Comparison Of Palonosetron With Placebo For Prevention Of Postoperative Nausea And Vomiting In Female Patients Undergoing Gynaecological Surgery Under Spinal Anaesthesia.

S K.S, S Shaikh

Citation

S K.S, S Shaikh. *Comparison Of Palonosetron With Placebo For Prevention Of Postoperative Nausea And Vomiting In Female Patients Undergoing Gynaecological Surgery Under Spinal Anaesthesia.*. The Internet Journal of Anesthesiology. 2012 Volume 30 Number 2.

Abstract

Background: Postoperative Nausea and Vomiting (PONV) can be a distressing problem in patients undergoing regional anaesthesia also, as patient and surgical risk factors for PONV continue to exist. In this randomized, double blind, prospective clinical study, we investigated and compared the efficacy of newer $5HT_3$ antagonist Palonosetron, compared to placebo, in preventing Postoperative Nausea and Vomiting in patients undergoing gynaecological surgeries under spinal anaesthesia.Material and Methods: 70 women, ASA 1 and 2, undergoing gynaecological surgeries, with risk for PONV (>/= 2 risk score) were randomly allocated to two groups containing 35 patients each. One group received 0.075mg of Palonosetron intravenously and other group received saline intravenously as placebo after administration of spinal anaesthesia. Peri-operative anesthetic care was standardized in all patients. The efficacy of study medication was assessed in terms of Complete Response (No emesis and no rescue antiemetic), incidence of emetic episodes, the incidence and severity of nausea in the postoperative study periods 0-6 hours, 6-24 hours and 24-72 hours. Results: The incidence of a Complete Response (no emesis, no rescue antiemetic) in 0-6 hour study period was 82.9% with palonosetron group and 45.7%with placebo group (P value-0.001 strongly significant).The corresponding incidence in 6-24 hour was 74.3% with palonosetron and 37.1% with placebo group (P value 0.002 strongly significant).During 24-72 hour, the incidence was 97.1% in palonosetron and 94.3% in the placebo group (P value not significant).Conclusion: A single intravenous dose of 0.075mg of Palonosetron significantly reduced emesis, nausea and use of rescue anti-emetics in female patients undergoing gynaecological surgeries under spinal anaesthesia compared to placebo.

INTRODUCTION

Postoperative Nausea and Vomiting (PONV) continues to be the most frequent complication of anesthesia and surgery in spite of availability of so many antiemetic drugs and regimens for prevention. J Lance Lichtor quotes in his editorial “we are tired of waiting for the ‘big little problem’ to be solved”.[1,2]

The overall incidence of PONV is reported to be between 20-30%, but it can increase up to 80% in high risk patients.[3]

Patients rate its avoidance and control of more importance than that of alleviating pain[4].In addition to economic implications, PONV has physical, metabolic and psychological effects on the patient which slow their recovery and reduce their confidence in future surgery and anaesthesia.

Much progress has been made in identifying the pathophysiology of nausea and vomiting including the receptor sites at which therapeutic interventions may be effective. Commonly used effective anti-emetics, selective serotonin hydroxytryptamine type $3(5\text{-}HT_3)$receptor antagonists like ondansetron, granisetron, dolasetron etc have similar efficacy for preventing PONV and they are relatively short acting(elimination time<12 hours).[1]

Palonosetron is the newest of $5HT_3$ receptor antagonists, successfully used in controlling chemotherapy induced emesis and approved by Food and Drug Administration (FDA) for prevention of PONV in march 2008.[5] It is being described as ‘second generation’ of $5\text{-}HT_3$ receptor

antagonists because of its unique pharmacology.[6] Palonosetron has far higher receptor affinity and a much longer half life than other 5-HT_3 antagonists, so has a prolonged duration of action.

Most of the research on PONV and efficacy of anti-emetics has been with general anaesthesia, while PONV could be a distressing problem in regional anaesthesia too,[7] as there is increasing use of neuraxial opioids. Moreover, the accepted risk factors for PONV like female gender, non smoking status, history of motion sickness or PONV, use of opioids could be present in patients undergoing regional anaesthesia, thus putting them in high risk group for PONV.[8,9,10]

So we designed this study to assess the antiemetic efficacy of new and much promising drug palonosetron in comparison with placebo in high risk group of female patients undergoing gynaecological surgeries under spinal anaesthesia.

MATERIALS AND METHODS

This prospective, randomized, placebo controlled, double blinded study was carried out, following an approval from the institutional ethics committee. Patients included in this study were informed about the procedure and written informed consent was taken from all of them.

