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Original Article

Anaesthesia Section

Comparison between Dexamethasone Alone and its Combination with 5-Hydroxytryptamine Receptor Antagonist for Antiemesis during Laparoscopic Surgeries: A Double-blind Randomised Clinical Study

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ABSTRACT

Introduction: Post Operative Nausea and Vomiting (PONV) are often associated with the laparoscopic surgeries under General Anaesthesia (GA). The PONV guidelines recommended the use of 5-hydroxytryptamine receptor antagonist (5-HT3RA) as the first-line prophylactic agents in patients categorised as high-risk for emesis perioperatively. There are very few studies comparing the efficacies of combinations of newer 5HT3 RA with dexamethasone.

Aim: To compare the severity of emetic episodes as well as the complete response rate to antiemetics like dexamethasone or its combination with palonosetron or ramosetron during the first 48 hours after laparoscopic surgeries.

Materials and Methods: This randomised clinical double-blind study was conducted in the Department of Anaesthesiology at Mysore Medical College and Research Institute, Mysuru, Karnataka, India, from November 2014 to August 2016 among 90 patients, aged between 18 to 60 years belonging to the American Society of Anaesthesiology (ASA) grade I and II scheduled for elective laparoscopic surgery under general anaesthesia. They were randomly allocated into three equal groups. Group D received dexamethasone 8 mg, group RD received ramosetron 0.3 mg with dexamethasone 8 mg, and group PD received palonosetron 0.075 mg with dexamethasone 8 mg. Postoperative Nausea and Vomiting (PONV), retching were recorded via direct questioning or by the spontaneous complaints from the patients at 2, 6, 24, 48 hours. A scoring system was used to assess PONV. Complete response rate was also noted i.e, percentage of patients in a group with absence of nausea, retching, vomiting and no requirement of rescue antiemetic medications within postoperative 48 hours.

Results: The baseline characteristics were similar in all three groups. Early and late PONV were significantly lesser with group PD compared to group D (p-value=0.01) and group RD (p-value=0.007). The complete response rate in group PD (86.6%) was significantly highest compared to group D (40%) and group RD (76%). Rescue anlgesics required was nil in group PD compared to group D (36.3%), and group RD (10%) over 48 hours.

Conclusion: Combination of palonosetron with dexamethasone is a better alternative to combination of ramosetron with dexamethasone in preventing PONV.

Keywords: Pneumoperitoneum, Postoperative nausea and vomiting, Prevention and control, Serotonin

INTRODUCTION

Mechanoreceptors and chemoreceptors from the gastrointestinal tract as well as the Chemoreceptor Trigger Zone (CTZ) in the brain identify emetic stimulus. CTZ is outside the blood-brain barrier which readily get stimulated by drugs or toxins. The afferent pathways via CTZ and vagal mucosal pathway in the gastrointestinal system are predominantly involved in Postoperative Nausea and Vomiting (PONV).These afferent impulse further interacts between brainstem and nucleus tractus solitaries which results in emesis. Then cholinergic, dopaminergic, histaminic and serotonergic receptors mediates the vomiting due to this afferent sensations [1].

The PONV is defined as any nausea, retching or vomiting occurring during the first 24-48 hours after surgery in inpatients [2] With modern anaesthesia practices, the incidence of PONV has come down by 50% especially with the use of non opioid medications [3]. The overall incidence of PONV is reported to be between 20-30%. [4]

The PONV is often associated with Laparoscopic Surgeries (LS) under General Anaesthesia (GA). This can be because of cabon dioxide (CO_2) absorption intravascularly which causes cerebral vasodilatation and raised intracranial pressure [5]. Also pneumoperitoneum causes mesenteric ischaemia releasing emetogenic mediators like serotonin [6].

Several factors increase PONV incidence [7]. Excess PONV can also lead to complications like wound dehiscence or anastomosis disruption, pulmonary aspiration, surgical site bleeding and dehydration and its consequences [8]. Eventually PONV becomes uneconomical to patients.

