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A COMPARATIVE STUDY OF ONDANSETRON WITH DEXAMETHASONE AND GRANISETRON WITH DEXAMETHASONE FOR PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING FOLLOWING ABDOMINAL SURGERIES UNDER GENERAL ANAESTHESIA.

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ABSTRACT

Aims and Objectives: To compare the effectiveness of Ondansetron with dexamethasone to that of Granisetron with dexamethasone for prevention of post operative nausea and vomiting (PONV) after abdominal surgery under general anaeshesia with respect to nausea, vomiting, requirement of rescue antiemetics and side effects. **Materials**: With Institutional ethical committee clearance, clinical Study conducted at R.L.J.H, Kolar. After obtaining informed written consent,60 patients of ASA(American Society of Anaesthesiologists) grade I and II in the age group of 18- 55 years of either sex undergoing elective surgeries were included. **Methods:** Patients were randomly allocated into 2 groups of 30 each.30 patients received Dexamethasone 8mg intravenously just after intubation, 4mg ondansetron intravenously 30min before extubation and 30 patients received Dexamethasone 8mg intravenously just after intubation, 2mg Granisetron intravenously 30min before extubation. PONV occurring up to 3hours was considered early and at 6, 12, 24 hour as delayed. A standard anaesthetic technique was used in all patients. Postoperatively, patients were assessed for episodes of nausea, retching and vomiting and the need for rescue antiemetic. Complete response defined as the absence of nausea, retching or vomiting and no need for rescue antiemetic during the 24-hour observation period. **Results:** Our report showed that administration of Granisetron 1 mg and Dexamethasone 8 mg or Ondansetron 4 mg and Dexamethasone 8 mg in patients undergoing abdominal surgeries under general anaesthesia, prevented PONV in a high percentage of patients with minimal side effects. We also found

during the early post operative period (0-3hrs) only 10% in Group with Granisetron and Dexamethasone had nausea while 26.7% in group with Ondansetron and Dexamethasone had nausea. This was found to be statistically significant (P<0.10). We did not find any statically difference between the two groups when we compared early versus late in terms of rescue antiemetic required and side effects. **Conclusion**: This study concludes Dexamethasone 8 mg in combination with Granisetron 1 mg or Ondansetron 4 mg was found to prevent nausea and vomiting in a high percentage of patients undergoing abdominal surgeries under general anaesthesia with minimal side effects. During the early post operative period, Granisetron with Dexamethasone is effective in preventing nausea than Ondansetron and Dexamethasone. There was no statistical significance difference between the two combinations concerning rescue antiemetic required or side effects.

KEYWORDS: General anaesthesia; PONV; abdominal surgery; Ondonsetron; Granisetron; Dexamethasone; nausea; retching; vomiting; rescue antiemetic; complete response.

INTRODUCTION

The most common and distressing symptoms following surgery and anaesthesia are pain, nausea and vomiting. Sometimes nausea and vomiting maybe more distressing especially after surgery, delaying the hospital discharge.[1]

There has been a general trend towards a decrease in the incidence and intensity of the problem because,use of less emetic anaesthetic agents, improved pre and post operative medication, refinement of operative techniques and identification of patient predictive factors. However in spite of these advances, nausea and vomiting still occurs with unacceptable frequency in association with surgery and anaesthesia.[2]

Dexamethasone was first reported to be an effective antiemetic agent in patients undergoing cancer chemotherapy in 19813. Since then randomized, placebo controlled studies have shown that the role of dexamethasone for the prevention of postoperative nausea and vomiting compared to placebo shows that dexamethasone treatment, reduced early and late PONV.[4]

