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A comparative study between palonosetron plus dexamethaxone with granisetron plus dexamethasone for prevention of postoperative nausea and vomiting following laparoscopic cholecystectomy under general anaesthesia

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Abstract:
Background: *Postoperative nausea and vomiting (PONV) are commonly observed undesirable and potential complications in patients after laparoscopic cholecystectomy (LC) and chemotherapy. PONV are commonly observed adverse effects of general anaesthesia (GA) and its incidence ranges between 60% to 72 % following laparoscopic cholecystectomy.*
Methods: *In a prospective, double blinded, randomized controlled study, and after Ethical Committee years who underwent elective LC under GA were studied during a two year period in a tertiary care teaching hospital, in Imphal were assigned in one of two groups viz: Group PD (n=50) received 0.075 mg palonosetron with 8 mg dexamethasone and group GD (n=50) received granisetron 40 µg/kg body weight plus 8 mg dexamethasone. Nausea, retching and vomiting (PONV), complete response, rescue antiemetic and any side effects were observed upto 48 hours postoperatively.* ***Results:*** *The incidence of ponv was 12% and 14% in group PD and group GD respectively in 0-2 hrs interval and 14% and 22% in 2-48 hrs interval, respectively. However group PD had lesser incidence of PONV than group GD* ***(p>0.05). Conclusion:*** *It may be concluded that prophylactic intravenous palonosetron with dexamethasone is as effective as granisetron and dexamethasone, in prevention of early PONV. Although statistically insignificant, palonosetron and dexamethasone was better than granisetron and dexamethasone in prevention of late PONV in LC under general anaesthesia.*

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I. Introduction

Postoperative nausea and vomiting are commonly observed undesirable and potential complications in patients after LC and chemotherapy. PONV are commonly observed adverse effects of anaesthesia and its incidence ranges between 23 % to 72 % following laparoscopic cholecystectomy.[1-3] Although PONV is rarely fatal, it can cause morbidity such as wound dehiscence, dehydration, electrolyte disturbance, esophageal rupture etc. So by understanding its neurophysiology, knowing the risk factors and knowledge about the various antiemetics available, PONV can be avoided.[4-6] Various risk factors like patient characteristics, drugs, operative procedures and others have been studied by previous studies but remains inconclusive.[7]

Dexamethasone, a glucocorticoid, can be used as adjunct to antiemetics. It causes better control of late PONV by inhibition of prostaglandin synthesis, decrease in 5 HT levels in central nervous system (CNS) or by anti-inflammatory actions at operative sites.[2,8] Granisetron is a highly selective and potent 5-HT_3 receptor antagonist. It acts specifically on the 5-HT_3 receptors on the vagal afferents nerves of the gut and produces irreversible block of the 5-HT_3 receptors and it may account for the long duration of this drug.[9,10] Palonosetron, a serotonin receptor antagonist which has been shown to be superior to other drugs in its class for prevention of acute, delayed and chemotherapy induced nausea and vomiting due to its allosteric binding to 5 HT_3 receptor and longer half life.[11-13]

The present study was undertaken to compare the antiemetic efficacy of combination therapy of palonosetron plus dexamethasone versus granisetron plus dexamethasone in the prevention of PONV in patients undergoing laparoscopic cholecystectomy under general anaesthesia.

II. Materials and methods

This prospective, double blinded, randomized controlled study was conducted in the Department of Anaesthesiology of a tertiary care hospital in Imphal, over a period of two years between September 2015 to August 2017. After obtaining Research and Ethics Board approval of the Institute, 100 adult patients, aged 18-65 years of both genders, weight < 70 kgs, American Society of Anaesthesiologist (ASA) physical status I&II scheduled for undergoing elective LC under general anaesthesia were randomly allocated into either of the two groups by a computer generated randomisation number chart viz:

Group PD - received 0.075 mg palonosetron i.v + 8 mg dexamethasone i.v &

Group GD - received granisetron 40 µg/kg bw i.v + 8 mg dexamethasone i.v.

Exclusion criteria included patients with history of hypersensitivity to the study drug, intake of antiemetic drugs within 24 hrs preoperatively, steroid therapy or immunocompromised, with intestinal, liver or renal disease, pregnant, lactating or menstruating, h/o psychiatric disorder, motion sickness and PONV, alcoholic and opioid addiction, difficult intubation during induction of anaesthesia, on cancer chemotherapy and emetogenic radiotherapy were excluded from the study.

