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Original Research Article

A comparative study of ondansetron and granisetron in combination with dexamethasone-in prophylaxis for postoperative nausea and vomiting (PONV) in laproscopic cholecystectomies

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ABSTRACT

Background: 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. PONV is difficult to treat and needs multiple drugs and combination of drugs. Granisetron and Ondansetron are among the commonly used 5HT3 antagonists and used in combination with dexamethasone for prophylaxis against PONV. The aim of the study was to compare the efficacy of combination of antiemetics-Ondansetron 4mg+Dexamethasone 8mg and Granisetron 1mg+Dexamethasone 8mg in prevention of post operative nausea and vomiting.
Methods: 75 patients of ASA 1 and 2 were randomly allocated to three groups-Group 1 (n=25) received Ondansetron 4mg+Dexamethasone 8mg; Group 2 (n=25)-received Granisetron 1mg+Dexamethasone 8mg; Group 3-received saline with dexamethasone 8mg. 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 24hrs. Severity was assessed using PONV Score (0=no nausea;1=nausea only;2=retching;3=vomiting). The adverse effects were also studied.
Results: The incidence of PONV was 16% in Group 1 and 2 and 68% in Group 3. The complete response after 24hr period was 32% in control group, 84% in Group 1 and Group 2. Rescue antiemetics were required only in control group. There was no statistical difference noted between Group 1 and Group 2 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.
Conclusions: 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 laproscopic cholecystectomies under general anaesthesia.

Keywords: Cholecystectomy, Dexamethasone, Granisetron, Laparoscopy, Ondansetron, PONV

INTRODUCTION

Post operative nausea and vomiting (PONV) is the most common and distressing symptom experienced by surgical patients. The incidence of PONV is 20-30 % in general anaesthesia.[1,2] The incidence of PONV is 70-80% in females, and more in ocular, middle ear, gynecological surgeries and laproscopic procedures.[2] Without antiemetic prophylaxis, the incidence 50-70% in laproscopic cholecystectomies. PONV causes harm to surgical site sutures, anastomoses.[3] It increases intra-ocular, intra-cranial pressure and may also cause tachycardia, electrolyte imbalance, wound dehiscence, oesophageal tears and aspiration pneumonitis.

Although various combinations of anti-emetic drugs with different modes of action have been tried, none has been proved to be 100% effective.[1,2] various studies have shown that double and triple combinations of antiemetics are effective in prophylaxis of PONV in high risk patients.[3]

Granisetron and Ondansetron are commonly used 5HT3 antagonists and used in combination with dexamethasone for prophylaxis against PONV. Ondansetron is commonly used in prophylaxis and treatment of PONV. Granisetron is also a cost-effective alternative. There are very few studies comparing the efficacy of ondansetron +dexamethasone combination with granisetron+ dexamethasone combination. In our study we intended to compare the combination of 5HT3 receptor antagonists-Granisetron and Ondansetron with Dexamethasone in prevention of PONV in females undergoing laproscopic cholecystectomy under general anaesthesia.

METHODS

The aim of the study was to compare anti emetic combination-Granisetron + dexamethasone; Ondansetron + dexamethasone for prophylaxis of PONV in elective laproscopic cholecystectomy cases performed under general anesthesia.

Institutional ethical committee clearance was obtained. The study was conducted at the superspeciality block of tertiary care hospital. The study was conducted over a period of six months (January-june2017). The study was a prospective randomized double-blind study. Pre-anesthetic evaluation was done on the previous day and assessed for risk factors. Written informed consent was taken from all willing patients. 75 female patients posted for elective laproscopic cholecystectomy surgery were enrolled for the study. Female patients in the age group of 20-60 years and ASA physical status class 1 and 2 were included for the study. Patients with known hypersensitivity or contra-indications to study drugs; History of nausea, vomiting or retching in 24 hours before anesthesia, pregnant patients, 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, obesity, endocrinal disorders, liver and renal diseases were excluded from the study.

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

Patients were randomly allocated by computed generated random numbers into the following three groups

- Group 1 (n=25) - received Ondansetron 4mg+ Dexamethasone 8mg I V (10ml),
- Group 2 (n=25) - received Granisetron 1mg+ Dexamethasone 8mg IV (10ml),
- Group 3 - control/placebo group received saline+ Dexamethasone 8mg saline IV (10ml).

Study drugs in each group were loaded in a single 10ml syringe and diluted to 10ml with normal saline (Granisetron (granidem, Aristo pharmaceuticals); 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 10ml filled identical syringes by an anaesthetsiologist who was not involved in the study. Standardized anaesthesia regimen was followed. Intravenous access was secured with 18gauge intravenous catheter Monitors for NIBP, SPO2 and ECG were connected, and baseline values were recorded.

