Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(1), 1822-1830 | ISSN:2251-6727

# Outcome of Pre-Emptive Intravenous Antiemetics Palonosetron Versus Combined Ondansetron and Dexamethasone in Caesarean Sections Performed Under Spinal Anaesthesia – A Prospective, Randomized, Comparative Study

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**(Received: 27 November 2023 Revised: 30 November 2023 Accepted: 03 December 2023)**

**KEYWORDS**
Spinal Anaesthesia, Caesarean Sections, Dexamethasone, Ondansetron, intra operative and vomiting and nausea after surgery.

**ABSTRACT**

**Introduction:** Patient pleasure is an important outcome of hospital treatment after anesthesia. PONV is a typical intraoperative side effect that can result in patient discontent and delayed discharge from the surgical institution.

**Aims:** A prospective, double-blind, randomized study to compare the preventive effects and synergistic efficacy of intravenous injection antiemetics that combined ondansetron, dexamethasone, and palonosetron to prevent nausea and vomiting during and after surgery in patients undergoing spinal anesthesia for a cesarean section.

**Materials and methods:** This study was a prospective, randomized, double-blind, comparative study. It was conducted from of 18 months, from February 2021 to July 2022, in the wards of Midnapore Medical College and Hospital, the post-anesthetic care unit (PACU), and the gynecology operation room complex. Total 100 patients were involved in this study.

**Result:** According to this study, during the intraoperative phase, 11 patients (22%) in Group OD and 4 patients (8%), in Group P, received rescue antiemetic. When rescue antiemetic was used intraoperatively, Group OD's value was significantly greater than Group P's (p Value = 0.049950).

**Conclusion:** Based on the findings and analyses of the current investigation, it may be deduced that, administration of pre-emptive intravenous 0.075mg palonosetron reduces the incidence of nausea and vomiting during surgery and consumption of antiemetics in female patients having an elective cesarean surgery under spinal anaesthesia compared to pre-emptive use of combination of 6mg ondansetron and 8mg dexamethasone.

## INTRODUCTION

Patient satisfaction after anesthesia is a critical result of hospital treatment. Post-operative nausea and vomiting (PONV) is a common intra-operative side effect that causes patient dissatisfaction and delays in release from the surgical facility. This issue is

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linked to age, gender, drugs, hemodynamic changes, and anesthetic procedures. Although the frequency of PONV in spinal anesthesia is lower (19%-22%) than in general anaesthesia (76%),[1] individuals may feel discomfort as a result, and support is required.

Vomiting and nausea after surgery is defined as nausea and/or vomiting occurring within a day of surgery. Seven neurotransmitters and three neurons stimulate the vomiting center, complicating therapy and prevention. Antiemetic premedication can reduce the frequency of nausea and vomiting after surgery. Many pharmacological therapies, procedures, and approaches have been developed over the years, however their efficacy is occasionally hampered by side effects. [2]

PONV has been found to be more common with particular operations, such as laparoscopic cholecystectomies and gynaecological surgeries. It is the most common and distressing adverse effect of spinal anesthesia (SA) during cesarean deliveries.[3] When antiemetic medication is not used as a preventive intervention, Caesarean sections conducted under regional anesthesia are associated with an increased risk of nausea and vomiting (50%-80%) during and after operation. PONV can cause gastrointestinal poisoning, as well as pneumothorax, oesophageal rupture, subcutaneous emphysema, and suture dehiscence. PONV affects 30-40% of the general population, but it reaches 75-80% in specific high-risk groups. Because to the use of less emetogenic anesthetic methods and the advent of innovative drugs for the prevention of PONV, the incidence of PONV has fallen by 50%. This decrease is particularly noticeable when non-opioid medication is used for pain treatment. Despite the efforts being made to reduce PONV, between 20% and 30% of cases occur on the first day. After surgery, effective PONV prevention and care are very important.Many factors, including those pertaining to the patient, the surgery, and anesthesia, can affect 10 PONV. Risk factors for surgery, anesthesia, and features of the patient have been determined. Risk factors for the patient include her gender, her non-smoking status, and her history of motion sickness or PONV. Using volatile anesthetics during surgery and using opioids both during and after surgery are risk factors linked to anesthesia [4] and use of nitrous oxide. Considerations about surgical risk may include the type and duration of the surgery.

To prevent PONV, a number of antiemetics from various pharmacological families are utilized, either singly or in combination, including antihistamines, [5] phenothiazine derivatives, anticholinergic, dopamine receptor antagonist20 and 5-HT3 antagonists.

