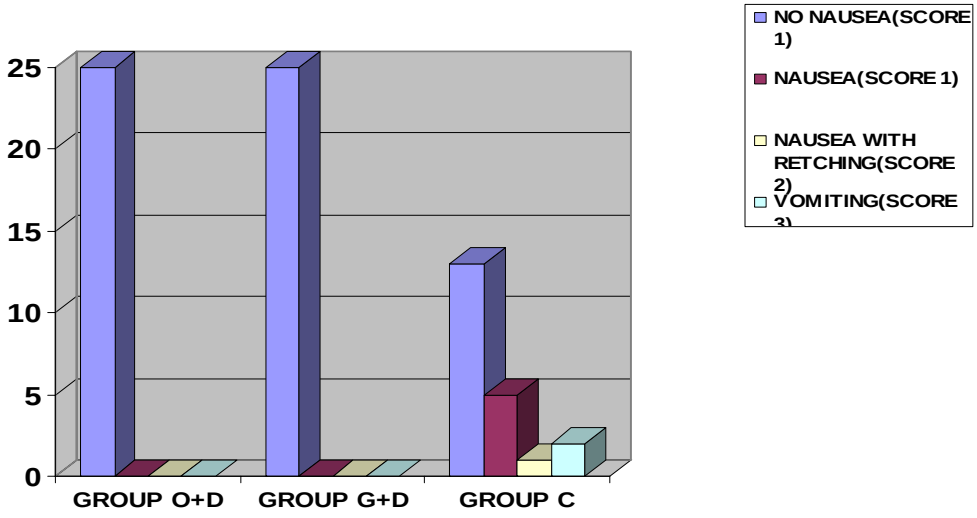
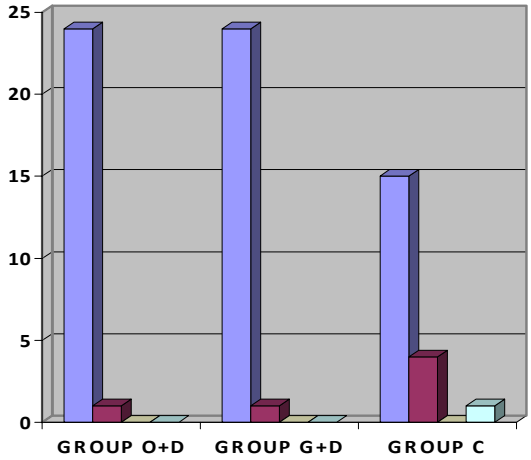


COMPARISON OFPONV SCORES IN FIRST 12-18 HOURS



COMPARISON OFPONV SCORES IN FIRST 18-24HOURS

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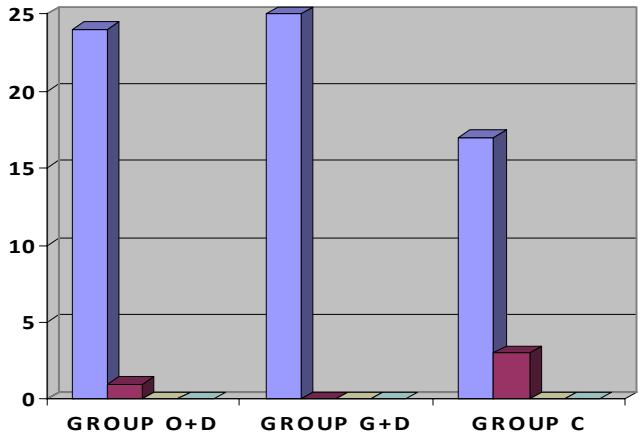

DISCUSSION

Post operative nausea and vomiting (PONV) is a common problem and distressing symptom in surgical patient population. General anaesthesia with inhalational agents is associated with an average PONV incidence of 20-30 % in surgical patients[11] The incidence largely depends on pre operative patient characteristics, operation, anaesthesia, gender, intensity of pain and its post operative management. Post operative vomiting will harm skin flaps, abdominal wall sutures, vascular anastomoses, and other areas recently operated on. It increases intra-ocular, intra-cranial pressure and may also cause tachycardia, electrolyte imbalance, wound dehiscence, oesophageal tears and aspiration pneumonitis[12]. PONV after minor and ambulatory surgery delays the hospital discharge. . **Apfel et al** described female gender, previous history of PONV or motion sickness, non-smoking status and postoperative use of opioids as important risk factors for PONV[13]. **Sinclair et al** described female gender, previous history of PONV or motion sickness, non-smoking status and postoperative duration, type of anesthesia and surgery as the important risk factors for PONV[13]. Among high-risk patients, the incidence of PONV can be as high as 70% to 80%. [14.] Use of volatile anesthetics ,nitrous oxide ,large-dose neostigmine(>2.5 mg) & use of intraoperative or postoperative opioids in general anaesthesia are associated with high incidence of PONV[4,14]