70 women, ASA grade 1 and 2, 23-65 years of age undergoing gynecological surgeries under spinal anesthesia, which were anticipated to complete within 3 hours (180min) were selected.

The risk factors considered in this study were

1) Gender-females

2) History of PONV or motion sickness

3) Non-smoking status

Exclusion criteria were pregnancy, body mass index>30,vomiting or retching within 24 hrs before surgery, administration of antiemetic or steroids within 24 hours of surgery, refusal of spinal anaesthesia.

A detailed medical history and patient characteristic information was noted. Any H/O PONV or motion sickness, smoking or tobacco chewing documented.

Patients were randomly allocated to receive either Inj.Palonosetron 75 mcg (diluted to 2cc) intravenously or 0.9%normal saline 2cc intravenously (placebo group) and identical syringes containing the above were prepared by personnel not involved in this study. Because rescue medication for relief of PONV was permitted, withholding active treatment was not considered detrimental to the patients randomized to placebo.[11]

All patients were kept fasting after midnight, received tab diazepam 10mg orally the night before surgery and on the morning of surgery at 6am with sips of water.

On arrival to operation theatre, routine monitors (electrocardiogram, pulse oximeter, NIBP) were attached and vital parameters like heart rate, respiratory rate, blood pressure and arterial oxygen saturation were observed throughout surgery.

An 18G intravenous cannula was secured and an intravenous infusion of 500ml (10-15ml/kg) of Ringer's lactate was given.

Patients were placed in the left lateral position and lumbar puncture was performed in the L2-3 or L3-4 space using a midline approach with 25G Quincke's spinal needle. As soon as there was free flow of cerebrospinal fluid, hyperbaric bupivacaine 0.5%, 3cc (15mg) +buprenorphine 100mcg was injected. Sensory blockade up to T7-8 level was achieved. Study medication was administered after spinal anaesthesia and before commencement of surgery.

Supplemental oxygen 4 lit/min was given via Hudson's face mask.

Any patients having inadequate block, requiring supplemental analgesics or general anaesthesia and patients who had episodes of severe hypotension were dropped from the study.

Monitoring of vital signs continued postoperatively.

All episodes of PONV (nausea, retching and vomiting) were recorded by direct questioning by trained nurses blinded to the study group or by the spontaneous complaints by the patients during the study periods. Study periods were every 2 hours during 0-6 hrs, every 6 hrs in 6-24hrs and every 12hrs during 24-72hrs.

Nausea was defined as the subjectively unpleasant sensation associated with awareness of urge to vomit; retching was defined as labored, spastic, rhythmic contraction of respiratory muscles without expulsion of gastric contents

and vomiting was defined as forceful expulsion of gastric contents from the mouth.[12] For the purpose of data collection, no distinction was made between vomiting and retching.

An emetic episode was defined as a vomiting or retching event or any combination of these events that occurred in rapid succession(less than 1 min interval between events).Complete response (CR) was defined as no emesis and no need for rescue antiemetic.

Nausea was assessed on Verbal rating scale (0-no nausea, 1-mild nausea, 2-moderate nausea, 3-severe nausea).[13]

If patient had an episode of emesis, Inj.metoclopramide 10mg intravenously was given as first rescue antiemetic. If the drug was not effective and patient continued vomiting, Inj.ondansetron 4 mg intravenously as second rescue antiemetic. To minimize the suffering from PONV, patients were informed and educated on how to request treatment when PONV occurred. Adverse events were evaluated and recorded by the investigator during the entire observation period.

Postoperative pain at the surgical site was assessed by using Visual Analogue Scale(0-no pain to 10-worst conceivable pain).Postoperative analgesia was provided with Inj.diclofenac sodium 75mg intramuscularly when VAS pain score was more than 4 in the immediate postoperative period and then continued twice daily postoperatively.

The efficacy of study medication was assessed in terms of % of complete response, the incidence of emetic episodes, the incidence and severity of the nausea in the study periods. Patients were also asked to rate their overall satisfaction with the anaesthetic experience on a three point scale (satisfied, neutral, dissatisfied).[14]

Descriptive statistical analysis has been carried out in the present study. Student t test(two tailed, independent) has been used to find the significance of study parameters on continuous scale between the two groups on metric parameters, Chi-square/Fisher exact test has been used to find the significance of study parameters on categorical scale between two groups. The statistical software namely SAS9.2, SPSS15.0, Stata 10.1, Medcalc9.0.1, Systat12 were used for the study. P value <0.05 was considered moderately significant and P value <0.01 was considered strongly significant. The results are expressed in mean+/- SD and number (%).

