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Comparative study of palonosetron with metoclopramide and ondansetron in prevention of PONV in laparoscopic cholecystectomy a randomized controlled trial

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Abstract

Background: Post-operative nausea and vomiting (PONV) is a 'big little' problem especially after laparoscopic surgeries. Palonosetron is a new potent 5 hydroxy tryptamine 3 antagonists. In this randomized double blind clinical study we compared the effects of i.v. palonosetron, ondansetron and metoclopramide administered at the end of surgery in preventing post-operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy under general anesthesia.

Methods: 90 ASA I/II patients of both sexes in the age group of 20-60 years over a period of 18 months undergoing laparoscopic cholecystectomy were included. The enrolled patients were randomised into three groups, Group G1 (Metoclopramide), Group G2 (Ondansetron) and Group G3 (Palonosetron). The incidence of nausea and vomiting were monitored immediately during 0-2 h, 2-6 h, 6-24 h and 24-72 h according to the VAS.

Results: Both palonosetron and ondansetron have comparable efficacy clinically and statistically in preventing nausea and were highly superior to metoclopramide in preventing nausea. Palonosetron had a better antiemetic effect than both ondansetron and metoclopramide in patients who underwent laparoscopic cholecystectomy. The number of complete responders was 8/30 (26.66%) in group G1, 20/30 (66.66%) in group G2 and 22/30 (73.33%) in group G3.

Conclusion: Palonosetron has a better profile of antiemetic action, and a lesser need for rescue antiemetic postoperatively and a comparable side-effects profile as compared to ondansetron and metoclopramide.

Keywords: laparoscopic cholecystectomy, ondansetron, palonosetron, metoclopramide, postoperative nausea and vomiting

Introduction

Postoperative nausea and vomiting (PONV) is one of the most distressing complaints in patients undergoing surgery under general anesthesia. The overall incidence of PONV is reported to be between 20-30%, but it can increase up to 80% in high risk patients [1]. Despite the increasing interest and efforts the incidence of Postoperative Nausea and Vomiting remains unacceptably high (40% to 75% in the first 24 hours, without active intervention) in patients undergoing laparoscopic cholecystectomy [2]. It is the legendary "Big, little problem" [3]. PONV constitutes the second most common complaint, pain being the most common [4]. PONV is a limiting factor in the early discharge of ambulatory surgery patients and is a leading cause of unanticipated hospital admissions, increased recovery room time, expanded nursing care, all factors that may increase total health care cost.

Postoperative Nausea and Vomiting (PONV) can be well tolerated by some patients but in others it can lead to serious consequences like aspiration of stomach contents into the trachea, especially when protective reflexes are impaired, dehydration and electrolyte imbalance especially due to depletion of potassium which cannot be easily accessed by blood sampling. It can also lead to tension in the suture lines that could lead to wound dehiscence and hematoma formation and increased bleeding under the skin flaps, esophageal rupture, venous hypertension and increase in the perception of pain and delayed discharge of the patient from post anesthesia care unit and even hospital discharge [5]. A number of pharmacological agents (phenothiazine, antihistaminics, butyrophenones,

benzamides and anticholinergics) have been tried for the prevention and treatment of PONV but undesirable adverse effect were inevitable. Unwanted sedation is one of the major drawbacks that preclude the use of phenothiazine and nonspecific antihistaminic group of drug.¹¹ Metoclopramide (benzamides) when used in low doses is not so clinically effective and at large doses that was being used earlier for prevention of Chemotherapy Induced Nausea and Vomiting (CINV), it lead to increased incidence of dyskinetic and extrapyramidal symptoms¹⁶. Anticholinergics were also tried for their potential antiemetic benefit but these drugs had their own set of varied side effects that ranged from blurred vision, dry mouth to dizziness and agitation¹⁷. Droperidol (butyrophenones) is a highly potent D₂-antagonist with well proven antiemetic properties at low intravenous dose but the major side effect of this group of drug was its tendency to cause fatal arrhythmias (Torsades de pointes) that led U.S. Food and Drug Administration (FDA) to issue FDA black box warning¹⁸. Dexamethasone has a well-documented antiemetic action but has a slower onset of action¹⁹.

