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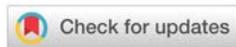
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Research Article

Comparison of dexamethasone, granisetron and haloperidol in prevention of postoperative nausea and vomiting following laparoscopic surgeries: A prospective, double-blinded study

Abstract

Background: Laparoscopic surgeries are most commonly performed surgeries. However, they are associated with increased incidences of postoperative nausea and vomiting.

Aim: We aimed to compare the effectiveness of dexamethasone, haloperidol, granisetron in prevention of postoperative nausea and vomiting following laparoscopic surgeries.

Methods: We conducted a randomized, double-blinded study including 90 patients both males and females undergoing laparoscopic surgeries in a tertiary hospital over 18 months. The subjects were randomized into three groups. Group I Dexamethasone 8mg, Group II Granisetron 2mg, Group III Haloperidol 1mg (n=30 each group). The study drugs were administered intravenously immediately after intubation. Patients were observed every 4th hourly till 24 hours for incidence of nausea, vomiting, pain and sedation.

Results: Incidence of vomiting was significantly less in dexamethasone group (p=0.047) as compared to granisetron and haloperidol and was statistically significant (p<0.047). There was no significant difference in the incidence of vomiting between other two groups. All other parameters were comparable in all the groups.

Conclusion: Dexamethasone in the dose of 8mg significantly reduces incidence of vomiting in laparoscopic surgeries than haloperidol and granisetron.

Trial Registry: Clinical Trial Registry of India 2018/03/018324

Abbreviations

PONV: Postoperative Nausea and Vomiting; ADR: Adverse Drug Reactions; GIT: Gastrointestinal Tract; CTZ: Chemoreceptor Trigger Zone; NTS: Nucleus Tractus Solitaries; IAP: Intraabdominal Pressure; FRC: Functional Residual Capacity; PACU: Post-Anesthesia Care Unit; IV: Intravenous; SVR: Systemic Vascular Resistance; ASA: American Society of Anesthesiologist; IM: Intramuscular; 5HT₃: Serotonin Receptor Antagonist; ANOVA: Analysis of Variance; VAS: Visual Analogue Scale; NPIS; Numeric Pain Intensity Scale; ES: Effect Size; SD: Standard Deviation

Introduction

Incidence of post-operative nausea and vomiting (PONV) is 20–30%. Nausea and vomiting are the second commonest complication for the surgeries done under general anesthesia and are slightly higher in the population undergoing laparoscopic surgeries [1]. Vomiting occurring after the surgery is usually self-limiting, if persistent results in morbidity and increases the duration of hospital stay. Vomiting and nausea are slightly higher in the population undergoing laparoscopic surgeries. It is higher especially in laparoscopic cholecystectomies [2]. The increased incidence is due to the creation of pneumo-

peritoneum which causes distension in the abdominal cavity leading to raised intra-abdominal pressure resulting in altered physiology. Increased wound tension, high venous pressure, water electrolyte disorders, acid base imbalance, aspiration, asphyxia are the complications resulting from PONV and hence prevention and treatment are mandatory.

There are different antiemetic drugs in practice for prevention and treatment of nausea and vomiting. These drugs act on different receptors like cholinergic, dopaminergic, serotonergic, anti-histaminic and corticosteroids [3]. Corticosteroids like dexamethasone are well known for their analgesic, anti-inflammatory, immunomodulatory and anti-emetic effects and are often used for prevention of PONV. It has been proved to be more effective than metoclopramide, droperidol, granisetron in prevention of PONV associated with chemotherapy. Dexamethasone either alone or in combination with other antiemetics is effective in decreasing the incidence of PONV [4]. Haloperidol belongs to the class of butyrophenones and has a similar structure to droperidol. It blocks the effect of dopamine and is given prophylactically for PONV. It is the drug with minimal toxicity and is effective for prevention of PONV. Both these drugs i.e. haloperidol and droperidol have been compared for prevention of PONV in laparoscopic surgery and were equally effective in preventing PONV [5].

Granisetron belongs to the class of serotonin 3 receptor antagonist and produce block of 5HT₃ receptors and is irreversible, which accounts for their longer duration of action. In patients with higher risk of PONV, granisetron with other antiemetics reduces the incidence of PONV [6]. Evaluation of ondansetron and granisteron is being done in preventing PONV in laparoscopic surgery and it is proved that granisetron is more effective than ondansetron in reducing the incidences of nausea and vomiting [7].

Although a variety of drugs, including droperidol, ondansetron, dolasetron decrease the incidence of PONV, none of these drugs either alone or in combination reduce incidence of PONV to 0%.

These drugs have been tried together as combinations in their groups and also individually. There are very few studies which have compared granisetron and haloperidol for their efficacy as anti-emetics. Though most of those studies have evaluated the drugs in combination the efficacy of each drug as agent for control of nausea and vomiting is not clear.

