EFFICACY OF SINGLE PARENTERAL DOSE OF PALONOSETRON VERSUS DEXAMETHASONE FOR PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERIES UNDER GENERAL ANAESTHESIA

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ABSTRACT

BACKGROUND

Postoperative Nausea and Vomiting (PONV) is an incessant postoperative complication of surgery associated with patient inconvenience and discomfort and can be an unpleasant experience. We designed this study to assess the antiemetic efficacy of palonosetron versus dexamethasone in the prevention of PONV among patients undergoing laparoscopic surgery under general anaesthesia.

MATERIALS AND METHODS

This prospective randomised double-blind study was conducted on 106 patients aged between 20 to 60 years of either sex belonging to ASA I and ASA II undergoing laparoscopic surgery under general anaesthesia after obtaining institutional ethical committee clearance and patient's written informed consent. The patients were randomly divided into two groups- group P (n=53) received palonosetron 0.075 mg IV and group D (n=53) received dexamethasone 8 mg IV five minutes before induction of anaesthesia. All the patients were observed for nausea and emetic episodes after recovery from anaesthesia during periods of 0-6 hours, 6-12 hours and 12-24 hours.

RESULTS

The demographical profile of the patients in both groups was comparable. In the first 0-6 hour postoperative period, 7 out of 53 patients (13.2%) in group P and 20 out of 53 patients (37.7%) in group D had vomiting. P value was significant (P=0.004). During the 0 to 6 hours postoperative period, the incidence of nausea was 9.4% in group P, whereas in group D, it was 24.5%. P value was significant (P=0.04). During the 6 to 24 hours postoperative period, the incidence of nausea and vomiting was comparable in both groups (P>0.05). In the 0-6 hours postoperative period, the number of complete responders (no vomiting, no rescue antiemetics) was 40/53 (75.5%) in group P and 30/53 (56.6%) in group D and the difference was clinically and statistically significant (P=0.040). In the next 6-12 hours and 12-24 hours postoperative period, the number of complete responders were comparable in both groups. No major adverse effects were seen in both groups due to the study drugs.

CONCLUSION

Single intravenous dose of palonosetron or dexamethasone given preoperatively prevented the incidence of postoperative nausea and vomiting in patients undergoing laparoscopic surgeries under general anaesthesia without any side effects. Palonosetron was comparatively more effective than dexamethasone in the early postoperative period to prevent the PONV than dexamethasone.

KEYWORDS

Dexamethasone, General Anaesthesia, Laparoscopic Surgery, Palonosetron, PONV.

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BACKGROUND

Postoperative Nausea and Vomiting (PONV) is an unpleasant experience and an incessant postoperative complication of surgery associated with a large amount of patient inconvenience and discomfort. The incidence of PONV is high in abdominal surgeries and female patients are particularly predisposed to this risk.[1] Incidence of PONV after surgery is in the range of 20-30%,[2] but it may be up to 50-70% after laparoscopic surgeries.[3] Although, the experience of PONV is generally self-limited, postoperative vomiting or retching can lead to rare, but serious medical complication such as aspiration of gastric content, suture dehiscence, oesophageal rupture, subcutaneous emphysema or pneumothorax. PONV may delay a patient's discharge from post-anaesthesia care units and can be leading cause of unexpected hospital admission after ambulatory

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anaesthesia. In July 2003, for Chemotherapy-Induced Nausea and Vomiting (CINV), the US Food and Drug Administration affirmed palonosetron hydrochloride for its treatment.[4] The mechanism of action of dexamethasone is poorly understood, but it seems to be most effective when it is administered before the start of surgery when it can also reduce surgery-induced inflammation.[5] The antiemetic property of dexamethasone is poorly understood. By centrally inhibiting the tractus solitarius nucleus and not the area of postrema in animal's experiments, it exerts its antiemetic property.[6] Slow mode of action facilitates its use at the beginning of a case, which appears superior to latter use.[5] Glucocorticoids bind to intracellular glucocorticoid receptors and exert their effects via gene transcription.[7] As changes to both gene expression and protein synthesis take time, most effects of corticosteroids are not instantaneous; rather, they only become apparent after several hours. Therefore, glucocorticoids usually take 1-2 hours to have biologic effects and this also depends on the route of administration.[8] This may explain why dexamethasone was found to significantly decrease PONV in the late postoperative stage (6-24 hours) rather than in the early postoperative stage (0-6 hours) in our data analysis.

