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Original Research Article

Comparison of efficacy of palonosetron-dexamethasone combination with palonosetron alone or dexamethasone alone for prophylaxis against post-operative nausea and vomiting in patients undergoing laparoscopic cholycystectomy

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ABSTRACT

Background and Aims: Post-operative nausea and vomiting (PONV) is highly distressing and unpleasant symptom. Palonosetron and dexamethasone are effective antiemetics with minimal side effect profile. This study compared the efficacy of palonosetron dexamethasone combination with palonosetron alone and dexamethasone alone for prevention of PONV after laparoscopic cholecystectomy.

Materials and Methods: This prospective, randomised, double-blind study was done on 150 adults, American Society of Anesthesiologists Grade I and II patients, aged 18-60 years undergoing laparoscopic cholecystectomy. They were allocated to three groups which were to receive either of the three treatment regimens: Group A, (n = 50) Dexamethasone 8 mg plus Palonosetron 0.075 mg OR GroupB (n = 50) Palonosetron 0.075 mg Alone OR Group C (n = 50) Dexamethasone 8 mg Alone. The primary outcome was incidence of PONV in 24 h and the secondary outcome was a number of rescue antiemetic required. One-way ANOVA test was used to compare the means amongst three groups. To compare the proportions in the groups, Chi-square test/Fisher's exact test/Two proportions Z-test was applied as appropriate.

Results: Overall incidences of PONV in the study 24 h postoperatively were 22% in group A, 42% in group B and 86% in group C in 24 h postoperatively ($P < 0.001$). Requirement of rescue antiemetic was more in dexamethasone group than other two groups.

Conclusion: Palonosetron alone and palonosetron-dexamethasone combination were equally effective in the prevention of PONV. Dexamethasone alone was least effective amongst the three groups. There is no difference between palonosetron and palonosetron-dexamethasone for PONV prevention.

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1. Introduction

Post-operative nausea and vomiting (PONV) is a highly unpleasant and distressing symptom and is the second common complaint in post-operative period after pain.[1]

Repeated episodes of PONV can lead to more serious and undesirable consequences such as electrolyte imbalance,dehydration, heightened perception of pain, aspiration of gastric contents, oesophageal rupture and suture dehiscence had also been reported.[2,3] Although such serious complications are rare but in surgeries especially laparoscopic cholecystectomy significantly increase the incidence of PONV to as high as 50%.[4,5]

According to Apfel's simplified risk score female gender, non-smoker, history of motion sickness and use of post-operative intravenous (IV) opioid additively contribute 20% each to incidence of PONV. Hence, PONV incidence can be as high as 80%, when all four risk factors are present.[6]

Palonosetron is a second-generation 5-HT3 receptor antagonist and is more effective than granisetron 1 mg and

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ondansetron 4 mg in preventing PONV. Dexamethasone reported to be safe and effective for prevention of PONV following different surgeries.

Although most of the previous studies favour the use of dexamethasone and palonosetron, some studies differ in opinion. In this context, we hypothesised that the combination of palonosetron and dexamethasone would be more efficacious as antiemetic for PONV prophylaxis than using each drug alone and this study was planned to accept or reject that hypothesis.

2. Materials and Methods

After obtaining approval from the Institutional Ethics Committee, a randomized, double-blinded interventional study was planned. One hundred and fifty adults who fulfilled the inclusion criteria (age: 18–60 years, American Society of Anesthesiologists (ASA) physical status I and II, undergoing laparoscopic cholecystectomy under general anaesthesia) were enrolled in the study from after getting informed and written consent. Patients who had any of the exclusion criteria (history of motion sickness, were pregnant or menstruating, having coexisting gastrointestinal pathology, known smokers, on chronic antiemetic medications, previously on opiates within 48 h before surgery and any history of allergy to palonosetron or dexamethasone) were excluded from the study

One independent investigator randomised the patients into three groups (as per computer-generated random numbers) which were to receive either of three treatment regimens: (Group A) dexamethasone 8 mg plus palonosetron 0.075 mg, (Group B) palonosetron 0.075 mg, (Group C) dexamethasone 8 mg. All the three drugs were drawn in identical 5 ml syringes and diluted up to 5 ml with normal saline and labelled as 'antiemetic'. The study drugs were injected slowly over 30 seconds just before the induction of anaesthesia. Patients, anaesthesiologist involved in intra-operative care and investigator collecting data in post-operative ward were unaware of the group allocation.

