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A COMPARATIVE STUDY OF PALONOSETRON AND PALONOSETRON WITH DEXAMETHASONE FOR PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING IN PATIENTS UNDERGOING CAESAREAN SECTION: A DOUBLE BLINDED, RANDOMIZED CONTROL STUDY.

Daili Khuo	PGT, Department of Anaesthesiology and Critical Care, Jawaharlal Nehru Institute of Medical Sciences (JNIMS), Imphal, Manipur.
S Thoibahenba Singh*	Associate Professor, Department Of Anaesthesiology And Critical Care, JNIMS *Corresponding Author
T R Kumaragurubaran	PGT, Department Of Anaesthesiology And Critical Care, JNIMS
Linthoingambi Samjetsabam	PGT, Department Of Anaesthesiology And Critical Care, JNIMS
Sonia Nahakpam	PGT, Department Of Anaesthesiology And Critical Care, JNIMS
Zarina Wahab	PGT, Department Of Anaesthesiology And Critical Care, JNIMS
Laishram Rani Devi	PGT, Department Of Anaesthesiology And Critical Care, JNIMS

ABSTRACT

BACKGROUND: Post-operative nausea and vomiting (PONV) is one of the most common complications and patients' complaints after surgery. Palonosetron, a newer generation of 5- HT antagonist has superior effects in prevention of PONV because of its unique action, longer duration of action and fewer side effects. Our study hypothesised that combination of dexamethasone with palonosetron would be more effective in prevention of PONV than palonosetron alone in pregnant patients undergoing caesarean section

AIM: To compare the effects of palonosetron versus palonosetron combined with dexamethasone in the prevention of PONV following caesarean section.

METHODS: 120 patients of ASA II posted for LSCS were enrolled in our study. The patients were grouped randomly into 60 each viz: Group Palonosetron (P) receiving 0.075mg palonosetron and Group palonosetron+dexamethasone (PD) receiving 0.075mg palonosetron and 8mg dexamethasone. The frequency of PONV, complete response, side effects were compared between the groups.

RESULTS: Patients experiencing episodes of PONV in Group P was found to be 15 (9%) as compared to 8 (4.8%) in Group PD. Complete response between group P and Group PD is 90% versus 96.3% respectively. Both these results when compared were not statistically significant. The occurrence of side effects were comparable between the two groups.

CONCLUSION: There was no significant difference between palonosetron and combination of palonosetron and dexamethasone in prevention of PONV.

INTRODUCTION:

Post operative nausea and vomiting (PONV) are two of the most common and unpleasant side effects following anaest hesia and surgery. Kapur described PONV as 'a big little problem'[1]. PONV is defined as nausea and/or vomiting occur ring within 24 hours of surgery.[2] It is one of the most common complications after surgery, and the most important peri-operative concern for patient.[3] The reported incidence of PONV in patients not receiving prophylaxis is about 20 to 30%. In patients with risk factors it can be as high as 80%.[4,5] Female gender, post puberty, non-smoking status, history of post-operative nausea and vomiting or motion sickness, increasing duration of surgery, use of volatile anaesthetics, nitrous oxide, intraoperative or postoperative use of opioids and types of surgeries like laparoscopy, strabismus surgery are some of the established risk factors.[6] Apfel et al[7] developed a simplified scoring system of risk factors to predict the incidence of PONV. These predictors were female gender, non-smoking status, history of PONV /motion sickness, and postoperative use of opioids. The predicted risk of PONV was 10%, 21%, 49%, 61% if one, two, three or four of these respectively were present. Pain, anxiety and dehydration may also increase the incidence of PONV.