Palonosetron is a 5-HT3 antagonist utilised as a part of treatment of Chemotherapy-Induced Nausea and Vomiting (CINV). It is the best of the 5-HT3 antagonists in controlling delayed CINV that occurs over 24 hours after the primary dosage of a course of chemotherapy and is the main medication of its class endorsed for this utilisation by the U.S Food and Drug Administration. Starting at 2008, it is the latest 5-HT3 antagonist to enter clinical use. Palonosetron is a specific serotonin 5-HT3 receptor antagonist. The antiemetic ability of the medication is achieved through the inhibition of 5-HT3 receptors involving both medullary chemoreceptor zone and GI tract.[9] This inhibition of 5-HT3 receptors, thus represses the visceral afferent acceleration of the vomiting focus likely in a roundabout way at the level of the region postrema and in addition through direct restraint of serotonin activity inside the zone of postrema and the chemoreceptor trigger zone.[10] Alternate mechanism seems to basically responsible for emetogenic chemotherapy-induced nausea and vomiting, since comparable temporal relationship have not been documented between serotonin and emesis caused beyond first day after a dose and these agents are generally not sole responsible in preventing or alleviating the delayed effect. The long plasma half-life of palonosetron may add to its observed adequacy in preventing delayed sickness and vomiting caused by emetogenic cancer chemotherapy.[11] The most common occurring adverse effects in clinical trials include headache and constipation. But, there are adverse effects involving cardiovascular system like tachycardia, sinus dysrhythmia, supraventricular tachycardia and QT interval prolongation and gastrointestinal system like diarrhoea, dyspepsia, constipation and abdominal pain. Apart from these effects, dry mouth, flatulence, dizziness, somnolence, insomnia, paraesthesia and altered hearing and vision maybe seen.

MATERIALS AND METHODS

This prospective randomised double-blind study was conducted on 106 patients aged 20-60 years of either sex belonging to ASA I and ASA II undergoing laparoscopic surgery under general anaesthesia after obtaining Institutional Ethical Committee clearance and patient's written informed consent. The participants were randomly divided into two groups- group P (n=53) received palonosetron 0.075 mg IV and group D (n=53) received dexamethasone 8 mg IV 5 minutes before induction of anaesthesia. Inclusion criteria were patients of either gender aged between 20 to 60 years belonging to ASA 1 and ASA 2 undergoing elective laparoscopic surgery. Exclusion criteria were those aged below 20 years and above 60 years, patients belonging to ASA 3 and ASA 4, emergency surgery, pregnant women, patients on chemotherapy and radiotherapy, patients sensitive to 5-HT3 antagonists, psychiatric diseases, diabetes, history of drug abuse, duration of surgery more than three hours, chronic obstructive pulmonary disease, previous history of motion sickness and PONV, patients in premenstrual phase and body mass index >35.

Sample size was calculated using the below formula.

$$N = \frac{2(Z_{1-\alpha}+Z_{1-\beta})^2 P (1-P)}{(P_1-P_2)}$$

$Z_{1-\alpha} = 1.96$ (at 95% confidence)

$Z_{1-\beta} = 0.842$ (at 80% power)

$P_1 = O.26 = 26\%$

$P_2 = O.06 = 6\%$

$$P = \frac{P_1 + P_2}{2} = \frac{0.26+0.06}{2} = 0.16$$

$$N = \frac{2\,(1.96+0.842)^2\,(0.16)\,(1-0.16)}{0.26-0.06}$$

N=53 in each group

Patients were randomly divided into two groups in a double-blinded manner with the help of computer-generated codes. The participating patients and investigators collecting the postoperative data were blinded to the randomisation. A thorough preoperative anaesthetic assessment was done the day before and the patients were premedicated with tablet alprazolam 0.5 mg the night before surgery. After a preoperative fasting of 8 hours, an intravenous cannula was inserted in the preoperative room. In the operation theatre, the patients were connected to a multipara monitor displaying ECG, heart rate, oxygen saturation, end-tidal carbon dioxide and core temperature. Premedication was given with intravenous midazolam 2 mg and fentanyl 2 µ/kg. Patients in group D received 8 mg of dexamethasone intravenously and those in group P received 0.075 mg

palonosetron intravenously 5 minutes before induction of anaesthesia. Preoxygenation was done with 100% oxygen for 5 minutes. Induction of anaesthesia was done with IV propofol 2 mg/kg and IV atracurium 0.5 mg/kg was administered for endotracheal intubation and muscle relaxation. After inserting the appropriate size endotracheal tube, position was confirmed by checking equal air entry bilaterally and capnographic trace. The cuff was inflated and tube was securely fixed. Anaesthesia was maintained with a mixture of 50% oxygen in air and sevoflurane. At the end of surgery, residual neuromuscular block was reversed with neostigmine and glycopyrrolate in all patients. Ketorolac (0.5-1.0 mg kg^{-1}) was administered for postoperative pain control. After surgery, patients were shifted to the post-anaesthetic care unit and monitored. The incidence of nausea and vomiting and use of rescue antiemetics were evaluated at 1, 6, 12 and 24 hours after surgery. Intravenous metoclopramide 10 mg was administered as rescue medication for patient's complaint of nausea or vomiting. Adverse events were evaluated and recorded by the investigator during the entire observation period. The primary outcome measured in this study was the incidence of PONV 0-24 hours after operation and the secondary outcome measured included the incidence of side effects and complete response.