All patients were premedicated with intravenous Midazolam (1mg) and intravenous fentanyl in the doses of 2µg/kg. Study drug was administered just before induction. General anesthesia was induced with Inj. Thiopentone sodium 5mg/kg IV and inj. Atracurium 0.5mg/kg was used for neuromuscular relaxation. Patients were intubated with 7.5mm I D Cuffed Endotracheal tube and anaesthesia was maintained on intermittent positive pressure ventilation with O2 (50%) + air (50%) with isoflurane 1-2%. Intra operative monitors used were NIBP, SPO2, ECG, capnogram, endtidal agent concentration and neuromuscular monitor.

Pneumoperitonium was created slowly and intrabdominal pressure was kept at 12mmhg. Tidal volume was frequently altered to maintain the minute ventilation and achieve end tidal CO2 levels of 35 to 45%. Intraoperative analgesia was achieved with bolus doses of fentanyl at 0.5µg/kg. Injection paracetamol 1g infusion was used 30minutes prior to extubation.

Before the removal of port, lidocaine 200mg was instilled at gall bladder site and maintained head low position for 10minutes. Surgical port sites were 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.glycopyrrolate 0.01mg/kg and extubated. Ryles tube was removed before extubation. Post operatively Inj. Ketorolac 30mg IM 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 24hrs post operatively. Post operative pain was assessed with VAS scale 0-10. Nausea was defined as a subjectively unpleasant sensation associated with an urge to vomit.[4] Retching was defined as spasmodic, rhythmic contraction of respiratory muscles without expulsion of gastric contents vomiting was defined as forceful expulsion of

gastric contents.[4] Nausea and vomiting occurring within first 6hrs was considered as early nausea and early vomiting. Complete response was defined as absence of nausea, retching, vomiting and no requirement of rescue antiemetic.[5] All patients were assessed every hourly for the first 6hours, three hourly for next 6hours and sixth hourly for subsequent 12hours using the following PONV scoring system score 0- no nausea, score 1-nausea only score 2-nausea with retching Score 3-vomiting.[6] Vomiting and Retching episodes separated by less than 5min were taken as a single episode.

All patients were given rescue anti-emetic Inj. Metoclopromide10mg IV only if they complained of nausea and vomiting for more than two episodes in 1hr period. Patients who received rescue antiemetics were excluded from the study. Patients were also being monitored for adverse effects like headache, dizziness, drowsiness, flushing and sedation in 24hr 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 24hrs post operatively. Any episode of Nausea, Retching and Vomiting was recorded and assessed using PONV score.[6] The groups were comparable with respect to age, weight and body mass index, consumption of analgesics, duration of surgery and anaesthesia were comparable (Table 1).

Table 1: Demographic and intra-operative parameters.

Parameter	Group 1 N=25	Group 2 N=25	Group 3 N=25
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)
Duration of surgery	90.11 (12)	88.16 (23)	93.46 (18)
Dose of fentanyl (MCG)	152 (5)	155 (12)	154 (33)

PONV scores were assessed and tabulated (refer to Tables 2,3,4).

Table 2: Incidence of nausea (score 1) in 24 hours.

Time	Group 1	Group 2	Group 3
0-6h	0	0	12%
6-12h	4%	8%	24% (*)
12-18h	4%	4%	20% (+)
18-24h	4%	0	15%
Total 24h	N=25	N=25	N=20

* Four patients received rescue antiemetics in group 3 and were excluded from further observation.

Table 3: Incidence of retching (score 2).

Time	Group 1	Group 2	Group 3
0-6h	0	0	4
6-12h	0	0	4.7%
12-18h	0	0	0
18-24h	0	0	0
Total 24h	N=25	N=25	N=20

Complete response (score 0) for 0-12 hour was 100%, 100%and 61.9%% in group 1, group 2 and group 3 respectively. There were no adverse effects noted in any of the groups in first 6hrs. (Refer Table 5).

Table 4: Incidence of vomiting (score 3) in 24 hours.

Time	Group 1	Group 2	Group 3
0-6h	4%	4%	16%
6-12h	0	0	9.5%
12-18h	0	0	5%
18-24h	0	0	0
Total 24h	N=25	N=25	N=20

Table 5: Comparison complete response (score 0) in 24 hours.

Time	Group 1	Group 2	Group 3
0-6h	92	88	40%
6-12h	100	100	61.9%
12-18h	96	96	75%
18-24h	96	100	85%
Total 24h	N=25	N=25	N=20

The incidence of PONV (score-1,2,3) are tabulated at intervals of 6 hours and complete response was noted in all three groups.

There was no statistical difference observed between group 1 and 2 in first 12 hours but significant difference was observed between group 1, group 2 and control groups (Table 6).

Table 6: Comparison of PONV scores.

Time	Group 1 and Group 2	Group1 and group 3	Group 2 and group 3
0-6h	0.7	<0.05	<0.05
6-12h	0.459	<0.05	<0.05
12-18h	0.76	0.81	0.65
18-24h	0.689	0.67	0.89
Significance	Not significant	Significant within 12h	Significant within 12h

Over 24hour period, the complete response was 84% in Group 1 (ondansetron + dexamethasone) and Group 2 (granisetron + dexamethasone). There was no statistically significant difference observed at 24 hours. Therefore, the incidence of PONV was 16% in Groups 1 and 2 (Table 7).