Conventional antiemetics used such as anticholinergics, dopamine receptor antagonist, antihistaminics although effective, possess clinical significant side effects like dry mouth, tachycardia and extrapryamidal symptoms [9]. Dexamethasone has been reported to be effective in reducing PONV. It is also anti-inflammatory at operative site [10,11].

Serotonin, which is present in gut enteroendocrine cells, becomes exocytosed due to mechanical stimulus, bacterial toxins or cytotoxic drugs. Serotonin can then trigger vomiting by increasing bowel movements or by stimulating primary afferent nerves via 5-hydroxytrptamine 3 receptors [12].

5-Hydroxytrptamine-3 Receptor Antagonist (5HT3RA) possesses property of superior antiemetic prophylaxis. Older 5HT3RA are the first generation 5HT3RA like ondansetron, granisetron and dolasetron which are carbazole, indazole and indole derivates, respectively [12]. Out of these, ondansetron with relatively shorter half-life of three hours was used widely to prevent PONV [13]. Ondansetron

received approval from the Food and Drug Administration (FDA) in 1991. Palonosetron and ramosetron are recently introduced 5HT3RA. It is different from the earlier 5HT3RA as ramosetron is tetrahydrobenzimidazole derivative [14]. Ramosetron also has higher 5-HT3 receptor affinity and slows dissociation when compared to the other older agents.It has a half-life of around five hours. Palonosetron is a second generation 5HT3RA with stereogenic centres and has more than 30-fold higher affinity for 5-HT3 receptors [12]. It is more potent compared to other 5HT3RA with elimination half-life of 40 hours. Palanosetron also inhibits responses induced by substance-P, the dominant mediator of delayed emesis [15].

Multimodal antiemetic treatment enhance individual antiemetic drug actions to control PONV among high risk patients. Dexamethasone combination with other 5HT3RA are effective to prevent PONV after laparoscopic surgeries [16,17].

Fonseca NM et al., study showed superior effect of palonosetron over ondansetron and dexamethasone to control PONV among patients posted for video cholecystectomy [3]. A combination of ramosetron with dexamethasone showed better control of PONV, followed by ramosetron alone, and then dexamethasone alone in laparoscopic cholecystectomy [16]. Most of the studies are of older 5HT3RA with dexamethasone rather than newer 5HT3RA [18]. Very few studies compared these two (palanosetron and ramosetron) antiemetic drugs.

Hence, the present study was done to know the difference in efficacy of dexamethasone alone and its combination with 5HT3RA like ramosetron and palonosetron. The primary objective was to compare the severity of PONV as well as complete response during the first 48 hours after LS. The secondary objective was to compare rescue antiemetics given in all the three groups and observe for any adverse effects.

MATERIALS AND METHODS

This randomised clinical double-blind study was conducted in the Department of Anaesthesiology at Mysore Medical College and Research Institute, Mysuru, Karnataka, India, from November 2014 to August 2016 among 90 patients. The study plan was approved by the Institutional Ethical Committee (ECR/134/Inst/KA/2013) and written informed consent was obtained from all patients.

Inclusion criteria: Patients belonging to American Society of Anaesthesiologist (ASA) grade I and II, posted for elective laparoscopic surgeries; of either sex, between the age group 18-60 years, and having body mass index between 18-25 kg/m^2. The study by Apfel CC et al., showed that four factors predicted the incidence of PONV which includes female gender, history of motion sickness or PONV, non smoking and the use of postoperative opioids. Incidences of PONV were 10%, 21%, 39%, 61% and 79% if none, one, two, three or four of these risk factors were present, respectively [19]. Patients having any of these two or less than two predictors were included in the study to minimise the bias.

