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A COMPARATIVE STUDY BETWEEN DROPERIDOL AND GRANISETRON FOR PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING AFTER LAPAROSCOPIC CHOLECYSTECTOMY

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ABSTRACT

Background: Post-operative nausea and vomiting (PONV) is a commonly observed undesirable consequence of laparoscopic cholecystectomy. Many pharmacological agents with varying effectiveness are investigated with none entirely effective in preventing PONV. This study was undertaken to compare the efficacy of granisetron and droperidol in reducing the incidence and severity of PONV after laparoscopic cholecystectomy.

Aims and Objectives: To compare the antiemetic efficacy of droperidol and granisetron following laparoscopic cholecystectomy, to study the incidence of PONV and to observe for side-effects in both the groups.

Materials and methods: Sixty patients posted for laparoscopic cholecystectomy were randomly allocated into 2 groups, each consisting of 30 patients. One group received 20mcgkg-1Droperidol and the other group received 60mcg kg-1Granisetron. Patients were assessed for first three hours and at 24hours postoperatively for presence and severity of PONV and any side effects.

Results: In droperidol group, 26 (86.7%) had no episodes of nausea at first two hours and 25 patients (83.3%) had no nausea at 24 hours postoperatively. Two (6.7%) patient had severe nausea at 2nd hour and 3rd hour postoperatively.2 patients (6.7%) reported of vomiting at 24hours postoperatively. In granisetron group, 27patients (90%) had no nausea at first two hours and 28 (93.3%) had no nausea at 24 hours postoperatively. No patients reported of severe nausea and vomiting in this group. The incidence of nausea and vomiting in droperidol group (17%) was not significantly higher than the granisetron group (11%,p = 0.321).

Conclusion: Droperidol and Granisetron are safe and equally effective in reducing the incidence and severity of PONV after laparoscopic cholecystectomy.

KEYWORDS : Laparoscopic Cholecystectomy, Postoperative nausea and vomiting, Granisetron, Droperidol.

Introduction

Most common and distressing symptoms following surgery and anesthesia are pain, nausea and vomiting. Sometimes nausea and vomiting may be more distressing especially after minor ambulatory surgeries, delaying the hospital discharge[1]. Post-operative pain management has received much more attention in past two decades than Post-operative Nausea Vomiting (PONV). The incidence of PONV is still very high in-spite of newer medications in our armamentarium. The incidence of PONV is 20-30%[2]. Anesthesia practice has progressed from opioid and deep ether anesthesia to non-opioid and non–ether anesthesia. Use of less emetic anesthetic agents, improved pre-operative and post-operative medication, refinement in operative techniques and identification of patient predictive factors have led to reduced incidence of PONV. However, despite these advances, nausea and vomiting still occur with unacceptable frequency in association with surgery and anesthesia. Hence it has been described as "big little problem"[3]. The present guidelines are developed under the auspices of the society of ambulatory anesthesia (SAMBA)[4]. These guidelines provide up-to-date information to practicing physicians and other healthcare providers about strategies to prevent and treat PONV.

Antiemetics such as hydroxyzine, droperidol and metoclopramide are used to prevent postoperative nausea and vomiting. Many physicians have stopped using droperidol. However the doses used for the management of PONV are low, and at these doses droperidol is unlikely to be associated with side effects like arrhythmias, sedation, extrapyramidal symptoms and dizziness.[5] The introduction of 5-HT3 receptor antagonists in 1991 has heralded a major advance in treatment of PONV because of absence of adverse effects that were observed with commonly used antiemetic drugs[6].This study was designed to assess the antiemetic efficacy and safety of droperidol versus granisetron for preventing postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy.

We hypothesized that granisetron would be more effective and safer than droperidol in the prevention of nausea and vomiting following laparoscopic cholecystectomy.

Aim and Objectives

1. To compare the efficacy of droperidol with granisetron for the prevention of PONV in laparoscopic cholecystectomy under general anesthesia.
2. Study the incidence of nausea and vomiting in both droperidol and granisetron groups.
3. Observe for any side-effects in both the droperidol and granisetron groups.

