



Original Research Article

Comparative study of ondansetron, granisetron and granisetron with dexamethasone for prevention of postoperative nausea and vomiting (PONV) in patients undergoing laparoscopic cholecystectomy

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ABSTRACT

Introduction: An assortment of drugs are being used for managing postoperative nausea and vomiting after laparoscopic surgeries. Combination anti-emetic therapy using 5HT₃ antagonists with dexamethasone as an adjunct is being tried owing to its improved efficacy for prevention or treatment of PONV.

Materials and Methods: This was a prospective, randomized, double blind, comparative study conducted on 150 patients aged between 18 to 65 years scheduled for laparoscopic cholecystectomy. Group O received 0.1 mg/Kg IV ondansetron upto a maximum dose of 8 mg. Group G received 0.04 mg/kg IV granisetron upto a maximum dose of 3mg. Group G+D will receive 0.04mg/kg IV granisetron and 8mg Dexamethasone.

Results: The three groups were comparable in terms of demographic data. Our results showed that the patients who had received combination of granisetron and Dexamethasone showed a better complete response as compared to patients who received ondansetron and patients who received granisetron alone. This was seen in all three time periods of 2-6 hours, 6-12 hours and 12-24 hours postoperatively with a p value less than 0.001 making it statistically significant.

Conclusion: Combination therapy with granisetron and dexamethasone IV used as prophylactic antiemetic is better than granisetron or ondansetron given IV alone. IV granisetron and dexamethasone combination has fewer side effects compared to ondansetron or granisetron. Need for the rescue antiemetic was least in the patients receiving granisetron and dexamethasone combination as compared to in patient receiving ondansetron and granisetron alone.

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1. Introduction

Postoperative nausea and vomiting (PONV) defined as nausea or vomiting occurring within 24 hours of surgery is one of the most common perturbing adverse effects of surgery. The incidence of PONV is between 60% to 72%.¹ It results from surgical, anaesthetic and patient factors and is mostly considered to be complex.

The cause of PONV after laparoscopic surgeries is credited to factors such as insufflation of the

peritoneum with Carbondioxide, peritoneal stretching and irritation of the peritoneum. PONV results in morbidity like wound dehiscence, bleeding from surgical site, pulmonary-aspiration of gastric contents, fluid imbalance and electrolyte disturbances, delayed recovery and hospital discharge and decreased patient satisfaction.² A variety of drugs are being used for preventing PONV. These include conventional antiemetic agents like metoclopramide (Dopamine receptor antagonist) as well as newer drugs such as ondansetron, granisetron and ramosetron (5HT₃ receptor blockers). An ideal antiemetic agent should have quick onset and relatively long duration of action with

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minimal side effects.

Ondansetron, the first 5-HT₃ receptor antagonist to be initiated in medical practice, is the most commonly used drug of this class.³ Granisetron is a comparatively newer 5HT₃ receptor antagonist that is found to be more effective than the other commonly used antiemetic drugs.⁴ Dexamethasone, a long-acting glucocorticoid with a half-life of 36–48 h after a single dose of 8 mg is usually given i.v. before induction of anesthesia.⁵ It increases the efficacy of other antiemetic drugs like metoclopramide, ondansetron and granisetron.⁶ The mode of action though not specific is attributed to anti-inflammatory and membrane stabilizing effects of the drug along with mood enhancing and appetite stimulating effects due to the release of endorphins.⁷ Adjunctive anti-emetic therapy using 5HT₃ antagonists and dexamethasone has provided good results and offered better efficacy for prevention or even treatment of PONV.^{8,9}

Wang et al. in a meta-analysis of randomized controlled trials on dexamethasone versus ondansetron in the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic surgery have reported that ondansetron was better at decreasing PONV than dexamethasone in the early postoperative stage (0–6 h), while in the late postoperative stage (6–24 h), dexamethasone was more effective than ondansetron.¹⁰

Gupta P et al., Erhan Y et al., Nadia B et al. and Bhattarai B et al. in separate studies have reported that Dexamethasone when used as an adjunct is more effective for prevention of PONV in comparison to individual ondansetron or granisetron.^{5,11–13}

The prophylactic potency and the clinical efficacy of these drugs in the prevention of PONV is a subject of keen interest in patients receiving general anaesthesia. We conducted this study to evaluate and compare the effect of ondansetron, granisetron and granisetron with dexamethasone for prevention of PONV in laparoscopic surgeries.

