

COMPARISON OF PROPHYLACTIC ANTIEMETIC EFFICACY OF HALOPERIDOL AND GRANISETRON FOR THE PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING FOLLOWED BY LAPAROSCOPIC SURGERIES

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ABSTRACT

BACKGROUND

Postoperative Nausea and Vomiting (PONV) continues to be a highly undesirable outcome of anaesthesia and surgery. For example, in the ambulatory care surgery setting PONV is among the most common complications with a frequency ranging from 30% to 50%.¹ In addition, significant or uncontrolled PONV in the ambulatory surgery Post Anaesthesia Care Unit (PACU) can lead to unanticipated hospital admission. Although routine antiemetic prophylaxis is clearly unjustified, patients at high risk for postoperative emesis should receive special considerations with respect to the prophylactic use of antiemetic drugs.² Retching or vomiting following surgery can put tension on suture lines, cause haematomas beneath surgical flaps and place the patient at risk for pulmonary aspiration of vomit if airway reflexes are depressed from the lingering effects of anaesthetic and analgesic drug.

AIM

To compare the prophylactic antiemetic efficacy of Haloperidol versus Granisetron groups for the prevention of postoperative nausea and vomiting in patients posted for laparoscopic surgeries.

MATERIALS AND METHODS

After obtaining Ethics Committee approval, adult patients with age from 18 to 65 yrs. with ASA grade 1 and 2 posted for laparoscopic surgeries were selected. Patients were divided into 2 groups of 30 patients each as Haloperidol group and Granisetron group. Balanced Anaesthesia was maintained with N₂O+O₂+Isoflurane+fentanyl and vecuronium 1 mg based on neuromuscular monitoring; 30 minutes prior to end of surgery group H patients received Haloperidol - 2 mg IV, group G patients received Granisetron - 1 mg IV. Results were statistically analysed using Student's unpaired t-test, Chi-square test and ANOVA analysis. P value less than 0.05 was considered statistically significant.

RESULT

Comparison of incidence of nausea and vomiting in the 2-24 hrs. postoperative period shows no statistically significant difference between 2 groups.

CONCLUSION

Prophylactic administration of antiemetics does reduce incidence and suffering due to PONV and its consequences. Prophylactic IV administration of Haloperidol 2 mg is as effective as Granisetron in reducing the incidence of PONV in laparoscopic surgeries. Granisetron causes headache as adverse effect, Haloperidol does not have serious adverse effect at doses used for PONV.

KEYWORDS

Granisetron, Haloperidol, Postoperative Nausea and Vomiting.

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INTRODUCTION

Nausea is defined as a subjective unpleasant sensation in which the patient is aware of the urge to vomit, but does not necessarily do so.

Vomiting is defined as an objective physical motion characterised by contraction of the abdominal muscles, descent of the diaphragm, and opening of the gastric cardia, resulting in expulsion of stomach contents from the mouth.

Nausea is mediated by neural pathways, whereas vomiting is initiated and coordinated by the vomiting center and the Chemoreceptor Trigger Zone (CTZ). After stimulation of the vomiting center, efferent pathways involving the salivary, respiratory and vasomotor centers and cranial nerves mediate vomiting.³⁻⁵ Activation of several receptors leads to nausea or vomiting; most antiemetic drugs exert their effects by blocking one or more of these receptors. "Dopamine type 2 (D₂) - receptors are located in the stomach, the Nuclei Tractus Solitarii (NTS), and the Chemoreceptor Trigger Zone (CTZ).

D₂-receptors in the stomach appear to mediate the inhibition of gastric motility that occurs during nausea and

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vomiting, and they participate in reflexes that relax the upper portion of the stomach and delay gastric emptying. D₂-receptors are also implicated in emetic signalling at the CTZ and in the NTS. Serotonin, acting at the serotonin type 3 (5-HT₃)-receptor is an important neurotransmitter in the afferent pathways from the stomach and small intestine as well as centrally in the CTZ, area postrema and NTS. Histamine type 1 (H₁)-receptors and muscarinic cholinergic type 1 (M₁)-receptors are concentrated in the NTS, CTZ and vestibular system.