Because 5-hydroxytryptamine receptor antagonists (5-HT3) are so effective at preventing PONV with few side effects, they are now considered first-line treatments because they do not have the extrapyramidal, dysphoric, or sedative side effects that other drugs have. When compared to other antiemetics, ondansetron is considered the "gold standard" of therapy. Because of its cheaper cost, it is the first 5-HT3 receptor antagonist and can be administered either alone or in combination for prophylaxis. [6] Its effectiveness as an antiemetic is well known. Its half-life, which is three to five hours, is rather brief. [6]

## MATERIALS AND METHODS

**Study Design:** prospective, double-blinded, randomized trial conducted in a hospital.

**Study Setting:** Institution based study done in Gynaecology Operation Room Complex, Post Anaesthetic Care Unit (PACU) and wards of Midnapore Medical College and Hospital

**Study Duration:** 18 Months (February 2021 to July 2022)

**Place of study:** Midnapore Medical College and Hospital, Paschim Midnapore, West Bengal.

**Study Population:** All ASA II patients who underwent caesarean section under spinal anaesthesia and fulfilled the inclusion criteria.

**Sample Design:** 100 patients were selected randomly in two groups, Group OD and Group P (50 each) by allotting a number in a sealed envelope from a computer-generated random number table only after getting the following-

1. Institutional ethics committee approval.
2. Written informed consent after having patient fully explained about the study procedure.

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According to the group patients received following injection before spinal anaesthesia. Group P: Palonosetron 0.075mg

Group OD: Ondansetron 6mg + Dexamethasone 8mg

**Inclusion Criteria:**

**1.** ASA grade II.

**2.** Age group of 18-40 years

**3.** Body Mass Index between 18.5 and 30.

**4.** Elective caesarean section under spinal anaesthesia

**Exclusion Criteria:**

**1.** Patients with severe cardio-respiratory disease

**2.** Patients with hepatic & renal disease

**3.** Patients with neurologic disorder

**4.** Patients with endocrine disorder

**5.** Subarachnoid block failure

**6.** Conversion to general anaesthesia

**7.** Patients with psychiatric problem

**8.** Any contraindication for spinal anaesthesia

**9.** Drug allergy to study drugs

**Outcome, Definition and Parameters:** PONV grading was done as per following scale measured in intra-operative and post-operative period up to 24 hours-

PONV score: 0 = no nausea and vomiting (complete responders) PONV score: 1 = nausea only

PONV score: 2 = vomiting once

PONV score: 3 = vomiting more than once

## RESULT

Duration of surgery between Group OD (65.26 ±14.51) and Group P (65.36 ±13.97). P-Value was 0.9721, which is statistically comparable.

Females, nonsmokers, postoperative opioid usage, and one of a history of motion sickness or PONV is one of the risk factors for PONV. Comparison of these risk factors were done between Group OD and Group P by using Apfel Score. P-Value calculated was 0.745912038, which was statistically comparable.

In Group OD 11 patients (22%) and in Group P 4 patients (8%) had nausea in intra operative period. Intra operative nausea was discovered to be considerably high in Group OD than in Group P (p Value = 0.04995). In Group OD 16 patients (32%) and in Group P 6 patients (12%) had nausea in post-operative period. Group OD experienced considerably more post-operative nausea than Group P (p Value = 0.0158).

In Group OD 10 patients (20%) and in Group P 3 patients (6%) had vomiting in intra operative period. Intra operative vomiting was found to be significantly high in Group OD than in Group P (p Value =0.0373924). In Group OD 13 patients (26%) and in Group P 4 patients (8%) had vomiting in post-operative period. Post-operative vomiting was found to be significantly high in Group OD than in Group P (p Value = 0.0166).

The anti-emetic rescue was used in 11 patients (22%) in Group OD and in 4 patients (8%) in Group P in intra operative period. Intra operative use of rescue anti emetic was found to be significantly high in Group OD than in Group P (p Value = 0.0291). Rescue anti emetic was used in 13 patients (26%) in Group OD and in 4 patients (8%) in Group P in post-operative period. Post-operative use of rescue anti emetic revealed that Group OD had a considerably higher value than Group P (p Value = 0.016577).