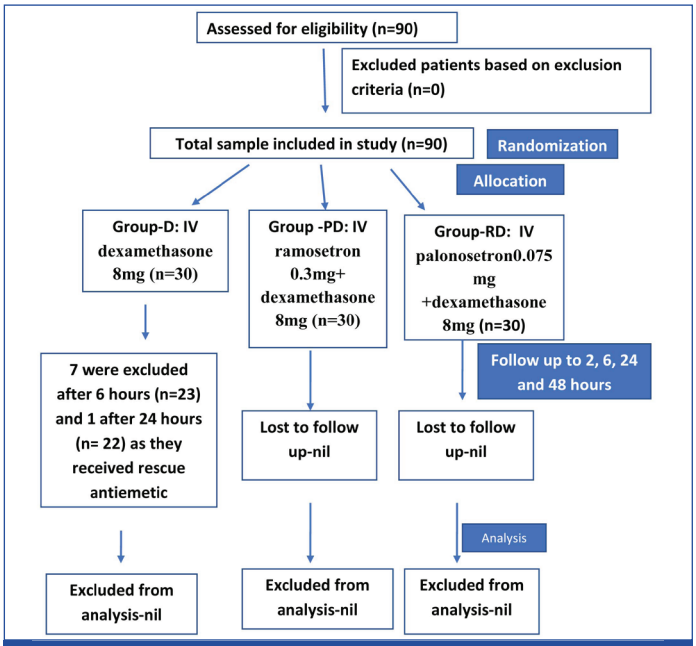
Exclusion criteria: Pregnancy, history of nausea, vomiting, retching or antiemetic consumption within 24 hours of LS, chronic opioid use or corticosteroid therapy, motion sickness, severe liver or renal disease and immunosuppression, LS converted to open surgeries and lasting for more than 120 minutes were excluded from the study.

Sample size calculation: Sample size was calculated by a power analysis, while designing the study. Allowing an α error of 5% and a β error of 20%; it was estimated that a minimum of 30 patients per group would be required to show a 30% difference (from 60% to 42%) in the incidence of PONV [20,21].

Cases were allocated randomly into three groups based on shuffled opaque sealed envelope technique, with 30 patients in each group [Table/Fig-1]. Antiemetic drugs were given intravenously (i.v.) as follows:

- **Group D:** Patients received dexamethasone (8 mg) alone
- **Group RD:** Patients received ramosetron (0.3 mg) with dexamethasone (8 mg)
- **Group PD:** Patients received palonosetron 0.075 mg with dexamethasone (8 mg).

The study drug containing required combinations diluted to volume of 5 mL using normal saline was prepared by the anaesthesiologist who was not involved in the study.



[Table/Fig-1]: Consolidated Standards of Reporting Trials (CONSORT) enrollment flow chart.

Study Procedure

Detailed preanaesthetic evaluation was done on the previous day. Subjects were nil per oral overnight. When patient were shifted to operation theatre, ASA recommended monitors were connected and baseline vital parameters recorded. Intravenous fluids started. Intravenous (i.v.) fentanyl 1 µg/kg and midazolam 0.02 mg/kg were given as a premedications followed by study drugs. After preoxygenation, patients were induced with i.v. thiopentone sodium 5 mg/kg and i.v. vecuronium bromide 0.1 mg/kg. Intubation was done with a proper sized endotracheal tube and its position was confirmed and fixed. Anaesthesia was maintained with oxygen 33%; nitrous oxide 66% and isoflurane 0.6%. Patients were ventilated to maintain end tidal carbon dioxide between 35-40 mmHg. Intra-abdominal pressure was maintained between 10-15 mmHg. After the completion of surgery patients were reversed with i.v. glycopyrrolate 0.02 mg/kg and i.v. neostigmine 0.5 mg/kg. After confirmation of the complete reversal, patients were extubated and shifted to postoperative care unit. Intramuscular diclofenac 75 mg was given for postoperative pain.

The intraoperative monitoring and postoperative observations were done by another anaesthesiologist who had administered the study drugs but unaware of the contents of the syringes. Thus, the patient and the observer were blinded for the study drugs.