Emetic symptoms during caesarean delivery can be due to anxiety, hypotension, and hypoperfusion of the CNS, surgical stimuli such as abrupt visceral movements, exteriorisation of the uterus, intra-abdominal manipulation or exploration and peritoneal traction during closure, concomitant opiate administration, increased intra-abdominal pressure and hormonal changes.[8]

PONV can complicate post-operative care in several ways: like aspiration of vomitus, electrolyte disturbances and dehydration, delay of nutrition, fluid intake, oral drug therapy, and wound dehiscence. It can delay recovery and cause prolonged hospital stay, unplanned admissions and increased health care costs.[9,10] Pain and the discomfort as a result of PONV can interfere in early mobilisation and prevent thrombo-embolic complications that are increased in pregnancy and also interfere in effective breastfeeding of the baby. A single episode of vomiting prolongs post-anaesthetic care unit stay by 25 minutes. It is also important to prevent PONV after discharge as it can affect patients' resumption of normal activities and readiness to return to work if PONV is prolonged.[11]

5-HT3 receptor antagonists ondansetron, granisetron, palono setron, are the most commonly used type of antiemetic, with ondansetron being the most prescribed type. Others are: Droperidol, a selective dopamine receptor antagonist, dexamethasone, a corticosteroid, transdermal scopolamine, a non-selective, muscarinic acetylcholine receptor antagonist and non pharmacological treatment modalities such as

acupuncture and electro-acupuncture have all been used to treat PONV.[12,13]

PONV has several aetiology and a single drug is not entirely effective in its management. Therefore, combination therapy of two drugs of different mechanism of action is frequently advocated. The administration of an antiemetic acting on one receptor type typically reduces the incidence of PONV by about 30%.[5] In a study conducted on pregnant women for caesarean section, one study concluded that combination of dexamethasone and ondansetron significantly reduced PONV than dexamethasone alone.[14] A similar study to ours was conducted on patients undergoing LSCS. It showed no significant difference in prevention of PONV between palonosetron versus palonosetron and dexamethasone combination.[15] The study, however, was done on patients receiving intrathecal morphine.

Taking into consideration the independent risk factors of PONV following surgery and anaesthesia associated with caesarean section under spinal anaesthesia, we intended to compare the effects of palonosetron monotherapy versus palonosetron and dexamethasone combination therapy in prevention of PONV under spinal anaesthesia with bupiv acaine alone.

MATERIALS AND METHODS:

After approval by the institutional ethical committee, we enrolled 120 patients undergoing caesarean section, aged 19-40 years of age, ASA II, and singleton pregnancy. Patients with other comorbid conditions, coagulopathy and those who took anti-emetic treatment 24 hours prior to surgery were excluded from our study. The study was a prospective, randomized and double-blinded study and conducted over 2 years from September 2017-september 2019. After obtaining informed consent and pre-anaesthetic check up, patients were fasted for 8 hours and premedicated with 300 mg ranitidine orally prior to surgery. Patients were randomly assigned to two groups: Group P and Group PD received drug palonosetron 0.075mg and palonosetron 0.075mg with dexamethasone 8 mg respectively. The drugs were prepared by another personnel not involved in study, in identical syringes with distilled water to make a total volume of 5ml and coded. Each patient was preloaded with 500 ml of RL before giving spinal anaesthesia. Baseline vitals were recorded. Study drugs were administered through the IV cannula. After positioning the patient in left lateral decubitus, under strict aseptic conditions, 25G Quincke spinal needle was introduced between L2-L3/L3-L4 interspace, and 10 mg of 0.5% Bupivacaine heavy was administered. Oxygen was administered though face mask and BP and Sp02 monitoring every 3 minutes. Inj. Mephentermine 3mg boluses was given if hypotension occurred. Rescue anti-emetic intraoperatively and postop eratively with Inj. metoclopramide 0.1mg/kg IV was given. After surgery, data was collected up to 24 hrs postoperatively. Patients were evaluated in the first 0-6 hrs, 6-12hrs and 12-24 hrs for PONV, side effects, and rescue emetics during this period of 24 hrs observation. Nausea was defined as the subjective unpleasant sensation associated with awareness of the urge to vomit. Vomiting was defined as the forceful expulsion of gastric contents from the mouth. A complete response was defined as no emesis and no rescue emetic required. The data collected was analysed using statistical package for Social Sciences (SPSS Inc. Chicago 2, USA) for window based version 20. Data were presented as mean ± standard deviation for continuous variables or number (percentage) for categorical variables. Data were analysed with independent t-test for continuous variables and chi-square test for categorical variables. P values <0.05 were considered statistically significant.

RESULTS:

Table 1: Demographic profiles and duration of surgery.