Statistical analysis was performed using SPSS for Windows (version 14, SPSS Inc., Chicago, IL, USA). Student's t-test was used to compare the continuous variables between the groups. A P-value of <0.05 was considered statistically significant. Data was presented as mean plus standard deviation, numbers or percentages.

RESULTS

Out of 110 patients enrolled, two patients required conversion to open appendicectomy and open herniorrhaphy respectively, and in two other patients, the surgical duration exceeded three hours and hence excluded from the study. Data obtained from the remaining 106 patients were analysed for interpretation.

Demographic Variables	Group P (n=53)	Group D (n=53)	P Value
Age (years)	34.04 ± 9.93	32.42 ± 9.81	0.399
Gender			
Male	28	29	0.846
Female	25	24	
Weight (kg)	54.19 ±10.05	54.19 ±10.08	0.954

Table 1. Demographical Profile of the Patients of Both the Groups

The demographic parameters were comparable in both the groups as shown in Table 1.

Type of Surgery	Group P	Group D	Total
Laparoscopic appendicectomy	10 (18.9%)	6 (11.3%)	16 (30.2%)
Laparoscopic cholecystectomy	7 (13.2%)	12 (22.6%)	19 (35.8%)
Diagnostic laparoscopy	11 (20.8%)	5 (9.4%)	16 (30.2%)
Laparoscopic-assisted vaginal hysterectomy	7 (13.2%)	16 (30.2%)	23 (43.4%)
Laparoscopic inguinal hernioplasty	3 (5.7%)	4 (7.5%)	7 (13.2%)
Laparoscopic tubal ligation	3 (5.7%)	3 (5.7%)	6 (11.3%)
Laparoscopic cystectomy	2 (3.8%)	3 (5.7%)	5 (9.4%)
Laparoscopic nephrectomy	4 (7.5%)	1 (1.9%)	5 (9.4%)
Laparoscopic fundoplication	4 (7.5%)	1 (1.9%)	5 (9.4%)
Total laparoscopic hysterectomy	2 (3.8%)	2 (3.8%)	4 (7.5%)

Table 2. Distribution of Patients According to Surgery

Table 2 shows the distribution of patients according to the nature of surgery in number and percentage.

Vomiting		Group P Palonosetron		Group D Dexamethasone		P value
		Number	Percentage	Number	Percentage	
0-6 hours	Present	7	13.2%	20	37.7%	0.004
	Absent	46	86.8%	33	62.3%	
6-12 hours	Present	4	7.5%	2	3.8%	0.411
	Absent	49	92.5%	51	96.2%	
12-24 hours	Present	1	1.9%	3	5.7%	0.308
	Absent	52	98.1%	50	94.4%	
Nausea		**Group P Palonosetron**		**Group D Dexamethasone**		**P value**
		Number	**Percentage**	**Number**	**Percentage**	
0-6 hours	Present	5	9.4%	13	24.5%	0.04
	Absent	48	90.6%	40	75.5%	
6-12 hours	Present	5	9.4%	2	3.8%	0.24
	Absent	48	90.6%	51	96.2%	
12-24 hours	Present	3	5.7%	1	1.9%	0.30
	Absent	50	94.3%	52	98.1%	

Table 3. Comparison of Incidences of Nausea and Vomiting in Both the Groups

Complete Response		Group P Palonosetron		Group D Dexamethasone		P value
		Number	Percentage	Number	Percentage	
0-6 hours	Present	40	75.5%	30	56.6%	0.040
	Absent	13	24.5%	23	43.4%	
6-12 hours	Present	44	83%	46	86.8%	0.586
	Absent	9	17%	7	13.2%	
12-24 hours	Present	45	84.9%	47	88.6%	0.576
	Absent	8	15.1%	6	11.4%	

Table 4. Distribution of Patient According to Complete Response

In the first 0-6 hour postoperative period, 7 out of 53 patients in group P and 20 out of 53 patients in group D had vomiting. P value was significant (P=0.004). During the 6 to 24 hours postoperative period, the incidence of vomiting was comparable in both groups (P>0.05) as shown in Table 3. During the 0 to 6th hour postoperative period, the incidence of nausea was 9.4% in group P, whereas in group D, it was 24.5%. P value was significant (P=0.04). The incidence of nausea during the 6 to 24 hours postoperative period was comparable in both groups (P>0.05).