5HT₃ receptor antagonists (5HT₃RA) belong to the cys-loop super family of ligand-gated ion channels and are first line therapies in the prevention of PONV¹⁰. Ondansetron was the first serotonin antagonist, and its introduction was a milestone in the prevention of early CINV and PONV. It has a relatively short half-life of 3 to 5 hours and may be given several times a day depending upon the severity of the symptoms. 5HT₃RA have an enviable safety profile, with minor side effects (no extrapyramidal symptoms or sedation) and rare cardiac conduction abnormalities compared with all previous antiemetics.

Palonosetron is a first second generation 5HT₃ receptor antagonist which was approved by Drug Controller General of India on 25.04.2009. Palonosetron is devoid of above mentioned side effects as seen with older antiemetic and is seen to be highly effective in prevention and treatment of Chemotherapy Induced Nausea and Vomiting¹¹. This unique 5HT₃ receptor antagonist has a greater binding affinity and prolonged mean elimination half-life of 40 hours which is substantially higher than older 5HT₃ receptor antagonist like ondansetron¹². Recent receptor binding studies suggest that palonosetron is further differentiated from other 5HT₃ by interacting with 5HT₃ receptors in an allosteric, positively cooperative manner with subsequent receptor internalization at sites different from those that bind with ondansetron and granisetron. In addition, this sort of interaction may be associated with long lasting effects on receptor ligand binding and functional responses to serotonin¹³.

Palonosetron has been compared with placebo for the prevention of PONV in patients undergoing open abdominal and gynaecological surgeries¹⁴. Studies pertaining to simultaneous comparison of drug palonosetron with drugs belonging to different groups are limited and results have been contradictory. In the light of the above facts we therefore intended to conduct this study in patients undergoing laparoscopic cholecystectomy in a tertiary care center with the aim of comparing palonosetron with ondansetron and metoclopramide in postoperative nausea and vomiting in laparoscopic cholecystectomy

Methodology

This prospective, randomised, controlled, single centered trial was conducted after approval by institutional ethical committee at Dr. RPGMC, Kangra, HP, India on 90 ASA I/II patients of both sexes in the age group of 20-60 years over a period of 18 months undergoing laparoscopic cholecystectomy.

The patients were allocated one of the 3 groups by systematic randomisation. The study drug solution was prepared and given to the patients by the principal investigator.

Group G₁: Metoclopramide 10mg

Group G₂: Ondansetron 4mg

Group G₃: Palonosetron 0.075mg

One of the allocated study drugs i.e. palonosetron, ondansetron or metoclopramide was given i.e. slowly before the induction of anesthesia.

The incidence of nausea and vomiting were monitored immediately during 0-2 h, 2-6 h, 6-24 h and 24-72 h according to the VAS scale and noted down in the postoperative monitoring proforma. Episodes of PONV were identified either by spontaneous complaints by the patient or by VAS on direct questioning. A score of more than or equal to 5 in VAS scoring was considered a significant and a criteria for rescue antiemetic. Metoclopramide 10 mg was used as rescue antiemetic, if two episodes of PONV occurred or VAS more than 5. If metoclopramide treatment is ineffective ondansetron 4 mg i.v was permitted. A complete response (CR) was defined as the absence of PONV and no use of rescue antiemetic during the whole observation period.

Results

Total number of patients enrolled during study period were 90 in all the three groups i.e. 30 in each group. All these patients were comparable to each other with respect to age, gender, weight and duration of surgery. (Table-1)

Table 1: Anthropometric characteristics of study participants

| Parameters | Groups | | | p value |
|----------------------------------------------|-----------------------------|-----------------------------|-----------------------------|---------|
| | Group G ₁ (n=30) | Group G ₂ (n=30) | Group G ₃ (n=30) | |
| Age(Yrs) mean±SD) | 37.43± 8.12 | 39.23 ± 8.47 | 42.30 ± 10.51 | >0.05 |
| Weight (Kg) (mean±SD) | 51.70±7.80 | 53.26 ± 9.97 | 51.46 ± 7.33 | >0.05 |
| (Male/female)n | 28/2 | 26/4 | 27/3 | >0.05 |
| Mean duration of anaesthesia(min.) (mean±SD) | 73.83 ±7.84 | 78.50 ±18.01 | 73.66± 13.88 | >0.05 |

All the three groups were comparable in terms of mean age, weight, sex and mean duration of anaesthesia with p value >0.05.