A potential new entry into the antiemetic pharmacopia in the year 1991 is ondansetron, of the class of selective 5 hydroxytryptamine subtype 3 (5HT3) receptor antagonists which lack effects on cholinergic adrenergic, dopaminergic or histaminergic receptors. The antiematic

property of ondansetron maybe mediated peripherally, centrally or both. Ondansetron has little effect on lower esophageal sphincter pressure, esophageal or gastric motility, or small bowel transit time. By 5HT3 selectivity, the undersirable side effects of using antagonists of dopaminergic, cholinergic or histaminergic receptors as antiemetic agents, such as dysphoria, sedation and extrapyramidal symptoms, are avoided. It has been proved to be extremely effective antiemetic in the group of patient receiving cytotoxic chemotherapy with no significant side effects. The use of ondansetron has now become extended to the management of PONV routinely. Extensive trails using oral and intravenous ondansetron in various types of patients posted for various surgeries have confirmed the efficacy of the drug with a less side effect profile.[5]

Granisetron is recently introduced, 5-hydroxy trypatamine receptor antagonist, with stronger 5HT3 binding. It is more potent and longer acting antemetic agent compared to Ondansetron against emesis associated with chemotherapy, and have been found to be very effective for preventing PONV after abdominal surgery. Granisetron has fewer incidences of side effects.[6]

There are many causes of PONV and so antagonising only one type of receptor is not sufficient in many patients .It is logical to give drugs which have different mechanism of action. The combination of dexamethasone with ondansetron or granisetron further decreased the risk of PONV. The best prophylaxis available is achieved by combining dexamethasone with 5HT3 receptor antagonist.[7]

Abdominal surgery is associated with a high incidence of nausea and vomiting[8]. The combination of ondansetron plus dexamethasone was more effective in the prevention of postoperative nausea and vomiting than ondansetron alone.[9] Also, the combination of granisetron and dexamethasone produced more effective PONV prevention in patients undergoing abdominal surgeries versus PONV prevention with granisetron alone.[6]

The present study was undertaken to compare the antiemetic effects of Ondansetron with dexamethasone and Granisetron with dexamethasone to prevent PONV in patients undergoing abdominal surgeries under general anaesthesia (GA).

MATERIALS AND METHODS

After obtaining the Institution ethical committee approval and written consent from the

patients of a either sex, 60 patients of ASA I and II of age group between 18 -55 years undergoing abdominal surgerieswere selected for study.

Patientsdocumented hypersensitivity to any of the study drugs,full stomach, with respiratory diseases,diabetes mellitus, patients who received anti emetic agents 48 hrs prior to surgery, with history of motion sickness or migraine,history of alcohol, drug abuse or smoking,pregnant or lactating female, renal impairment and hepatic disease, with neurological and endocrinal abnormalities, patients with history of vomiting and ryle's tube in situ in the past 24 hours, history of ischaemic heart disease, patients with uncontrolled hypertension and pheochromocytomawere excluded from the study.

A prospective double blind randomized clinical study was carried out on all these patients. Patients were randomly divided into two groups of 30 each using computer generated random numbers.

Group – "O+D" – Ondansetron and Dexamethasone group (n = 30)

Group – "G+D" – Granisetron and Dexamethasone group (n = 30)

Patients were visited on the previous day of the surgery, a detailed clinical history was taken, General and Systemic examinations were done. The patients were explained about the study and written consent is taken.

All patients received Tab. Alprazolam 0.5 mg and Tab. Ranitidine 150 mg on the previous night of surgery. Patients were instructed to remain nil orally after 10PM on the previous night of surgery. All abdominal surgeries were carried out under GA by anaesthesiologist being unaware of the prophylactic treatment given.

On day of surgery in the preoperative room, iv line was secured. Patients were randomly assigned to receive either Granisetron (G)1 mg plus Dexamethasone 8mg(D) (G+D) i.v. or Ondansetron (O) 4 mg plus Dexamethasone (D) 8 mg (O+D) i.v. The randomization lists were computer-generated, centrally determined, and the randomization numbers were allocated sequentially in the order in which patients were enrolled. Study medications were prepared by the site anaestesiologist, who was not involved in any other part of the study, and presented to blinded investigators as identical 2-mL filled syringe. The anaesthetic regimen and surgical procedures were standardized for all patients.