PONV score was compared between two groups. PONV score 0 was given for complete responders (no nausea or vomiting in post-operative period). PONV score 1 was given to patients who had only nausea, PONV score 2 was given to patients who had vomiting only once and PONV score 3 was given to patients who had vomiting more than once during post-operative period. Complete responders having PONV score 0, were more in Group P than in Group OD. Number of patients with PONV score 1 and 2 was less in Group P than in Group OD. No patient of Group P compared to 6 patients of Group OD had PONV score 3, i.e., vomiting more than once. P Value (0.0402) calculated by chi square test was significant.

During the intraoperative and postoperative periods, Group OD experienced a much greater frequency of nausea than in Group P (p values < 0.05). Incidence of vomiting was significantly high in Group OD than in Group P during intra operative and post-operative period (p values <0.05). Use of rescue anti emetic was significantly high in Group OD than in Group P during intra operative and post-operative period (p values <0.05). Incidence of headache was compared between Group OD and Group P during intra

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operative and post-operative period. P values were >0.05, statistically comparable. Incidence of dizziness was compared between Group OD and Group P during intraoperative and post-operative period. P values were >0.05, comparable.

**Table 1: Comparison of Duration of Surgery and Apfel Score**

| | Group OD | | Group P | | P-VALUE |
|---|---|---|---|---|---|
| | MEAN | SD | MEAN | SD | |
| DURATION OF SURGERY | 65.26 | 14.51 | 65.36 | 13.97 | 0.9721 |
| Apfel Score | 2.24 | 0.66 | 2.20 | 0.57 | 0.74591 |

**Table 2: Comparison of Intra-operative Nausea and Post-operative Nausea**

| | | No Nausea | Nausea | Total | Incidence of Nausea | P-value |
|---|---|---|---|---|---|---|
| Intra-operative Nausea | Group OD | 339 | 11 | 50 | 22% | 0.0499 |
| | Group P | 46 | 4 | 50 | 8% | |
| | Total | 85 | 15 | 100 | | |
| Post-operative Nausea | Group OD | 34 | 16 | 50 | 32% | 0.0157 |
| | Group P | 44 | 6 | 50 | 12% | |
| | Total | 78 | 22 | 100 | | |

**Table 3: Comparison of Intra-operative Vomiting and Post-operative Vomiting**

| | | No Vomiting | Vomiting | Total | Incidence of Nausea | P-value |
|---|---|---|---|---|---|---|
| Intra-operative Vomiting | Group OD | 40 | 10 | 50 | 20% | 0.0373 |
| | Group P | 47 | 3 | 50 | 6% | |
| | Total | 87 | 13 | 100 | | |
| Post-operative Vomiting | Group OD | 37 | 13 | 50 | 26% | 0.0165 |
| | Group P | 46 | 4 | 50 | 8% | |

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|---|---|---|---|---|---|---|
| | **Total** | 83 | 17 | 100 | | |

**Table 4: Comparison of Intra-operative Rescue antiemetic use and Post-operative Rescue antiemetic use**

| | | **Rescue anti-emetic not-required** | **Rescue anti-emetic required** | **Total** | **Incidence of Nausea** | **P-value** |
|---|---|---|---|---|---|---|
| **Intra-operative Rescue antiemetic use** | **Group OD** | 39 | 11 | 50 | 22% | 0.0499 |
| | **Group P** | 46 | 4 | 50 | 8% | |
| | **Total** | 85 | 15 | 100 | | |
| **Post-operative Rescue antiemetic use** | **Group OD** | 37 | 13 | 50 | 26% | 0.0165 |
| | **Group P** | 46 | 4 | 50 | 8% | |
| | **Total** | 83 | 17 | 100 | | |

**Table 5: Comparison of Incidence of Nausea and Vomiting**

| | | **Group OD** | **Group P** | P-value |
|---|---|---|---|---|
| **Nausea** | Intra-operative | 22 | 8 | 0.0499 |
| | Post-operative | 32 | 12 | 0.0157 |
| **Vomiting** | Intra-operative | 20 | 6 | 0.0211 |
| | Post-operative | 26 | 8 | 0.0165 |
| **Rescue antiemetic use** | Intra-operative | 22 | 8 | 0.0499 |
| | Post-operative | 26 | 8 | 0.0165 |
| **Headache** | Intra-operative | 20 | 8 | 0.7268 |
| | Post-operative | 14 | 12 | 0.7152 |
| **Dizziness** | Intra-operative | 22 | 14 | 0.2978 |
| | Post-operative | 16 | 22 | 0.4444 |

**Table 6: Comparison of PONV Score**

| **PONV Score** | **Group OD** | **Group P** | **Total** |
|---|---|---|---|
| **0** | 34 | 44 | 78 |

