DEXAMETHASONE WITH EITHER GRANISETRON OR ONDANSETRON FOR POSTOPERATIVE NAUSEA AND VOMITING IN LAPAROSCOPIC SURGERY

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Abstract

In a prospective randomized double-blind study, we compared the effectiveness of dexamethasone 8 mg with either granisetron 1 mg or ondansetron 4 mg in the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic surgery. Hundred ASA I and II patients scheduled for laparoscopic surgery were enrolled in the study and 84 patients completed it. Following induction of anesthesia, group I (n = 42) received granisetron 1 mg and dexamethasone 8 mg, group II (n = 42) received ondansetron 4 mg and dexamethasone 8 mg. Nausea and vomiting episodes, pain scores as well as side effects were recorded during the first hour and subsequently during the first 6 and 24 hours postoperatively. Satisfaction scores were obtained at discharge. There was no statistically significant difference between the 2 groups during the 1st 24 hours following surgery in regards to pain scores, satisfaction and side effects manifestations. At 0-1 hour interval, 100% of patients in group I and 97.6% in group II had no vomiting. Total response (no moderate or severe nausea and no rescue antiemetics) was 83.3% in group I and 80.95% in group II, and metoclopramide was used in 7.1% of patients in both groups. At 1-6 hours interval, 97.6% of patients in group I and 100% in group II had no vomiting. Total response was 92.8% in group I and 90.9% in group II, and metoclopramide was used in 4.76% of patients in group I and 2.38% in group II. At 6-24 hours no vomiting occurred in 97.6% of patients in group I and 100% in group II. Total response was 95.2% in both groups, and metoclopramide was used in 2.38% of patients in both groups. In conclusion, the combination of dexamethasone 8 mg 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 and excellent patient satisfaction.

Key Words: Postoperative nausea and vomiting, Granisetron, Ondansetron, Dexamethasone, Laparoscopy.

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Introduction

Postoperative nausea and vomiting (PONV) are two of the most common and unpleasant side effects following anesthesia and surgery[1]. Laparoscopic surgery is associated with a high incidence of nausea and vomiting[2,3]. In a recent review on postoperative recovery profile after laparoscopic cholecystectomy, PONV was seen in 11% of patients and severe PONV in 2% of patients despite prophylaxis with dexamethasone, ondansetron and the use of total intravenous anesthesia technique[4]. PONV remains to be a predictor of complicated recovery profile and deserves further attention. The combination of ondansetron plus dexamethasone was more effective in the prevention of postoperative nausea and vomiting than ondansetron alone[5]. Also, the combination of granisetron 40 μg/kg and dexamethasone 8 mg produced 98% PONV free in patients undergoing laparoscopic cholecystectomy versus 83% PONV free with granisetron alone[6]. In another study, the same combination produced 95% PONV free versus 83% for granisetron alone[7]. Although the combination of dexamethasone and 5-hydroxytryptamine type 3 (5HT3) antagonists has been previously described, our report is the first to compare the combination of granisetron 1 mg and dexamethasone 8 mg versus ondansetron 4 mg and dexamethasone 8 mg for PONV prophylaxis in patients undergoing laparoscopic cholecystectomy and herniorraphy.

The aim of this study is to compare the effectiveness of granisetron 1 mg and dexamethasone 8 mg (group I) versus ondansetron 4 mg and dexamethasone 8 mg (group II) in the prevention of early and late PONV in patients undergoing laparoscopic cholecystectomy and herniorraphy.

Materials and Methods

After obtaining our institutional review board (IRB) approval and informed written consents from all human subjects, 100 patients, ASA I or II, scheduled for laparoscopic cholecystectomy or herniorraphy were enrolled in this prospective randomized double-blinded study. 84 patients completed the study (42 in group I and 42 in group II). Exclusion criteria included: Known allergies or hypersensitivity to the study drugs, history of chronic nausea and vomiting or experienced nausea and vomiting in the past 24 hours prior to anesthesia, had received any antiemetics or any drug with antiemetic properties during the 24 hours before anesthesia, had a body mass index ≥35 kg/m^2, aged >70 years, were pregnant or breast feeding or had a condition requiring chronic opioid use.

Using a computer generated randomization method; Patients were randomized into 2 groups. Group I received granisetron 1 mg and dexamethasone 8 mg while group II received ondansetron 4 mg and dexamethasone 8 mg. The study medications were prepared by a resident, who was not involved in any other part of the study, and were presented to blinded investigators as identical 2 ml filled syringes.