In the 0-6 hours postoperative period, the number of complete responders (no vomiting, no rescue antiemetics) was 40/53 (75.5%) in group P and 30/53 (56.6%) in group D and the difference was clinically and statistically significant (P=0.040). In the next 6-12 hours postoperative period, the number of complete responders was 44/53 (83%) in group P and 46/53 (86.8%) in group D and the difference was not statistically significant (P=0.586). During the next 12-24 hours postoperative period, the number of complete responders was 45/53 (84.9%) in group P and 47/53 (88.6%) in group D and the difference was not statistically significant (P=0.576).

Side Effects	Group P	Group D
Headache	4	5
Dizziness	5	2
Extrapyramidal symptoms	0	0
Cardiac arrhythmias	0	0
Hypotension	1	0
Insomnia	2	0
Constipation	3	0
Urinary retention	2	4

Table 5. Side Effects in Both the Groups Represented as Numbers

Minor side effects were seen in the patients because of the study drugs. Four patients in group P and five in group D had headache. Five patients in group P and two in group D had dizziness. One patient in group P had transient hypotension, two had insomnia and three had constipation. Two patients in group P and four in group D had urinary retention. None of the patients had any cardiac arrhythmias or extrapyramidal symptoms.

DISCUSSION

In our study, during the first six hours, the incidence of vomiting and nausea was significantly higher in patients who received dexamethasone compared to palonosetron. The late onset and prolonged antiemetic efficacy of dexamethasone maybe attributed to its prolonged biological half-life (36-72 hours).[12] Dexamethasone has proven antiemetic properties.[13]

In the early postoperative stage (0-6 hours), palonosetron was better at decreasing PONV than dexamethasone. However, in the late postoperative stage (6-24 hours), there was no significant difference between both drugs and effects on PONV was comparable. However, single parenteral dose of 0.075 mg of palonosetron significantly increased the CR rate (no emetic episodes and no rescue medication) up to 24 hours postoperatively. Dexamethasone is not particularly effective in preventing nausea and vomiting occurring early in the postoperative period. Thomas and Jones have shown a failure of prophylaxis during the first 3 hours in 28.3% of patients who had received dexamethasone compared to 22 and 8.6% of patients who had received ondansetron and ondansetron plus dexamethasone, respectively.[14] Compared to its combination with ondansetron, whereas ondansetron alone is less effective against late PONV as compared with combination therapy. This is in concordance with our study results. Bisgaard et al observed that preoperative dexamethasone compared to placebo reduces the incidence of PONV in patients undergoing laparoscopic cholecystectomy and recommended its routine use in laparoscopic cholecystectomy.[15]

Our study results show that the number of complete responders during 6-12 and 12-24 hours postoperative period in the two groups P and D did not differ significantly (P=0.576, P=0.586), which is in accordance with studies by Blitz et al. In their study of 118 patients undergoing laparoscopic surgery randomised to receive a combination of 8 mg dexamethasone, plus 0.075 mg palonosetron and 0.075 mg palonosetron alone found no significant difference in the incidence of PONV between the groups in the late postoperative period.[16] Anaesthetic agents initiate the vomiting reflex by stimulating the central 5-HT3 receptors on the Chemoreceptor Trigger Zone (CTZ). The relation between pneumoperitoneum and PONV is not exactly known. The abdominal insufflation during laparoscopic surgeries increases the abdominal pressure with subsequent dilatation of intestinal loops, which could influence the secretion of 5HT. The mucosal enterochromaffin cells of the intestinal tract contain approximately 90% of 5HT present in the body.[17] In our study, palonosetron was used in a dose of 0.075 mg, which has been found to be the minimum-effective dose in various studies.[18,19] Dexamethasone 8 mg is the most commonly used dose for the prophylaxis of PONV in various studies.[20,21]

Limitations of this study- The obvious limitations of this study include the lack of assessment of frequency, duration and severity of nausea and vomiting. Similarly, the study was not extended beyond 24 hours after recovery from anaesthesia. In addition, satisfactions of the patients with regards to overall management were not assessed.

CONCLUSION

Single intravenous dose of palonosetron or dexamethasone given preoperatively prevented the incidence of postoperative nausea and vomiting in patients undergoing laparoscopic surgeries under general anaesthesia without any side effects. Palonosetron, a unique second-generation 5-HT3 receptor antagonist is comparatively more effective than dexamethasone in the early postoperative period to prevent the PONV after anaesthesia in laparoscopic abdominal surgery due to its prolonged duration of action than dexamethasone. A single 0.075 mg IV dose of palonosetron significantly increased the CR rate (no emetic episodes and no rescue medication) during the first 0 to 6 hours as compared to dexamethasone.

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