PONV: All episodes of PONV were recorded via direct questioning, by an observer (blinded to the study group) or by the spontaneous complaints from the patients at 2, 6, 24, 48 hours. PONV assessment scores were:

- 0- no nausea;
- 1- nausea only;
- 2- nausea with retching;
- 3- vomiting

Nausea was defined as a subjectively uncomfortable sensation associated with awareness of urge to vomit. Retching was defined as forceful contraction of the respiratory muscle without expulsion of gastric contents. Vomiting was defined as forceful expulsion of gastric contents by mouth. Complete response rate was defined as percentage of patients in a group with absence of nausea, retching, vomiting and no requirement of rescue antiemetic medications within postoperative 48 hours.

Rescue antiemetic: PONV score of 2 or 3, received rescue antiemetic i.v. metaclopramide 10 mg. Early PONV and late PONV were considered, if it occurs within or after 6 hours respectively.

Adverse effects: Patients were monitored for adverse effects like headache, dizziness, drowsiness, flushing and sedation.

STATISTICAL ANALYSIS

Continuous data was expressed as mean±standard deviation or median (interquartile range) whereas number or percentage was used for categorical data. Independent t-test was used for continuous variables and Chi-square test was used for categorical variables. Analysis of Variance (ANOVA) was used to test the hypothesis of several means are equal. All the statistical calculations were done through Statistical Package for Social Sciences (SPSS) for windows (version 17.0). A p-value <0.05 was considered to be significant association.

RESULTS

Demographic characteristics of patients and surgical characteristics did not differ among the three groups [Table/Fig-2].

Variables		Group D (Mean ±SD)	Group PD (Mean ±SD)	Group RD (Mean ±SD)	p-value
Age (years)		35.97±7.12	38.30± 8.18	36.36± 8.22	0.82
Gender					
Male (n)		14	14	14	1
Female (n)		16	16	16	
Weight (kg)		63.66±7.09	65.73± 4.74	62.43± 5.23	0.088
Height (cms)		160±6.82	160.53± 7.88	158.83± 7.75	0.67
BMI (kg/m^2)		24.83±1.96	25.60± 2.35	24.81± 2.21	0.288
Duration of surgery (min)		62.16± 28.48	65.2± 27.89	60.5± 27.83	0.806
Type of laparoscopic surgeries	Cholecystectomy (n)	14	11	11	0.85
	Appendicectomy (n)	8	10	10	
	Tubal ligation (n)	6	7	7	
	Hysterectomy (n)	2	2	1	
	Others (n)	0	0	1	

[Table/Fig-2]: Demographic and surgical characteristics.
p-value <0.05 was considered as statistically significant

Whenever the patients had PONV score of more than 2, they were not followed up for the next time interval and accordingly the number of patients were decreased in that respective group during the next time interval [Table/Fig-3]. Early PONV score was significantly lower in the combination drug groups PD and RD, compared to the dexamethasone alone group D. But there was no significant difference between group D and group RD with respect to the incidence of late PONV (after 24 hours). Though the early PONV was better controlled by both the antiemetic combination, late PONV was significantly better controlled in the group PD [Table/Fig-3].

Scores	Group D n (%)	Group RD n (%)	Group PD n (%)	p-value among the groups		
				D vs PD	D vs RD	PD vs RD
PONV scores <2 hours						
0	25 (83.33%)	30 (100%)	29(96.66%)	0.042	0.032	0.15
1	5 (16.66%)	0	1(3.33%)			
2	0	0	0			
3	0	0	0			
PONV scores at between 2- 6 hours						
0	18 (60%)	30 (100%)	29 (96.66%)	0.0012	0.00315	0.155
1	5 (16.66%)	0	1 (3.33%)			
2	4 (13.33%)	0	0			
3	3 (10%)	0	0			
PONV scores at less than 6-24 hours						
0	18 (78.26%)	29 (96.66%)	30 (100%)	0.012	0.0352	0.329
1	4 (17.39%)	1 (3.33%)	0			
2	1 (4.34%)	0	0			
3	0	0	0			
PONV scores at between 24-48 hours						
0	16 (72.72%)	26 (86.66%)	29 (96.66%)	0.01	0.7	0.007
1	3 (13.63%)	1 (3.33%)	1 (3.33%)			
2	2 (9.09%)	3 (10%)	0			
3	1 (4.54%)	0	0			