2. Materials and Methods

This was a prospective, randomized, double blind, comparative study conducted in a superspeciality Hospital over a period of 12 months from January 2015 to December 2016 after obtaining Hospital Ethical Committee approval. A total of 150 patients aged between 18 to 65 years, belonging to ASA (American Society of Anaesthesiologists Physical Status) I–II, scheduled for laparoscopic cholecystectomy under general anaesthesia were randomly enrolled for the study after obtaining written informed consent.

Sample size was calculated using 95% Confidence interval and power of study 80% as 50 patients in each arm. With an allocation ratio of 1:1:1, samples were randomised by closed envelope method using the numbers generated by the computer or from the random number table to obtain

randomization code for enclosing the numbers in the closed envelopes used for randomization and were divided into 3 groups each having n=50. Group O received 0.1 mg/Kg IV Ondansetron upto a maximum dose of 8 mg, Group G received 0.04 mg/kg IV Granisetron upto a maximum dose of 3mg, Group G+D will receive 0.04mg/kg IV Granisetron and 8mg Dexamethasone.

Patients unwilling to participate in the study, patients who were haemodynamically unstable, posted for emergency surgeries, severe gastrointestinal, respiratory, cardiovascular, renal or hepatic disorders, or chronically on opioid analgesics were excluded from the study. Any drug with a potential anti-emetic effect was withheld 24 hours prior to the administration of anaesthesia.

Pre-anaesthetic evaluation was done for all the patients and fasted as per standard protocols. Patients were given IV Ranitidine 50 mg 2 hours before surgery and once shifted to the operation theatre, electrocardiography (ECG), pulse oximeter (SpO₂) and non-invasive blood pressure (NIBP) monitors were attached. IV access was secured and crystalloid infusion started. The study drug was given IV prior to induction. (All the study drugs were delivered in equivalent volume in 5 ml syringe with a coded label. The anesthesiologist who anesthetized the patient and all hospital personnel involved were unaware of the content of the syringe.) Inj. Fentanyl (2µg/kg) was given IV for analgesia. Anaesthesia was then induced with Inj. Propofol 1–2 mg/kg. Inj. Vecuronium (0.1 mg/kg body weight) was used as muscle relaxant. Patient was then intubated using an appropriate sized endotracheal tube. Patient was mechanically ventilated and an end tidal carbon-dioxide (ETCO₂) between 30–35 mm Hg was maintained. Anaesthesia was maintained with 66% Nitrous oxide in Oxygen and Isoflurane. ECG, NIBP, SpO₂, ETCO₂ were monitored throughout the procedure. At the end of the procedure, muscle relaxation was reversed with injection Neostigmine 0.05 mg/kg and Glycopyrrolate 0.01 mg/kg. Patient was extubated after attaining complete reversal and shifted to the post-operative ward. ECG, NIBP and SpO₂ were monitored in the post-operative ward. 100% O₂ at the rate of 5l/min was given via face mask for 30 minutes postoperatively. Post operative analgesia was provided with paracetamol infusion 1gm IV over 20 minutes.

Postoperatively all patients were observed for every episode of nausea, vomiting and retching and recorded by persons who were unaware of the study drug. (Nausea was defined as unpleasant sensation associated with the awareness of urge to vomit. Retching was defined as labored rhythmic contraction of abdominal muscles without expulsion of gastric contents.) Rescue antiemetic was given in the form of Inj. Metoclopramide 0.2 mg/kg if patient vomited twice or more. Post operative data was collected over 24 hours.

Severity of nausea and vomiting was assessed as:

- Score 0 (no nausea or vomiting),
- Score 1 (nausea),
- Score 2 (retching or mild vomiting),
- Score 3 (two or more episodes of vomiting in 30 min duration).