RESULTS

Patient characteristics including age, Body Mass Index(BMI),risk factors like non smoking status, history of PONV or motion sickness, duration and types of surgery were similar between the two groups[table 1].The incidence of a Complete Response(no emesis, no rescue antiemetic) in 0-6 hour study period was 82.9% with palonosetron group and 45.7%with placebo group(P value-0.001 strongly significant).The corresponding incidence in 6-24 hour was 74.3% with palonosetron and 37.1% with placebo group(P value 0.002 strongly significant).During 24-72 hour, the incidence was 97.1% in palonosetron and 94.3% in the placebo group(P value not significant).

During the period 0-6 hours postoperatively, 19 patients (54.3%) in the placebo group required rescue anti-emetics where as only 5 patients (14.3%) in the palonosetron group received them. The number of patients receiving rescue anti-emetics were 14(40%) in placebo group and 8(22.9%) in palonosetron group in 6-24 hour period. Only 1 (3.3%) patient received rescue antiemetic in placebo group and none n palonosetron group in 24-72 hour period.

The commonly observed adverse effects were headache, dizziness, pruritis and constipation, but those were not clinically serious and incidence statistically insignificant between the two groups. There was no difference between the pain scores among two groups.

Figure 1

TABLE 1. Patient Characteristics

	PALONOSETRON(n=35)	PLACEBO (n=35)
Age (years)	46.06+/- 12.07	44.03+/- 10.29
BMI (kg/m^2)	25.16+/- 1.29	25.45+/- 1.53
Duration of surgery	98+/- 28	97+/-25
Non smoking status	34(97.1%)	35(100%)
H/O PONV or motion sickness	1	2
Types of surgery		
Mayoward's	19	13
Total abdominal Hysterectomy	12	15
Haeney's	2	2
Fothergill's	1	3
Ovarian cystectomy	1	2
ASA physical status		
1	19(54.3%)	13(37.1%)
2	16(45.7%)	22(62.9%)

Figure 2

TABLE 2. Incidence of Postoperative Nausea and Vomiting

	Palonosetron	Placebo	P value
0-6 hours			
Complete response	29(82.9%)	16(45.7%)	0.001
Nausea	13(37.1%)	25(71.4%)	0.003
Vomiting	6(17.14%)	19(54.3%)	<0.001
Rescue antiemetics	5(14.3%)	19(54.3%)	
6-24 hours			
Complete response	26(74.3%)	13(37.1%)	0.002
Nausea	15(42.8%)	29(82.8%)	<0.001
Vomiting	9(25.7%)	22(62.8%)	0.016
Rescue antiemetics	9(25.7%)	22(62.8%)	
24-72 hours			
Complete Response	34(97.1%)	33(94.3%)	1.000
Nausea	2(5.7%)	3(8.6%)	0.614
Vomiting	1(2.8%)	1(2.8%)	1.000
Rescue antiemetics	1(2.9%)	0	

Figure 3

TABLE 3. Incidence of Patient Satisfaction

Patient satisfaction	Palonosetron	Placebo
Satisfied	33(94.3%)	22(62.85%)
Neutral	2(5.7%)	11(31.42%)
Dissatisfied	0	2(5.7%)

Figure 4

FIG. 1 Comparison of incidence of nausea in two groups of patients

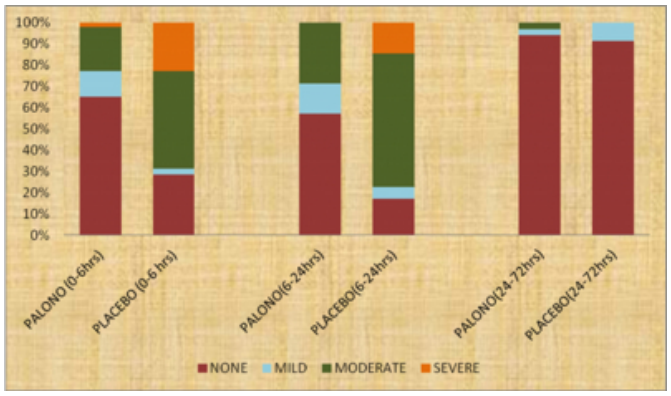
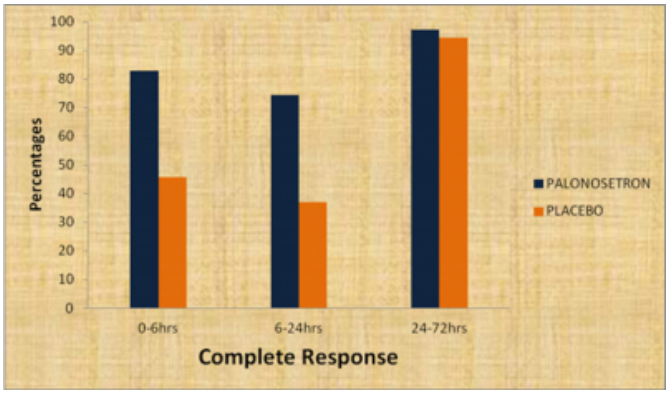