	Group P	Group PD	P value
Age (yrs) (Mean ± SD)	28.68 ± 5.61	28.61 ± 6.33	0.95
Weight (kgs)(mean ± SD)	64.15 ± 5.94	65.92 ± 6.8	0.13
BMI (kg/m2) (mean ± SD)	27.62 ± 3.05	27.86 ± 3.49	0.69
Duration of surgery (mins)(mean ± SD)	43.25 ± 6.13	44.16 ± 5.97	0.41

SD: standard deviation; BMI: body mass index.

The mean age, weight, and BMI between group P and group PD are 28.68 years and 28.61 years, 64.15kgs and 65.92 kgs, 27.62 kg/m^2 and 27.86 kg/m^2 respectively. There was no statistically significant difference of parameters between these groups with P values 0.95, 0.13 and 0.69 respectively.

Table 2: Comparison of risk factors between the two groups.

Risk factors	Group P	Group PD	P value
H/o PONV	9 (15)	5 (7)	0.25
H/o motion sickness	11(18.3)	11(18.3)	1.00
Non-smoking status	60 (100)	60 (100)	NA

Data are presented as: number of patients (%) h/o= history of. PONV= postoperative nausea and vomiting.

The number of patients having history of previous PONV and history of motion sickness were respectively 9 (15%) and 11(18.3) in palonosetron group and 5 (7%) and 11 (18.3) in palonosetron plus dexamethasone group. All the patients in both groups were non-smokers. There was no statistical difference of risk factors between the two groups.

Table 3: Comparison of Nausea and vomiting between two groups.

Time Intervals	Symptoms	Group Palonosetron	Group Palonosetron+ Dexamethasone	P value	Inference
0-6 hours	Nausea	4 (6.7)	3 (5)	0.69	Not significant
	Vomiting	6 (10)	2 (3.4)	0.15	Not significant
6-12 hours	Nausea	3 (5)	1 (1.7)	0.31	Not significant
	Vomiting	0	0		
12-24 hours	Nausea	2 (3.3)	2 (3.3)	0.98	Not significant
	Vomiting	0	0		

Data are expressed as: number of patients (%)

The frequency of nausea during 0-6 hours was almost compa rable in both the groups i.e. 4 patients (6.7%) in group palonosetron and 3 patients (5%) in group palonosetron+ dexamethasone combination group. In the same duration, 6 patients (10%) in Group P and 2 patients (3.4%) from group PD experienced vomiting. The difference was statistically not significant. (p value=0.15). Comparison of patients experiencing nausea during 6-12 hours duration between the two groups was also found to be statistically not significant (p value= 0.31). Total PONV episodes was found to occur more in 0-6 hours duration (15 patients, 65.21%) than 6-12 hours duration (4 patients with nausea) and 12-24 hours (4 pts with nausea). No patients experienced vomiting in both 6-12 hours duration and 12-24 hours duration in both the groups.

Table 4: Total number of PONV episodes both the groups

Groups	Total episodes of PONV	P value
Group P	15	0.104
Group PD	8	

PONV: postoperative nausea and vomiting.

The episodes of PONV in palonosetron group was found to be 15 (9%) as compared to 8 (4.8%) episodes of PONV in combined palonosetron and dexamethasone group. The difference between PONV episodes in these groups was not statistically significant.

Table 5: Anti-emetics and complete response

	Group P	Group PD
Anti-emetics	6 (10)	2 (3.3)
Complete response	54 (90)	58 (96.3)

Data are represented as: number of patients (%)

All patients who experienced vomiting required rescue anti-emetic. 6 patients (10%) required anti-emetic in Group P as compared to 2 patients (3.3%) in Group PD. 90% of patients P showed complete response to palonosetron and 96.3 % of group PD showed complete response to palonosetron and dexamethasone combined therapy.

Table 6: Adverse effects between the two groups

	Group P	Group PD
Headache	4 (7)	3 (5)
Dizziness	2 (3)	1 (2)
Others	0	0
Total	6 (10)	4 (7)
P value	0.509	

Data represented as: number of patients (%)

The incidences of adverse effects were comparable in both groups.