For an α value of 5% and β value of 0.2 (power =1- β=0.8, i.e 80%), assuming a complete response of 67% and 90% in granisetron and palonosetron respectively in 24-48 hrs, the sample size was 46 in each group, which was rounded to 50 in each group assuming a 5% dropout, based on an earlier study.[14]A placebo group was not included as it would be unethical to expose the patients to go through the ponv.

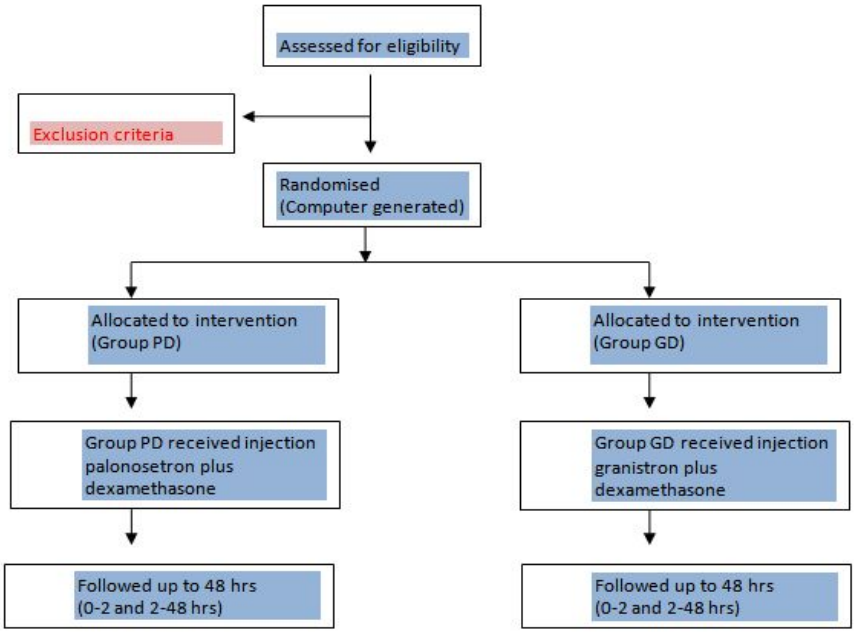

Figure 1. Flowchart of the study

After preanaesthetic evaluation a day before the scheduled day for operation and overnight fasting, on arrival in the operation theatre, an intravenous (IV) line was accessed with 18G cannula in the non-dominant hand. All patients were premedicated with injection ranitidine 50 mg by intravenous (IV) route, one hour before the anaesthetic procedure. The study drugs were prepared in identical syringes (5ml) by the anaesthesiologist blinded to the study, and administered 10 minutes before induction of anaesthesia according to the randomisation table. Routine standard monitoring devices were attached like non-invasive blood pressure (NIBP), heart rate, electrocardiography (ECG), oxygen saturation (SpO_2), end-tidal carbon dioxide ($ETCO_2$), then the patients were preoxygenated for 3 minutes. Anaesthesia was induced with IV 2.5% thiopentone 5 mg/kg bw and fentanyl 2 µg/kg bw and the anesthetic regime and surgical procedure were standardised for both the groups.The patients were intubated with IV rocuronium (0.6 mg/kg) under vision by direct laryngoscopy with appropriate size endotracheal tube. The anaesthesia was maintained with nitrous oxide plus traces of isoflurane in oxygen plus intermittent bolus doses of rocuronium bromide (0.1-0.2 mg/kg) plus intermittent positive pressure ventilation (IPPV).

Ventilation was maintained at $ETCO_2$ at 30-35 mm Hg and intra-abdominal pressure to a maximum of 14 mm Hg. Before extubation tramadol 2 mg/kg bw and diclofenac 75 mg IM were given to all patients. At the end of the operation, residual neuromuscular blockade was reversed with inj neostigmine 2.5 mg and glycopyrrolate 0.5 mg. Extubation was done after suction of the oropharynx and adequate recovery, judged on a clinical basis.

After the surgery, data were collected upto 48 hrs (hours) postoperatively. The follow up of the patients during the first 2 hrs were undertaken in the post-anaesthetic care unit (PACU) and thereafter 2-48 hrs in the ward. During the first 2 hrs in PACU, vital signs such as NIBP, HR and SpO_2 were monitored in all the patients. All patients were also evaluated for PONV, rescue antiemetic and adverse effects of drugs for the first 48 hrs after anaesthesia. Metoclopramide 10 mg was given as rescue antiemetic to patient on request or when vomiting occurs.

The data collected were checked for completeness and consistency and data were entered in Statistical package for social sciences (SPSS) version 21 (Armonk, NY; IBM Corp.). Descriptive statistics like mean, standard deviation, percentage were used to describe the socio-demographic variables like age, sex etc and comparisons between groups was performed by using inferential statistics like independent 't' test and Chi Square, to test the significance. P value <0.05 was taken as statistically significant.

