

# Prophylactic Antiemetic Therapy Using Combinations Of Granisetron, Dexamethasone And Droperidol In Patients Undergoing Laparoscopic Cholecystectomy

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## Citation

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## Abstract

**Purpose:** Postoperative nausea and vomiting (PONV) after laparoscopic cholecystectomy remains a common problem despite routine antiemetic prophylaxis. Therefore, this study was undertaken to compare the combinations of granisetron, droperidol and dexamethasone with each other for reducing the incidence and severity of PONV after laparoscopic cholecystectomy. **Methods:** One hundred & sixty patients, aged 20-70 years, scheduled for elective cholecystectomy were enrolled in a randomized, double-blinded manner and assigned to one of four treatment regimens: 5ml normal saline (Group P), granisetron 3mg + droperidol 1.25mg (group GDr), granisetron 3mg + dexamethasone 8mg (group GDx) or dexamethasone 8mg + droperidol 1.25mg (group DxDr). The study drugs were administered I.V. immediately before the induction of anesthesia. A standard general anesthetic technique was used throughout. A blinded observer recorded the emetic episodes. Rescue antiemetics and side effects were assessed during the first 24 hours after anesthesia. **Results:** Complete response, defined as no PONV and no administration of rescue antiemetic medication, was 40%, 95%, 92.5% and 70%, respectively in group P, GDr, GDx and DxDr ( $p < .05$ , among all the groups except between group GDr and GDx). **Conclusion:** Granisetron droperidol and granisetron-dexamethasone are more effective than droperidol-dexamethasone for reducing the incidence and severity of PONV during the first 24 hours postoperatively after laparoscopic cholecystectomy.

## INTRODUCTION

Postoperative nausea and vomiting (PONV) are distressing and frequent adverse events of anaesthesia and surgery, with a relatively high incidence after laparoscopic cholecystectomy (25-42%) when no antiemetic is provided [12]. Numerous antiemetics have been studied for the prevention of PONV in patients scheduled for laparoscopic cholecystectomy. None of the available antiemetics is entirely effective, perhaps because most of them act through the blockade on one type of receptor [345]. It has been demonstrated in the past that combined antiemetics with different sites of activity are more effective for the prevention of PONV following laparoscopic cholecystectomy. The efficiency of a combination of serotonin receptor antagonist (granisetron) and droperidol is superior to monotherapy with either of them [678]. Similarly, adding dexamethasone to 5-HT3 antagonists improve antiemetic efficacy in PONV [791011]. In a recent study haloperidol or droperidol with dexamethasone has been used

for antiemetic prophylaxis in laparoscopic cholecystectomy [12] but this combination has not been compared with other combinations till date. Therefore, we designed this study to compare droperidol – dexamethasone combination with granisetron-droperidol and granisetron-dexamethasone combination for antiemetic prophylaxis in patients undergoing laparoscopic cholecystectomy.

## PATIENTS & METHODS

This was a prospective, double blind, placebo-controlled, randomized study. After approval from the Ethical Committee of the University and written informed consent, one hundred and sixty (160) patients of either sex belonging to ASA physical status I - II, aged 20 - 60 years, scheduled for laparoscopic abdominal surgery, were recruited in this study. Patients with gastrointestinal disease, previous history of postoperative nausea and vomiting (PONV), history of motion sickness, those who had received opioids, antiemetics, steroids or NSAIDs or who had hypersensitivity to any of the three drugs used, were

## Prophylactic Antiemetic Therapy Using Combinations Of Granisetron, Dexamethasone And Droperidol In Patients Undergoing Laparoscopic Cholecystectomy

excluded from this study. All patients were kept fasting for at least 8 hours before surgery and received alprazolam 0.5 mg orally on the night before surgery. Patients were randomly allocated to one of the four groups using a computer generated table of random numbers.

Group P: Patients received 5ml normal saline as placebo,

Group GDr: Patients received intravenous granisetron 3 mg in combination with droperidol 1.25 mg,

Group GDx: Patients received intravenous granisetron 3 mg in combination with dexamethasone 8 mg,

Group DxDr: Patients received intravenous dexamethasone 8 mg in combination with droperidol 1.25 mg.