Other Considerations in the Prevention of PONV Anaesthetic Factors

Soon after propofol was approved for marketing as an IV anaesthetic agent, a number of articles were published indicating that propofol was associated with a significant decrease in PONV.^{6,7} In animal models, propofol has been shown to decrease synaptic nerve transmission in the olfactory cortex and to decrease serotonin levels in the area postrema.⁸ A systematic review of PONV following maintenance anaesthesia with propofol or an inhalational anaesthetic agent found that patients receiving propofol had a significantly lower frequency of PONV regardless of induction agent, choice of inhalational agent, use of nitrous oxide, patient age or use of an opioid.⁹ Another systematic review found that propofol may be effective in reducing PONV in the short term, but only when given as a continuous infusion for maintenance of anaesthesia and when the PONV event rate is greater than 20% (e.g. in moderate to high-risk patients).¹⁰ There is evidence of a relationship between plasma propofol concentration and antiemetic efficacy. Gan et al found that a median plasma propofol concentration of 343 ng/mL was associated with a reduction in Postoperative Vomiting (PV) in surgical patients.¹¹ Therefore, the common practice of selecting propofol for inducing anaesthesia, because of its antiemetic effects in day care procedures.

Nitrous Oxide

Nitrous oxide is known to cause nausea and vomiting when it is administered as the sole anaesthetic agent.¹² Nitrous oxide also causes PONV due to changes in middle ear pressure¹³ or bowel distention due to diffusion into closed cavities.¹⁴ In an animal model, nitrous oxide activated the medullary dopaminergic system.¹⁵ Three systematic reviews concluded that omitting nitrous oxide from a general anaesthetic in high-risk patient (e.g. those undergoing gynaecological procedures) decreases the risk of PONV.¹⁶⁻¹⁸

Hydration Status

Postoperative outcomes such as thirst, dizziness, drowsiness and nausea may be influenced by the surgical patient's fluid status before and after surgery. Pre-operative dehydration may occur due to the preoperative nothing-by-mouth (NPO) orders that often go into effect many hours before surgery. Preoperative dehydration may be compounded in a patient whose scheduled surgery is delayed. Aggressive perioperative hydration with infusions at rates of up to 20 mL/kg/hr. has been shown to effectively deter Postoperative Nausea (PN) as well as thirst, dizziness and drowsiness.¹⁹

Recently, more liberal preoperative NPO guidelines have been introduced in an effort to avoid preoperative dehydration.²⁰

Reversal Agents

Anticholinesterase drugs are routinely administered at the end of surgery to antagonise any residual effect of non-depolarising neuromuscular blocking agents. These agents may contribute to PONV, because they increase gastrointestinal motility and gastric secretions. In actual practice, these effects are usually countered by concurrent administration of an anticholinergic agent, such as glycopyrrolate. A systematic review of the effect of omitting reversal agents on the risk for PONV found little evidence of benefit unless large doses (>2.5 mg of neostigmine methylsulfate) were used.²¹

Oxygen

It has been hypothesised that the high frequency of PONV seen with abdominal procedures may be related to surgical compression and manipulation causing tissue ischaemia and the release of serotonin from gastrointestinal tissues.^{22,23} High inspired-oxygen concentrations may counter the tissue hypoxia resulting from surgical manipulation, thereby preventing serotonin release.