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| | | | |
|---|---|---|---|
| **1** | 3 | 2 | 5 |
| **2** | 7 | 4 | 11 |
| **3** | 6 | 0 | 6 |

**DISCUSSION**

Since spinal anesthetic is so affordable and simple to apply, it is the most often utilized procedure for cesarean sections. Compared to general anesthesia, it lowers the death rate related to cesarean sections sixteen times. The dangers associated with general anesthesia, such as aspiration of stomach contents, trouble managing the airway, respiratory distress in infants, and mothers' awareness during the procedure, are avoided with spinal anesthesia.132 An additional benefit of this approach is that it preserves consciousness and offers a superb surgical field, prolonged pain relief, low incidence of thromboembolism, and an early recovery of gastrointestinal function. It also plays a significant part in lowering acute post-operative discomfort and enabling ambulatory anesthesia. Insufficient pain following surgery causes a patient's recuperation to be delayed, lengthening their hospital stay and, eventually, raising health care expenses and impeding mother-child bonding.

Spinal anesthetic has different affects on women who are pregnant and women who are not. The anesthetic drug's distribution into the cerebrospinal fluid is less predictable in pregnant women, which is linked to changes in the protein contents and acid-base balance of the cerebrospinal fluid as well as increased pressure on the spinal canal as a result of pregnancy-related physiological changes. Additionally, these parturient women who undergo spinal anesthesia for a caesarean section run the risk of experiencing emetic sensations during and after the procedure. This may be related to post-induction hypotension, which may activate the vomiting center and cause brainstem hypoxia.

There are numerous types of receptors and their mediators that have been linked to PONV, and the pathophysiology of PONV is intricate. (1) Type 3 serotonin (5HT 3 receptor), (2) type 2 dopamine receptor, (3) type 1 histamine receptor, (4) type 1 receptor muscarinic cholinergic, (5) hormone receptor and (6) receptor for NK1, or neurokinin type 1.

According to historical statistics, 60–80% of individuals who undergo a cesarean section and then receive neuraxial opioids without receiving antiemetic prophylaxis suffer PONV. Due to PONV's complex etiology and multiple receptor locations, no medication can fully prevent or treat the disease, notwithstanding the development of novel antiemetic drugs. Therefore, rather of employing a single antiemetic medication, combination therapy utilizing multiple antiemetics targeting diverse receptor sites is advised for individuals at high risk for PONV. Therefore, the latest consensus guidelines recommend using either a single, effective anti-emetic medication or a combination of two medications from separate categories to prevent PONV in high-risk individuals. So, In order to examine the effectiveness of palonosetron combination therapy (ondansetron with dexamethasone) and monotherapy in avoiding PONV in patients undergoing caesarean sections, we decided to conduct this randomized double-blind trial.

Since palonosetron by itself was found to be more successful in lowering the incidence of PONV than when combined with dexamethasone, we opted to employ palonosetron monotherapy in our investigation. The FDA has also approved a dose of 0.075 mg palonosetron, which was found to be beneficial in lowering PONV at the beginning of surgery based on prior trials. Palonosetron takes 30 minutes to start working, thus we chose to start the surgery with 0.075 mg of the medication before placing the subarachnoid block.

A dose of 6 mg of ondansetron, a first-generation 5HT3 antagonist was selected since it works just as well at treating and preventing post-operative nausea and vomiting as a larger dose. Furthermore, at this dosage, there won't be any negative effects. Pearman et al. suggested that for pregnant women who are more likely to have nausea and vomiting, the effects of 6 mg ondansetron may be more beneficial than 4 mg ondansetron. [7]

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JCHR (2024) 14(1), 1822-1830 | ISSN:2251-6727

It has been suggested that dexamethasone works well as an antiemetic following both general and pediatric surgery. Additionally, dexamethasone has been suggested to lessen the risk of PONV after neuraxial opioid. [8] The study **by Tzeng et al**. suggested that after a caesarean section, dexamethasone may reduce the nausea and vomiting brought on by the epidural morphine. [9] The 8 mg dexamethasone dosage was selected based on findings from another trial that shows giving 8 mg intravenously to individuals having a lower segment cesarean section while under spinal anesthetic lengthens the duration of sensory block. The incidence of PONV was significantly (51%) lower in the research involving 120 parturients who received 8 mg IV of dexamethasone as opposed to a placebo. Nonetheless, its antiemetic effect could be mediated, at least partially, by blocking the corticoreceptors in the brain's nucleus tractus solitarius. It might possibly work against vomiting by way of a supplementary pathway.

