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Original Research Article

Dexamethasone or Promethazine as an adjuvant to Granisetron for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: a prospective, randomized double blind study

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Abstract: Postoperative nausea and vomiting (PONV) after laproscopic cholecystectomy remains a common problem in spite of introduction of newer antiemetics with better efficacy and safety profiles. None of the available antiemetics is entirely effective, perhaps because most of them act through the blockade on a particular type of receptor. The addition of adjuvants like dexamethasone and promethazine to antiemetics like granisetron can improve the outcome. However, lack of knowledge limits its acceptance. The aim of the present study was to compare the effects of dexamethasone and promethazine as adjuvant to granisetron for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy. In Method 120 patients, aged 25-55 years, scheduled for elective cholecystectomy were enrolled in a randomized, double blinded manner and assigned to one of three treatment regimens: granisetron2mg + 5ml normal saline (Group I), granisetron2mg + dexamethasone 8mg (Group II) and granisetron2mg + promethazine 12.5mg (Group III). Occurrence of PONV along with need for rescue antiemetic during the first postoperative day was compared between groups as a primary outcome. In Results the Complete control of PONV (no emesis, no rescue treatment for 24 hours after administration of study agent) was achieved in only 72.5% of cases in group I, in 95% of cases in group II which is significant ($p<0.05$) and 87.5% of cases in group III which is not significant ($p>0.05$). In conclusion, in the surgical setting of laparoscopic cholecystectomy, dexamethasone is better adjuvant than promethazine in reducing the incidence and severity of PONV during the first 24 hrs postoperatively.
Keywords: Postoperative nausea and vomiting (PONV), dexamethasone and promethazine.

INTRODUCTION

The most common and distressing symptoms, which follow anaesthesia and surgery, are pain and emesis. The syndrome of nausea, retching and vomiting is known as 'sicknesses and each part of it can be distinguished as a separate entity [1]. PONV (postoperative nausea and vomiting) has been characterized as the "big little problem" by Kapur[2] and has been common complication for both in patients and out patients undergoing virtually all types of surgical procedures. Sometimes nausea and vomiting may be more distressing especially after minor and ambulatory surgery, delaying the hospital discharge. The consequences of PONV are physical, surgical and anaesthetic complications for patients as well as financial implications for the hospitals or institutions[3]. Physical consequences include sweating, pallor, tachycardia, and stomach ache, increased chances of oesophageal tear, wound dehiscence and electrolyte imbalance. Surgical consequences include disruption of vascular anastomoses and increased intracranial pressure[4]. The anaesthetic consequences are aspiration pneumonitis and discomfort in recovery. Institutions are already over burdened with financial restraints because of increased nursing care, delayed discharge from Phase I and II recovery units and unexpected admissions. Hence, prophylactic antiemetic therapy is needed for all these patients. Laparoscopic surgery is one such condition, where risk of PONV is particularly prolonged. This increased risk of PONV is due to pneumoperitoneum causing stimulation of mechanoreceptors in the gut[5].

None of the available antiemetics is entirely effective, perhaps because most of them act through the blockade on a particular type of receptor. There is possiblity that combined antiemetics with different sites of activity would be more effective than one drug alone

for the prophylaxis against PONV. Combination of antiemetic therapy is often effective for the prevention of PONV following laparoscopic cholecystectomy.

The present study was designed to compare the clinical efficacy of a single, preoperative, intravenous titrated dose of granisetron alone, granisetron plus promethazine and granisetron plus dexamethasone for prevention of nausea and vomiting after laparoscopic cholecystectomy under general anaesthesia.

MATERIALS AND METHODS

After taking approval from ethical committee the present study was conducted in the department of Anaesthesiology in JawaharLal Nehru Medical college, Aligarh on 120 patients between 25 to 55 years ASA grade I &II, Hb> 10 gm% planned for laparoscopic cholecystectomy under general anaesthesia. Patients with gastrointestinal disease other than gall bladder 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 known hypersensitivity to any of the three drugs, were excluded from this study.

Written and informed consent was taken from all. Preanaesthetic assessment was done a day before surgery. Patients were randomly divided into three categories:

Group I: Patients who received intravenous granisetron 2 mg in combination with 5ml Normal saline.

Group II: Patients who received intravenous granisetron 2 mg in combination with Dexmethasone 8 mg.

Group III: Patients who received intravenous granisetron 2 mg in combination with Promethazine 12.5 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.

All patients were premedicated with oral alprazolam (0.25mg) and ranitidine (150 mg) night before they started NPO. A standardised protocol for general anaesthesia was followed for all patients.