Materials and Methods

After approval from Hospital Ethical Committee and written informed consent, sixty patients aged 25 to 65yrs belonging to physical status ASA classes 1 and 2, undergoing elective laparoscopic cholecystec omy were randomly allocated into 2 groups of 30 patients each. Randomization was done using computer based numbering system. The study was double blinded. Patients with gastrointestinal disease, motion sickness and abnormal ECG findings were excluded. Patients received one of the two drugs either droperidol 20mcg kg^{-1} or granisetron 60mcg kg^{-1} intravenous just before the induction of anesthesia.

All patients were premedicated with glycopyrrolate 0.2mg intramuscu larly, 30 minutes before induction of anaesthesia. Patients received a single dose of either droperidol (20mcg kg^{-1}) or granisetron (60mcg kg^{-1}) intravenous over two to five minutes immediately before induction of anaesthesia. Anaesthesia was induced with thiopentone sodium 5mg kg^{-1} and fentanyl 2mcg kg^{-1} intravenous. Vecuronium 0.2mgkg^{-1} intravenous was given to facilitate tracheal intubation. After tracheal intubation, anesthesia was maintained with O_2 + N_2O + 1% - 2% Isoflurane. Ventilation was controlled mechanically and adjusted to maintain $EtCO_2$ between 30 and 35mm Hg. Intraoperative, Heart Rate, Blood pressure and, SPO_2were noted at frequent intervals in both the groups. Patients were reversed with neostigmine 0.05mgkg -1and glycopyrrolate 0.01mgkg-1and the trachea was extubated. The awakening time was defined as the period between cessation of nitrous oxide administration and eyes opening on command. Patients were shifted to post anesthesia care unit.

After recovery from anesthesia, PONV experienced by patients were recorded during the first three (0-3) hours and the next 3-24hour by direct questioning by anaesthetist who was blinded to the group assignment.

PONV was recorded by the Severe Emetic Scale7(Table 1).

Table 1: Definition of Severe Emetic Scale[7]

Post-operative nausea and vomiting	Score
No nausea	1
Mild nausea	2
Severe nausea	3
Vomiting	4

Metoclopramide 10mg intravenous was administered if two or more episodes of vomiting occurred within 24 hours after recovery from anaesthesia as the rescue antiemetic.

Adverse events like hypotension, headache, dizziness and constipation were also recorded throughout the study period (0-24hr after anaesthesia) by either general questioning or by spontaneous report of the patients.

Drowsiness / sedation was graded on a two – point scale (0 =awake, 1= drowsy/sedated)[7]

Statistical analysis

Sample size: Power analysis was based on the study by S Ozmen et al[7]. Considering an alpha error of 5% and beta error of 80%, a sample size of 60(30 in each group) was arrived at.

The Descriptive and inferential statistics were used for analysis.
The Independent-Samples T Test has been used to compare means for two groups of cases.

Repeated measure ANOVA analysis has been used to measure dependent variables over different periods of time All the statistical methods were carried out through the SPSS for Windows (version 16.0)

Results

Sixty patients were enrolled in the study. Both the groups i.e droperidol and granisetron had 30 patients each.s

The mean age, weight and sex distribution of the patients were similar among both the groups Table 2.

The mean duration of anesthesia, duration of surgery and awakening time were also comparable between both the groups (Table 2)

TABLE 2 : Patient characteristics and operation times

PARAMETERS	DROPERIDOL	GRANISETRON	OVERALL	p - value
AGE	47.5±6.9	48.5±6.57	48.0±6.7	0.719
SEX(M/F)	21/9	22/8	43/17	0.774
WEIGHT	60.3±6.34	61±6.63	60.65±6.	0.678
ASA I/II	14/16	15/15	29/31	0.796
DURATION OF ANAESTHESIA(MIN)	102.07±7.48	101.53±7.53	102±7.48	0.585
DURATION OF SURGERY (MIN)	89.6±7.48	89.27±7.52	89.4±8	0.873
AWAKENING TIME (MIN)	6.7±0.61	6.52±0.56	6.6±0.59	0.238

All values are expressed as mean±SD

There was no significant difference in the hemodynamic parameters like Heart rate and Blood pressure between both the groups as depicted in Figure 1 and Figure 2 respectively at all periods of study.