To our knowledge the three drugs, dexamethasone, granisetron and haloperidol have not been compared against each other for laparoscopic surgeries. Hence, this study was conducted to compare the efficacy of dexamethasone, granisetron and haloperidol for prevention of PONV in laparoscopic surgeries.

Materials and Methods

This prospective, randomised, double blinded study was done over a period of 18 months. All the patients who underwent elective laparoscopic surgeries between the age of

18-60yrs of both sexes belonging to ASA (American society of anaesthesiologists) physical status I and II in tertiary care hospital were included in the study. Patients with use of antiemetic, glucocorticoids and opioids within 24 hours of surgery, pregnant patients, those suffering from psychotic illness and motion sickness were excluded from the study.

After obtaining institutional ethics committee approval and written informed consent in patient's own language, 90 patients were randomly allocated into three groups (n=30 each) by computer generated list of random numbers and were given drugs according to the groups: Group I-Dexamethasone 8mg, Group II- Granisetron 2mg(Roche laboratories UK), Group III- Haloperidol 1mg(Rpg life sciences Ltd,India). An operation theatre assistant who was not involved in the study prepared the drug solutions based on randomisation for each group. All three drugs were taken in identical 5ml syringes and were labelled as antiemetic. An independent investigator who was not involved in the anesthetic management and monitoring of the patients gave the study drug to the patient. Patients, anesthesiologists involved in intraoperative and postoperative care of the patient and investigator collecting the data were unaware of the group allocation. Pre anesthetic checkup was done for all the patients. Patients were given oral tablet ranitidine 150mg and tablet alprazolam 0.5mg night before surgery. Patients were shifted to operation Theatre (OT). Standard monitors like pulse oximeter, electrocardiography and non-invasive blood pressure were connected. An iv access was established with 18 gauge intravenous cannula. Patients were preloaded with 5ml/kg of crystalloids. All the patients were given premedication drugs, inj.glycopyrrolate iv in a dose of 5mcg/kg iv, inj. midazolam 0.02mg/kg iv. Patient were given inj.fentanyl 2mcg/kg iv for analgesia .Patients were induced with inj.propofol 2mg/kg iv and inj. vecuronium 0.1mg/kg iv. Patients were intubated with appropriate size endotracheal tube and connected to circle system.The study drugs were administered right after intubation was done. Ventilation was controlled mechanically. Anesthesia was maintained with vecuronium 0.03mg/kg and isoflurane and N₂O and O₂, 70: 30 ratio. Ryles tube was inserted to deflate the stomach for better laparoscopic visualisation. Time of start of inhalation agent and surgery was noted. Vitals were monitored every 15 min. Time of switching off of inhalational; agent and end of surgery were noted. At the end of surgery neuromuscular blockade was reversed with inj.neostigmine iv in the dose of 50 mcg/kg and inj. glycopyrolate in the dose of 10mcg/kg. Eye opening time was noted. Patients were extubated. Duration of surgery and duration of anesthesia was noted. After the surgery, patients were observed for 24 hours. Patients were shifted to post-anesthesia care unit (PACU). Monitors were connected and pulse rate, blood pressure, oxygen saturation were monitored. All the patients were monitored and given oxygen in the PACU unit. Nausea scores were monitored according to visual analogue scale (VAS scale, 0-10 where 0=No nausea, and 10=worst possible nausea). Vomiting was noted as number of emetic episodes. 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.

Second episode of vomiting was treated with metoclopramide 10mg IV. Vomiting episodes were recorded every 4 hourly for 24 hours. Sedation scores were monitored with Ramsay sedation scale.

Ramsay sedation scale

Sedation score - Clinical scale

- 1 Anxious, Restless, Agitated
- 2 Oriented
- 3 Responds to commands
- 4 Brisk response to light glabellar tap
- 5 Sluggish response to light glabellar tap
- 6 No Response

Pain score were monitored as numeric pain intensity scale of 0-10)0=no pain and 10 worst possible pain (NPIS). Pain score of more than 3 was be taken as patient experiencing pain. Time of demand of first rescue analgesic was noted. inj. diclofenac 1.5mg/kg im was given for pain. Total number of analgesics required was noted. Any other side effects were also noted. End of 24 hours was taken as end of study point and patient's proforma was returned to the principal investigator in a sealed envelope.

Primary outcome of the study was incidence of vomiting in 24 hours.

Secondary outcomes were the number of rescue antiemetic required, incidence of nausea and nausea scores, pain score and sedation scores.

Sample size calculation: Sample size calculation were done based on previous studies when incidence of nausea and vomiting with granisetron and haloperidol was 83% [8] and 39% [9], respectively. Applying effect size(ES) of 0.89 to the ANOVA for three groups, sample size of 25 patients per group were needed for 5% significance and 90% power of study.30 patients per group were included to allow possible drop out .