Patient was premedicated with injection glycopyrrolate 0.01 mg/kg, injection midazolam 0.03 mg/kg, fentanyl 2mcg/kg and induction done with thiopentone 2–5 mg/kg. Endotracheal intubation was facilitated by injection atracurium 0.5mg/kg. Controlled mechanical ventilation and anaesthetic gases (sevoflurane in 50% O_2 and nitrous oxide) were provided. Intra-operative monitoring was done with 5-lead electrocardiogram, SpO_2, $EtCO_2$, non-invasive blood pressure. At the end of surgery, extubation done after reversing any residual muscle paralysis by injection neostigmine 0.05 mg/kg plus injection glycopyrrolate 4 mcg/kg. After extubation patients shifted to post-anaesthesia care unit (PACU). Injection diclofenac 1 mg/kg was given as postoperative analgesia and repeated after every 8 hours.

All patients were monitored in the PACU. Primary outcome was incidence of nausea and vomiting in 24 h. Secondary outcome was the number of rescue antiemetic required. Injection metoclopramide 10 mg IV was used as rescue antiemetic. Nausea was defined as the unpleasant sensation associated with awareness of the urge to vomit; vomiting was defined as the forceful expulsion of gastric contents from the mouth. Failure of PONV prophylaxis was defined as any episode of nausea, vomiting, retching and/or use of rescue antiemetic. Incidence of any PONV, a number of rescue antiemetic required was measured at 0, 1, 2, 6, 12 and 24 h postoperatively. We measured PONV, as PONV 1 = no nausea and vomiting; 2 = nausea but no vomiting; 3 = nausea and vomiting.

2.1. Statistical analysis

Sample size of 45 patients in each of 3 groups were required at 80% study power and α error of 0.05 assuming incidence of PONV in 23.4%, 27.2% and 56.14% of cases in A, B, C group respectively based on previous study.[7] It is further enhanced and rounded off to 50 patients in each of 3 groups as final sample size expecting 10% attrition.

One-way ANOVA was used to compare the means among three groups. To compare the proportions in the groups, Chi-square test/Fisher's exact test was applied as appropriate. Two proportions Z-test was used to compare the proportions between two independent groups [when sample size multiply by proportion (n*p) was $\geq$ 5]. $P < 0.05$ was considered as statistically significant. Statistical analysis was performed with the SPSS, version 21 for Window statistical software package.

3. Results

There were no statistically significant differences between the groups in age, sex, ASA physical status.(Table 1) Immediately after shifting the patient to post-operative area, incidence of PONV was measured as 6%, 10% and 40% in A, B and C group, respectively ($P < 0.001$). After 1 h postoperatively, 16% in A group, 16% in B group and 26% in C group reported PONV ($P = 0.343$). At 2 h postoperatively, nobody in A group complained of PONV, whereas 6% in P group and 12% in C group reported PONV ($P = 0.007$). No patient in A group and 8% in P group and 8% in C group reported PONV at 6^{th}. ($P = 0.121$) (Table 2). No patient reported any incidence of nausea and vomiting after 6^{th}. till 24^{th}. postoperatively in our study.

Overall incidences of PONV in our study (primary outcome) were 22% in A, 42% in B and 86% in C group in 24 h postoperatively ($P < 0.001$). Table 2

Rescue antiemetic requirement was significantly more in C > B > A groups (Table 3)

Proportion of occurrence of postoperative nausea and vomiting in the three groups in 24 h postoperatively had

Table 1: Demographic profile in three study groups

Groups	A	B	C	P value
Age	41.96±13.23	39.90±15	43.44±12.86	0.602
Sex ratio	14/36	12/38	16/34	0.502
ASA physical status I II	36(72%) 14(28%)	38(76%) 12(24%)	36(72%) 14(28%)	0.650 0.448

Table 2: Incidence of postoperative nausea and vomiting in postoperative period in three study groups

PONV		A (%)		B (%)		C (%)		p value
		No.	%	No.	%	No.	%	
0 h	Yes	3	6	5	10	20	40	p<0.001 (S)
	No	47	94	45	90	40	80	
1 h	Yes	8	16	8	16	13	26	0.343 (NS)
	No	42	84	42	84	37	74	
2 h	Yes	0	0	3	6	6	12	0.041(S)
	No	50	100	47	94	44	88	
6 h	Yes	0	0	4	8	4	8	0.121(NS)
	No	50	100	46	92	46	92	
12 h	Yes	0	0	0	0	0	0	-
	No	50	100	50	100	50	100	
24 h	Yes	0	0	0	0	0	0	-
	No	50	100	50	100	50	100	