PONV is multifactorial and combination of drugs with different mechanisms of action is more effective [12] Many treatments are available for PONV, but none has been described as a panaecea[7]. Anti emetic drugs including anti histamines, butyrophenonoes, dopamine receptor antagonists were used a few years ago. These antiemetics had undesirable side effects like excessive sedation, hypotension, dry mouth, dysphasia, hallucinations and extra pyramidal

symptoms and they are now rarely used. ***SAMBA[3] guidelines*** *suggest that adults at moderate risk for PONV should receive combination therapy with one or more prophylactic drugs from different classes. Combination therapy has superior efficacy compared to monotherapy for PONV prophylaxis*[3,6].

In 1981, Dexamethasone was found to be an effective anti emetic in patients undergoing chemotherapy with limited side effects and its use in prophylaxis for PONV was started 2 years later [7, 15]. . *The mechanism of action of corticosteroids is unknown but may be related to inhibition of prostaglandin synthesis, decrease in 5HT3 levels in central nervous system or by an anti inflammatory action at operative sites.*[10]

In 1990, 5HT3 antagonists were introduced [16,17,18]. Gregory et al reported the effectiveness of 5HT3 antagonists in prevention of chemotherapy induced nausea and vomiting[17, 19]. McKenzie demonstrated that dexamethasone in combination with ondensetron was effective than single drug therapy[18] **Elhakim M et al** [20] concluded that dexamethasone 8mg represented the minimal effective dose for combination with ondansetron 4mg for prophylaxis of PONV[20]**. Fujii et al** in 1995 recommended granisetron 20 mcg /kg as the dose for combination with dexamethasone 8 mgs in prophylaxis of PONV[21,22] The FDA labeled dose of granisetron recommended for PONV prophylaxis is 1mg and this dose was based on the dose range study by Wilson et al. SAMBA guidelines recommended 1mg as the dose of granisetron for prevention of PONV[3].

In view of these observations, in the present study combination of antiemetics and dosages recommended for combination was employed. [23]. Spinal and epidural anaesthesia is the most popular and most frequently used technique for abdominal and pelvic surgeries in adults, we opted to administer general anaesthesia to all female cases posted for major gynaecological surgery, as the incidence of PONV is high in general anaesthesia and also to study the efficacy of antiemetic combinations in surgeries performed under general anaesthesia. Although use of volatile anaesdthetics, neostigmine >2.5 mg , nitrous oxide and intra operative ue of opioids increases the incidence of PONV, we followed a standard general anaesthetic protocol and studied the incidence of PONV. Pain was managed in a multimodal way as discussed in methodology.

Olando et al[19], Rajeeva et al[24], Thomas et al[25], Kushwaha et al [8]and Sri Raman et al [9] have administered ondansetron and Granisetron for prevention of PONV at the time of induction.5 HT3 receptor antagonists are metabolized via CYP2D6 and genetic polymorphisms of the P450 enzyme can lead to decreased efficacy due to ultra rapid metabolism[26,27]. Because of this reason there is a growing opinion that ondansetron and Granisetron are more effective when given at the end of surgery. However because of the literature support of the efficacy of 5 HT3 receptor antagonists in preventing PONV while being administered at the time of induction itself, we chose to employ these drugs at the time of induction.

Metoclopramide was chosen as rescue antiemetic as Serotonin antagonists when used for prophylaxis tend to block almost all available receptors [28]thus, subsequent use of serotonin antagonists for rescue treatment would be ineffective [29]. Therefore, it is currently assumed that after administering an antiemetic it is most effective to choose an antiemetic of another class for later rescue treatment[30].

Olando et al [19], Rajeeva et al [24] and **Kushwaha et al [8]** have used Inj.Metoclopramide 10mg as recue antiemetic when Ondansetron and Granisetron were employed as primary antiemetics.