Nausea was defined as unpleasant sensation associated with awareness of the urge to vomit. Vomiting was defined as the forceful expulsion of gastric contents from the mouth. Complete response was defined as no PONV and no need for any rescue medication.

III. Results

The two groups were comparable with respect to their demographic profile (Table 1).

Table1. Distribution of the patients (demographic profile, duration of anaesthesia, co-morbidities)

	Group PD (mean ±SD)	Group GD (mean ±SD)	P value
Age	40.18±11.55	40.94±11.75	0.745
Sex (M:F)	7:43	11:39	0.298
Body Weight (kg)	57.06±7.99	59.30±8.75	0.185
Height (cms)	159.60±5.07	160.76±4.57	0.233
ASA (I:II)	35:15	38:12	0.499
Duration of surgery	53.94±12.61	52.34±13.71	0.545
Duration of anaesthesia	64.42±14.02	62.94±14.56	0.606
Co-morbidities-Presence : absence	4:46	5:45	1.00

***(P<0.05, considered significant)**

The comparison of incidence of PONV, complete response and rescue antiemetics during 0-2 hrs and 2-48 hrs and 0-48 hrs are shown in table 2. The incidence was similar in both the groups in 0-2 hrs but during 2-48 hrs incidence of PONV was more in group GD than in group PD, although statistically insignificant (p>0.05). Also, the incidence of overall PONV in group PD was 12 (24%) and in group GD was 16 (32%). Although not statistically significant, higher percentage of PONV was observed in group GD than group PD.

Table 2: Showing PONV, Complete Response, Rescue Antiemetic during 0-2, 2-48 and 0-48 hrs postoperative period.

Duration (hrs)	Factors	Group PD (50) No. of patients (%)	Group GD(50) No. of patients (%)	P value
0-2	Nausea	5 (10)	6 (12)	0.749
	Retching	-	-	-
	Vomiting	3 (6)	3 (6)	1
	PONV	6 (12)	7 (14)	0.766
	Complete Response	44 (88)	43 (86)	0.766
	Rescue antiemetic	6 (12)	7 (14)	0.766
2-48	Nausea	3 (6)	9 (18)	0.065
	Retching	1 (2)	-	1
	Vomiting	3 (6)	8 (16)	0.110
	PONV	7 (14)	11 (22)	0.298
	Complete Response	43 (86)	39 (78)	0.298
	Rescue antiemetic	7 (14)	11 (22)	0.298
0-48	Nausea	8 (16)	14 (28)	0.148
	Retching	1 (2)	-	1
	Vomiting	5 (10)	9 (18)	0.249
	PONV	12 (24)	16 (32)	0.373
	Complete Response	38 (76)	34 (68)	0.373
	Rescue antiemetic	12 (24)	16 (32)	0.373

***(P<0.05, considered significant)**

The incidence of adverse effects between the two groups (table 3) was not significant statistically.

Table 3: Showing adverse effects

Factor	Group PD (50) No. of patients(%)	Group GD(50) No. of patients (%)	P value
Headache	1 (2)	2 (4)	1
Dizziness	5 (10)	6 (12)	0.749
Constipation	1(2)	-	1

***(P<0.05, considered significant)**

IV. Discussion

Four important risk factors are mentioned as important predictors of post operative nausea and vomiting, namely gender, non-smoking status, history of PONV or motion sickness and use of postoperative opioids.[5] It is mostly believed to be multifactorial in origin. According to Tramer,[5] post-operative nausea and vomiting (PONV) is a nuisance. The anaesthetist is usually blamed, despite the fact that PONV results from several factors, some related to anaesthesia, others to surgery, and some to the patients themselves. The importance of PONV is generally underestimated because it is self limiting, never becomes chronic and almost never kills. However, PONV is unpleasant, associated with patient discomfort and dissatisfaction, and delayed discharge from the recovery room and prolonged hospital care.[4]

The two groups in this study i.e palonosetron-dexamethasone and granisetron-dexamethasone, were comparable with respect to their demographic profile , duration of anaesthesia and surgery, ASA status and presence of comorbidities (Table 1) with no statistical significance. So, we can presume that the difference in effects between the two groups can be attributed to the administered drugs.

