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Effectiveness of Prophylactic Intravenous Granisetron for the Prevention of Nausea and Vomiting after Laparoscopic Cholecystectomy: A Prospective Randomized Study

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Abstract: ***Postoperative nausea and vomiting (PONV) are most common symptom after laproscopic surgeries. Various approaches have been proposed for the management of PONV but not without adverse effects. One of the potent drug granisetron has longer acting properties has introduced for the antiemetic treatment in chemotherapy patient and fewer studies in treating patient of laparoscopic surgeries. We undertake this study to evaluate the efficacy and safety properties of granisetron in prophylaxis PONV in laproscopic cholecystectomy. Aims: To study the efficacy of single prophylactic antiemetic therapy with granisetron@40μg/kg I.Vin patients undergoing laparoscopic cholecystectomy. Material and Methods: Total 120 patients of either sex age between 20 to 60 yrs posted for laparoscopic chloecystectomy with no history of PONV, non obesity ,non pregnant, no antiemetic intake for last 24 hour has been selected and standard protocol of general anesthesia were followed. Randomly patients received different doses of iv granisetron and placebo. Postoperatively, emetic episodes during the first 24 hours after anesthesia were recorded by nursing staff blind to which treatment the patients had received. The details of any adverse effects were noted throughout the study, whether obtained through general questioning of the patients by follow-up nurses, through observation by these nurses, or spontaneously mentioned by the patients. Results: Efficacy to control postoperative nausea and vomiting were more when granisetron were used against pacebo. Conclusion: Intravenous granisetron has effectiverole in treating PONV in laparoscopic cholecystectomy.***

Keywords: Granisetron, PONV, Laproscopic Surgeries, Antiemetics.

1. Introduction

Incidence of nausea and vomiting after laparoscopic cholecystectomy with no antiemetic treatment varies from 25% to 42%.[1,2] A variety of pharmacological approaches (antihistamines, butyrophenones, dopamine receptor antagonists) have been investigated for the prevention and treatment of postoperative nausea and vomiting, but adverse effects such as excessive sedation, hypotension, dry mouth, dysphoria, hallucinations, and extra pyramidal signs have been noted.[3] Ondansetron hydrochloride, a serotonin type 3 receptor antagonist, reduces the incidence of nausea and vomiting after gynaecological surgery.[4] Granisetron hydrochloride, another antagonist of serotonin receptors, is effective for the treatment of emesis in patients receiving cytotoxic drugs. Granisetron is more potent and has longer-acting properties against cisplatin induced emesis than ondansetron. We have recently demonstrated that granisetron reduces the incidence of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy.[5] The purpose of this study was to evaluate the efficacy and safety of prophylaxis with I.V granisetron for the prevention of nausea and vomiting after laparoscopic cholecystectomy.

2. Material and Methods

After obtaining institutional review board approval and informed consent from each patient, we studied 130 patients who were classified as physical status 1 according to the American Society of Anesthesiologists. The group was composed of 98 women and 32 men, between 25 and 63 years old, undergoing general anesthesia for elective laparoscopic cholecystectomy. Indications for this surgical procedure in the current clinical trial are symptomatic cholelithiasis, chronic cholecystitis, and cholecystic polyp. Exclusion criteria were antiemetics given within 24 hours before surgery; active, acute cholecystitis in the 6 months prior to admission; regular corticosteroid therapy; serum μ-glutamyltransferase, alkaline phosphatase, or direct bilirubin levels twice normal or laparoscopy replaced by laparotomy.

No patients received preanesthetic medication. Anesthesia was induced intravenously (IV) with thiopentone sodium at 5 mg/kg and fentanyl citrate at 2 μg/kg, and IV vecuronium bromide at 0.1 mg/kg was used to facilitate tracheal intubation. After intubation of the trachea, anesthesia was maintained with isoflurane, nitrous oxide and oxygen, with controlled ventilation adjusted to maintain an end-tidal carbon dioxide concentration between 35 and 40 mm Hg using an anesthetic/respiratory gas analyzer. A nasogastric tube was inserted, and suction was applied to empty the stomach of air and other contents. Before extubation of the trachea, the nasogastric tube was again suctioned and then removed. At the completion of the surgical procedure isoflurane and nitrous oxide administration was stopped. Residual neuromuscular blockade was antagonized with IV atropine sulfate at 0.02 mg/kg and IV neostigmine

methylsulfate at 0.04 mg/kg. Before extubation of the trachea, the nasogastric tube was again suctioned and then removed. Postoperatively, all patients were admitted to the hospital for 2 days. Postoperative analgesia was provided I.V Paracetamol and NSAIDs.

Postoperatively, emetic episodes during the first 24 hours after anesthesia were recorded by nursing staff blind to which treatment the patients had received. The nurses asked the patients if retching or vomiting had occurred and if they felt nauseated. These nurses observed the patients at various intervals according to the normal ward routine. Nausea was defined as the subjectively unpleasant sensation associated with awareness of the urge to vomit; retching was defined as the labored, spasmodic, rhythmic contraction of the respiratory muscles without the expulsion of gastric content; and vomiting was defined as the forceful expulsion of gastric contents from the mouth.3 The details of any adverse effects were noted throughout the study, whether obtained through general questioning of the patients by follow-up nurses, through observation by these nurses, or spontaneously mentioned by the patients.

Statics Analysis: Patients were randomly allocated via a computer-generated random numbers list to receive 1 of 4 treatment regimens (n = 30 of each): granisetron at 3 different doses (10 mcg, 20mcg, or 40 mcg) or placebo. These drugs were given intravenously 30 minutes before surgery.