In the comparison of VAS in three groups it was found that mean VAS was high in group G₁ than G₂ and G₃ at 0-2, 2-6 and 6-24 hours (p<0.01). Table – 2, Figure – 1.

Table 2: Comparison of VAS in three groups at different time intervals

| VAS | Study group | mean±SD(mean rank) | Kruskal- wallis test statistic | p value |
|----------|----------------|--------------------|--------------------------------|---------|
| 0-2 Hrs | G ₁ | 4.10±2.95(58.83) | 15.554 | 0.001 |
| | G ₂ | 1.73±2.80(40.95) | | |
| | G ₃ | 1.23±2.52(36.72) | | |
| 2-6 Hrs | G ₁ | 3.53±2.97(59.90) | 21.050 | 0.001 |
| | G ₂ | 0.86±2.06(39.25) | | |
| | G ₃ | 0.70±1.82(37.35) | | |
| 6-24 Hrs | G ₁ | 1.57±2.67(53.50) | 17.322 | 0.010 |
| | G ₂ | 0.00±0.00(41.50) | | |
| | G ₃ | 0.00±0.00(41.50) | | |

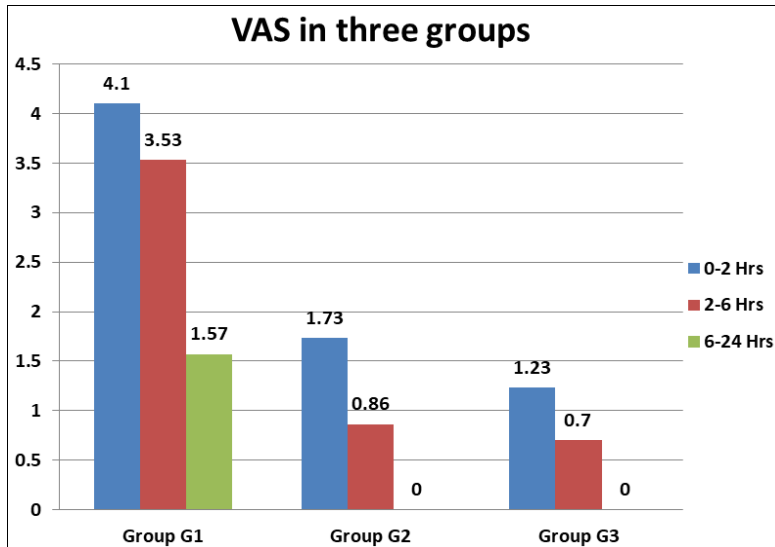


Fig 1: VAS in comparison to three groups.

In the comparison to episodes of vomiting in three groups it was found that mean of vomiting was very high in group G₁

in comparison to G₂ and G₃ (p value <0.01). Table – 3, Figure - 2

Table 3: Comparison of vomiting in three groups at different time intervals

| Vomiting | Study group | mean±SD (mean rank) | Kruskal-Wallis test statistic | p value |
|----------|----------------|---------------------|-------------------------------|---------|
| 0-2 Hrs | G ₁ | 0.70±0.74(57.48) | 16.192 | 0.001 |
| | G ₂ | 0.23±0.50(41.82) | | |
| | G ₃ | 0.10±0.30(37.20) | | |
| 2-6 Hrs | G ₁ | 0.63±0.71(58.52) | 22.546 | 0.001 |
| | G ₂ | 0.13±0.43(40.57) | | |
| | G ₃ | 0.03±0.18(37.42) | | |
| 6-24 Hrs | G ₁ | 0.30±0.79(51.50) | 12.706 | 0.017 |
| | G ₂ | 0.00±0.00(42.50) | | |
| | G ₃ | 0.00±0.00(42.50) | | |