Patient was premedicated withGlycopyrollate 5µgkg-1 intravenous and Fentanyl 2µg per kg intravenous & induced by Propofolintravenousat the dose of 2 mg per kg body weight. Tracheal intubation was facilitated by inj. scoline 2mgkg-1 i.v.Anaesthesia was maintained by N2O + O2 + Isoflurane (0.6 to 0.8 %). Intermittent doses of Vecuronium were given during anaesthesia to maintain adequate muscle relaxation. Intra operative HR, BP, SpO 2, ECG and urine output was monitored. Dexamethasone was given immediately after induction of anesthesia in both treatment groups. Neuromuscular blockade was reversed with IV neostigmine (up to 0.07 mg/kg) and glycopyrrolate (up to 0.02 mg/ kg). Granisetron or Ondansetron was administered approximately 30 min before tracheal extubation (defined as end of surgery).

Fentanyl (up to 50 microgram IV) was permitted as needed for the management of postoperative pain. Patients were transported to the recovery room and later to the ward after confirming an adequate level of consciousness and intact reflexes.

The time of each vomiting episode and the time and intensity of each nausea episode were recorded immediately before anesthesia and 2, 6, 12 and 24 h after tracheal extubation. An episode of vomiting was defined as either vomiting (expulsion of stomach contents) or retching (an involuntary attempt to vomit but not productive of stomach contents). Vomiting and/or retching episodes separated by less than 5 min were recorded as a single episode. The intensity of each nausea episode was graded as mild (discomfort noticed but no disruption of anticipated normal activity), moderate (discomfort sufficient to reduce or affect anticipated normal activity), or severe (inability to perform anticipated normal daily activity). Rescue medication could be administered to any patient who experienced an episode of moderate or severe nausea, an episode of vomiting, the initial rescue medication was Granisetron 1 mg administered as a single IV push. Nausea and vomiting assessments were made 30 min after rescue medication administration, and response was defined as improvement or resolution of PONV symptoms. Subsequent PONV symptoms could be treated with an alternative rescue medication at the discretion of the investigator. If rescue medication was used, both the time of administration and type of medication were recorded. Adverse events were evaluated and recorded by the investigator during the entire observation period.

“Complete response” was defined as the absence of nausea, retching or vomiting and no need for rescue antiemetic during the 24-hour observation period.

Statistical analysis

Study design: A Comparative two group study.

Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

The following assumptions on data are made, Assumptions:

1.Dependent variables should be normally distributed,

2.Samples drawn from the population should be random, Cases of the samples should be independent Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Significant figures

P value: P<0.10

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data.

RESULTS

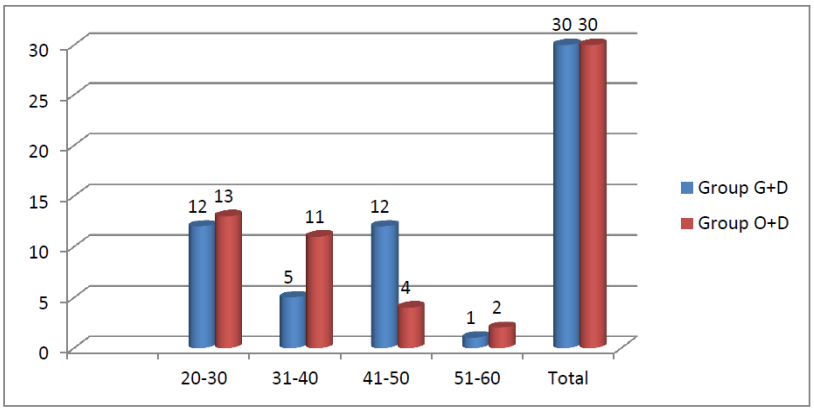
Table 1: Age distribution of patients studied.