[Table/Fig-3]: Postoperative Nausea and Vomiting (PONV) scores between 6-24 hours and between 24-48 hours.
p-value <0.05 was considered as statistically significant

Complete response rate for early PONV (upto six hours postoperatively) was significantly lowest in group D compared to groups RD and PD. Both the combination drugs were statistical significantly effective than dexamethasone alone. Complete response rate for late PONV (from 6 hours to 48 hours postoperatively) was highest in group PD. But when complete respose rate for late PONV was compared between group D and group RD specially after 24 hours there was no significant difference indicating better control of late PONV in group PD rather than group D or group RD [Table/Fig-4]. No rescue antiemetics were required in the groups PD at all over 48 hours. No rescue antiemetics were required in group RD to control PONV in the early postoperative period, but it was required in late postoperative period which was significantly higher compared to group PD. Rescue antiemetics were given to control both early and late PONV in group D [Table/Fig-5].

There were no adverse effects noted in any of the groups during first 2 hours; 2-6 hours; 6-24 hours or 24-48 hours follow-up.

Time interval (hrs)	Group D	Group RD	Group PD	p-value D vs RD	p-value D vs PD	p-value PD vs RD
0-2	25 (83.3%)	30 (100%)	29 (96.6%)	0.011	0.046	0.157
2-6	18 (60%)	30 (100%)	29 (96.6%)	0.00013	0.00054	0.157
6-24	18 (78%)	29 (96.6%)	30 (100%)	0.017	0.0042	0.157
24-48	16 (73%)	26 (86.6%)	29 (96.6%)	0.097	0.0067	0.083

[Table/Fig-4]: Complete response rate at various study intervals.
p-value <0.05 was considered as statistically significant

Rescue antiemetics	Group D	Group RD	Group PD	p-value D vs RD	p-value D vs PD	p-value PD vs RD
For early PONV	7 (23.33%)	0	0	0.0034	0.0034	0.5
For late PONV	4 (13%)	3 (10%)	0	0.3585	0.024	0.042
Overall in 48 hours	11 (36.33%)	3 (10%)	0	0.016	0.0005	0.042

[Table/Fig-5]: Rescue antiemetics received.
p-value <0.05 was considered as statistically significant

DISCUSSION

In the present study, the early and late PONV incidence rate was significantly higher and complete response rate was significantly lower in the group receiving dexamethasone alone, compared to the antiemetic drug combination group. Rescue antiemetic received was also higher in the former group compared to the combination drugs groups.

In a systematic review by Heinz et al., a number of randomised controlled trials were compared where dexamethasone alone or its combination with 5HT3RA were used to control PONV. They concluded that the combination has a superior antiemetic effect. In their study an average incidence rate of PONV was derived. The average incidence of nausea during early and late postoperative period were 4% and 28%, respectively; the average incidence of vomiting during early and late postoperative period were 2% and 23%, respectively, with the combination of dexamethasone and 5HT3RA [17]. However, the review was based on studies using dexamethasone with i.v. ondansetron 4 mg or i.v. granisetron 40 µg/kg. Hence, the incidence of PONV was slightly higher with the combination drugs compared to the present study, where palonosetron and ramosetron combined with dexamethasone were used.

In the index study, the number patients that needed the rescue analgesics were 23.3% and 13%, respectively, at early and late postoperative period with dexamethasone. The number of patients requiring rescue analgesics with dexamethasone alone as antiemetic was higher compared to its combination with 5HT3RA. The biological half-life of dexamethasone is 36-72 hours. Its antiemetic effect is due to prostaglandin antagonism or endorphin release; it can also change the blood brain barrier permeability to serum proteins [11,17]. These mechanism of actions of dexamethasone, when combined with 5HT3RA, exhibits synergism by changing receptor affinity and sensitivity to 5HT3RA [22].

In the present study, among the combination drugs, early PONV was nil in both the groups, whereas, the late PONV rate was higher in group RD compared to group PD. Overall, the complete response rate was also higher in group PD (96.6%) compared to group RD (86.2%) at 48 hours.