Data was recorded & results were statistically evaluated. The outcome measures were: Incidence of nausea and vomiting in the 3 groups at 0-2, 2-6, 6-24 hrs and Severity of nausea and vomiting in the 3 groups at 0-2, 2-6, 6-24hrs.

The primary objective of the study was to compare the efficacy of the combination granisetron + dexamethasone with each of granisetron and ondansetron. Previous studies indicate that the combination is able to substantially reduce the incidence of PONV. The analysis of the data was focused on estimating the reduction in incidence of these adverse outcomes. For this purpose the usually used statistical test is 'z' test for proportion which compares two groups at a time. We also proposed to use the same test but in view of multiple applications to the same data the significance level was adjusted for Bonferroni correction. Thus these studies were carried out at 1.7% level of significance. Since the previous studies indicate the definitive decline, we assumed that there is no chance of increase incidence of adverse outcomes in the combined drug group. Thus the statistical test was used for one sided alternative hypothesis.

3. Results

One hundred and fifty patients were recruited and all of them completed the study (n = 50 in each group). Data was compiled on Microsoft Excel 2010 software (Microsoft Corporation, Redmond, Washington, 2010). Data was analysed using SPSS 20 (IBM Corporation, New York, 2014). The data collection was accomplished from January 2016 to January 2017. For statistical analysis, descriptive statistics – minimum, maximum, mean and standard deviation was used. Confidence interval was calculated to 95%. Normality test was done. Independent sample t test was used for data following normal distribution. Chi square test was used for data not following normal distribution. P value less than 0.05 was considered statistically significant.

3.1. Age and gender distribution

Most of the study subjects belonged to the age group 31-40 years (38.6%). The three groups were clinically and statistically comparable with a p value of 0.728. Hence, all groups are comparable in terms of age.

There were 109 females and 41 males in our study. However, there was no statistically significant difference between the groups in terms of gender distribution. (p=0.849)

3.2. Primary outcome measures (Table 1)

3.2.1. 0-2 hrs

In the first two hours, the total number of patients with score 0 were 56%(28) in group O, 70% (35) in group D, and 96%(48) in group G+D. In group O total number of patients with score 1 were 38%(19), score 2 were 4%(2) and 2%(1) with score 3. In group G total number of patients with score 1 were 13, two patients with score 2 and 0 patients with score 3, where as in group G+D only two patients were with score 1 and no patients were with score 2 and score 3 which makes it statistically significant (p value<0.001) as shown in Table 1.

3.2.2. 2-6 hrs

2-6 hrs post surgery total number of patients with score 0 were 14%(7) in group O, 34%(17) in group G and 86%(43) in group G+D. In group O patients with score 1 are 68%(34), score 2 are 16%(8) and 2%(1) with score 3. In group G patients with score 1 were 56%(28) and score 2 were 10%(5) and no patients with score 3, where as in group G+D 14%(7) patients were with score 1 and no patients with score 2 and score 3 which is statistically significant (p value <0.001)

3.2.3. 6-24 hrs

6-24 hrs post surgery total number of patients with score 0 were 14%(7) in group O, 40%(20) in group G and 74% (37) in group G+D. In group O patients with score 1 were 78%(39), 4%(2) patients each with score 2 and 3. In group G patients with score 1 were 22%(11), 2%(1) with score 2 and no patients with score 3, where as there were only 22%(11) patients with score 1, 4%(2) with score 2 and no patient with score 3 in group G+D which makes it statistically significant (p value <0.001).

3.3. Comparison of patients needing rescue antiemetic among three groups: (Table 2)

3.3.1. RA 0-2 hrs

Requirement of rescue antiemetic in group G+D was 0% compared to group G 4%(2) and group O 6%(3) required rescue antiemetic which was statistically insignificant (p value 0.235).