Age in years	Group G+D		Group O+D	
	No	%	No	%
20-30	12	40.0	13	43.3
31-40	5	16.7	11	36.7
41-50	12	40.0	4	13.3
51-60	1	3.3	2	6.7
Total	30	100.0	30	100.0

The average age of patients in Group G+D was 34.16 years, whereas it was 33.46 years in Group O+D (p>0.05).

The distribution of the patients in the groups, G+D and O+D according to the age group is shown by Table 1 and Graph 1

Graph 1 : Age Distribution of Study groups



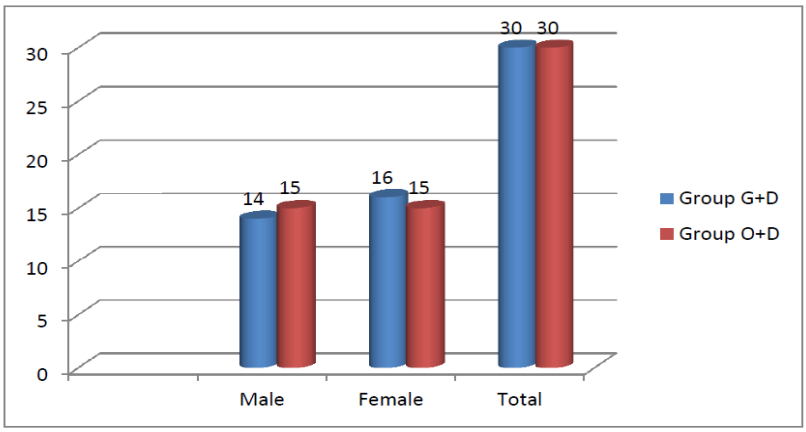
There were 14 male patients (46.7%) and 16 female patients (53.3%) in Group G+D and 15 male patients (50%) and 15 female patients (50%) in Group II as shown in Table and Graph. This distribution of the sample among both the groups was found to be statistically non-significant.

Table 2: Gender distribution of patients studied

Gender	Group G+D		Group O+D	
	No	%	No	%
Male	14	46.7	15	50.0
Female	16	53.3	15	50.0
Total	30	100.0	30	100.0

P value=0.796

Graph 2 : Sex Distribution of Study Groups



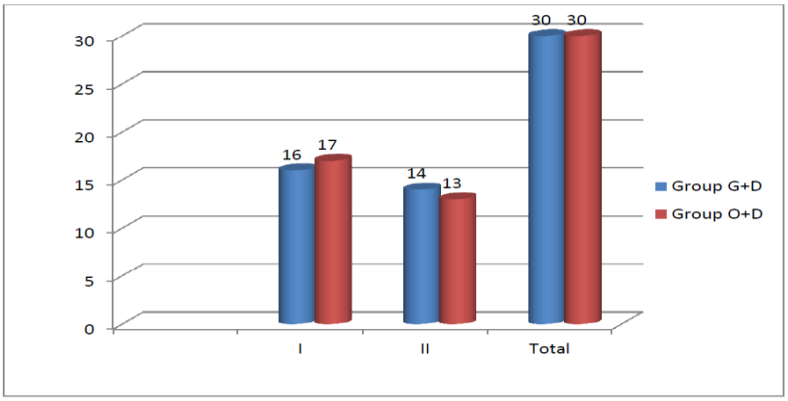
The overall distribution of patients by sex is given by graph 2 which shows that 48.33% were male and 51.66% were female patients. This was found to be statistically non-significant.

Table 3: ASA Grade of patients studied

ASA Grade	Group G+D		Group O+D	
	No	%	No	%
I	16	53.3	17	56.7
II	14	46.7	13	43.3
Total	30	100.0	30	100.0

P=0.795

Graph 3: ASA grade distribution



Both groups had almost similar numbers of ASAI and ASAII.