Gastric Suctioning

Gastric suctioning may be useful in reducing PONV following procedures involving the nose, mouth and oropharynx, in which large amounts of blood (a potent emetogenic) can enter the stomach. Gastric distention resulting from vigorous positive-pressure ventilation through a facemask may also cause vomiting.² Gastric distention can be reduced by suctioning before extubation. In general however gastric suctioning has not been shown to reduce PONV; in fact, the presence of a nasogastric tube during the postoperative period may stimulate the gag reflex.²⁴

Inhalational (Volatile) Anaesthetic Agents

The use of inhalational anaesthetic agents was the strongest risk factor in the development of PONV. However, this emetogenic effect was primarily evident in the early postoperative period (up to two hours) and was mostly dependent on the duration of anaesthesia, particularly in procedures lasting longer than three hours. Therefore, omitting inhaled anaesthetics may be more efficacious for avoiding PONV in high-risk patients than administering a prophylactic antiemetic.²⁵

MATERIAL AND METHODS

After obtaining Ethics Committee approval, adult patients with age from 18 to 65 yrs. with ASA grade 1 and 2 posted for laparoscopic surgeries were selected. Patients were divided into 2 groups of 30 patients each as Haloperidol group and Granisetron group.

Other exclusion factors are patients with obvious airway problems, obesity with BMI >25, pregnant patients, patients with chronic cough/psychiatric illness/significant major organ disease, patient who has consumed an antiemetic medication within 24 hrs. prior to commencing study were also excluded from the study. Informed and written consent was taken, anaesthesia was standardised.

All patients were premedicated with Fentanyl 2 mcg/kg body wt. Patients were connected to monitors like non-invasive blood pressure, pulse oxymeter, ECG. Induction was done with propofol 2 mg/kg body wt. Intubated after

neuromuscular blockade with vecuronium 0.1 mg/kg/body wt. Anaesthesia was maintained with N₂O+O₂+Isoflurane +vecuronium 1 mg based on neuromuscular monitoring; 30 minutes prior to end of surgery group H patients received Haloperidol-2 mg IV and group G patients received Granisetron - 1 mg IV. All patients received Inj. Diclofenac 50 mg IM 30 minutes before the end of the surgery. After the surgery was over, residual neuromuscular blockade was reversed with neostigmine - 0.05 mg/kg/body wt. and glycopyrrolate - 0.01 mg/kg/body wt. Extubation was done when patient was fully awake. For evaluation postoperative period was divided into 3 periods, early postoperative period as 0-2 hrs., late postoperative period as 2-24 hrs. and third period as 0-24 hrs. time period following anaesthesia.

Following Observations were Made

1. Recovery time (in minutes): From the time of discontinuation of anaesthesia until opening of eyes.
2. Sedation level: After recovery from anaesthesia was assessed by Modified Observer’s Assessment of Alertness/Sedation scale (OAA).²⁶

Responsiveness	Score
A. Response readily to name spoken in a normal time	5
B. Lethargic response to name spoken in a normal time	4
C. Response only after name is called loudly and Repeatedly	3
D. Response only after mild prodding /shaking	2
E. Does not respond to mild prodding /shaking	1
F. Does not respond to test stimulus	0

3. Pain score was assessed by 10 cm Visual Analog Scale, where 0 cm is taken as no pain and 10 cm as worst pain.
4. Nausea Score: The intensity of each nausea episode was graded as:
 - Mild - Discomfort noticed, but no disruption of anticipated normal activity.
 - Moderate - Discomfort sufficient enough to affect anticipated normal activity.
 - Severe - Inability to perform normal activity.
5. Episodes of Vomiting: A vomiting episode was defined as vomiting events occurring in rapid sequence within a one-minute period. If the interval between two bouts of emesis exceeded one minute, they were considered separate episode.
6. Rescue Antiemetic: Inj. Metoclopramide 10 mg IV was given if patient vomited.
7. ECG - Monitoring was done with lead-II for measurement of QT_c interval 10 minutes after administration of study drug.
8. Side effects profile of haloperidol and granisetron like headache, constipation, dizziness, extrapyramidal symptoms were observed and noted.
9. Inj. Diclofenac Sodium 50 mg IM was given at the end of surgery.

Statistical Analysis

Students unpaired t-test, Chi-square test and ANOVA was used for analysis. P value less than 0.05 was considered statistically significant.

RESULTS

60 patients selected and they were divided into 30 patients in each group. Table 1 shows mean age distribution in haloperidol group of 40 yrs., in granisetron group of 41.37 with P value of 0.833, which is statistically not significant. There has been no significant difference in gender and weight distribution between 2 groups. Duration of surgery in 2 groups shows no significant difference between them with p value of 0.182.