All patients were premedicated with granisetron 2 mg i.v.And fentanyl 2ug/kg i.v. just before induction of anaesthesia. Patients in all 3 groups were administered antiemetics as adjuvants diluted in 5 ml normal saline i.v. slowly over 30 sec., one minute before induction of anaesthesia. The patients were induced with thiopentone 5.0 mg/kg body weight i.v. after adequate preoxygenation and tracheal intubation was facilitated with vecuronium bromide 0.1 mg/kg i.v., 3 minutes after its administration. Anaesthesia was maintained with N_2O and O_2 mixture (60% : 40%) and repeated dose of vecuronium (0.02 mg/kg) for muscle relaxation supplemented with isoflurane as and when required. Residual neuromuscular block of vecuronium was antagonized with i.v. neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg) at the end of the surgery. Intraoperative and postoperative monitoring of patients was done by recording pulse, blood pressure and oxygen saturation carefully. No other sedatives or antiemetic drugs were administered. The postoperative analgesia was standard for all and was provided with tramadol 50 mg plus diclofenac sod. 75 mg, both i.m. 15 – 20 min. after the trachea was extubated and patients were fully conscious.

Episodes of postoperative nausea, vomiting and retching experienced by the patients within first 24 hours of anaesthesia i.e. immediately after extubation and thereafter in postoperative ward at different intervals were observed and recorded. Complete response of prophylactic antiemetic is defined as no PONV and no need for rescue antiemetic medication 24 hours after anaesthesia. Incidence of postoperative nausea and vomiting was evaluated on the scoring system :- 0 = none; 1 = nausea; 2 = nausea with retching; 3 = vomiting[6].

Severity of postoperative nausea and vomiting was evaluated by total score after 24 hours. Occurrence of incidence of any adverse effects supposed to be due to granisetron, promethazine and dexamethasone were looked for.

All the observed parameters and results were carefully recorded and analysed statistically. Statistical analysis of data was done using arithmetic mean and standard deviation. Comparison of results among two groups was done using Chi-square test through Minitab software. “P” value < 0.05 was considered statistically significant.

RESULTS

The treatment groups were comparable with regards to patient demographics having no significant difference between them (Table I) ($p>0.05$). The control and experimental groups were also comparable with regard to duration of anaesthesia.

Complete control of PONV (no emesis, no rescue treatment for 24 hours after administration of study agent) was achieved in only 72.5% of cases in group I, in 95% of cases in group II which is significant ($p<0.05$) and 87.5% of cases in group III which is not significant ($p>0.05$) (Table II). Total number of patients with PONV was highest in group I (27.5%) followed by group III (12.5%) and least in group II (5%). PONV score was highest in group I (15) and was 4 and 6 in group II, III respectively (Figure 1).

The emetic episodes in group I was maximum during the first 2 hrs while in group II and group III were maximum during 2-6 hrs (Figure 2). There were no emetic episodes in any of the groups after 12 hrs. Rescue antiemetic treatment required by group II was lower than in group I and III, highest in group I (Figure 3).

The common side effects in group III are drowsiness (15%) and dizziness (12%). The common side effects in group I are dizziness (5%) and drowsiness (5%). There are no significant side effects in group II.

Table 1: Demographic Data (Mean + SD)

Variables	Group - I	Group - II	Group - III	p-value
Mean Age (years)	36.20+6.13	38.50+6.11	37.3+4.88	0.355
Mean Weight (Kg)	56.36+5.90	54.56+6.15	55.40+5.24	0.765
Sex (Male : Female)	8:17	6:19	8:17	0.713
Mean Duration of anaesthesia (in minutes)	106.80+10.39	108.72+10.44	107.20+9.90	0.924

Table 2: PONV scores during 24 hours postoperatively in different groups

PONV Score	Group - I n (%)	Group - II n (%)	Group – III n (%)
0	29 (72.5%)	38 (95%)	35 (87.5%)
1	8 (20%)	2 (5%)	4 (10%)
2	2 (5%)	0 (0%)	1 (2.5%)
3	1 (2.5%)	0 (0%)	0 (0%)
Patients with PONV	11 (27.5%)	2 (5%)	5(12.5%)