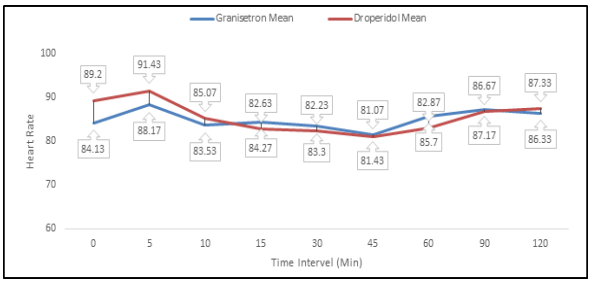

Figure 1: Intraoperative heart rate during different time intervals between the two groups. The data are listed as mean ± standard deviation

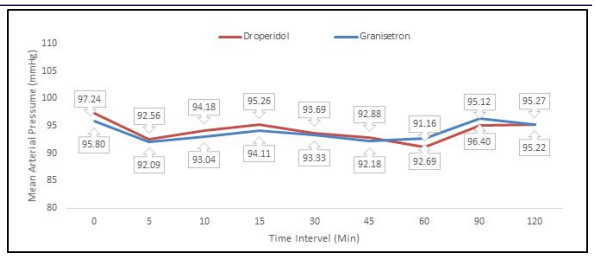

Figure 2 : Intraoperative Mean arterial pressure during different time intervals between the two groups. The data are listed as mean ± standard deviation

The number of patients experiencing nausea and vomiting during 0-3hrs and 24hrs postoperatively are shown in Table 3. The overall PONV incidence up to 24 hours post operatively were 17% in droperidol and 11% in granisetron group which was statistically insignificant (p = 0.321).

TABLE 3 Number (%) of patients experienced nausea and vomiting during 0-24 hours after anaesthesia in the two groups

GROUPS	TIME(hr)	SCORE 1 NO NAUSEA	SCORE 2 MILD NAUSEA	SCORE 3 SEVERE NAUSEA	SCORE 4 VOMITING
DROPERIDOL n=30(%)	0	26(87.7%)	4(13.3%)	-	-
	1	26(86.7%)	4(13.3%)	-	-
	2	26(86.7%)	3(10%)	1(3.3%)	-
	3	23(76.7%)	6(20%)	1(3.3%)	-
	4	22(73.3%)	8(26.7%)	-	-
	24	25(83.3%)	3(10%)	-	2(6.7%)
GRANISETRON n=30(%)	0	27(90%)	3(10%)	-	-
	1	28(93.3%)	2(6.7%)	-	-
2	27(90%)	3(10%)	-	-	
3	27(90%)	3(10%)	-	-	
4	23(76,7%)	7(23.3%)	-	-	
24	28(93.3%)	2(6.7%)	-	-	

n = number of patients in each group

In droperidol group, 26 patients (86.7%) had no episodes of nausea at first two hours and 25 patients (83.3%) had no nausea at 24 hours postoperatively. Mild nausea was present in 4 patients (13.3%) in first two hours and 3 patients (10%) at 24 hours postoperatively. One (3.3%) patient had severe nausea at 2nd hour and 3rd hour postoperatively. 2 patients (6.7%) reported of vomiting at 24hours postoperatively (Table3).

In granisetron group, 27 patients (90%) had no nausea at first two hours and 28 (93.3%) had no nausea at 24 hours postoperatively. Patients having mild nausea were 3 (10%) at 0, 1 and 3rd hour and 2 (6.7%) patients each at the end of 2nd hour and 24 hours postoperatively. No patients reported of severe nausea and vomiting in this group (Table3). Side effects like sedation, hypotension and headache were absent in both the groups. 2 patients reported constipation in granisetron group which was not significant.