24 hour period

Complete response

In our study Complete response at 24 hrs in group O+D and group G+D was similar i.e 88% in each group. **Kushwaha et al [8]** compared O+D and G+D groups and noted a complete response in 24 hour period to be 88% and 92% respectively. Thus the results of the present study concur with **Kushwaha et al [8].**

In the present study, the complete response in control group at 24 hours was 40%. **Fujii et al [10] and Olando et al [19]** reported a complete response in the control group as 45%and 20% respectively. Therefore the results observed in control group concurs with study by **Fujii et al [10]**

Total incidence of PONV in our study (24 Hours)

The total incidence of PONV in our study, in G+D and O+D was 12% and 12% respectively. The incidence was similar to the findings in **Kushwaha et al [8]** [O+D-12%;G+D-8%] Incidence of PONV in our study in control group was 60% and **Kushwaha et al [8] and Fuji et al [10]** in their control group reported the incidence of 55% and 44% respectively.

Gan T J et al [31] and **Sriraman et al [9]**compared the incidence of nausea in 24 hours with O+D and G+D groups. In the studies by **Gan TJ et al [31]**, nausea was observed in 49% of patients in O+D and 52% in G+ D group. In the studies by **Sriraman et al [9]** , nausea was noticed in 8% of the patients in O+D and 6% in G+D, where as in the present study, the incidence of nausea in 24 hours was 12% in O+D group and 12% in G+D group. As already explained, this difference may be due to the difference in the surgical procedure or the dosages and timing of antiemetics employed. However, both **Gan T J et al [31]**and **Sriraman et al [9]** have noted that there is no statistical difference in G+D and O+D group. In the present study also, the difference in nausea between O+D and G+D groups was also not statistically significant.

Gan T J et al[31] and **Kushwaha et al [8]** et al compared the incidence of vomiting 24 hours in O+D and and G+D groups. In the studies by Gan T J et al[31] , vomiting was observed in 13% of patients in O+D and 17% in G+ D. In the studies by **Kushwaha et al[8]**, vomiting in 24 hour period was noticed in 36% of the patients in O+D and 28% in G+D, where as in the present study, the incidence of vomiting was 4% in O+D group and 4% in G+D group. This difference may be due to the difference in the surgical procedure or the timing and dosage of antiemetics employed by these authors. However, both **Gan T J et al[31] and Kushwaha et al[8]** have noted that there is no statistical difference in G+D and O+D group. In the present study also, the difference in vomiting in 24 hour period between O+D and G+D groups was also not statistically significant.

In our study, there was no requirement of rescue antiemetic in groups G +D and O+ D. whereas 25% of patients in control group required rescue antiemetic in the total period of 24 hrs

and 16% of these patients required rescue antiemetic in first 6 hrs suggesting the incidence of PONV to be high and severe in first 6hrs post operatively. **Elhakim et al** [20] also reported that 30% of patients in the control group required rescue antiemetics.

Thomas et al [25] reported adverse effects like fatigue, dizziness and flushing & **Gan T J et al** [31] reported drug related adverse effects as 3% in O+D group**. Fujii et al** [21] observed the adverse effects like headache, dizziness, drowsiness and sedation in G+D group. In our study, we did not observe any adverse effects like headache, drowsiness, itching & dizziness in any of the three study groups

The incidence of PONV was low in all groups after 12 hrs. There was similar incidence of PONV between the all three study groups after 12 hrs. There was no statistical difference observed after 12 hrs among the groups. The incidence of nausea and vomiting was slightly high in control group which was clinically significant. This finding concurs with study by **Kushwaha et al** [8]

In 24 hrs, Prophylaxis with ondansetron 4mg or granisetron 1mg in combination with dexamethasone 8mg had reduced the incidence of nausea from 72% to 12% and vomiting from 28% to 4% .complete response was noted in 88% in groups which had prophylactic antiemetic combination in comparison to 40% in placebo/control group.

CONCLUSION

From the present study

1. The incidence of PONV is high (60%) in female patients undergoing T AH under general anaesthesia with standard technique when no antiemetics are employed for prevention of PONV.

2. PONV in the post operative period can last upto 24 hours, though the incidence and severity is maximum in the first 6 hours.

3. Combination of ondansetron 4mg with dexamethasone 8 mg administered at the time of induction effectively reduces the incidence of PONV in vast majority of patients (88% complete response)

4. Combination of granisetron 1mg with dexamethasone 8 mg administered at the time of induction effectively reduces the incidence of PONV in vast majority of patients(88% complete response)

5. Administration of combination of granisetron plus Dexamethasone and Ondansetron plus Dexamethasone are equally effective in preventing PONV and are not associated with adverse effects.

6. Both combinations- granisetron 1mg plus dexamethasone 8mg ; ondansetron 4mg plus dexamethasone 8 mg , can be effectively employed at the time of induction to prevent PONV in high risk patients.

7. Both Granisetron and Ondansetron are cost effective for prevention of PONV.

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