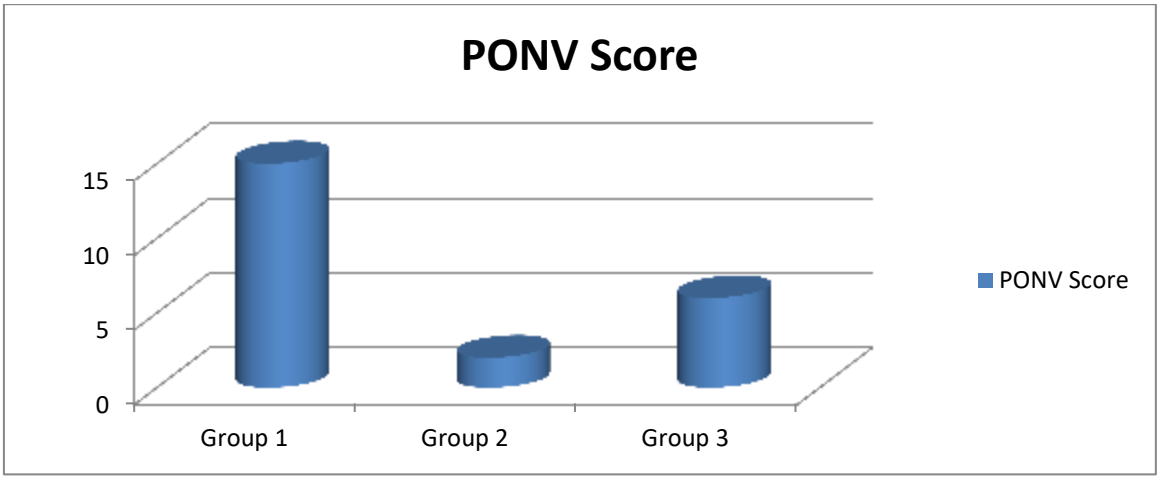

Fig 1: PONV scores in different groups

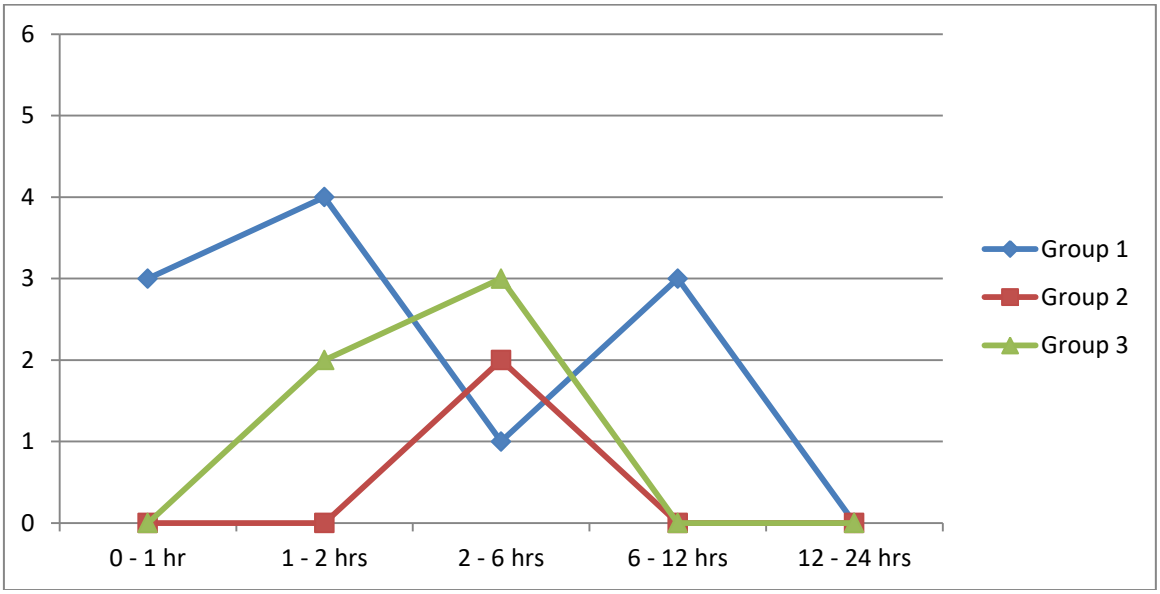

Fig 2: Emetic episodes among groups at different time intervals

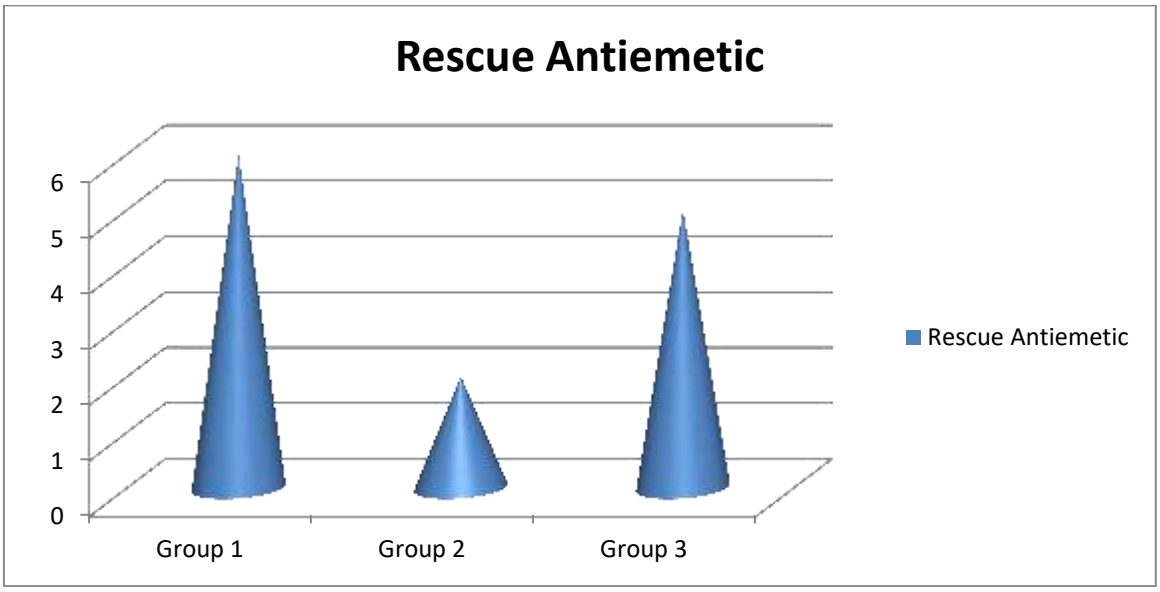

Fig 3: Rescue Antiemetic Treatment

Table 3: Adverse Effects

Adverse effects	Group - I	Group - II	Group - III
Dizziness	2	1	5
Drowsiness	2	1	6
Headache	1	-	-
Hypotension	1	-	-
Constipation	1	-	-
Extra pyramidal symptoms	-	-	-
Hypersensitivity	-	-	-

DISCUSSION

Although the laparoscopic approach for cholecystectomy has decreased surgical morbidity and has become a popular procedure, the incidence of PONV is appreciably high when no prophylactic antiemetic is given[7]. The etiology behind the PONV following laparoscopiccholecystectomy is complex and multifactorial [3]. A number of factors including anesthetic technique, sex, pain, postoperative care and

patients demographic data, are considered to influence the incidence of emesis.

The recent consensus panel guidelines of the Society of Ambulatory Anesthesia (SAMBA) recommend that combination antiemetic therapy be used in high-risk subjects [8]. The 5-HT3-receptor antagonist has demonstrated their superior efficacy, safety, and tolerability over conventional antiemetics[9]. Granisetron is highly selective 5-hydroxytriptamine type-3 receptor (5HT3) antagonist with negligible adverse effects, whereas promethazine has few like – drowsiness, hypotension and extra pyramidal syndrome. Dexamethasone, a glucocorticoid has been used as an antiemetic in patients receiving chemotherapy, with limited side effects[10] and has also been reported to decrease chemotherapy induced emesis when added to antiemetic regime.

Y.Fujii*et al.;* [11] reported that the effective dose of oral granisetron for prophylaxis of prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy, the incidence of emesis free period was 60% with granisetron1mg, 83% with 2mg and 83% with 4mggranisetron dose ($p<0.01$). In our study also 2mg (40ug/kg) dose of Granisetron was used. Our study demonstrated a complete response in 72.5% in patients who had received granisetron alone which is comparable to 70% observed in the previous study conducted by Erhan*et al.*[12].