DISCUSSION:

Post operative nausea and vomiting is one of the most common complaints of patients after surgery, general or spinal anaesthesia. In a study of 220 patients, 49% patients rated PONV as the primary concern after surgery and general anaesthesia, pain as the concern was lesser (27%).[3] Multiple episodes of PONV, in addition to discomfort to the patient, can hamper the proper care of the baby and breastfeeding, delayed mobilisation and can cause apprehension and anxiety in subsequent pregnancy and surgery.

The pathophysiology behind nausea and vomiting is multifactorial in origin involving various afferents from GIT, CTZ, cerebral cortex, cerebellum and vestibular apparatus where several receptors and mediators are involved. This suggests the use of combination of drugs with different mechanisms in treatment of PONV. Combination therapy of 5HT3 receptor antagonists with dexamethasone has been frequently studied. In this prospective, double blinded study, we compared the antiemetic effects of palonosetron monotherapy (Group P) with palonosetron and dexamet hasone combination therapy (Group PD) in patients undergoing Caesarean section.

Palonosetron is a 2nd generation 5HT3 receptor antagonist. It has unique properties by exhibiting allosteric binding activity with a prolonged elimination half life of 40 hours. Candiotti KA et al,[16] demonstrated that palonosetron 0.075mg was more effective than 0.025 mg and 0.05mg in patients undergoing major gynaecological surgery and laparoscopic surgery. We also used palonosetron 0.075 mg for this study.

Jodan A et al[17] found dexamethasone to reduce the incidence of PONV as compared with placebo (P=0.015) in patients undergoing caesarean section. The effectiveness of dexamethasone as an anti-emetic was also seen in a number of studies[18,19] including a meta-analysis by Allen TK et al.[20]

The demographic profiles, duration in our study were comparable between the two groups. The frequency of risk factors were comparable in both groups. Other risk factors responsible for PONV might be due to the independent risk factors associated with pregnancy and caesarean section such as increased intra-abdominal pressure, decreased lower oesophageal tone, intraoperative spinal hypotension, hormonal changes, exteriorisation of uterus and use of uterotonic drugs. The absence of significant difference between the two groups with respect to demographic profile, duration of surgery and risk factors could imply that any difference in the frequency of PONV between the two groups can be attributed to the effects of the drugs used.

In our study, the episodes of PONV in group P was 15 (9%) and group PD was 8 (4.8%) with no significant difference between the two groups (p=0.104). This finding was similar to a recent study conducted by Swaro S et al[15] in parturients undergoing CS under spinal anaesthesia. The proportion of PONV in their study during the first 24 hours postoperative period was 8 (26.6%) in the Group P, 12 (40%) in Group D and 6 (20%) in Group PD. There was no significant difference in the 24 hour PONV between group P and PD (p value= 0.29). The percentage of total episodes of PONV was lesser in our study in both the groups throughout the 24 hours. This could be due to the use of intrathecal morphine in their study, while we used only bupivacaine heavy for spinal anaesthesia.

The overall incidence of PONV was more at 0-6 hours duration (65.21%). This finding was also similar in other studies where incidence of PONV was more during early postoperative period.[14,15] The incidence of adverse effects were comparable between the two groups.

Studies on combination of 5HT3 receptor antagonist and dexamethasone for prevention of PONV showed varying results. Ondansetron and dexamethasone combination therapy was found to be more effective in prevention of PONV than ondansetron monotherapy.[21] whereas others did not find a significant difference with the combination therapy.[50,51]

Similarly, studies between palonosetron and palonosetron and dexamethasone combination therapy did not show consistent results. Two studies found that combination therapy was found to be better in preventing PONV than palonosetron monotherapy.[22,23] Others did not find difference between palonosetron monotherapy and combination therapy with dexamethasone.[24-26] The inconsistency in these results could be attributed to the non-uniformity of risk factors of these studies such as: types of surgery, study populations and the use of intraoperative or postoperative opioids.