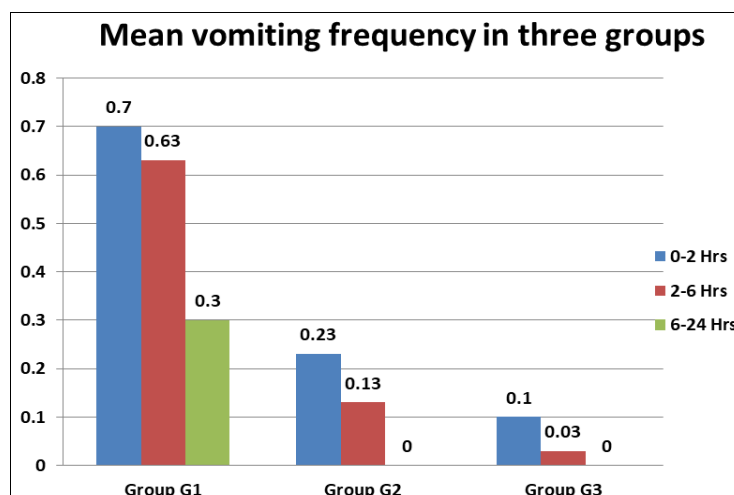


Fig 2: Mean vomiting frequency in three groups.

In the comparison between three groups it was found that mean use of rescue antiemetic was very high in group G₁ than G₂ and G₃ (p <0.01). Table – 4, Figure - 3

Table 4: Comparison of use of rescue antiemetics in three groups at different time intervals

| Rescue antiemetic | Study group | mean±SD(mean rank) | Kruskal-Wallis test statistic | p value |
|-------------------|----------------|--------------------|-------------------------------|---------|
| 0-2 Hrs | G ₁ | 0.73±0.82(54.90) | 9.203 | 0.001 |
| | G ₂ | 0.30±0.59(42.12) | | |
| | G ₃ | 0.23±0.56(39.48) | | |
| 2-6 Hrs | G ₁ | 0.83±0.79(60.90) | 26.094 | 0.001 |
| | G ₂ | 0.13±0.43(38.00) | | |
| | G ₃ | 0.10±0.30(37.60) | | |
| 6-24 Hrs | G ₁ | 0.33±0.60(53.50) | 17.338 | 0.001 |
| | G ₂ | 0.00±0.00(41.50) | | |
| | G ₃ | 0.00±0.00(41.50) | | |

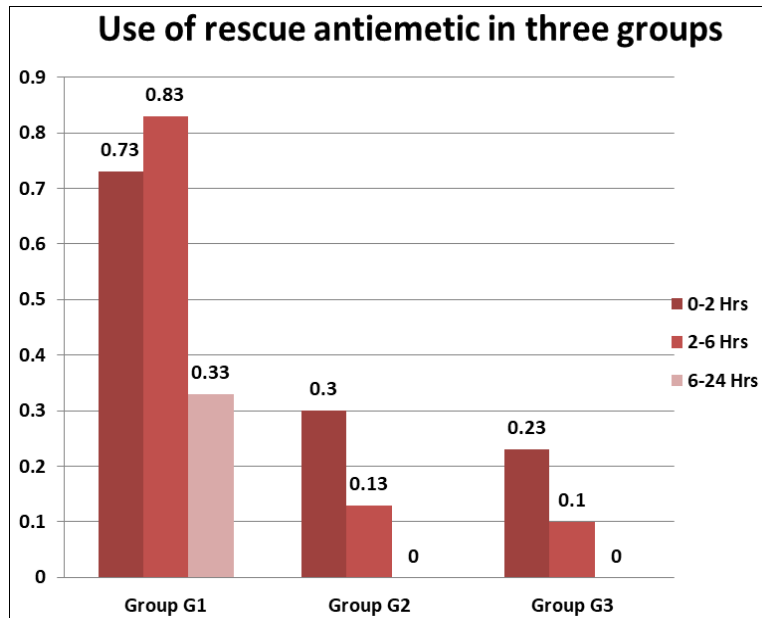


Fig 3: Use of rescue antiemetic in three groups.

In the comparison between three groups, the number of patients who had headache was 5 in G₃, 4 in G₂ and 3 in G₁ over 0-72 hour study period and it was statistically not significant. The number of patients who had dizziness was 4 in G₃, 3 in

G₂ and 4 in G₁ over 0-72 hour study period and it was statistically not significant. In the comparison between three groups, the no of patients who had complete response were 22 in G₃, 20 in G₂ and 8 in G₁ over 0-72 h study period Table – 5, Figure – 4.