Patient demographic data were determined by analysis of variance with the Bonferroni adjustment for multiple comparison or y^2 test. The number of patients who were emesis free or experiencing nausea, retching, or vomiting and the incidence of adverse effects were compared with the Fisher exact probability test. A *P* value less than .05 was considered significant. All values were expressed as mean (SD) or number (percentage). Power analysis was used to determine the number of patients in the current study based on the assumptions that the incidence of an emetic-free period (which was regarded as the primary end- point) in patients receiving placebo would be 50%, an improvement between 50% and 80% was considered of clinical importance, and a=.05 and 1 − þ=.8. Based on these assumptions, 30 patients per group were required.

3. Observation & Result

6 men and 4 women were excluded from the study, according to the exclusion criteria. Patient profile and information on surgery and anesthesia are summarized in **Table 1**. There were no differences in patient demographics among the treatment groups. No differences were observed with regard to the number of patients with either nausea, retching, or vomiting. The only difference was found in the incidence of patients who were emesis free up to 24 hours after anesthesia, which occurred in 16 (53%), 18(60%), 25 (83%), and 25 (83%) of 30 patients who had received placebo, 10 mcg/kg of granisetron, 20 mcg/kg of granisetron, and 40 mcg/kg of granisetron, respectively. Thus, an emesis free period was same in patients who had received granisetron at either 20 mcg/kg or 40 mcg/kg than in those who had received placebo,P value for comparative data shows highly significant (*P*<.05). However, there was no difference between the patients who had received 10 mcg/kg of granisetron and those who had received placebo (**Table 2**). The clinically serious adverse effects due to the study drug were not observed in any of the groups.

Table 1: Patient Demographics

Characteristic	Placebo (n = 30)	Granisetron, 10 mcg/kgwt (n = 30)	Granisetron, 20 mcg/kgwt (n = 30)	Granisetron, 40 mcg (n = 30)
Mean (SD) age, y	48 (9)	46 (8)	46 (10)	48 (8)
Sex (M/F)	7/23	8/22	7/23	6/24
Mean (SD) height, cm	158 (12)	158 (13)	156 (11)	158 (13)
Mean (SD) weight, kg	55 (12)	56 (13)	55 (12)	56 (14)
Mean (SD) duration of operation, min	85 (34)	88 (32)	85 (33)	87 (35)
Mean (SD) duration of anesthesia, min	109 (35)	111 (34)	107 (32)	110 (35)
Indication for laparoscopic cholecystectomy, No. of patients Symptomatic cholelithiasis	22	21	22	22
Chronic cholecystitis	3	3	3	3
Cholecystic polyp Analgesic used postoperatively, No. of patients	5	6	5	5
Paracetamol	18	17	18	17
NSAIDs	3	3	3	3

Table 2: Number of Patients Who Were Emesis-free or Experiencing Nausea, Retching, or Vomiting Up to 24 Hours After Anesthesia*

Symptoms	Placebo	Granisetron, 10 mcg/kgwt	P	Granisetron, 20 mcg/kgwt	P	Granisetron, 40 mcg/kgwt	P
Emesis-free	16 (53)	18 (60)	.40	25 (83)	.01	25 (83)	.01
Nausea	7 (23)	6 (20)	.5	3 (10)	.15	3 (10)	.15
Retching	2 (7)	1 (3)	.5	1 (3)	.5	2 (7)	>.9
Vomiting	6 (20)	6 (20)	>.9	2 (7)	.13	1 (3)	.05

4. Conclusion

Patients undergoing elective laparoscopic cholecystectomy have a relatively high incidence of postoperative nausea and vomiting.[1,2] This problem is multifactorial in origin, including patient demographics, nature of the underlying

disease, type of surgery, anesthetic technique, and postoperative care.[3] The main patient related factors are age, sex, obesity, previous post- operative nausea and vomiting. Surgical factors include the effect of intraperitoneal carbon dioxide insufflation on residual stretching and irritation of the peritoneum.[2] In the current study, however, these factors were well balanced among the treatment groups, so differences regarding an emesis free period for the first 24 hours after anesthesia can be attributed to the study drug.

Recently, we have demonstrated that this drug reduces the incidence of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy. A Prophylactic regimen of Intravenous granisetron is effective for the treatment of vomiting in patients undergoing Laparoscopic cholecystectomy.[5] In the current study, the chance of an emesis free period during the first 24 hours after anesthesia was greater in patients who had received 20 or 40 mcg/kgwt of granisetron than in those who had received placebo (P<.05). The exact mechanism of granisetron for the prevention of postoperative nausea and vomiting remains unclear, but it has been suggested that this drug may act on sites containing serotonin type 3 receptors with demonstrated anti- emetic effects.

In this clinical trial, however, we demonstrated that antiemetic efficacy of 20 mcg/kgwt of granisetron was similar to that of 40 mcg/kgwt of granisetron and that no differences existed in emesis-free periods between patients who had received placebo and those who had received 10 mcg/kgwt of granisetron. These findings suggest that granisetron at 20 mcg/kgwt may be an effective antiemetic for the prevention of nausea and vomiting after laparoscopic cholecystectomy[6] and that increasing the dose to 40 mcg/kgwt provides no demonstrable benefit.

Granisetron does not cause the sedative, dysphoric, and extrapyramidal symptoms associated with nonserotonin type 3 receptor antagonists (eg, droperidol, metoclopramide).[3] Adverse effects due to granisetron observed in the present study were not clinically serious in any group. Therefore, Intravenous granisetron at 3 different doses (10 mcg, 20 mcg, 40 mcg) is considered to be relatively free of adverse effects for the prevention of nausea and vomiting after laparoscopic cholecystectomy.

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