Table 7: summary of Incidence of PONV, Complete response and adverse effects in 24 hours.

	Incidence of PONV	Complete response	Adverse effects
Group 1	16%	84%	0%
Group 2	16%	84%	0%
Group 3	68%	32%	0%

In the control group who received only dexamethasone, the complete response over 24 hours was 32% and the incidence of PONV was 68%. The VAS score for pain was 3.5 to 4.2 in all groups. No adverse effects were listed.

DISCUSSION

Laproscopic cholecystectomy is a well-accepted procedure for gall bladder removal. Its known for the benefits of faster recovery, less pain, early discharge and better cosmetic result. However, laproscopic surgeries have high incidence of PONV. Laproscopic cholecystectomies have the incidence of 50-70%.[1,2,7,8] PONV within 24hours of surgery may negate the benefits by causing wound dehiscence, longer hospital stays, pain at port sites, electrolyte disturbances, disruption of sutures and aspiration of gastric contents too.

Therefore, prophylaxis of PONV is important. As the incidence of PONV is high in laproscopy, combination of antiemetics are recommended. Several studies have proved that combination of antiemetic-5HT3anatagonists with dexamethasone, effectively reduces the incidence of PONV.[7-9]

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.[10] 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 and in the gut or by an anti-inflammatory action at operative sites.[11]

Gregory et al reported the effectiveness of 5HT3 antagonists in prevention of chemotherapy induced nausea and vomiting.[9,12] 5HT3 anatagonists are the first line therapy in prevention of PONV. Currently ondanstron, granisetron and palonosetron are commonly used. Combination of corticosteroid with 5HT3 receptor anatagonist is proved to have better antiemetic effect. The mechanism could be by shunting away tryptophan from 5HT pathway in neural tissues, increasing the sensitivity of receptors for antiemetic drugs.[12]

Studies have shown that combination of granisetron with dexamethasone is effective in prevention of PONV as the combination therapy with ondansetron and dexamethasone.[8,9,12] Fuji et al concluded that -granisetron 20mcg/kg is the recommended dose for combination with dexamethasone 8 mg in prophylaxis of PONV.

The FDA and SAMBA guidelines recommended 1mg as the dose of granisetron for prevention of PONV. Elhakim M et al concluded that dexamethasone 8mg represented the minimal effective dose for combination with ondansetron 4mg for prophylaxis of PONV.[3] Hence our dose selection is justified.

The total incidence of PONV in our study, in two groups 1 and 2 (O+D and G+D) was 16%. Complete response was 84% in both the groups. Dabbos et al reported the incidence of PONV over 24hours was 4.8% and complete response was 95.2% in G+D group and O+D groups.[13] There was no statistically significant difference between granisetron and ondansetron combinations. Similarly, Kushwaha et al reported 12% and 8% in combination of granisetron and odansetron.[6] Gan T J et al and Kushwaha et al have noted that there is no statistical difference in G+D and O+D group.[14,6] In the present study also, the difference in vomiting in 24hour period between O+D and G+D groups was also not statistically significant. The results of our study concur with earlier studies.

Sanjowal et al reported complete response of 92% with ondansetron and dexamethasone combination.[15] Ahsan et al study with O +D combination in cholecystectomy had

incidence of 12%.[16] In our study the incidence is 16%. Results of our study concur with the results of metaanalysis proving that antiemesis with combination of 5HT3 and dexamethasone is effective than single drug therapy.[17,18] Dexamethasone administered as single antiemetic drug too has a significant reduction in PONV. In our study too, dexamethasone group (group 3) had incidence of PONV of 68% and complete response was 32%. Significant difference was observed between group 1 with group 3 and between group 2 and group 3. Therefore, combination of anti-emetic drugs has better control over PONV.

In our study, there was no incidence of adverse effects like headache, dizziness, drowsiness and sedation, however, Thomas et al reported adverse effects like fatigue, dizziness and flushing and Gan T J et al reported drug related adverse effects as 3% in O+D group.[19,14] Fujii et al observed the adverse effects like headache, dizziness, drowsiness and sedation in G+D group.[12]

CONCLUSION

The incidence of PONV was low in all groups after 12hrs. There was similar incidence of PONV between the all three study groups after 12hrs. There was no statistical difference observed after 12hrs among the groups. In 24hrs, Prophylaxis with ondansetron 4mg or granisetron 1mg in combination with dexamethasone 8mg had reduced the incidence of nausea and the complete response achieved in our study was 84% in Group 1 and Group 2 and 32% in Group 3. Combination of 5HT3 receptor antagonists with dexamethasone has better control of PONV than administration of single drug therapy in high risk cases. We conclude that, combination of dexamethasone 8mg with either granisetron 1mg or ondansetron 4mg is effective in prophylaxis of PONV in laproscopic cholecystectomy.

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