Table 5: Comparison of side effects and complete response in three groups at different time intervals

| Parameters | Groups | | |
|-------------------------|-----------------------------|-----------------------------|-----------------------------|
| | Group G ₁ (n=30) | Group G ₂ (n=30) | Group G ₃ (n=30) |
| Headache (Y/N) | 5/25 | 4/26 | 3/27 |
| Dizziness (Y/N) | 4/26 | 3/27 | 4/26 |
| Complete Response (Y/N) | 8/22 | 20/10 | 22/8 |

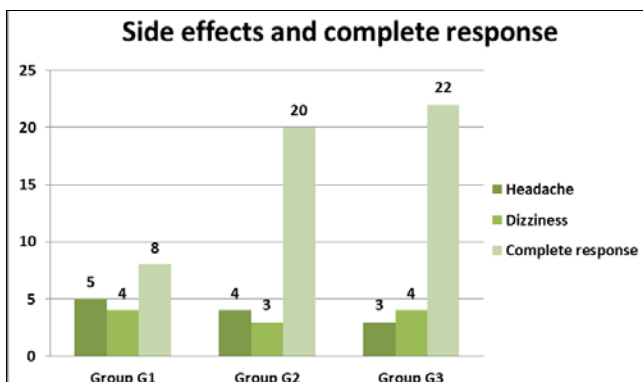


Fig 4: Side effects and complete response.

Discussion

This prospective, randomised, controlled study was done in 90 patients belonging to ASA grade I/II undergoing laparoscopic cholecystectomy under general anaesthesia with a similar surgical and demographic profile. All the three groups in our study were comparable in respect to mean age, weight, gender and duration of anaesthesia. Our study demonstrates that palonosetron given as antiemetic has a better profile as far as nausea, vomiting and use of rescue antiemetic is concerned in comparison to ondansetron over the entire study period taken together but it is not statistically significant. Both ondansetron and palonosetron was far superior to metoclopramide in

preventing PONV in patients undergoing laparoscopic cholecystectomy under general anaesthesia. The study results also showed that the use of rescue antiemetic was lesser in patients given palonosetron and ondansetron than those patients who were given metoclopramide. The overall complete response profile was also significantly better in palonosetron and ondansetron group in comparison to metoclopramide group. The side effects of all the three study drugs were also not statistically significant.

In their prospective, randomized, double-blind study by Naguib M *et al.* (1996)^[15] they observed that the percentage of emesis free patients during the 24 h recovery period after surgery were 65.5% in the ondansetron group and 29.2% in the metoclopramide group. Our study results were also similar to the above with 70% emesis free period in ondansetron group and 33.33% emesis free patients in metoclopramide. Similar results in both the study could be because of same dose of drugs being used in both the study in patients undergoing similar surgery i.e. laparoscopic cholecystectomy.

Palonosetron is an antiemetic with highly selective 5HT₃ receptor antagonist mechanisms of action. Dose selection of palonosetron was based on findings of an earlier study that evaluated i.v. doses of palonosetron ranging from 0.1 to 30 µg/kg^[16]. Candiotti and colleagues (2008)^[17] in their study concluded that a single 0.075mg IV dose of palonosetron significantly increased the CR rate (no emetic episodes and no rescue medication) from 0 to 24 h and it decreased severity of nausea also in comparison to group that received 0.025mg, 0.050 mg or placebo. CR rates for placebo and palonosetron 0.075 mg were 26% and 43% respectively for the 0 to 24 h postoperative interval (p= 0.004). In our study also with the same dose of 0.075 mg palonosetron given just before induction, we observed a CR rate of 73.33% during 0 to 24 h study period. The percentage of patients with vomiting episodes during 0 to 24 h period was 16.67%. The relatively higher rates of CR and lower incidence of vomiting is seen in our study as we have excluded the patients who had any risk factors for PONV, whereas Candiotti and colleagues took patients with at least two PONV risk factors.