After standard monitoring techniques consisting of EKG, pulse oximetry, and blood pressure, patients received 1 mg of midazolam intravenously as a premedication. General anesthesia was induced with intravenous (IV) propofol 2 mg/kg, lidocaine 1 mg/Kg, fentanyl 2 μg/kg, and muscle relaxation was achieved with rocuronium 0.6 mg/kg to facilitate endotracheal intubation. Maintenance of anesthesia was achieved by sevoflurane, oxygen: air mixture (1:1), additional doses of fentanyl up to 4 μg/kg and rocuronium as needed to keep a train of four ratio <0.7. The study medications dexamethasone and granisetron or dexamethasone and ondansetron were administered immediately after induction of anesthesia in both treatment groups. Neuromuscular blockade was reversed at the end of surgery with IV neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg). Patients were transferred to the post anesthesia care unit (PACU) and the PACU team was instructed to assess pain scores according to the visual analogue scale VAS. If pain score >5 the patients were given either paracetamol (Prodafalgan™) 1 g IV drip or demerol 20 mg IV bolus. The time of each vomiting episode and the time and intensity of each nausea episode were collected from the nursing chart upon arrival to PACU, at 1 hour, 6 and 24 hours postoperatively. An episode of vomiting was defined as expulsion of stomach contents with no relief of nausea symptoms. 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 activity). The initial rescue medication was metoclopramide 10 mg administered as a single IV bolus dose and was given if the patients vomited, complained of moderate or severe nausea and if they requested the treatment medication. Nausea and vomiting assessments were made up to 30 minutes following rescue medication administration and response was defined as improvement or resolution of PONV symptoms. Adverse events were evaluated and recorded by a resident who was blinded to the study drugs used. Postoperative pain was also followed up at 1, 6 and 24 hours postoperatively. Patient satisfaction was recorded just before discharge.

Statistical Analysis

All values were reported as means ± standard deviation, or numbers and percentages. Data were analyzed using independent sample t-test and chi-squared test. A P value less than 0.05 was considered statistically significant.

Results

Of the 100 patients initially signing the informed consent, 84 patients (42 in group I, 42 in group II) completed the study. There was no statistically significant difference between the two groups in regards to gender, history of PONV and history of motion sickness, age, weight, type of surgery (laparoscopic cholecystectomy or laparoscopic herniorraphy), duration of surgery, history of prolonged gastric emptying, and smoking history (Table 1).

Table 1
Demographic data

	Granisetron + Dexamethasone (n = 42)	Ondansetron + Dexamethasone (n = 42)
Age (years)	46.5 ± 11.7	47.4 ± 14.2
Gender (male/female)	22/20	20/22
Weight (kilograms)	75.8 ± 16.1	77.5 ± 14.1
Type of surgery: Lap cholecystectomy Lap Herniorraphy	 31 11	 30 12
History of PONV	5	4
History of motion sickness	1	2
History of delayed gastric emptying	4	5
History of smoking	20	18
Duration of surgery (min)	61 ± 8.4	62 ± 7.4

There was no statistically significant difference between the two groups at the three time intervals (0-1, 1-6, 6-24 h) with respect to total response, number of patients who vomited and the use of antiemetics (metoclopramide) (P>0.05) (Table 2).

Table 2
Efficacy outcome

	Granisetron + Dexamethasone (n = 42)	Ondansetron + Dexamethasone (n = 42)
No Vomiting		
0-1 hr	42 (100%)	41 (97.6%)
1-6 hrs	41 (97.6%)	42 (100%)
6-24 hrs	41 (97.6%)	42 (100%)
Total response		
0-1 hr	35 (83.3%)	34 (80.95%)
1-6 hrs	39 (92.8%)	38 (90.9%)
6-24 hrs	40 (95.2%)	40 (95.2%)
Metoclopramide		
0-1 hr	3 (7.1%)	3 (7.1%)
1-6 hrs	2 (4.76%)	1 (2.38%)
6-24 hrs	1 (2.38%)	1 (2.38%)

Total response = no moderate nausea, no severe nausea and no rescue antiemetic use.

All patients who received metoclopramide once were satisfied and did not receive any other antiemetics. In this randomized double-blind study, granisetron 1 mg plus dexamethasone 8 mg was shown to be as effective as ondansetron 4 mg plus dexamethasone 8 mg; At 0-1 hour, 100% of patients in group I had no vomiting and 97.6% of patients in group II had no vomiting. Total response (i.e. no moderate or severe nausea and no rescue antiemetic use) was present in 83.3% in group I and 80.95% in group II. The percentage of patients who received metoclopramide was 7.1% in both groups at 0-1 hour interval as well. At 1-6 hours interval, 97.6% of patients in group I and 100% in group II had no vomiting. Total response was 92.8% in group I and 90.9% in group II, and metoclopramide was used in 4.76% of patients in group I and 2.38% in group II. At 6-24 hours no vomiting occurred in 97.6% of patients in group I and 100% in group II. Total response was 95.2% in both groups, and metoclopramide was used in 2.38% of patients in both groups. Two out of 42 patients in group I, and 2 out of 42 patients in group II complained of dizziness in the PACU; 3 out of 42 patients in group I and 3 out of 42 patients in group II complained of headache in the PACU; one out of 42