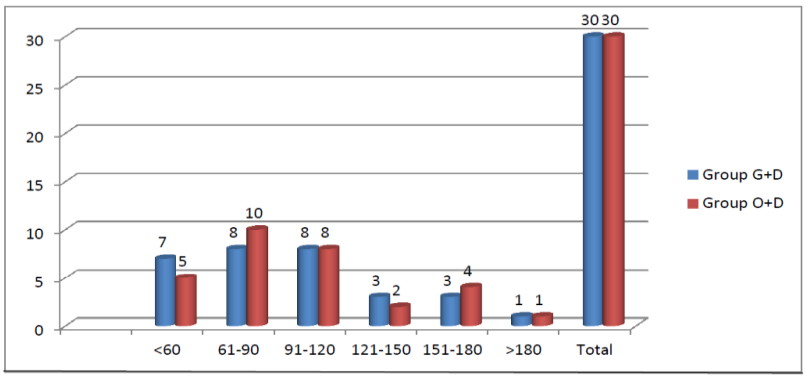
Duration of anaesthesia and surgery in the two groups were compared. There is no statistical significance noted between the two groups.

Table 4: Duration (mins) of surgery

Duration (mins)	Group G+D		Group O+D	
	No	%	No	%
<60	7	23.3	5	16.7
61-90	8	26.7	10	33.3
91-120	8	26.7	8	26.7
121-150	3	10.0	2	6.7
151-180	3	10.0	4	13.3
>180	1	3.3	1	3.3
Total	30	100.0	30	100.0

The mean duration of surgery was 98.5 minutes in group G+D and 101.5 minutes in group G+D. Both groups have almost equal duration.

Graph 4 : Duration of surgery



Postoperative Data

Table 5: Comparative evaluation of Incidence of Nausea/Retching/Vomiting in early and delayed

	Early		Delayed	
	No	**%**	**No**	**%**
Nausea				
• Group G+D (n=30)	3	10.0	4	13.3
• Group O+D (n=30)	8	26.7	7	23.3
• P value	0.095+	-	0.217	-
Retching				
• Group G+D (n=30)	2	6.7	0	0.0
• Group O+D (n=30)	5	16.7	1	3.3
• P value	0.228	-	1.000	-
Vomiting				
• Group G+D (n=30)	1	3.3	0	0.0
• Group O+D (n=30)	3	10.0	2	6.7
• P value	0.612	-	0.492	-

Early nausea During the early peroid only 3 patients out of 30 (10%) in Group G+D had nausea while 8 patients (26.7%) in group O+D had nausea. This was found to be statistically significant (P<0.10).

Only 3 patients in group G+D had mild nausea compared to 8 patients in group O+D. No patients in group G+D had moderate nausea compared to 1 patient in group O+D. None of the patients in both groups had severe nausea.

Delayed nausea : During the delayed period only 4 patients out of 30 (13.3%) in Group G+D had nausea while 7 patients (23.3%) in group O+D had nausea. This was not found to be statistically significant.

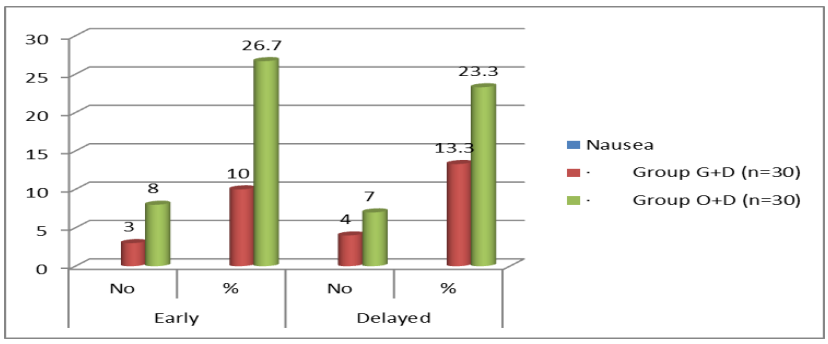
In group G+D, 3 patients had mild episodes compared to 6 patients in group O+D. 1 patient in group G+D had moderate episodes compared to 2 episodes in group O+D. None of the patients had severe nausea.