The study medications were prepared by the technician in identical syringes and in equal volume to make the study double blind. Neither the patient nor the observer was aware of the medication received by the patient. A standard protocol for general anesthesia was followed for all the patients. All patients were premedicated with glycopyrrolate 0.2 mg intramuscularly 30 minutes before induction of anesthesia. Fentanyl 3µg/kg and midazolam 0.01mg/kg was given intravenously before induction. Test drug was administered just before induction of anesthesia. Anesthesia was induced with sodium pentothal 4 to 6mg/kg intravenously and endotracheal intubation was facilitated with succinylcholine 1.5 to 2.0 mg/kg. Anesthesia was maintained with 60% nitrous oxide in oxygen with vecuronium bromide 0.04 to 0.08 mg/kg and intermittent fentanyl 1-2µg/kg. A nasogastric tube was inserted in all patients and was removed before extubation after suctioning. Intraoperative monitoring was done by recording heart rate, blood pressure, ECG, EtCO<sub>2</sub>, and oxygen saturation every 5 minutes. Mechanical ventilation was adjusted so as the EtCO<sub>2</sub> remained between 30-35mmHg. At the end of the surgery residual neuromuscular blockade was antagonized with neostigmine 0.05 mg/kg and glycopyrrolate 0.02mg/kg and extubation was done following complete recovery from general anesthesia. Postoperatively vitals monitoring (heart rate, blood pressure and oxygen saturation) were done. Any episode of nausea, vomiting and retching experienced by the patients were recorded immediately after extubation and thereafter in postoperative period at 0-4, 4-8, 8-12 hours, 12-18 hours and 18-24 hours. Complete response of prophylactic antiemetic is defined as no PONV and no need for rescue antiemetic medication 24 hours after anesthesia. Other adverse effects of drugs like headache, giddiness,

constipation and allergic reaction if any, were recorded throughout the postoperative period. To assess severity of postoperative nausea and vomiting, the scoring system was evolved (no nausea- Score 0, nausea only- Score 1, nausea with retching Score-2 vomiting – Score 3. When vomiting occurred or on patient's request 4 mg IV Ondansetron was given. For postoperative pain all patients received 75mg Diclofenac Sodium IM.

Sample size was predetermined. We expected at least 30% difference in all treatment groups as compared to placebo, in the proportion of patients requiring rescue IV Ondansetron for nausea and vomiting. The  $\alpha$  error was set at 0.05 (two sided) and  $\beta$  error at 0.10. Analysis showed that 40 patients per group would be sufficient [13]. Statistical analysis of data among the groups was performed by one way analysis of variance (ANOVA) with Bonferroni correction for multiple comparisons, Chi-Square test, or Fischer's exact test, as appropriate. A p value <0.05 was considered significant.

## RESULTS

Patient profile and information regarding surgery and anesthesia are summarised in Table I.

### Figure 1

Table 1 : Demographic Data

Groups	P	GDr	GDx	DxDr
Age (in years)	35.94±10.12	36.50±9.4	38.48±10.12	28.9±10.22
Weight (in kg)	55.18±7.52	56.32±9.4	54.42±10.25	55.34±8.92
Duration of anaesthesia (in min)	108.10±9.52	106.25±10.68	108.90±9.18	107.10±8.12
Sex (Male:Female)	8:32	10:30	9:31	8:32

The treatment groups were comparable with regards to patient demographics and types of operation. A complete response was observed in 40%, 95%, 92.5% and 70% patients, respectively in group P, GDr, GDx and DrDx (p < 0.05 among all the groups except between group GDr and GDx) (Table II). Rescue antiemetic was required by 40% and 7.5% patients of group P and DrDx, respectively. None of patients in GDx and GDr group required rescue antiemetic (Table II).

**Figure 2**

Table 2: Data regarding PONV in different groups

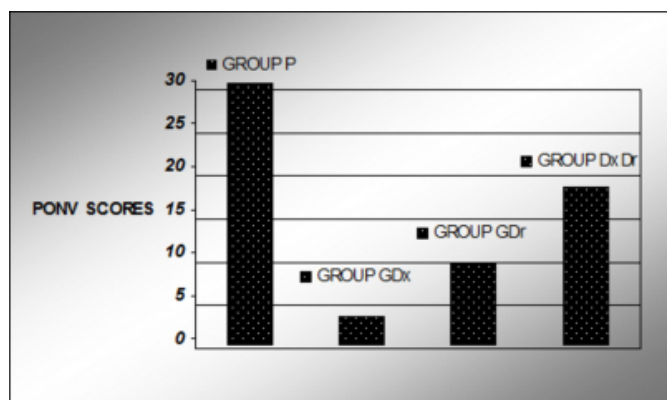
Groups	P n (%)	GDr n (%)	GDx n (%)	DxDr n (%)
Complete response	16 (40%)	38 (95%)*	37 (92.5%)*	28 (70%)*
Nausea	12 (30%)	1 (2.5%)*	2 (5%)*	8 (20%)*
Retching	6 (15%)	1 (2.5%)*	1 (2.5%)*	2 (5%)
Vomiting	6 (15%)	-	-	2 (5%)*
Rescue antiemetic	16 (40%)	-	-	3 (7.5%)*

- \* p<0.05 (in comparison to the placebo group)
- + p<0.05 (group II Vs group IV)
- p<0.05 (group III Vs group IV)

PONV score was highest in group P (30) and was 3, 9 and 18 in group GDr, GDx and DxDr, respectively (Figure 1).