3.3.2. RA 2-6 hrs

Rescue antiemetic was not required for patients in group G+D, where as in group O 16%(8) patients and group G 10%(5) patients required rescue antiemetic in 2-6 hrs postoperative period which is statistically significant (p value 0.016)

3.3.3. RA 6-24 hrs

During this period 4%(2) patients needed rescue anti emetic in group G+D, in group G 2%(1%) and group O

8%(4) patients required antiemetic which is not statistically significant. (p value 0.350)

3.4. Comparison of patients needing rescue antiemetic among three groups in 24hrs post operative period (Table 3)

In 24 hrs post-operative period 4%(2) patients in group G+D compared to group G 16%(8) patients, group O 30%(15) patients required rescue anti emetic which is statistically significant (p value 0.002).

3.5. Side effects

In group G+D only 2%(1) patient had side effect compared to those in group O 18%(9) and group G 8%(4) hence making it statistically significant (p value 0.024). (Table 4)

4. Discussion

Postoperative nausea and vomiting is one of the most perturbing experiences associated with surgery, and many patients find it more bothersome than post-operative pain. Occurrence of unmanageable vomiting can prolong the duration of hospital stay and hence the economic burden on the patient also assume greater meaning.

The problem of PONV is multifactorial, and includes age, obesity, known motion sickness, previous PONV, type of surgery, anaesthetic procedure and technique and degree of postoperative pain. The scheme for the prevention of early and late PONV has progressed from single drug therapy to combination antiemetic therapy, (also called balanced antiemesis). More lately, multimodal management strategies incorporating changes in anesthetic technique, combative fluid management and pain relief strategies have produced even better results.

The present study was undertaken to compare the efficacy of 3 different group of drugs ondansetron, granisetron and granisetron with dexamethasone for prevention of postoperative nausea and vomiting in 150 ASA I and ASAII patients posted for laparoscopic cholecystectomy. The incidence of a complete response (i.e. no PONV or rescue antiemetics), nausea, retching, vomiting and the need for rescue antiemetic were recorded up to 24 hours post surgery.

Patients were divided into three groups, one group of patients receiving ondansetron, second and third groups receiving granisetron and granisetron with dexamethasone combination respectively. We observed incidence and severity of post operative nausea and vomiting during three different time intervals 0-2hrs, 2-6hrs, 6-24 hrs post operatively and compared three groups. Episodes of nausea, retching, and vomiting were recorded for 0-2, 2-6 and 6-24 h, respectively of the postoperative period in all the three groups and categorized into 4 scores-score 0, score 1, score 2, score 3.^{5,14,15}

All the three groups were comparable in terms of age with a p value of 0.71 which is not significant. We noticed that there was a preponderance of females undergoing laparoscopic cholecystectomy in all three groups though there was no statically significant intergroup difference in terms of gender. (p value 0.849) This can be attributed to the increased incidence of cholelithiasis in females.¹⁶ ASA physical status was statistically similar in two groups with p = 0.765. All the three groups had similar weight distribution (p=0.619).

In first two hours post operative period, patients who had received combination of granisetron and dexamethasone had least incidence of nausea i.e only 4%. While patients who received ondansetron showed an incidence of 38%. Patients who received granisetron had 26% incidence of nausea. Incidence of retching was nil in the group of patients receiving combination of granisetron and dexamethasone while patients receiving granisetron and ondansetron showed retching in 4% of the patients in each group.

In the second interval of 2-6 hrs post-operative period maximum incidence i.e 68% of nausea was seen in patients receiving ondansetron while least incidence i.e in 14% noted in the group of patients receiving combination of granisetron and dexamethasone, 56% of patients in the granisetron group complained of nausea during this interval. Incidence of retching in different groups exhibited a similar pattern. None of the patients who received granisetron and dexamethasone complained of retching while 10% of patients who received granisetron and 16% of patients receiving ondansetron complained of retching. In this time interval one patient in ondansetron group vomiting more than one occasion while none of the patients in granisteron group complained of vomiting.

