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Original Research Article

Effects of palonosetron and dexamethasone on postoperative nausea and vomiting in adult patients undergoing laparoscopic abdominal surgery: a randomized, double-blind, clinical trial at a tertiary care hospital

Sifna Tahir[1*], Altaf Ahmad Mir[2], Abdul Hameed[1]

[1]Department of Anaesthesiology and Critical Care, GMC, Srinagar, Jammu & Kashmir - 190006, India
[2]Department of Biochemistry, PGIMER, Chandigarh- 160012, India

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***Correspondence:**
Dr. Sifna Tahir,
E-mail: sifna.tahir@gmail.com

ABSTRACT

Background: Post-operative nausea and vomiting (PONV) is one of the common problems after laparoscopic abdominal surgery. It hampers the postoperative recovery in spite of the availability of many antiemetic drugs and regimens for its prevention. We evaluated the effectiveness of intravenous (IV) palonosetron in counteracting PONV during the first 48hrs following laparoscopic abdominal surgery, using dexamethasone as the comparator drug.
Methods: In this study a single pre-induction IV doses of palonosetron (75mcg) or dexamethasone (8mg) were administered to adult patients of either sex undergoing elective laparoscopic abdominal surgery. There were 40 subjects per group. The pre-anesthetic regimen, anesthesia procedure and laparoscopic technique were uniform. The primary effectiveness measure was total number of PONV episodes in the 48 hours period following end of surgery. The frequencies of individual nausea, retching and vomiting episodes, visual analog scale (VAS) score for nausea at 2, 6, 12, 24 and 48 hours, use of rescue antiemetic (metoclopramide), number of complete responders (no PONV or use of rescue in 48 hours) and adverse events were secondary measures. SPSS software version 16 was employed to using student's t-test, chi-square test or fisher's exact tests. Value of $P < 0.05$ was considered significant.
Results: The incidence of nausea and vomiting was maximal during the first six hours postoperatively. The complete control of postoperative nausea and vomiting for first 24 hours was achieved in 80% patients of palonosetron group and 60% patients of dexamethasone group. During 24-48 hours the incidence of PONV was 17.5% and 22.5% respectively in palonosetron group and dexamethasone group. The use of rescue medication is about 50% less in the use of palonosetron as antiemetic than dexamethasone. Safety profile was similar in both the groups.
Conclusions: Palonosetron is comparatively highly effective to prevent the PONV after anaesthesia in elective laparoscopic abdominal surgery when administered as single pre-induction dose due to its prolonged duration of action than dexamethasone.

Keywords: Abdominal surgery, Dexamethasone, Laparoscopic, Palonosetron, PONV, Randomized controlled trial

INTRODUCTION

Postoperative nausea and vomiting (PONV) continues to be a common and distressing complication of surgery under general anesthesia. It is considered one of the most unpleasant postoperative discomforts. PONV can lead to serious complications of aspiration of gastric contents, suture dehiscence, oesophageal rupture, subcutaneous

emphysema or pneumothorax and electrolyte imbalance. This may lead to delay in resumption of normal activities after elective surgery. The deleterious effects of PONV are not only limited to patient's health but can also produce a negative financial impact on hospital resources and the patient. The incidence of PONV is 30-40% in normal population and touches a peak of 75-80% in certain high-risk groups.[1] Following laparoscopic cholecystectomy the incidence of PONV remains unacceptably high (40-75% in the first 24 hours, without active intervention).[2,3] With the introduction of lesser emetogenic anesthetic techniques and advent of newer drugs for the prophylaxis of postoperative nausea and vomiting, the incidence of PONV has come down by 50%, especially with the use of non-opioid medication for pain relief.

Postoperative nausea and vomiting is defined as nausea and/or vomiting occurring within 24 hours after surgery. The aetiology of PONV is not still known well, but it is probably a multifactorial phenomenon.[4,5] Patient characteristics, type of surgical procedure, duration of anesthesia and surgery are few of the important determinants for risk of PONV. Creation of pneumoperitoneum is an essential part of laparoscopy, leading to stretching of mechanoreceptors, increased serotonin (5HT) synthesis and PONV.[6]

Prolonged entrance of CO_2 leads to pneumoperitoneum, peritoneal distension and diaphragmatic stimulation. Intra-abdominal manipulation is one of the causes of PONV.[4,5] 5HT3 receptor antagonists (5HT3RA) have a definite role in the prevention of PONV. 5HT3 receptors are found in the gut and in areas of the central nervous system (CNS and are abundant in the chemoreceptor trigger zone (CTZ) of the area postrema, which has projections to the vomiting centre located in the lateral reticular formation of the medulla oblongata.[7] Vagal nerve terminals are the sites of peripheral 5HT3 receptors, which are linked to the vomiting centre via the nucleus tractus solitaries.[8] Competitive antagonism with 5HT3RA at these sites, and probably others, can block initiation of the vomiting reflex, caused by emetogenic stimuli.