Statistical methods: Data was analyzed using statistical package for social sciences (SPSS) VERSION 23, Microsoft USA, Armonk, NY: IBM Corporation and its licensors 2015. Descriptive statistics was calculated such as frequency and percentage. Continuous variables were expressed in standard deviation and mean. Data was analyzed by Shapiro-wilk test. Demographic parameters were assessed with analysis of variance between the groups and are expressed as Mean and standard deviation (SD). Incidence of nausea and vomiting were compared using Chi square test and expressed as frequency and percentage. Two-proportion comparison between the three groups for incidence of vomiting was done using 2 proportion Z – test. Number of patients experiencing pain and nausea were assessed with Chi square test and expressed as number and %. Intraoperative – vitals were compared between two groups using Chi square test and expressed as percentage, frequency. P value<0.05 was taken as statistically significant for 2 sided test.

Results

All the 90 patients randomised were analysed for the study and there were no dropouts. The demographic profile was comparable in all the three groups in terms of age, height, weight and gender. The duration of anesthesia and surgery were not statistically significant (Table1).

The incidence of nausea and vomiting in all the groups are shown in table 2,3. The incidence of vomiting in dexamethasone group was significantly less than in granisetron and haloperidol group (P=0.047). Requirement of rescue antiemetic was comparable between the three groups. The incidence of nausea was comparable between the three groups until the 20th postoperative hours and was statistically significant at 24th hour (P=0.013).

The proportion of occurrence of postoperative vomiting in all the three groups and the inter-group comparison for two out of three groups is shown in table 4. The proportion between groups I, II and I, III were statistically significant (P=0.02, P=0.04 respectively).The proportion between group II and III was not statistically significant (P=0.158).

Table 1: Demographic profile between groups.

Demographic data	Group I (Mean ± SD) (n=30)	Group II (Mean ± SD) (n=30)	Group III (Mean ±SD) (n=30)	P value
Age	32.3000 ± 9.94173	34.4000 ± 11.28197	31.7667 ± 9.16396	0.572
Weight	60.5000 ± 9.05062	60.6000 ± 10.65315	57.3333 ±12.08117	0.406
Height	159.3333 ± 7.21461	160.2333 ± 7.36573	158.4000 ±10.22708	0.696
Gender(M/F)	9/21	12/18	8/22	
Duration of Anesthesia	132.7333±49.60390	115.8000±45.55966	125.4000±35.64538	0.332
Duration of Surgery	117.867±50.26326	99.4333±46.08888	105.6000±29.20038	0.243

SD= Standard deviation

Table 2: Incidence of nausea.

Variable	Group 1	Group 2	Group 3	P value
Nausea at 4hrs	1(3.3%)	1(3.3%)	1(3.3%)	1.000
Nausea at 8hrs	3(10%)	6(20%)	5(16.7%)	0.667
Nausea at 12hrs	3(10%)	9(30%)	6(20%)	0.172
Nausea at 16hrs	2(6.7%)	7(23.3%)	3(10%)	0.218
Nausea at 20hrs	1(3.3%)	7(23.3%)	4(13.3%)	0.084
Nausea at 24hrs	0(100%)	7(23.3%)	4(13.3%)	0.013

Table 3: Incidence of Nausea.

Group I	Group II	Group III	P value
16.7%	43.3%	43.3%	0.047

Table 4: Two proportion Z test for occurrence of Postoperative nausea and vomiting (PONV).

Groups comparison	Z	P	Inference
Group I and II	1.678	0.99	Not significant
Group I and II	3.317	0.002	Significant
Group II and III	1.429	0.158	Not significant

The distribution of pain scores among the three groups are shown in figure1 and were not statistically significant ($P=0.465$). Sedation scores were comparable in all the three groups and was not significant ($P=0.408$).

Discussion

The result of our study has shown a significantly low incidence of nausea and vomiting in the dexamethasone group compared to other groups ($P=0.013$ at 24 hrs for nausea, $P=0.047$ for vomiting). Overall incidences of vomiting in our study were 16.7% in group I, 43.3% in group II and group III.

In the era of day care and minimally invasive laparoscopic surgeries, post-operative nausea and vomiting remains a problem to be addressed. With the availability of many antiemetic agents, the ideal agent is debatable. Dexamethasone has shown to be safe and effective in the prevention of post-operative nausea and vomiting following laparoscopic surgeries in many studies.

Chu et al, compared 5mg of dexamethasone with 2mg of haloperidol in patients undergoing laparoscopic assisted vaginal hysterectomy [10]. They found that incidence of vomiting in dexamethasone was 12% and in haloperidol was 14% and was not statistically significant. In our study incidence of vomiting in dexamethasone was 16.7% and in haloperidol 43.3% and was statistically significant ($P=0.047$). Incidence of vomiting in dexamethasone was almost similar in both the studies. We used 8mg of dexamethasone in our study.