Figure 5

FIG. 2 Incidence of complete response in two groups of patients



DISCUSSION

PONV has a multifactorial pathogenesis with activation of target receptors in the Chemoreceptor Trigger Zone (CTZ), vestibular system, the cerebral cortex and visceral afferents from gastrointestinal tract. The $5HT_3$ receptor antagonists involve both central and peripheral mechanisms in the control of nausea and vomiting. They bind competitively and selectively to $5HT_3$ receptors in CTZ and also block the receptors in gastrointestinal tract and inhibit emetic symptoms.

Palonosetron is a novel $5HT_3$ receptor antagonist. Rojas et al have described the unique pharmacology of palonosetron compared with the other $5HT_3$ receptor antagonists including differences in half life and receptor internalization that may provide a longer duration of action.[6] Its efficacy in preventing chemotherapy induced nausea and vomiting has been demonstrated in various studies.[15,16]

Kovac et al have concluded that a single 0.075mg intravenous dose of palonosetron significantly reduced emesis, intensity of nausea and the use of rescue anti-emetics in addition to delaying emesis and treatment failure.[12] Keith A, Candiotti et al also confirmed that 0.075mg of palonosetron was effective antiemetic dose in a study conducted in out patients.[10] Lower doses were not effective. So in our study we used this dose as it was found to have best treatment effect. We compared it with placebo instead of a standard antiemetic, as it is a new drug and its role in preventing PONV is still being defined. Also, risk reduction can be assessed easily.

Regional anaesthesia is associated with lower incidence of PONV than general anaesthesia, but its occurrence in this

group of patients seems to be more dependent on risk factors such as female gender, non smoking status, use of opioids, history of motion sickness or PONV and type of surgery.

Studies dealing with PONV have discussed almost exclusively general anaesthesia and largely ignored regional anaesthesia. Usage of neuraxial opioids has recently been increased. Buprenorphine is a long acting, highly lipophilic opiod, which has proved to be a promising analgesic by intrathecal route.[17,18] It is commonly being used in our institution as an intrathecal additive to spinal anaesthesia for its excellent intra operative and post operative analgesia with relatively better safety profile.

In this study, treatment groups were comparable with respect to patient demographics, types of surgery, type of anaesthesia and analgesics used postoperatively. Therefore the difference in the Complete Response between the groups can be attributed to the study drug.

Our study demonstrated that palonosetron was statistically superior to placebo for most of the end points during the first 24 hours, including Complete Response (CR), emesis and nausea rates, and requirement of rescue anti-emetics. This effect was not seen during 24-72 hours mainly because even the patients in the placebo group had reduced incidence of vomiting probably due to regional anaesthesia and no opioid usage in the postoperative period. Less intense nausea in palonosetron group compared to placebo group could indicate its anti nausea effect and it is a first $5HT_3$ antagonist to have shown this property and it needs to be researched further.

Dhurjoti Prosad Bhattacharjee et al compared palonosetron and granisetron in preventing PONV after laparoscopic cholecystectomy under general anaesthesia in female patients.[19] Complete Response rates for palonosetron for postoperative periods 0-3 hours,3-24 hours and 24-48 hours were 90%,90% and 90% respectively which was comparable with our study where CR rates for 0-6,6-24 and 24-72 hours were 82.9%,74.3% and 97.1% respectively.

Another study was conducted by Sukhminderjit Singh Bajwa et al in 60 female patients who underwent bilateral laparoscopic tubal ligation under general anaesthesia. They compared antiemetic efficacy of palonosetron with ondansetron.[20] They concluded that palonosetron is comparatively better drug in preventing PONV and reported that 6.67% of patients in palonosetron group experienced significant post-operative head ache as compared to 20% in ondansetron group. This is comparable to our findings of adverse effects where 5.7% patients in the palonosetron group suffered post-operative head ache which was statistically insignificant compared to placebo.

LIMITATIONS of the study:*modest population size

*Although our study was placebo controlled, the lack of an active comparator limits the ability to directly compare palonosetron with older, established members of $5HT_3$antagonists like ondansetron.