PONV prophylaxis has seen many advances over recent years. These include use of non-pharmacological measures to reduce baseline risk, a change to less emetogenic anesthetic techniques and the use of new antiemetic drugs. However, in PONV management, the use of antiemetic, either alone or in combination, remains the mainstay.

Drugs used include metoclopramide, haloperidol, dexamethasone and the selective 5-HT3 receptor antagonists. 5-HT3 receptor antagonists are now a first line option because of effectiveness and general lack of adverse drug reactions.[9,10] In 5-HT3 receptor antagonists group ondansetron has been used most in clinical research, and its antiemetic efficacy in chemotherapy-induced emesis and in the treatment and prevention of PONV is well established. However, several alternatives to ondansetron (e.g. granisetron, tropisetron, dolasetron, ramosetron) are now available.

Palonosetron is the most recently introduced member of this class of drugs in India. It was approved by the Drugs Controller General of India on 25.04.2009. Interaction pattern of Palonosetron with the 5-HT3 receptor is different from earlier 5-HT3 receptor antagonists, enabling a higher binding affinity and longer half-life.[10,11]

In contrast to the older 5-HT3 receptor antagonists, palonosetron's allosteric binding and positive cooperativity triggers receptor internalization, which result in persistent inhibition of 5-HT3 receptor function and long duration of action.[12] Following single intravenous (IV) dose the mean terminal elimination half-life is approximately 40 hours. Therefore the duration of action exceeds 24 hours and may extend to 48 hours. It was reported that palonosetron was more effective than ondansetron in preventing chemotherapy-induced nausea and vomiting (CINV) and PONV.[13,14]

Corticosteroids like dexamethasone are thought to exert antiemetic properties by inhibiting prostaglandin synthesis or the release of endogenous opioids with negligible side effects.[15] Dexamethasone is a low price corticosteroid which has anti-inflammatory effects, and some studies have also evaluated its effect on nausea and vomiting prophylaxis after chemotherapy.[4,5] Palonosetron has been compared with placebo for the prevention of PONV in patients undergoing open abdominal and gynaecological surgery.[16,17] Comparison with other antiemetic drugs and in other types of surgery is still limited.

Therefore, the present double-blind, randomized prospective study was aimed to assess and compare the antiemetic efficacy, duration of action, and side effects of palonosetron and dexamethasone for antiemetic prophylaxis of postoperative nausea and vomiting after undergoing laparoscopic abdominal surgery under general anesthesia.

METHODS

After approving the study protocol by the institution ethical committee, informed consent was obtained from every patient. In this study 80 patients, scheduled for elective laparoscopic abdominal surgery under general anesthesia, were enrolled. Age ranged from 20-60 years (mean = 46 years).

Patients with one or more of the following were excluded from the study: American society of anaesthesiologists (ASA) physical status III–IV; administration of antiemetic medication within 24 hours before surgery; administration of steroids within 24 hours before surgery or during the 24 hours after surgery; gastrointestinal,

renal, or hepatic disease; insulin-dependent diabetes mellitus and conversion to open cholecystectomy. Patients with vomiting or retching in the 24 hours preceding surgery, those who had received cancer chemotherapy within 4 weeks or emetogenic radiotherapy within 8 weeks before study entry, and patients with ongoing vomiting from gastrointestinal disease were also excluded.

Study design and treatment

Through a computer generated randomization schedule, patients were randomly allocated into two groups (n = 40 each) to receive one of the following regimens: palonosetron 0.075 mg in 2.5 ml (group P) or dexamethasone 8 mg in 2.5 ml (0.9% saline was added to make the desired volume) (group D). The study medications were administered immediately before the induction of anaesthesia. Trained anaesthesia technicians who did not participate in the study prepared the drugs according to manufacturer's instructions and placed them in numbered, sealed envelopes assigned by computer generated random numbers. The envelopes were opened before anesthetic induction by a physician not involved in the study.