Erhan et al, compared the effectiveness of granisetron 3mg and 8mg dexamethasone in patients undergoing laparoscopic cholecystectomy [11]. Incidence of vomiting was 10% in both the groups and was not significant. In our study it was 43.3% for granisetron and 16.7% for dexamethasone and was significant. In our study incidence was more in granisetron group as only 2mg dose was used whereas Erhan et al, used 3mg. Granisetron in the dose of 5–20mcg/kg has proven to be better antiemetic than other 5HT₃ antagonist.

Sunil et al, compared the antiemetic efficacy of haloperidol vs granisetron for prevention of PONV in patients undergoing laparoscopic surgeries [12]. Comparison was done with 2mg haloperidol and 1mg granisetron. Noted incidence of vomiting

in haloperidol was 43.3% and 43.3% in granisetron. Authors have quoted this difference as not significant in their study. In our study incidence of vomiting was equal in both the groups 43.3% and was not significant. Haloperidol in dose of 0.5–2mg iv or im is effective in postoperative nausea and vomiting.

Rao et al, measured the difference between granisetron and granisetron with dexamethasone for PONV prophylaxis in laparoscopic surgery [13]. Granisetron 40mcg/kg iv in one group and 40mcg/kg with 8mg dexamethasone in other group was given. Vomiting in granisetron group was 30% and granisetron plus dexamethasone 3.3%. In our study we used granisetron in the dose of 2mg and found that vomiting was 43.3% and in dexamethasone group it was 16.7%. Nausea was significantly reduced in granisetron and dexamethasone combination. In our study nausea at 24th hour with dexamethasone was 0 and with granisetron it was 23.3%.

Erhan et al, studied 3mg of granisetron vs 8mg of dexamethasone and found that incidences of nausea were nil in both the groups [11]. In our study incidence of nausea up to 20 hours was 6–9% in granisetron group and 1–5% in dexamethasone group. The higher dose of granisetron used in their study could be responsible for less incidence of nausea. In our study nausea was comparable at every 4 hours and was significant only at 24th hour, which was zero in dexamethasone group and granisetron 23.3% and was statistically significant. In study done by Sunil et al, incidence of nausea in haloperidol group was 13.3% and 23.3% in granisetron group and was not significant [14].

Chu et al, requirement of analgesia was 13% in haloperidol and 18% in dexamethasone group which was comparable. In our study need for analgesia for dexamethasone was 36.7% had pain and 53.3% in haloperidol and was not statistically significant. Rescue analgesic needed in dexamethasone was at 153 min and 189 min for haloperidol. There was no difference in the level of sedation in the two groups [10].

In our study sedation scores were comparable between haloperidol and other two groups. The incidence of pain in our study was 36.7% in dexamethasone group and 43.3% in granisetron group which was not significant.

Though many studies have evaluated the efficacy of dexamethasone in laparoscopic surgeries, we compared the drug with two other classes of antiemetic and found to significantly reduce the incidence of PONV. Dexamethasone being a glucocorticoid is easily available, cheap and safe with a single dose compared to other classes of drugs.

There were few limitations in our study. Prophylactic effects of drugs could not be studied for more than 24 hours due to hospital policies. Geriatric age group is a risk factor for PONV but we could not include that in our study due to ethical issues. Study population did not include patients above ASA II Physical status. All the three drugs were given in fixed doses and were not calculated as per kg requirement.

Future studies are needed comparing different doses of haloperidol and granisetron with each other. More research

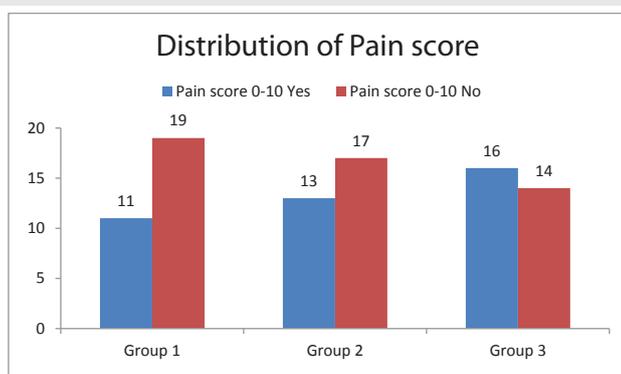


Figure 1: Distribution of pain scores.

is needed to study combined efficacy of granisetron and haloperidol against the superiority of dexamethasone for prevention of postoperative nausea vomiting following laparoscopic surgeries.

Conclusion

We conclude that dexamethasone is better than granisetron and haloperidol for prevention of postoperative nausea and vomiting following laparoscopic surgeries. All the three drugs are similar in efficacy for postoperative pain relief, and sedation.

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