Early retching : During the early period only 2 patients out of 30 (6.7%) in Group G+D had retching while 5 patients (16.7%) in group O+D had retching.

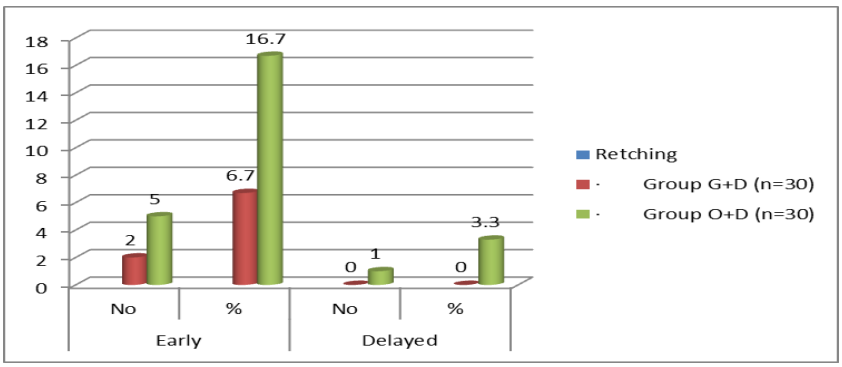
Only 1 patient in group G+D had mild retching compared to 5 patients in group O+D. Only1 patients in group G+D had moderate retching compared to 2 patients in group O+D. None of the patients in both groups had severe retching.

Delayed retching : Only 1 patient (3.3%) in group G+D had mild retching compared to 5 (16.7%) patient in group O+D who had mild retching.

Graph 5: Nausea episode



Graph 6: Retching Episodes



Early Vomiting:During the early period only 1 patients out of 30 (3.3%) in Group G+D had Vomiting while 3 patients (10%) in group O+D had Vomiting. Only 1 patient in group G+D had mild Vomiting compared to 3 patients in group O+D. None of the patients in both groups had moderate and severe nausea.

Delayed vomiting: During the delayed period none of patients out of 30 (13.3%) in Group G+D had Vomiting while 2 patients (6.7%) in group O+D had Vomiting. Among later 1 patient each had mild and moderate vomiting.