All patients were kept fasting after midnight and received tablet (tab.) alprazolam 0.25 mg orally as premedication. On the operation table, routine monitoring of pulse oximetry (SpO2), electrocardiogram (ECG) and non-invasive blood pressure (NIBP) was started. Baseline vital parameters like heart rate (HR), blood pressure and SpO2 were recorded. An intravenous line was secured. Patients were premedicated with Injection (inj.) Rabeparazole-20 mg IV and Inj. Midazolam 1 mg IV Preoxygenation with 100% O_2 was done with a facemask. Subsequent induction was done with Inj. propofol 2 mg/kg body weight and relaxation and intubation was accomplished with Inj. atracurium besylate 0.5 mg/kg body weight. Anaesthesia was maintained with oxygen and nitrousoxide mixture (50:50).

Isoflurane (0.7-1.3 MAC) and Inj. atracurium besylate 0.1 mg/kg body weight was used as a muscle relaxant. Positive pressure ventilation was delivered with tidal volume and respiratory rate adjusted to maintain end tidal CO_2 between 30-40 mmHg. Inj. Tramadol HCl 2 mg/kg body weight and injection paracetamol 20 mg/kg body weight was administered intravenously (IV) for intraoperative analgesia. During surgery Ringer lactate was infused in accordance with maintenance of volume requirements. A nasogastric tube was inserted to make the stomach empty of air and other contents.

For laparoscopic surgical procedure, peritoneal cavity was insufflated with carbon dioxide to keep intra-abdominal pressure <14mmHg. At the end of surgical procedure, residual neuromuscular block was adequately reversed using IV glycopyrrolate 0.02 mg/kg body weight and neostigmine 0.05 mg/kg body weight. Before tracheal extubation, the nasogastric tube was suctioned and removed and patient subsequently extubated. For postoperative analgesia, diclofenac transdermal patch was applied on body surface. All patients were observed postoperatively by resident doctors who were unaware of the study drug.

Patient monitoring

All episodes of PONV (nausea, retching and vomiting) were recorded for 0-2 hours in postanaesthesia care unit and from 2-48 hours in postoperative ward. The incidence of nausea and vomiting was recorded at 2, 6, 12, 24 and 48 hours after extubation by direct questioning to the patient or His/Her attendents. The severity of PONV was graded as follows (Wilson's Score):

- No PONV - Absence of any emesis or nausea
- Mild PONV - Patient having only mild nausea, or one emetic episode or nausea lasting for less than 10 minutes and where no antiemetic is required
- Moderate PONV - patient has 1-2 emetic episodes or moderate to severe nausea and antiemetic therapy is required
- Severe PONV - Patient has more than 2 emetic episodes or is nauseated more than twice and more than one antiemetic required. The use of rescue antiemetic drug use was monitored at 0-48 hours post-surgery.

Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit, whereas an episode of vomiting was defined as forceful expulsion of gastric contents from the mouth and retching included laboured, spasmodic, rhythmic contractions of the respiratory muscles without expulsion of gastric contents. Metoclopramide (10 mg IV) was permitted as a rescue antiemetic when two episodes of PONV occurred. If metoclopramide treatment was ineffective, ondansetron 4 mg IV was permitted. A complete response was defined as the absence of PONV and no use of rescue antiemetics.

Details of any adverse effects (including headaches, dizziness, constipation and myalgia) were recorded. The primary outcome measure of this study was the incidence of nausea and vomiting during the first 48 h after anaesthesia. Secondary outcome measures were the severity of nausea, need for rescue medication, patient satisfaction and incidence of adverse effects.

Statistical analyses

All statistical analyses were performed using SPSS® statistical package, version 17.0 (SPSS Inc., Chicago, IL, USA) for Windows®. The Student's t-test was used to compare intergroup differences and the $\chi 2$ or Fisher's exact tests were used for categorical variables. The p-values were corrected by the Bonferroni method and a p-value < 0.05 was regarded as statistically significant.

RESULTS

In total, 80 patients were recruited, all of whom completed the study. There were no statistically significant differences between palonosetron and dexamethasone treated groups in terms of patient characteristics, PONV risk factors or operative data (Table 1 and Table 2).The groups were comparable with respect to age, weight and duration of surgery (Table 1 and Table 2).

Table 1: Patient characteristics.

		Group D (n = 40)	Group P (n = 40)	p value
Age (Years)		43.9±14	39.9±13.4	0.6
Gender	Male	18	14	0.4
	Female	22	26	
Weight (Kgs)		61.75±9.5	60.8±10.01	1
Duration of surgery (minutes)		42.1±13.05	45.1±14.8	1

*p<0.05 is significant

Table 2: Risk distribution in the two study groups.