In the time interval of 6-24 hrs post-operatively 22% of patients who had received granisetron and dexamethasone combination had nausea, 4% patients in this group had retching, none of the patients in this group had more than one episode of vomiting while in the patients receiving ondansetron 78% had nausea, 4% patients had retching and 4% patients had more than two episodes of vomiting. 58% had nausea and 2% patients had retching in the group of patients receiving granisetron.

Our results showed that the patients who had received combination of granisetron and dexamethasone showed a higher incidence of a complete response as compared to patients who received ondansetron and patients who received granisetron alone. In other words, patients who had no incidence of nausea or vomiting were higher in number than the patients who had received combination of Granisetron and Dexamethasone. This was seen in all three time periods of 2-6 hours, 6-12 hours and 12-24 hours postoperatively with a p value less than 0.001 making it statistically significant. Similar results were

Table 1: Primary outcome measures among the three groups

| | | O | Group G | G+D | Total | P value |
|----------|---|----------|------------|----------|------------|---------|
| 0-2 Hrs | Score 0 (no nausea or vomiting) | 28 (56%) | 35 (70%) | 48(96%) | 111(74%) | <0.001 |
| | Score 1 (nausea) | 19 (38%) | 13 (26%) | 2 (4%) | 34 (22.7%) | |
| | Score 2 (retching or one episode of vomiting) | 2 (4%) | 2 (4%) | 0 | 4 (2.7%) | |
| | Score 3 (two or more episodes of vomiting in 30 min duration) | 1 (2%) | 0 | 0 | 1 (0.7%) | |
| 2-6 Hrs | Score 0 (no nausea or vomiting) | 7 (14%) | 17 (34%) | 43 (86%) | 67 (44.7%) | <0.001 |
| | Score 1 (nausea) | 34 (68%) | 28 (56%) | 7 (14%) | 69 (46%) | |
| | Score 2 (retching or one episode of vomiting) | 8 (16%) | 5 (10%) | 0 | 13 (8.7%) | |
| | Score 3 (two or more episodes of vomiting in 30 min duration) | 1 (2%) | 0 | 0 | 1 (0.7%) | |
| 6-24 Hrs | Score 0 (no nausea or vomiting) | 7 (14%) | 20 (40%) | 37 (74%) | 64 (42.7%) | <0.001 |
| | Score 1 (nausea) | 39 (78%) | 29 (58%) | 11 (22%) | 79 (52.7%) | |
| | Score 2 (retching or one episode of vomiting) | 2 (4%) | 1 (2%) | 2 (4%) | 5 (3.3%) | |
| | Score 3 (two or more episodes of vomiting in 30 min duration) | 2 (4%) | 0 | 0 | 2 (1.3%) | |

Table 2: Rescue antiemetic requirement among the three groups

| Rescue Anti-emetic | | O | Group G | G+D | Total | P value |
|--------------------|-----------|----------|------------|-----------|-------------|---------|
| 0-2 Hours | Not Given | 47 (94%) | 48 (96%) | 50 (100%) | 145 (96.7%) | 0.235 |
| | Given | 3 (6%) | 2 (4%) | 0 | 5(3.3%) | |
| 2-6 Hours | Not Given | 42 (84%) | 45 (90%) | 50 (100%) | 137 (91.3%) | 0.016 |
| | Given | 8 (16%) | 5 (10%) | 0 | 13 (8.7%) | |
| 6-24 Hours | Not Given | 46 (92%) | 49 (98%) | 48 (96%) | 143 (95.3%) | 0.350 |
| | Given | 4 (8%) | 1 (2%) | 2 (4%) | 7 (4.7%) | |

Table 3: Rescue antiemetic requirement in total 24hrs post-operative period among the three groups

| Rescue antiemetic | O | Group G | G+D | Total | P value |
|-------------------|----------|------------|----------|-------------|---------|
| Given | 15 (30%) | 8 (16%) | 2 (4%) | 25(16.7%) | 0.002 |
| Not given | 35 (70%) | 42 (84%) | 48 (96%) | 125 (83.3%) | |