Graph 7 : Vomiting episodes

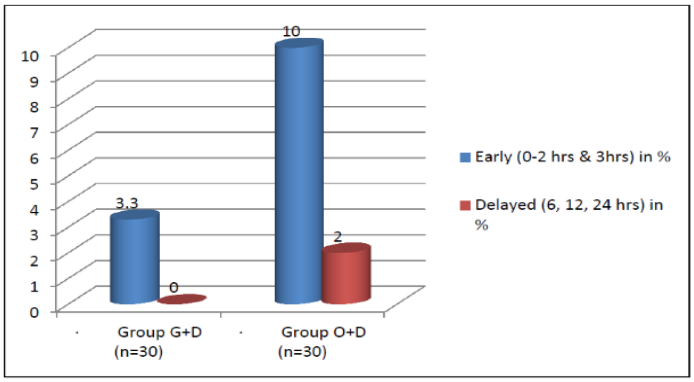


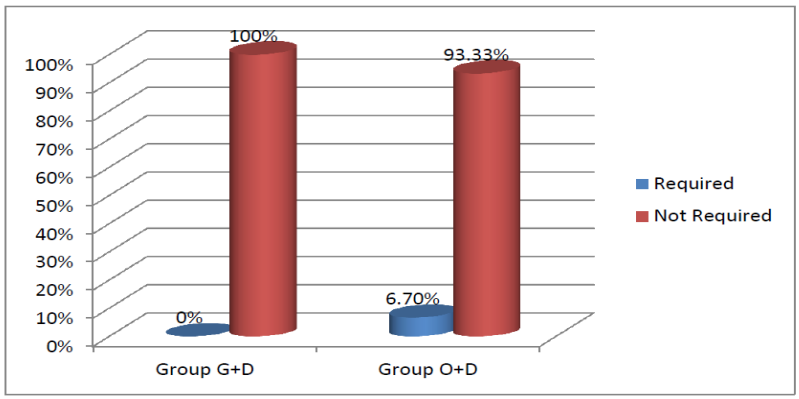
Table 6 : Rescue antiemetic

	Group G+D	Group O+D
Required	0	2(6.7%)
Not Required	30(100%)	28 (93.33%)

P Value =0.253

Need for rescue antiemetic was found to be not statistically significant. 2 patients in group O+D compared to no patients in group G+D needed rescue antiemetic.

Graph 8 : Rescue antiemetic



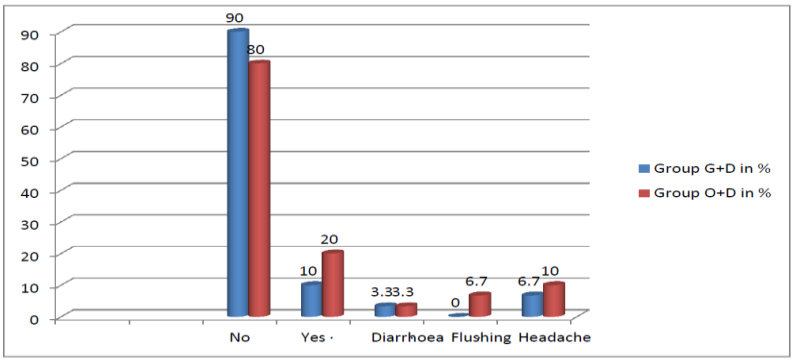
1 patient each in both groups had diarrhea. In group G+D, 2 patients experienced headache compared to 3 patients in group O+D. 2 patients in group O+D had flushing of face while in group G+D , no patients had this side effect. The difference was found to be statistically insignificant.

Side effects

Table 9: Side effects

Side effects	Group G+D (n=30)		Group O+D (n=30)	
	No	%	No	%
No	27	90.0	24	80.0
Yes	3	10.0	6	20.0
• Diarrhoea	1	3.3	1	3.3
• Flushing	0	0.0	2	6.7
• Headache	2	6.7	3	10.0

Graph 9 : Side effects



DISCUSSION

Post operative nausea and vomiting are the most common complaints after anaesthesia and surgery. PONV can contribute to the development of medical problems and patients with PONV consume more resources and require additional health care professional time compared with patients in whom these complications are avoided.

The over all incidences may be larger depending on preoperative patient characteristics, factors related to operation and anaesthesia, the intensity of pain and its management in the postoperative period.[10]

The 5HT3 receptor antagonists are highly specific and selective for nausea and vomiting. Members of this group exert their effects by binding to the serotonin 5HT3 receptor in the chemorecptor trigger zone (CTZ) and at vagal afferents in the gastrointestinal tracts.[11] Granisetron is highly selective in its ability to bind the 5HT3 receptors 1000:1 to other receptors such as (5HT1A, 5HT1B, 5HT1C, 5HT1, 5HT2) or α1 and α2 adrenergic, dopamine D2, histamine H1, benzodiazepine, β adrenergic, and opioid receptors, while the selectivity for ondansetron is only250-400:1.[9]