In our study, the incidence of nausea in group PD was 10% in 0-2 hrs interval and 6% in 2-48 hrs in terval. Mansour[15] reported incidence of nausea in 8% in 0-6 hrs, 12% in 6-12 hrs, 12% in 12-24 hrs intervals and Devi et al.[16] observed it in 14% in 0-2 hrs, 6% 2-48 hrs which were both comparable to our study. The incidence of nausea in group GD was 12% in the 0-2 hrs interval and 18% in the 2-48 hrs interval which was higher than those of Wadaskar et al.[17] i.e 6.6% in 0-4 hrs, 3.3% in 4-24 hrs and, Biswas and Rudra[18] i.e 3% in 0-4 hrs, 3% in 4-24 hrs. However, it was lower than The Italian Group for Antiemetic Research[19] (28.1% in 0-24 hrs, 35.6 in 24-48 hrs) and and Saito et al.[20] (40.1% in 0-24 hrs, 72.8% in 24-120 hrs) respectively.The difference in the incidence of nausea might be due to the different time intervals as compared to their study.

The incidence of retching in the present study in both the groups was 0% in the 0-2 hrs interval. During 2-48 hrs interval, the incidence of retching was 2% in group PD and 0% in group GD. This was comparable to that of Bhattacharjee et al.[14] who found negligible incidence in palonosetron (3.3% in 0-3 hrs, 3.3% in 3-24 hrs and 0 in 24-48 hrs) and granisetron (3.3% in 0-3 hrs, 3.3% in 3-24 hrs and 6.6% in 24-48 hrs) groups.

In the present study, the incidence of vomiting in the group PD was 6% in both 0-2 hrs and 2-48 hrs intervals. This was comparable to the results of Mansour[15] (4% in 0-6 hrs, 2% in 6-12 hrs, 4% in 12-24 hrs) and

with Bala et al.[21] (4.8% in 0-2 hrs, 7.1% in 2-24 hrs, 0% in 24-48 hrs) though the time intervals were different. The incidence of vomiting in the group GD in the present study was 6% in 0-2 hrs and 16% in 2-48 hrs intervals respectively. Dabbous et al.[22] (0% in 0-1 hr, 2.4% in 1-6 hr, 2.4% in 6-24 hr) observed lower incidence. The Italian Group for Antiemetic Research[19] found comparable incidence of vomiting (7.4% in 0-24 hrs and 10.4 % in 24-48 hrs) though the time intervals were different. Saito et al.[20] reported higher incidence of vomiting (23.6 % in 0-24 hrs, 45.8 % in 24-120 hrs). Palonosetron has more profound anti nauseating effect which might explain the similar incidence of vomiting in both the groups during the early period.[23]

In the present study, complete response in the group PD was 88% and 86% of the patients in the 0-2 hrs and 2-48 hrs intervals respectively in accordance with earlier studies,[15,16,21] while in group GD it was 86% and 78% of the patients in 0-2 hrs and 2-48 hrs intervals respectively which is also similar with earlier studies.[17,20,22] The rescue antiemetic medication was given to 12% in 0-2 hrs and 14% in 2-48 hrs intervals in the group PD and it was 14% in 0-2 hrs and 22% in 2-48 hrs intervals in group GD with no significance between the groups. We used metoclopramide as it is recommended that rescue antiemetic should be of a different class other than the prophylactic antiemetic used.

At the end of the total study period of 0-48 hrs, the incidence of complete response in our study in the group PD was 76% which was comparable with Srivastava et al.[24] (75.5%), Mansour[15] (84%), Devi et al.[16] (86 %) and Ghosh et al.[25] (86.66%), but higher than Saito et al.[20] (51.5%). In the group GD complete response in our study was 68% which was lower than Biswas and Rudra[18] (95%) and Wadaskar et al.[17] (86.67%) but higher than Saito et al.[20] (40.4%), Monohar et al.[26] (50%).

The adverse effects were found to be similar in both the groups and statistically insignificant with no serious adverse effects observed among the patients.

However, there are certain limitations in our study. Only the patient undergoing surgery for LC under GA were included and complete response from PONV could not be achieved due to use of inhalational agents, nitrous oxide, tramadol, neostigmine and glycopyrrolate as a part of standard anaesthesia practice which are itself emetogenic.

V. Conclusion

It can be concluded from the present study that prophylactic intravenous palonosetron 0.075 mg with dexamethasone 8 mg is as effective as granisetron, 40 µg/kg and dexamethasone 8 mg, in preventing early (0-2 hrs) postoperative nausea and vomiting. Although statistically not significant, due to lesser incidence of PONV and increased rate of complete response, palonosetron and dexamethasone is better than granisetron and dexamethasone in prevention of late (2-48 hrs) onset nausea and vomiting in patients undergoing laparoscopic cholecystectomy following general anaesthesia without any major adverse effects. Further studies in other laparoscopic surgeries are recommended to apply the findings to the general population.

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