In a study done by Bajwa *et al.* (2011)^[18] comparing 8 mg of ondansetron i.v. with palonosetron 0.075 mg i.v. in patients undergoing day care gynaecological surgery found out that 20% and 13.33% of the patients in ondansetron group (group I) had nausea and vomiting episodes postoperatively as compared to 6.67% and 3.33% respectively in palonosetron group (group II) which was statistically significant (p<0.05). Their study also demonstrated a 20% incidence of post-op headache in group I compared to 6.67% in group II. The mean rescue dose of antiemetic was significantly higher (10.6 mg) in the group I as compared to group II (6.4 mg) (p=0.036).

Park SK and colleagues (2011)^[19] in their randomized, double-blind study enrolled 90 patients of ASA grade I/II undergoing gynaecological laparoscopic surgery to determine the efficacy between palonosetron and ondansetron in PONV. Patients received either palonosetron 0.075 mg (n=45) or ondansetron 8 mg (n=45) intravenously, immediately before induction of general anaesthesia. The incidence of PONV was significantly lower in the palonosetron group compared with the ondansetron group (42.2% vs 66.7%, respectively). There were no significant statistical differences in the visual analogue scale for

nausea. In our study also there were no significant statistical differences in the VAS for nausea between both palonosetron and ondansetron (p=0.601). However, the incidence of vomiting over 0-24 h was comparatively lesser in palonosetron group than in ondansetron group, but statistically it was not significant (16.67% vs 30.00%, p=0.169). The incidence of use of rescue antiemetic was also lesser in patients receiving palonosetron than ondansetron, but statistically it was also not significant (16.67% vs 33.34%, p=0.255). The higher incidence of PONV seen in Park SK and EJ Cho study could be because of background infusion of patient controlled analgesia started to deliver fentanyl 4 µg bolus with 16 µg/h infusion for postoperative pain relief.

In our study also nausea, vomiting and use of rescue antiemetic was comparable at all time periods specified in the study supported by the fact that p value data was not significant statistically for any of the three variable mentioned above at any time points. It was further seen in our study that with palonosetron 5 subjects (16.67%) required rescue antiemetic medication, while 9 subjects (33.34%) did so with ondansetron, but the statistical result between the two groups were not significant with p value being 0.255. The numbers of complete responders were 22 subjects (73.33%) in palonosetron group compared to 20 subjects (66.67%) in ondansetron group and statistically it was also not significant (p=0.625).

In the literature reviewed so far our study is the first study in which palonosetron has been simultaneously compared with ondansetron and metoclopramide in patients undergoing laparoscopic cholecystectomy. To summarize the results of our study support the hypothesis that palonosetron is a better antiemetic in comparison metoclopramide clinically and statistically. Further palonosetron 0.075 mg and ondansetron 4mg are at any time better antiemetic than metoclopramide 10 mg. However, when palonosetron and ondansetron are compared together, palonosetron has got a better clinical antiemetic effect though not statistically significant.

Our study has its share of limitations. Since VAS was used for assessing nausea some degree of subjectivity is inevitable. Secondly had our study been a double blind comparison it would have carried a greater weight.

There is increasing evidence supportive of multimodal approach and combination of antiemetic drugs in management of PONV. So palonosetron as a part of combination therapy has scope for further research. At the time our study was being carried out, use of palonosetron was not approved in pediatric and pregnant women. So, further research is warranted for providing antiemetic benefits of palonosetron in these population groups.

The final conclusion deduced was palonosetron 0.075 mg given as a single intravenous dose compared to ondansetron and metoclopramide significantly reduced emesis, nausea and use of rescue antiemetic and had longer duration of action in patients undergoing laparoscopic cholecystectomy under GA. Palonosetron seems to be a promising agent as a prophylactic antiemetic, even in patients with high susceptibility for developing PONV.

Conclusion

In conclusion, the results of the present study clearly convey the facts that palonosetron has a better profile of antiemetic action, and a lesser need for rescue antiemetic postoperatively and a comparable side-effects profile as

compared to ondansetron and metoclopramide. Palonosetron and ondansetron has got a prolonged duration of action in comparison to metoclopramide. Thus providing the patients who underwent laparoscopic cholecystectomy under general anaesthesia a smooth postoperative period with lesser episodes of nausea and vomiting.

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