Park JW et al., compared the antiemetic effect for PONV between palonosetron alone and its combination with dexamethasone, among patients posted for gynaecological LS. The incidence of PONV was 9.8% with palanosetron monotherapy, whereas, it was 14% with the combination therapy [23]. Hence, the study showed the antiemetic effect produced by palonosetron as a monotherapy was almost similar with its combination with dexamethasone. This is because the authors used a lower dexamethasone dose of 4 mg, whereas, in the present study, the standard antiemetic dose of 8 mg was used. Because of this lower dose of dexamethasone in Park JW et al., study, early and late PONV incidence were higher and complete response rate was lower in combination group over a period of 24 hours compared to the palonosetron and dexamethasone combination group in the present study [23]. Also, this might be because of Rhodex index which they used to detect PONV. This index uses eight questionnaires which get sensitised to even small emetic feeling as the questions are related to detailed individual's perception of duration and frequency of nausea, retching and vomiting. It also assesses distress raised due to PONV [23].

In the study conducted by Cho E et al., immediately after induction dexamethasone 8 mg or normal saline was given according to the allocated group and postoperatively fentanyl 20 µg/kg with palonosetron 0.075 mg infusion was started to be delivered over 48 hours. There was significant lower rate of PONV with combination drugs compared to palonosetron alone. The PONV rate was 47% and 52% at early and late postoperative period respectively with palonosetron and dexamethasone combination. This was higher than what PONV rate was derived in the present study with similar combination of drugs. This might be because of fentanyl infusion used postoperatively as analgesia in the former study. Fentanyl is an opiod which by acting on µ receptors at CTZ can trigger vomiting [22].

A meta-analysis was conducted to study the efficacy of palonosetron and ramosetron which included eleven studies and 1373 patients. The authors included only the studies which used standard doses of palonosetron (0.075 mg) and ramosetron 0.3 mg without any other adjuncts. Palonosetron as antiemetic was found to be more effective in delayed postoperative period after 24 hours (relative risk-0.56; p-value=0.033), especially in laparoscopic surgeries whereas ramosetron was more effective for PONV at early postoperative period upto 6 hours (relative risk-8.47; p-value=0.013) especially in spine surgeries. Even in the present study, palonosetron with dexamethasone combination significantly better controlled PONV at late postoperative period than ramosetron and dexamethasone combination [24].

This superior action of palonosetron over ramosetron can be attributed to its additional substance-P inhibitory action as well as its 5HT3 receptor interaction in an allosteric, positively cooperative manner, at sites different from where other 5HT3RA bind. This also explains for its long duration of action [25].

There are also studies showing the results that ramosetron is better than palonosetron to control PONV. Ahn EJ et al., compared PONV with palonosetron and ramosetron in patients posted for gynecological laparoscopic surgeries receiving intravenous opioid based patient controlled analgesia. They inferred that ramosetron has better PONV control than palonosetron. This could be because of higher consumption of opioid based infusion postoperatively in palonosetron than ramosetron group [26].

Swaika S et al., found ramosetron to be more effective than palonosetron to control PONV [27]. This effect of ramosetron was significant during early postoperative period with 2 hour period whereas at late postoperative period after 2 hours up to 24 there was no significant difference between palonosetron and ramosetron antiemetic efficacy. In the present study, the antiemetic efficacy up to 48 hours postoperatively was studied. There was a significantly higher number of patients with PONV with ramosetron than palonosetron between 24 to 48 hours monitoring interval.

Limitation(s)

Different types of laparoscopic surgeries were included. The number of patients with Nasogastric Tube (NGT) were not evaluated seperately, because NGT itself can trigger PONV.

CONCLUSION(S)

Combination of antiemetics with dexamethasone prevents early PONV than dexamethasone alone. Combination of palonosetron 0.075 mg with dexamethasone 8 mg is effective in preventing late PONV, in patients undergoing laparoscopic surgeries under general anaesthesia, compared to the combination of ramosetron 0.3 mg with dexamethasone 8 mg or dexamethasone 8 mg alone.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
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- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

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