The findings of our study was similar with that of other studies[15,24-26] in that there were no statistically significant difference present between palonosetron versus palono setron and dexamethasone combination therapy in preve nting PONV. However, in all these studies, the frequency of PONV was lower in the combined therapy group, with the most PONV occurring in the early post-operative period. As these studies were conducted on patients undergoing laparoscopic surgeries or intrathecal morphine were used, this might explain partially the reason for lower incidence of total PONV episodes in our study as compared to these studies. Dahl JB et al[27] reported that the incidence of PONV is increased by 22% in patients receiving intrathecal morphine. The use of intrathecal or intravenous opioids might decrease pain scores postoperatively but at the expense of increased incidence of PONV and pruritis.

Our study showed that combination of dexamethasone with palonosetron did not offer a significant advantage over palonosetron monotherapy in preventing PONV following caesarean section. However, combination therapy reduced the frequency of PONV episodes during both early and late

post-operative period.

There were few limitations to our study. First, we did not include a placebo group because we believe it to be unethical to include as we evaluated patients belonging to moderate to high risk category for PONV. Second, the intra-operative vitals of the patients were not included in the comparison. However, all the patients were preloaded with the same volume of IV fluids, left uterine displacement was done just after spinal anaesthesia was given, and made sure that hypotension, whenever present, was promptly corrected with fluids and injection mephentermine 3mg boluses before shifting the patient from OR to PACU to ward. Third, we did not evaluate PONV after 24 hours as the incidence of PONV after this period was minimal.

CONCLUSION:

In our study, the combination of palonosetron and dexame thasone did not show any statistically significant decrease in the incidence of PONV as compared to palonosetron monotherapy in patients undergoing elective caesarean section under spinal anaesthesia.

The total number of episodes of PONV was also lower in our study as compared to other similar studies on parturients undergoing caesarean section. This might be due to the use of intrathecal morphine in those studies, while we used only bupivacaine heavy for spinal anaesthesia and other non-opioid analgesics in the post-operative period..

The incidence of PONV was however, lower in combination therapy even though it was not statistically significant. Therefore, a study of wider variants of subjects where intrathecal and parenteral opioids are to be used liberally could be done to further evaluate the efficacy of this combination therapy over monotherapy.

REFERENCES:

1. Kapur PA. The big little problem. AnaesthAnalg 1991; 73:243-45.
2. McCracken G, Houston P, Lefebvre G Society of Obstetricians and Gynecologists of Canada. Guideline for the management of postoperative nausea and vomiting. J Obstet Gynaecol Can 2008;30:600–07.
3. Eberhart L, Morin AM, Wulf H, Geldner G. Patient preferences for immediate postoperative recovery. Br J Anaesth 2002;89:760–61.
4. Bayter M, Peña P, Marquez M, Cárdenas-Camarena L, Macias A, Rubio J, et al. Incidence of postoperative nausea and vomiting when total intravenous anaesthesia is the primary anaesthetic in the ambulatory patient population. Ambul Surg 2018;24:8-11.
5. Gan TJ. Postoperative nausea and vomiting-can it be eliminated? JAMA. 2002; 287: 1233-6.
6. Gan TJ. Risk factors for postoperative nausea and vomiting. Anesth Analg. 2006 Jun;102(6):1884-98.
7. Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: Conclusions from cross-validations between two centers. Anesthesiology 1999;91:693-700.
8. Balki M, Carvalho JC. Intraoperative nausea and vomiting during cesarean section under regional anesthesia. Int J Obstet Anesth 2005 Jul;14(3):230-41.
9. Whatcha MF, White PF. Postoperative nausea and vomiting: its etiology, treatment and prevention [review]. Anaesthesiology 1992;77:162-84.
10. Gold BS, Kitz DS, Lecky JH, Neuhaus JM Unanticipated admission to the hospital following ambulatory surgery. Journal of the American Medical Association 1989;262:3008-10.
11. Carroll NV, MiederhoffP, Cox FM, Hirsch JD. Post operative nausea and vomiting after discharge from outpatient surgery centers. Anesth Analg 1995; 80:903-9.
12. Horn CC, Wallisch WJ, Homanics GE, Williams JP. Pathophysiological and neurochemical mechanisms of postoperative nausea and vomiting. Eur J Pharmacol 2014;722(1):55–66.
13. Stoicea N, Gan TJ, Joseph N, Uribe A, Pandya J, Dalal R, Bergese SD. Alternative Therapies for the Prevention of Postoperative Nausea and Vomiting. Front Med (Lausanne). 2015;2:87.
14. Imeh A, Olaniyi O, Simeon O, and Omotola O. Dexamethasone versus a combination of dexamethasone and ondansetron as prophylactic antiemetic in patients receiving intrathecal morphine for caesarean section. Afr Health Sci. 2014 Jun; 14(2): 453–9.
15. Swaro S, Karan D, Banerjee A. Comparison of palonosetron, dexamethasone, and palonosetron plus dexamethasone as prophylactic antiemetic and antipruritic drug in patients receiving intrathecal morphine for lower segment caesarean section. Anesth Essays Res 2018;12:322-7.
16. Candiotti KA, Kovac AL, Melson TI, Clerici G, Joo Gan T. 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. Anesth Analg 2008 Aug;107(2):445-51.
17. Jadon A, Sinha N, Agrawal A, Jain P. Effect of intravenous dexamethasone on postoperative nausea-vomiting (PONV) after intrathecal morphine during caesarean Section. SOJ Anesthesiol Pain Manag 2016;3(1):1-5.
18. Bisgaard T, Klarskov B, Kehlet H, Rosenberg J. Preoperative dexamethasone improves surgical outcome after laparoscopic cholecystectomy-a rand omized double blind placebo controlled trial. Ann Surg 2003;238:651–60.
19. Backes JR, Jared C. Bentley JC, Joel R. Politi JR, Bryan T. Chambers BT. Dexamethasone Reduces Length of Hospitalization and Improves Postoperative Pain and Nausea After Total Joint Arthroplasty A Prospective, Randomized Controlled Trial Jeffrey R. J Arthroplasty 2013 Sep; 28(8):11-7
20. Allen TK, Jones CA, Habib AS. Dexamethasone for the prophylaxis of postoperative nausea and vomiting associated with neuraxial morphine administration: a systematic review and meta-analysis. Anesth Analg 2012 Apr;114(4):813-22.
21. Song JW, Park EY, Lee JG, Park YS, Kang BC, Shim YH. The effect of combining dexamethasone with ondansetron for nausea and vomiting associated with fentanyl-based intravenous patient-controlled analgesia. Anaesthesia 2011 Apr; 66(4): 263-7
22. Demirhan A, Tekelioglu YU, Akkaya A, Ozlu T, Yildiz I, Bayir H, et al. Antiemetic effects of dexamethasone and ondansetron combination during cesarean sections under spinal anaesthesia. Afr Health Sci 2013;13:475-82.
23. Szarvas S, Chellapuri RS, Harmon DC, Owens J, Murphy D, Shorten GD. A comparison of dexamethasone, ondansetron, and dexamethasone plus ondansetron as prophylactic antiemetic and antipruritic therapy in patients receiving intrathecal morphine for major orthopedic surgery. Anesth Analg 2003;97:259–63.
24. Ghosh S, Pal A, Acharya A, Biswas C, Ghosh TR and Ghosh S. Palonosetron and palonosetron plus dexamethasone to prevent postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: A prospective, randomized, double-blind comparative study. Anesth Essays Res 2011 Jul-Dec; 5(2): 134–7.
25. Park JW, Jun JW, Lim YH, Lee SS, Yoo BH, Kim KM, Yon JH, and Hong KH. The comparative study to evaluate the effect of palonosetron monotherapy versus palonosetron with dexamethasone combination therapy for prevention of postoperative nausea and vomiting. Korean J Anesthesiol. 2012 Oct; 63(4):334-9.
26. Srivastava A, Raghavendra K P, Parate LH. A comparative study of palon osetron versus palonosetron and dexamethasone for the prevention of postoperative nausea and vomiting in subjects undergoing laparoscopic surgeries: A randomized double-blind control study. Karnataka Anaesth J 2016;2:19-24
27. Dahl JB, Jeppesen IS, Jørgensen H, Wetterslev J, Møiniche S. Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia: A qualitative and quantitative systematic review of randomized controlled trials. Anesthesiology 1999;91:1919-27.