Table 3: No of patients requiring rescue antiemetic

	Group A (N=50)		Group B (N=50)		Group C (N=50)		Result (P value)
	No.	%	No.	%	No.	%	
0 hrs	5	10.00	5	10.00	17	34.00	0.001 (S)
1 hrs	9	18.00	7	14.00	3	26.00	0.302 (NS)
2 hrs	0	0	2	4.00	6	12	p<0.001 (S)
6 hrs	0	0	3	6.00	4	8	p<0.001 (S)
12 hrs	-	-	-	-	-	-	-
24 hrs	-	-	-	-	-	-	-

S = Significant ; NS = Non Significant

Table 4: Proportion of occurrence of post operative nausea and vomiting

Group comparison	Z	P	Inference
A versus B	0.5	0.600	Group A and B are equal, no significant difference
A versus C	3.5	0.001	Significant
B versus C	3.1	0.001	Significant

Two proportions Z-test was used to compare between two groups

been shown in Table 4.

4. Discussion

Palonosetron is a highly effective 5-HT3 antagonists and has favourable side effect profile in comparison to others drugs used in the past for prevention and treatment of PONV. Dexamethasone is reported to be an effective antiemetic having central antiemetic action through an activation of the glucocorticoid receptors in the bilateral nuclei tractus solitarii in the medulla. With a better understanding of pathophysiology of PONV involving different sets of receptors, combination therapy with antiemetics acting through different pathways appear to be the logical choice. A fair number of trials had shown the efficacy of dexamethasone as an antiemetic. However, in our study, dexamethasone was least effective as a single medication and addition of it to palonosetron increased the efficacy as compared to when dexamethasone used alone medications.

Overall incidence of PONV in first 24 h was highest in dexamethasone alone group whereas palonosetron alone and combination groups had a significantly lesser incidence of PONV. There was no statistically significant difference in incidence of PONV between Palonosetron and combination group. It suggests that addition of dexamethasone with

palonosetron did increase the antiemetic efficacy in comparison of dexamethasone alone.. Palonosetron and palonosetron-dexamethasone combination - both are effective and the combination is not better than palonosetron alone.

In a study done by Park JW, Jun JW et al[8] they had shown the overall incidence of PONV as 9.8% in palonosetrone - dexamethason group and 14% in palonosetrone group which was stastically non significant, we also found statistically insignificant difference in PONV between palonosetron and palonosetron dexamethasone combination.

Henzi et al[9] compared the combination of dexamethasone with palonosetron with monotherapy of palonosetron. However, in their study combination did not show satistically significant difference with palonosetrone alone. Thus finding in our studies was in agreement with their study.

Injection metoclopramide (10 mg) was used as rescue antiemetic for patients who complained of PONV. Although pharmacologically metoclopramide is a weak antiemetic in comparison to 5-HT3 blocker, we chose it, because it is widely available and used as an antiemetic drug in our institute with reasonably acceptable side effects profile. Its mechanism of action (D2 receptor blockade) is also different from the studied drugs. Requirement of rescue antiemetic was more in patients in dexamethasone group than other two groups.

In a study done by Chatterjee, Sahu et al, where they compared efficacy of palonosetron dexamethasone combination with palonosetron alone or dexamethasone alone in prophylaxis of PONV in laparoscopic cholycystectomy surgery, they found that highest number of patients with severe PONV in group Dexamethasone and least number of patients with severe PONV in group palonosetrone dexamethason combination. Thus finding in our study was similar to above mentioned study.

We also studied the trend of incidence of PONV overtime for first 24 h and we found that no patient complained of PONV in three study groups after 6 h. This result is variable from other studies,[10,11] which showed a variable incidence of PONV continuing in the first 24 h and beyond. Probable explanation for this may be the possible emetic effect of different anaesthetic agents used intraoperatively. Residual effect of these emetic intraoperative anaesthetics can be implicated as the cause of PONV in first 6 h, by which time, most of these drugs' plasma concentrations would have been reduced by metabolism and elimination.

There are few limitations in our study. Pre-operative medications for chronic co-morbidity (diabetes and hypertension etc.,) could not be controlled. Post-operative nil per oral status and diet were not identical in all patients. Incidence of PONV and antiemetic effects of study drugs beyond 24 h could not be studied because of our study design. Our study population was limited to ASA physical Status I and II. We could not include ASA physical status III (and beyond) patients in view of ethical issue as well as limitations arising due to fixed intraoperative anaesthetic technique.

5. Conclusion

Palonosetron and palonosetron-dexamethasone combination were better than dexamethasone alone for preventing PONV in laparoscopic cholecystectomy patients. Statistically insignificant difference was found ($P > 0.05$) in efficacy between palonosetron alone and palonosetron-dexamethasone combination which suggests they are equally effective in the prevention of PONV.

6. Source of Funding

Nil.

7. Conflicts of Interest

There are no conflicts of interest.

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