	Group D (n = 40)	Group P (n = 40)	p value
Obesity n (%)	5 (12.5)	7 (17.5)	
Non obese n (%)	35 (87.5)	33 (82.5)	0.57
Smokers n (%)	7 (17.5)	5 (12.5)	
Non smokers n (%)	33 (82.5)	35 (12.5)	0.53
H/O motion sickness n (%)	8 (20)	5 (12.5)	
No H/O motion sickness n (%)	32 (80)	35 (87.5)	1

*p<0.05 is significant

Table 3: Group wise incidence of post-operative nausea and vomiting (PONV) in patients undergoing elective abdominal laparoscopic surgery during 48 hours post operation who received Palonosetron 0.075 mg (group P) and Dexamethasone 8 mg (group D) intravenously 10 seconds before induction of anesthesia.

	Group P (n =40)	Group D (n = 40)	p value
0 - 2 hours			
Nausea n (%)	4 (10)	24 (60)	<0.05
Vomiting n (%)	2 (5)	5 (12.5)	0.43
Overall PONV n (%)	6 (15)	29 (72.5)	<0.05
2 - 6 hours			
Nausea n (%)	5 (12.5)	21 (52)	<0.05
Vomiting n %)	2 (5)	5 (12.5)	0.43
Overall PONV n (%)	7 (17.5)	26 (64.5)	<0.05
6 - 24 hours			
Nausea n (%)	6 (15)	12 (30)	0.1
Vomiting n (%)	2 (5)	4 (10)	1
Overall PONV n (%)	8 (20)	16 (40)	0.05
24 - 48 hours			
Nausea n (%)	4 (10)	8 (20)	0.34
Vomiting n (%)	3 (7.5)	1 (2.5)	0.61
Overall PONV n (%)	7 (17.5)	9 (22.5)	0.57
Rescue antiemetics n (%)	6 (15)	17 (42.5)	<0.05

*p<0.05 is significant

The incidence of PONV (Table 3) during 0-2 hours in the postoperative period was 15% (n = 6) with group P (Palonosetron) and 72.5% (n = 29) with group D (Dexamethasone) and the incidence during 2-6 hours postoperatively was 17.5% (n = 7) with group P (Palonosetron) and 64.5% (n = 26) with group D (Dexamethasone). The difference was statistically significant (p value <0.05). During 6-24 hours, the incidence was 20% (n = 8) and 40% (n = 16) respectively (Table 3). The difference was statistically insignificant (p value<0.05). During 24-48 hours the incidence of PONV in group P (Palonosetron) was 17.5% (n = 7) and in group D (Dexamethasone) it was 22.5% (n = 9). Although the difference is statistically insignificant ((p value<0.05), the

antiemetic efficacy of dexamethasone shows an improvement as post-operative hours increase. Overall use of rescue medication is 15% (n = 6) in group P (palonosetron) and 42.5% (n = 17) in group D (dexamethasone).

Table 4: Group wise incidence of adverse effects in patients undergoing elective abdominal laparoscopic surgery.

Postoperative period	Group D (n = 40)	Group P (n = 40)	p value
0-2 hours			
Headache n (%)	6 (51)	5 (12.5)	0.36
Constipation n (%)	8 (20)	8 (20)	1
Drowsiness n (%)	1 (2.5)	1 (2.5)	1
2-6 hours			
Headache n (%)	3 (7.5)	3 (7.5)	1
Constipation n (%)	5 (12.5)	8 (20)	1
Drowsiness n (%)	1 (2.5)	1 (2.5)	1
6-24 hours			
Headache n (%)	1 (2.5)	3 (7.5)	1
Constipation n (%)	4 (10)	3 (7.5)	0.31
Drowsiness n (%)	1 (2.5)	1 (2.5)	
24-48 hours			
Headache n (%)	2 (5)	0	0.99
Constipation n (%)	0	0	1
Drowsiness n (%)	0	0	1

*$p<0.05$ is significant.

The use of rescue medication is about 50% less in the use of palonosetron as antiemetic than dexamethasone. During late post-operative period the antiemetic effect of dexamethasone shows an improvement. Thus a complete response during 0-48 hour in the postoperative period was significantly more in patients who had received palonosetron than in those who had received dexamethasone.

Headache, dizziness, drowsiness and constipation were the commonly observed adverse effects but those were not clinically serious or significant. Also, the incidences of adverse effects were statistically insignificant between the groups (Table 4).