The first clinical trial suggesting that dexamethasone may prevent PONV was published in 1993 [13] Subsequent studies indicated that dexamethasone alone[14, 15] or in combination with a 5-HT3 receptor antagonist[16, 17] may indeed be an interesting alternative for the control of emetic symptoms in the postoperative period. Granisetron Dexamethasone and Granisetron Promethazine combination both have been used and compared with Ganisetron in separate studies [18,19] but no published studies comparing the efficacy of these combinations together were found.

In present study, the incidence of PONV in group-II patients receiving granisetron dexamethasone combination was significantly reduced to 5% from 27.5% in control group ($p<0.05$). This 95% complete response in our combination group is in very well accordance with 95% response observed in a study conducted by Biswas*et al.*[17] and 90% response recorded in a study conducted by Tarek*et al.*[20]. Also, the incidence of postoperative nausea and vomiting in group- III patients receiving granisetron promethazine combination was 12.5% compared to the control group (27.5%) ($p>0.05$). This 87.5% complete response is slightly more than the 70% response recorded in a study conducted by Ganet al.[19]**.** This difference may be due to the higher doses of granisetron and promethazine used by us.

The adverse effects observed in this study were relatively mild, and there were no significant difference in the incidences of headache, dizziness and drowsiness. Excessive sedation and extra pyramidal symptoms were also not observed in any of the patients.

CONCLUSION:

In conclusion, in the surgical setting of laparoscopic cholecystectomy, dexamethasone is better adjuvant than promethazine in reducing the incidence and severity of PONV during the first 24 hrs postoperatively. Granisetron alone is less effective than the above mentioned combinations in preventing PONV.

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