Recovery time in minutes after ANOVA analysis shows no statistically significant difference between 2 groups. The sedation score is significantly more in haloperidol group compared to granisetron group with a P value of 0.033.

Pain score are comparable between the two study groups. There has been no statistically significant difference in the incidence of nausea and vomiting in 0-2 hrs. postoperative period between 2 groups. Comparison of incidence of nausea and vomiting in the 2-24 hrs. postoperative period shows no statistically significant difference between 2 groups.

We identified increased incidence of adverse effect as headache with granisetron of 20%, which is statistically significant.

DISCUSSION

PONV is one of the main complaints in patients undergoing laparoscopic surgeries under General Anaesthesia. It is one of the most important factor that determines the length of the hospital stay after ambulatory anaesthesia.²⁷ Numerous factors can affect PONV such as age, gender, obesity, motion sickness, history of PONV, duration of surgery, anaesthetic technique, use of opioids and pain. Haloperidol is used effectively in prevention of PONV by many observers at various doses and combinations. T. F. Wang et al²⁸ evaluated the prophylactic effect of low-dose haloperidol (1 mg) on post-operative nausea and vomiting (PONV) in women undergoing ambulatory laparoscopic surgery. Concluded that like droperidol (0.625 mg), prophylactic intravenous haloperidol (1 mg) significantly reduced the incidence of PONV in women undergoing ambulatory laparoscopic surgery. Grecu L²⁹ et al studied haloperidol 1 mg and ondansetron 4 mg for postoperative nausea and vomiting prophylaxis. They concluded that the postoperative nausea and vomiting prophylaxis with both drugs was significantly more effective and longer lasting than ondansetron alone. There was no detectable increase in side effects. Rosow et al²⁷ studied two hundred and forty four adults who were randomised to receive IV haloperidol 1 mg or ondansetron 4 mg during general anaesthesia. They concluded that in a mixed surgical population, the efficacy and toxicity of postoperative nausea and vomiting prophylaxis with haloperidol 1 mg was not significantly different from ondansetron 4 mg.

Our selection of the drug dosages was based on the previous work by Lee Y.³⁰ Buttner et al³¹ for haloperidol and Wilson et al³² for Granisetron. Lee Y et al³⁰ compared the prophylactic antiemetic efficacy of haloperidol vs. ondansetron for the prevention of Postoperative Nausea and Vomiting (PONV) after general anaesthesia. Approximately 30 mins. before the end of surgery, patients were randomly assigned to receive either haloperidol 2 mg IV or ondansetron 4 mg IV, respectively. Concluded that haloperidol 2 mg IV given 30 mins. before the end of surgery was effective in preventing PONV with efficacy comparable to ondansetron 4 mg IV for the

first 24 hrs. after general anaesthesia. Buttner et al³¹ observed that haloperidol 2 mg is better than 1 mg in preventing PONV. Wilson J A et al³⁰ studied the single dose IV granisetron in the prevention of PONV in adult patients undergoing elective open abdominal surgery or vaginal hysterectomy during general anaesthesia.

The two higher doses of granisetron (1.0 mg and 3.0 mg) provided effective prophylaxis against vomiting with 78% and 77% of patients respectively, being free from vomiting in the first 6 hrs. after surgery, and 63% and 62% in the first 24 hrs. He concluded that 1 mg granisetron is the optimum dose. Mikawa et al³³ conducted study defining the optimal dose of granisetron for prophylaxis against PONV after gynaecological surgery and they found that granisetron markedly decreases PONV at doses of 5 mcg/kg or larger. In our study drug was given 30 minutes before the end of surgery as peak plasma concentration from IV injection is >15 mins. Vella-Brincat et al 2004.³⁴ In contrast Yang YL et al suggested that the timing of administration of haloperidol 2 mg IV did not influence its antiemetic efficacy.³⁵