DISCUSSION

In patients undergoing laparoscopic cholecystectomy the incidence of PONV has been reported 50-72% when no prophylactic antiemetic is provided.[18,19] The aetiology of PONV following laparoscopic cholecystectomy remains unclear. But intraperitoneal CO_2 insufflation leading to stretching and irritation of peritoneum is a probable reason. Among the other 5-HT3 antagonists, palonosetron exhibits far higher receptor affinity and more potent binding with 5-HT3 receptors.[16] Also, palonosetron triggers functional effects that persist beyond its binding to the 5-HT3 receptor at the cell surface leading to prolonged duration of action and longer half-life (40 hours).[17]

In addition, palonosetron also exhibits antinauseatic property which is in contrast to other 5-HT3 blockers. In Kovac et al.[20] study, complete response rates of 56% and 70% between 0-24 hours and 24-72 hours respectively were demonstrated in palonosetron pre-treated patients after gynaecological surgeries. Also, in a similar study, Candiotti et al reported complete response rate of 43% between 0-24 hours and 49% during 24-72 hours postoperatively in patients receiving palonosetron 0.075 mg.[21]

Present complete response rate was 80% and 92.5% in palonosetron group during 0-24 h and 24-48 h respectively. The differences in the incidence of PONV in these studies seem to be associated with the use of different anesthesia technique and the different patient population. Present patients were at high risk for PONV due to non-smoking habits, female gender and laparoscopic surgery. Though, all these factors were well balanced among the groups. Dexamethasone, a corticosteroid, is a cheap, long acting antiemetic drug with an excellent side effect profile. Its prophylactic use has been found to be effective in reducing the incidence of PONV during 24 hours after laparoscopic cholecystectomy.[4,22,23] The antiemetic properties have been suggested to be due to various mechanisms like, prostaglandin antagonism, release of endorphins and bradykinin reduction.[24,25] It can potentiate the effect of other antiemetics also. In patients at high risk for PONV, the combination therapy using dexamethasone and 5-HT3 antagonists, ondansetron, granisetron, ramosetron as well

as dolasetron, appears to be more effective than single-drug prophylaxis.[26-28]

In a recent study, the ramosetron and dexamethasone combination was found to be superior to ramosetron alone with 93% patients showing complete response at 12-24 hours after laparoscopic cholecystectomy.[27] The dose of dexamethasone used was also chosen based on recommendations of previous studies that addressed its efficacy for treating PONV and postoperative pain.[23,29] In the current study, a single dose of dexamethasone 8 mg was not related to any adverse effects. In the present study, 20% patients receiving palonosetron experienced PONV during 0-24 hours while 17.5% patients during 24-48 hours. Addition of palonosetron to antiemetic prophylaxis also reduced the requirement of rescue antiemetic medication and were associated with greater patient satisfaction.

Palonosetron 0.075 mg conferred significant antiemetic benefits compared to dexamethasone 8 mg. When comparing the antiemetic efficacy of the two groups, the benefits conferred by the palonosetron 0.075 mg were more superior than those of dexamethasone 8 mg since it resulted in an improved emesis control, and a lower incidence of PONV for longer durations with a higher level of statistical significance at 0-2 hours, 2-6 hours and 6-24 hours when compared to dexamethasone alone. During 24-48 hours there was a difference in the incidence PONV being lower in palonosetron group but it was statistically insignificant. Of particular interest, the overall need of rescue antiemtic was 6 (15) for group P compared to 17 (42.5) for group D. fujii and Itakura also reported that prophylactic therapy with dexamethasone 8 mg was effective in reducing PONV as well as analgesic requirement after laparoscopic cholecystectomy.[23]

In a recent study, Murphy et al reported that the use of preoperative dexamethasone enhanced post discharge quality of recovery after laparoscopic cholecystectomy and reduced nausea, pain, and fatigue in the early postoperative period.[30] There were no severe adverse effects in any group of patients in our study. In particular, there were no wound infections or healing delays in patients receiving dexamethasone. The main limitation of our study is that we did not include a placebo group which is required to calculate the absolute risk reduction of PONV. As per Aspinall and Goodman if you have active drugs available, placebo controlled trials may be unethical because PONV are very much distressing after laparoscopic surgery.[31] Second, the patients with underlying diseases were excluded, so the results of the study should not be generalized to other patients with severe underlying diseases. Further studies should consider these limitations.

CONCLUSION

Compared with dexamethasone, palonosetron was more effective in reducing the incidence of PONV during first 24 hours after surgery in patients undergoing laparoscopic abdominal surgery without apparent side effects. During 24-48 hours the antiemetic effect of dexamethasone showed an improvement but palonosetron continued to be a better choice in late post-operative period as well. Addition of dexamethasone to palonosetron can reduce the requirement of rescue antiemetic and improve the patient satisfaction with the management of PONV symptoms.

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