Discussion

Postoperative nausea and vomiting continues to be a common complication of surgery[8]. It is a limiting factor in early discharge of patients and a leading cause of unanticipated hospital admission. Patients report that avoidance of PONV is of greater concern than the avoidance of post- operative pain[9]. Hence it is called "big little problem".

Incidence of PONV is reported to be higher in laparoscopic procedures when compared to laparotomy procedures. Etiology of PONV following laparoscopic cholecystectomy remains unclear, but is probably multifactorial associated with operative factors. Age, sex, obesity, history of motion sickness and or previous PONV, menstruation, anesthetic technique and postoperative pain are considered important factors in determining the incidence of PONV. Therefore during surgical procedures such as laparoscopic cholecystectomy, anti-emetic prophylaxis is commonly used[10].

Several antiemetic drugs have been recommended for the prevention and control of PONV[11].

Granisetron is a selective $5HT_3$ receptor antagonist[7]. 5HT-3 antagonists have a favorable side effect profile and are considered safe. In contrast, droperidol is a tranquilizer and the anti-emetic effect attributed to its dopamine receptor antagonist property[12]. The efficacy of droperidol is equivalent to that of Ondansetron for PONV prophylaxis. Droperidol and granisetron have different mechanisms of action for their antiemetic property. Hence we chose to compare these two drugs for prevention of PONV. Incidence of PONV is higher is laparoscopic surgery, incidence varying from 25 – 42% hence we chose patients posted for laparoscopic cholecystectomy surgery for our study.

In our study, both the groups were similar with regard to patient demographics, surgical procedure, anesthetics administered and analgesics used postoperatively. Duration of surgery and the duration of anesthesia were also similar in both the groups. Hence the difference in the incidence of PONV among the groups can be attributed to the difference in the agents administered.

Kortilla et al[13] and Madej et al[14] reported that 1.25mg (approximately 25mcgkg^{-1}) and 2.5mg (approximately 50mcgkg^{-1}) of droperidol reduced the incidence of PONV following gynecological surgery. However, higher doses of this drug (2.5 – 5.0mg) were associated with side effects such as drowsiness and extrapyramidal symptoms[7].Pandit et al[15] gave 5, 10 and 20mcgkg^{-1} of droperidol after laparoscopic surgeries. They concluded that droperidol in the doses of 10mcgkg^{-1} and 20mcgkg^{-1} are very effective (66% and 75% reduction in nausea respectively) for prevention of PONV after laparoscopic surgeries. Yoshitaka Fujii et al[16] during their study found that the antiemetic efficacy of granisetron in the doses of 40mcgkg^{-1} and 60mcgkg^{-1} was superior to that of granisetron 20mcgkg^{-1} and placebo during the 24hrs period postoperatively. Naguib et al[17] demonstrated that 3mg granisetron (i.e 60mcgkg^{-1} and 4mg Ondansetron were effective is reducing the incidence of PONV following laparoscopic cho lecystectomy. In this study therefore, the antiemetic efficacy of droperidol(20mcgkg^{-1}) in the prevention of PONV was compared with granisetron(60mcgkg^{-1})

Fujii et al[18] in their study found a relatively high incidence of PONV (42%) during the first 24hrs after recovery from anesthesia for laparoscopic cholecystectomy in patients who had received placebo. This incidence was in accordance with the previous reports about the incidence of PONV that ranged between 25% and 42%. The incidence of PONV was 41% in patients who had received droperidol and 15% in the patients who had received granisetron as antiemetics. Thus they concluded that the incidence of PONV was lower in patients who had received granisetron when compared to those who had received droperidol or placebo.

In this study we found the incidence of PONV was 17% in the droperidol group and 11% in the granisetron group during the first 24hrs after recovery from anaesthesia. As this difference was statistically not significant, we in our study concluded that granisetron and droperidol were equally effective in reducing the incidence of PONV and that no drug was superior to the other.