The recovery profiles were also similar whether haloperidol was administered at the start or at the end of surgery. In our study, incidence of nausea in Haloperidol group was 4 cases (13.3%), all of mild intensity. In granisetron group nausea episodes were seen in 7 cases (23.3%), of which 5 cases mild and 2 cases had moderate nausea. Incidence of vomiting in Haloperidol group was 5 cases (16.7%), of which one case had 2 episodes of vomiting. In contrast, Lee Y et al³⁰ had an incidence of PONV of 28% with haloperidol where study was done on different kind of surgeries. In granisetron group, 3 cases (10%) had vomiting of which one case had 2 episodes. So there was no statistical significant difference in incidence of vomiting between Haloperidol group and Granisetron group. In control group 13 cases (43.33%) had vomiting, of which 3 patients had 2 episodes of vomiting. Incidence is 43.33% in early postoperative period compared to 10% in late postoperative period. Apfel C C et al²⁵ suggested volatile anaesthetics were the leading cause of early postoperative vomiting.

In patients at high risk for PONV, it would therefore make better sense to avoid inhalational anaesthesia rather than simply to add an antiemetic, which may still be needed to prevent or treat delayed vomiting. Paul F. White et al³⁶ designed prospective observational study to assess the relationship between common patient risk factors for developing PONV and the occurrence of early (0–24 hrs.) versus late (24–72 hrs.) emetic symptoms. It was concluded that despite the frequent use of multiple antiemetic drugs for prophylaxis, an Apfel risk score of three or four (vs 2) was associated with a higher incidence of emetic sequelae in the first 24 hrs. after surgery.

However, the occurrence of late (24–72 hrs.) emetic symptoms was low and appeared to be unrelated to the patient's Apfel risk score. Regarding the role of neostigmine, Ching-Rong Cheng et al³⁷ re-evaluated the effect of neostigmine on postoperative nausea and vomiting, while considering the different anticholinergics as potentially confounding factors.

They found the combination of neostigmine with either atropine or glycopyrrolate did not significantly increase the incidence of overall (0–24 hrs.) vomiting (relative risk, 0.91; 95% confidence interval, 0.70–1.18; P=0.48) or nausea

(relative risk, 1.24; 95% confidence interval, 0.98–1.59; P = 0.08). In our study in all patients who had episode of vomiting, duration of surgery was long compared to patients who did not vomit.

Regarding surgical duration, Tseng L et al³⁸ estimated the incidence of Postoperative Nausea and Vomiting (PONV) in women undergoing major gynaecologic laparoscopic surgery with an expected surgical duration exceeding 1 hour and anticipated overnight hospitalisation. It was concluded that a long surgical period may have great impact on the PONV in women who undergo gynaecologic laparoscopic surgery, which implies the need for skilled gynaecologic laparoscopists. During our study, all the patients who had vomiting were given 10 mg of Inj. Metoclopramide intravenously as rescue antiemetic. Buttner et al³¹ observed sedation and extrapyramidal side effects at higher doses >4 mg. In our study, sedation was significantly more in haloperidol group (P = 0.033) when compared to granisetron.

But sedation score was comparable between haloperidol and control group. But recovery time from anaesthesia was not significantly different from granisetron. In our study, none of the patients had QTc interval prolongation. Considering side effect profile of granisetron in our study, 6 cases (20%) in granisetron group had headache which is statistically significant. Limitations of our study: Patients with history of motion sickness are known to have a higher incidence of PONV. This study does not evaluate such patients and their response to being treated with haloperidol or granisetron. Patients with previous history of PONV were also not evaluated separately. This study has not assessed cost-effectiveness of PONV prophylaxis.

CONCLUSION

Prophylactic administration of antiemetics does reduce incidence and suffering due to PONV and its consequences. Prophylactic IV administration of Haloperidol 2 mg is as effective as granisetron in reducing the incidence of PONV in laparoscopic surgeries, Granisetron causes headache as adverse effect, Haloperidol does not have serious adverse effect at doses used for PONV.

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