patients in group I and 3 out of 42 patients in group II were sedated in the PACU; 38 out of 42 patients in group I and 37 out of 42 patients in group II were satisfied with the antiemetic prophylaxis. Pain scores in group I at 0-1 hour were 5 ±1.1 , at 1-6 hours 4.8 ±0.5 and at 6-24 hours 2 ± 0.4. Pain scores in group II at 0-1 hour were 4.7 ± 0.5, at 1-6 hours 4.4 ± 0.4 and at 6-24 hours 2.3 ± 0.4. There was no significant difference between the two groups concerning the side effects and the pain scores.

Discussion

Laparoscopic surgery without antiemetics prophylaxis is associated with a high incidence of nausea and vomiting[2,3]. Studies have shown that substituting propofol for a volatile anesthetic reduces the risk of postoperative nausea and vomiting by about 19%, whereas substituting nitrogen for nitrous oxide reduces the risk by about 12%[8]. Combining these two anesthetic management strategies (i.e., total intravenous anesthesia) reduces the risk by about as much as any single antiemetic[8]. A 70 percent reduction in the relative risk of postoperative nausea and vomiting is the best that can be expected, even when total intravenous anesthesia is used in combination with three antiemetics[8]. Therefore, 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.

In this prospective randomized double-blind study, we found no statistically significant difference in the incidence of PONV, during the first 24 hours following surgery, when dexamethasone was combined with either granisetron or ondansetron. Multiple previous studies had shown that combination regimens of antiemetics provide significantly better PONV prophylaxis compared with a single antiemetic therapy. Of note, the combination of dexamethasone and ondansetron was better than ondansetron alone[5] also, dexamethasone and granisetron was better than granisetron alone[6,7]. Furthermore, different combination therapies had been proven to be similar in outcome and efficacy[8]. Our results confirms the results published by Apfel et al where different antiemetic interventions are found to be similarly effective and different antiemetic combinations are found to be similar in outcome and efficacy[8]. Another meta-analysis found no statistically significant difference in the incidence of early or overall PONV when a 5-HT_3 receptor antagonist was combined with either droperidol or dexamethasone. Both combination regimens provided significantly better PONV prophylaxis compared with 5-HT_3 receptor antagonists alone[9]. Gan et al reported a similar study to ours using different dosages and different timing of administration for abdominal hysterectomy. They also found that both combinations were equally effective in preventing PONV in the first two hours postoperatively[10]. Our study however extends the observation period to 24 hours postoperatively.

Dexamethasone is a glucocorticoid that produces strong antiemetic effect, by an undetermined mechanism. It may act through prostaglandin antagonism, serotonin inhibition in the gut and by releasing endorphins. The prophylactic antiemetic effect of dexamethasone has been documented in laparoscopic surgery[11-14]. There are no reports of dexamethasone related adverse effects in the doses used for management of PONV although even meta-analyses and systemic reviews may have insufficient power to detect rare complications[15,16]. When dexamethasone is used alone, late efficacy seems to be most pronounced[11].

The prophylactic antiemetic effect of ondansetron[17] and granisetron[18] has been documented in laparoscopic surgery. The 5HT3 receptor antagonists are highly specific and selective for nausea and vomiting[1]. 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[1]. 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 only 250-400:1[19]. We did not find any difference between the two groups when we compared early versus late in terms of antiemetic efficacy, total response and side effects.

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compared to placebo shows that dexamethasone treatment, reduced early PONV by 35%, and late PONV by 50%[15]. The dose most frequently used was 8 or 10 mg IV. The combination of dexamethasone with ondansetron or granisetron further decreased the risk of PONV[11,15]. The best prophylaxis available is achieved by combining dexamethasone with 5HT3 receptor antagonist[11,15].

Our report showed that administration of granisetron 1 mg and dexamethasone 8 mg or ondansetron 4 mg and dexamethasone 8 mg following induction of anesthesia in patients undergoing short laparoscopic operations, prevented PONV in a high percentage of patients with minimal side effects and excellent patient satisfaction.

In conclusion, 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 laparoscopic cholecystectomy and herniorraphy, with minimal side effects and excellent patient satisfaction. There was no statistically significant difference between the two combinations concerning its efficacy or side effects.

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