FUTURE research: 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 required for providing anti-emetic benefits of palonosetron in these population groups.

In conclusion, a single intravenous dose of 0.075mg of palonosetron, compared to placebo, significantly reduced emesis, nausea and use of rescue anti-emetics in female patients undergoing gynaecological surgeries under spinal anaesthesia. Palonosetron seems to be a promising agent as a prophylactic antiemetic, even in patients with high susceptibility for developing PONV and has a favorable side effect profile.

References

1. J.Lance Lichtor. We’re Tired of Waiting. Editorial. Anaesthesia Analgesia 2008;107:353-355
2. Fisher DM. The “big little problem” of postoperative nausea and vomiting: do we know the answer yet? Anaesthesiolgy 1997;87:1271-3
3. Tong J Gan, Tricia Meyer, Christian C Apfel et al. Consensus Guidelines for Managing Postoperative Nausea and Vomiting. Anesthesia Analgesia 2003;97:62-71.
4. Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. Anesthesia Analgesia 1999;89:652-8
5. Neil A Muchatuta, Michael J Paech. Management of postoperative nausea and vomiting: focus on palonosetron. Therapeutics and Clinical Risk Management 2009;5:21-34
6. Camilo Rojas, Mariago Stathis, Ajit G.Thomas. Palonosetron Exhibits Unique Molecular Interactions with the 5HT3 Receptor. Anaesthesia Analgesia 2008;107:469-78
7. Alain Borgeat, Georgios Ekatodramis, Carlo A.Schenker. Postoperative Nausea and Vomiting in Regional Anaesthesia, A Review. Anesthesiology 2003;98:530-47
8. C C Apfel, P Kranke, L H J Eberhart, A Roos. Comparison of predictive models for postoperative nausea and vomiting. British Journal of Anaesthesia 2002;88(2):234-40
9. Tong J. Gan. Risk Factors for Postoperative Nausea and Vomiting. Anaesthesia Analgesia 2006;102:1884-98

10. Michaela Stadler, Francois Bardiau, Laurence Seidel. Difference in Risk Factors for Postoperative Nausea and Vomiting. Anesthesiology 2003;98:46-52
11. Keith A. Candiotti, Anthony L. Kovac, Timothy I. Melson. A randomized, Double Blind Study to Evaluate the Efficacy and Safety of Three Different Doses of Palonosetron Versus Placebo for Preventing Postoperative Nausea and Vomiting. Anaesthesia Analgesia 2008;107:445-51
13. Anthony L kovac, Leopold Eberhart, Christian Apfel. A Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Three Different Doses of Palonosetron Versus Placebo in Preventing Postoperative Nausea and Vomiting Over a 72-Hour period. Anaesthesia Analgesia 2008;107:439-44.
14. S I Kim,S C Kim,Y H Baek,S Y Ok. Comparison of ramosetron with ondansetron for prevention of postoperative nausea and vomiting in patients undergoing gynaecological surgery. British Journal of Anaesthesia 2009;103(4):549-53.
15. Aapro MS, Macciocchi A, Gridelli C. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting in elderly patients. J Support Oncol 2005;3(5):369-74.
16. Aapro MS, Grunberg SM, Manikhas GM, Olivares G et al. A phase 3,double blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy .Ann Oncol 2006;17(9):1441-49.
17. Shaloo ipe, Sara Korula, Sreelatha Varma et al. A comparative study of intra-thecal and epidural buprenorphine using combined spinal-epidural technique for caesarean section. Indian Journal of Anaesthesia 2010;54(3):205-09.
18. Sunil Dixit. Post Operative Analgesia after Caesarean section: An experience with Intra-thecal Buprenorphine. Indian Journal of Anaesthesia 2007;51(6):515-18.
19. Dhurjoti Prosad Bhattacharjee, Satrajit Dawn, Sushil Nayak et al. A comparative study between Palonosetron and Granisetron to prevent Postoperative Nausea and Vomiting after Laparoscopic Cholecystectomy. J Anaesth Clin Pharmacol 2010;26(4):480-83.
20. Sukhminderjit Singh Bajwa, Sukhwinder Kaur Bajwa, Jasbir Kaur et al. Palonosetron: a novel approach to control postoperative nausea and vomiting in day care surgery. Saudi J Anaesth 2011;5(1):19-24.

Author Information

Sushma. K.S, M.D
Asst Professor, Dept of Anaesthesiology, Karnataka Institute of Medical sciences

Safiya. I. Shaikh, M.D
Professor and Department Head, Dept of Anaesthesiology, Karnataka Institute of Medical sciences