**Figure 3**

Figure 1: PONV Scores in different groups



The most common adverse effects were headache, dizziness and constipation, and their incidence was highest in group P, although, statistically there was no difference among the groups (Table III). No extra-pyramidal symptoms were observed in any of the groups.

**Figure 4**

Table 3: Adverse Events

Groups	P		GDr		GDx		DxDr	
	n	%	n	%	n	%	n	%
Headache	4	10	2	5	3	7.5	4	10
Dizziness	4	10	2	5	2	5	3	7.5
Constipation	2	5	1	2.5	2	5	2	5
Extra pyramidal	-	-	-	-	-	-	-	-
Hyper sensitivity	-	-	-	-	-	-	-	-

**DISCUSSION**

The major finding of this study was that a complete response, no PONV and no rescue antiemetic medication during the first 24 hours after anesthesia in patients who had received granisetron–droperidol combination (95%) and granisetron–dexamethosone combination (92.5%) was greater than in those who had received placebo (40%) or droperidol–dexamethosone combination (70%) (p<0.05).

Patients undergoing laparoscopic surgery have a relatively high incidence of PONV (25 –42%) [12]. The etiology of PONV is not exactly known, but it is probably multifactorial [14]. A number of factors which includes age, sex, obesity, and history of motion sickness and / or previous PONV, menstruation, operative procedure, anesthetic technique and postoperative pain are considered to increase the incidence of PONV. In this study, however, these factors were well balanced among all the groups, so that the differences in the incidence of PONV among them can be attributed to the differences to the drugs administered.

Granisetron has been reported to effectively reduce the incidence of PONV after laparoscopic cholecystectomy [15]. The precise mechanism induced in the prevention of PONV is not known, but it has been suggested that it may act on sites containing 5-HT3 receptors with demonstrated antiemetic effects [16]. Droperidol is a major tranquilizing drug possessing antiemetic activity as a result of its antagonistic property at dopamine receptor [14]. The role of dexamethasone in the surgical setting is less well understood. The first clinical trial suggesting that

dexamethasone may prevent PONV was published in 1993 [17]. Subsequent studies indicated that dexamethasone alone [1819] or in combination with a 5-HT<sub>3</sub> receptor antagonist [789101116], may indeed be an interesting alternative for the control of emetic symptoms in the postoperative period.

Granisetron-dexamethasone and granisetron-droperidol combinations has been used in past [6710], but no published studies comparing the efficacy of droperidol-dexamethasone combination with other combination were found. We demonstrated in this study that a complete response was significantly greater in patients who had received droperidol-dexamethasone combination (70%) than in placebo group ( $p < 0.05$ ), but it was lesser than those of granisetron-droperidol (95%), and granisetron-dexamethasone combination (92.5%) ( $p < 0.05$ ). In the previous study, complete response with granisetron-dexamethasone 10 and granisetron-droperidol [6] combination seen was 95% & 98%, respectively. However, the difference observed by us may be attributed to our smaller sample size.

It has been demonstrated that 3 mg granisetron and 12.5 mg droperidol reduces the incidence of PONV in patients undergoing laparoscopic cholecystectomy [68]. On the other hand, the dose of dexamethasone (8mg) used in this study was based on several recent reports [57]. They demonstrated that 8 mg dexamethasone was effective for the prevention of PONV. This study also showed that 7.5% patients in dexamethasone- droperidol group and 40% patient in placebo group required another rescue antiemetic for the treatment of PONV compared none who had received granisetron-dexamethasone / droperidol combination ( $p < 0.05$ ). This suggests that granisetron in combination with either of the drugs (droperidol/dexamethasone) is superior in reducing the severity of PONV after laparoscopic cholecystectomy.

One of the important problems with droperidol for prophylactic antiemetic therapy is the risk of undesirable adverse events, such as excessive sedation and extra-pyramidal signs [14]. In this study, however, these symptoms were not observed in any of the group. Thus, the risk of undesirable side effects may not be increased with the combination used in our study.

In conclusion, in the surgical setting of laparoscopic cholecystectomy, granisetron-droperidol and granisetron-dexamethasone effectively reduces the incidence and severity of PONV during the first 24 hrs postoperatively.

Droperidol-dexamethasone is not as effective as the above mentioned combinations in preventing PONV. We recommend further trials of this combination using different doses to be effective in reducing PONV after laparoscopic cholecystectomy.

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