Table 4: Comparison of individual side effects among the three groups

| | | O | Group G | G+D | Total |
|--------------|---------------------|----------|------------|----------|-------------|
| Side Effects | Nil | 41 (82%) | 46 (92%) | 49 (98%) | 136 (90.7%) |
| | Dizziness | 2 (4%) | 0 | 0 | 2 (1.3%) |
| | Headache | 3 (6%) | 3 (6%) | 1(2%) | 7 (4.7%) |
| | Headache, Dizziness | 2 (4%) | 1 (2%) | 0 | 3 (2%) |
| | Rash | 2 (4%) | 0 | 0 | 2 (1.3%) |

obtained by Pushpalata and Shilpi in their study wherein the incidence of complete response (no PONV, no rescue medication) was 96% in patients receiving granisetron and dexamethasone combination, as compared with 86% with granisetron and 4% with ondansetron during 0-3h after surgery which was clinically significant ($P < 0.05$).⁵ Similarly in a study conducted by Fuji et al., a complete response during 0-3 h after anesthesia was 51%, 82% and 96% in patients who had received placebo, granisetron and G + D combination, respectively. The corresponding incidence during 3-24 h after anesthesia was 56%, 84% and 96%, respectively and concluded that prophylactic use G + D combination is more effective than granisetron alone for the prevention of PONV after breast surgery.¹⁷ Our study was in concordance with the above study. But our study was performed in both male and female patients undergoing laparoscopic cholecystectomy. We also compared the efficacy of granisetron and dexamethasone combination with granisetron and ondansetron for prevention of PONV. B. N. Biswas, A. Rudra too in their study noticed a significant incidence of complete response with combination therapy (granisetron plus dexamethasone) than granisetron alone.¹⁸

The incidence of nausea, vomiting and retching was highest in patients who had received ondansetron as antiemetic in each of the time periods. Rescue antiemetic was given in patients who had a score 2 or 3 in any time interval during the study. Need for the rescue antiemetic was maximum in patients receiving ondansetron i.e. 30%, it was 16% in patients receiving granisetron alone and least in patients receiving granisetron and dexamethasone combination (4%) with a p value 0.002 making it statistically significant.

Rescue antiemetic was required in maximum number of patients during 2-6hrs time interval i.e in patients receiving ondansetron only 6% patients required rescue antiemetic during 0-2hrs, but in 2-6 hrs time interval 16% patients and 6-24hrs time interval 8% patients required rescue antiemetic. In patients receiving granisetron 4%, 10%, 2% patients required rescue antiemetic in 0-2hrs, 2-6hrs, 6-24 hrs respectively. In patients receiving granisetron and dexamethasone, rescue antiemetic was required only in 6-24 hrs time interval in 4% patients. This finding was in accordance with the study done by Nadia Bano et al. in which they concluded that combination therapy with ondansetron and dexamethasone required less rescue antiemetics post-operatively.¹²

In a comparative study between ondansetron and granisetron done by Chaudhari S.A. it was noted 4% patients receiving ondansetron, had mild headache during 24hrs of postoperative period. While a systematic review and meta-analytic study done by Karanicolas, Paul J. on Dexamethasone showed no increase in the incidence of headaches or dizziness.¹⁹ In our study side effects like headache, dizziness, rash were maximum seen in patients

receiving ondansetron (18%) and least in group of patients receiving granisetron and dexamethasone (2%), in patients receiving granisetron incidence is 8% with a p value of 0.024 making it statistically significant. These symptoms can also be attributed to the hypercarbia due to CO₂ insufflation in laparoscopic surgery.

Hence, it can be summarized from our study that combination therapy with granisetron and dexamethasone significantly reduces the incidence of PONV as compared to ondansetron or granisetron alone and with lesser side effects in patients undergoing laparoscopic cholecystectomy.

5. Conclusion

Combination therapy with granisetron and dexamethasone i.v used as prophylactic antiemetic is better than granisetron or ondansetron given i.v. alone. I.V Granisetron and dexamethasone combination has fewer side effects compared to ondansetron or granisetron. Need for the rescue antiemetic was least in the patients receiving granisetron and dexamethasone combination as compared to in patient receiving ondansetron and granisetron alone.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

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