In the study conducted by Hiroyoshi Tanaka et al [19], the frequencies of PONV in patients who received granisetron (12%), droperidol 1.25mg (16%) and droperidol 2.5mg (12%) were lower than those who had received placebo (60%) during the 0–3 hour period after recovery from anesthesia. Similarly in our study the frequency of PONV in patients who received droperidol (15%) and granisetron (10%) during the 0-3 hour period after recovery from anesthesia, suggesting that both the drugs were equally effective for prevention of PONV during the 0 -3 hours postoperatively. In our study, there was no incidence of vomiting in the granisetron group during the 24hour postoperative period. Though two patients reported of vomiting in the droperidol group with an incidence of 6.7% at the end of 24hrs after recovery from anesthesia, this was statistically not significant.

Yoshitaka Fujii et al [10] in their study reported that "complete response" which they defined as no PONV and no requirement of rescue antiemetic medication during the first 24hrs postoperatively, was 98% in patients who had received granisetron–droperidol combination. This was greater than in those patients who had received granisetron alone 86% and droperidol alone 64%. In our study complete response was 88.9% in patients receiving granisetron and 82.2% in patients receiving droperidol during the 24hrs postoperative period. There was again no statistically significant difference among both the groups p=0.321

Hiroyoshi Tanaka et al[19] in their study found that there was prolongation in awakening time and reported drowsiness and sedation in the patients who had received droperidol in the dose of 2.5mg, but there were no differences in the awakening time and frequency of side effects among the group of patients who had received droperidol in dose of 1.25mg, granisetron and or placebo for the prophylaxis of PONV. In our study, however there was no prolongation in awakening time in patients who received droperidol in comparison to those patients who received granisetron (p = 0.23). Hence droperidol used in the doses for prevention of PONV i.e 20 mcg/kg does not cause delay in recovery.

Yoshitaka Fujii et al[18] observed that the adverse events noted in their study were relatively mild and there were no differences in the incidence of headache, dizziness and drowsiness among the groups receiving either droperidol or granisetron. One of the important problems with droperidol for prophylactic antiemetic therapy is the risk of undesirable adverse events such as excessive sedation and extrapyramidal signs[19]. Hiroyoshi et al and S Ozmen et al in their studies concluded that the risk of undesirable side effects was not increased with added droperidol. Studies by Lamond et al [20] and Tramer et al[21] reported a lower incidence of PONV with lower doses of droperidol without sedation.

Falkson et al [22] reported that mild headache occurred in patients who received granisetron to prevent chemotherapy induced nausea and vomiting.

Schaub.L et al[23] performed randomized comparison of single shot intravenous low dose droperidol (<1mg or 15mcg kg^{-1}) with placebo for prevention of PONV in adults undergoing general anesthesia. They concluded that risk of sedation and time of awakening were not increased In our study, adverse events such as headache, hypotension, drowsiness or sedation were not observed in either of the groups receiving droperidol or granisetron as antiemetics in the 24hrs postoperative period.

However, in our study two patients (6.7%) in the granisetron group reported of constipation which was not significant as to receive any treatment. Hence use of droperidol for prevention of PONV in the doses of 20mcgkg^{-1} does not increase the incidence of side effects during the 24hrs postoperative period.

The limitation of the study was that we used monotherapy for prevention of PONV but studies have shown that polytherapy would be more effective for prevention of PONV.

Conclusion

We concluded that both droperidol and granisetron are equally effective and safe antiemetic drugs for reducing the incidence and severity of PONV after laparoscopic cholecystectomy. Droperidol when used in low dose does not increase risk of side effects. Although antiemetic prophylaxis cannot eliminate the risk of PONV completely, it can significantly reduce the incidence of PONV to large extent. Though monotherapy is effective for prophylaxis of PONV there is increasing evidence that the combination of several potentially beneficial factors (multimodal approach) may lead to improved outcome. Double and triple antiemetic combinations hence are recommended for the prophylaxis of PONV is patients at high risk of PONV.

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