Combination therapy using antiemetics acting at different neuroreceptor sites is more effective than using individual components alone. This is particularly true when dexamethasone is combined with a serotonin receptor antagonist such as granisetron or ondansetron. The mechanism of antiemetic action of corticosteroids is unknown, but may be related to inhibition of prostaglandin synthesis, decrease in 5-HT3 level in the CNS and by an anti-inflammatory action at operative site.[12] Nucleus tractussolitarius in the medulla and Area Postrema are the main regions in which dexamethasone exerts its central antiemetic action. 67 A wide dose range study of dexamethasone (2-16 mg) has been used in the management of PONV and emesis related to chemotherapy and after paediatric and gynaecological surgeries. Dexamethasone 8 mg was used most widely and found to be most cost effective and was the reason behind our selection for the present study. [13]

Of note, the combination of dexamethasone and ondansetron was better than ondansetron alone[9]. Also, dexamethasone and granisetron was better than granisetron alone.[6]

In our study of group O+D 26.7% patients experienced early nausea while 23.3% patients experienced delayed nausea. In group G+D, 10% of patients had early nausea, 13.3% had delayed nausea. Similar to finding of Lopez et al[14], where only 12% of patients in ondensetron with dexamethasone group had delayed nausea.

Our study regarding incidence of early vomiting in ondansetron with dexamethasone group was 10% and delayed vomiting was 6.7%.. It correlates with the study ofBiswas et al[15] in which the incidence of postoperative vomiting was 7% in ondansetron plus dexamethasone group. In Granisetron with dexamethasone group incidence of early vomiting was 3.3% with no delayed vomiting episode. This correlates with Dabbous. A. et al[16] study where Granisetron with dexamethasone group showed 3.3% of both early and delayed vomiting.

In this prospective randomized double-blind study, we found during the early post operative period (0-3hrs) only 3 patients out of 30 (10%) in Group with Granisetron and Dexamethasone had nausea while 8 patients (26.7%) in group with Ondansetron and Dexamethasone had nausea. This was found to be statistically significant ($P<0.10$).

In our study Granisetron with Dexamethasone group during early period, showed lesser incidence of retching (6.7%) and vomiting (3.3%) when compared to Ondansetron and Dexamethasone group with incidence of retching was 16.7% and vomiting was 10%. But

these were statistically not significant. In delayed period Granisetron with Dexamethasone group showed lesser incidence of nausea (13.3%) and there were no incidence of retching and vomiting compared to Ondansetron and Dexamethasone group where incidence of nausea, retching and vomiting were 23.3%, 3.3% and 6.7% respectively. It was statistically not significant. We did not find any statistical difference between the two groups when we compared early versus late in terms of rescue antiemetic required and side effects.

Gan et al reported a similar study to ours using different dosages for abdominal hysterectomy. They also found that both combinations were equally effective in preventing PONV in the first two hours postoperatively. [17]

Another similar study by Dabbous A et al also found that the combination of dexamethasone 8mg with either granisetron 1 mg or ondansetron 4 mg following induction of anesthesia in patients undergoing laparoscopic surgery showed no statistically significant difference in antiemetic efficacy with minimal side effects.[16]

Our report showed that administration of granisetron 1 mg and dexamethasone 8 mg orondansetron 4 mg and dexamethasone 8 mg in patients undergoing abdominal surgeries under general anaesthesia, prevented PONV in a high percentage of patients with minimal side effects and excellent patient satisfaction. We also found during the early post operative period (0-3hrs) only 10% in Group with Granisetron and Dexamethasone had nausea while 26.7% in group with Ondansetron and Dexamethasone had nausea. This was found to be statistically significant ($P<0.10$). We did not find any statistical difference between the two groups when we compared early in terms of rescue antiemetic required and side effects.

CONCLUSION

This study concludes Dexamethasone 8 mg in combination with Granisetron 1 mg or Ondansetron 4 mg was found to prevent nausea and vomiting in a high percentage of patients undergoing abdominal surgeries under general anaesthesia with minimal side effects. During the early post operative period (0-3hrs) Granisetron with Dexamethasone is effective in preventing nausea than Ondansetron and Dexamethasone. There was no statistically significant difference between the two combinations concerning rescue antiemetic required or side effects.

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