One benzamide derivative that works by opposing serotonin and dopamine 5-HT3 receptors is metoclopramide. a common antiemetic medication, metoclopramide 10 mg, is generally and safely administered at this dosage in people with PONV. Here 100 patients were selected randomly to be separated into Group P and Group OD. In each group, there were fifty patients. Group P was given intravenous palonosetron (0.075mg) and group OD was given intravenous ondansetron (6 mg) and dexamethasone (8mg) immediately before spinal anaesthesia. The demographic data (age and weight) were matched between the study groups and were found comparable. In the present study showed that in group OD 22% patients and in group P 8% patients needed intra-operative rescue antiemetic whereas use of post-operative rescue antiemetic is 26% in group OD and 8% in group P. From figure 18 it is clear that both the incidences of nausea following surgery and intraoperative vomiting are significantly high in group OD (22% and 20% respectively) than group in P (8% and 6% respectively). It is also clear from the results that the same pattern is seen in post-operative nausea and vomiting (PONV), with a considerably higher frequency in group OD than in group P. Granisetron, ondansetron, and palonosetron: a comparison in terms of preventing nausea and vomiting during surgery by **Singh et.al** also showed that incidences of PONV in 24 hrs are more in patients of ondansetron group than in palonosetron group for middle ear surgeries under general anaesthesia.**[10]** Another comparative study of palonosetron, dexamethasone, and palonosetron plus dexamethasone to prevent PONV **by Swaro et.al.** demonstrated the patients in Group D (40%) received dexamethasone 8 mg intravenously; this was substantially higher than patients in Group P (27%), who received 0.075 mg of palonosetron intravenously, and patients in Group PD (20%), who received Dexamethasone 4 mg with palonosetron 0.075 mg of intravenously. Additionally, they demonstrated that Group D (30%) required more rescue antiemetic than did Group P (6%) and Group PD (3%). **[11]**

Though all these studies are showing that incidence of PONV is significantly less when palonosetron is used as antiemetic than the other antiemetics such as, ondansetron, granisetron, dexamethasone but a study **by Kim et.al. [12]** Shows that Palonosetron and ondansetron had similar efficacy on preventing PONV in high-risk patients undergoing gynecological laparoscopic surgery and receiving opioid-based IV-PCA. Twelve while opioid-based patient-controlled analgesia was provided to these individuals, opioid-based analgesia was not used in our study.

In our study the overall incidence of post-operative nausea (PONV Score 1) in 24hrs was 6% in patients among group OD and 4% in patients of group P. The incidence is higher in group OD and the difference between two groups was statistically significant. The overall incidence of vomiting once (PONV Score 2) in a 24-hour period varied statistically significantly between the ondansetron and palonosetron groups, at 14% and 8%, respectively. In the ondansetron group, the total incidence of vomiting more than thrice in a 24-hour period (PONV Score 3) was 12%, while in the palonosetron group, it was 0%. This is in accordance with the studies **by Y.E. Moon et.al., [13] T. Singh et.al.[10] and N. Chakravarty and S.K. Raghuwanshi.[14]**

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So, it is demonstrated from our study that, an antiemetic prophylaxis with palonosetronan antagonist of 5-hydroxytryptamine subtype 3 (5-HT3) offered a clinically superior means of preventing postoperative nausea and vomiting. Their effectiveness and length of action differ statistically significantly from those of the combined therapy of ondansetron and dexamethasone.

**Studies by Tiwari et.al. [15]** and **Swaro et.al. [16]** concluded that palonosetron alone and in combination with dexamethasone both work well in treating postoperative nausea and vomiting; however, in this aspect, palonosetron alone is not superior to the combination of palonosetron and dexamethasone.

Compared to earlier antagonists, it has a greater affinity for the 5HT3 receptor and a longer plasma half-life (more than 12 hours), palonosetron, a second generation 5HT3 antagonist, prolongs the suppression of receptor function. The following features set palonosetron apart from first-generation antagonists:

- Palonosetron has a different chemical makeup. In contrast to earlier medications that had three substituted indole structures similar to serotonin, in this one, a quinuclidine moiety is linked to a fused tricyclic ring structure.
- When it binds to the 5HT3 receptor, it demonstrates allosteric binding and positive cooperativity, which causes receptor internalization and a sustained suppression of receptor activity.
- Palonosetron also suppresses substance P-induced reactions, which are the main cause of chemotherapy-induced delayed emesis, by selectively blocking 5HT3/NK1 receptor crosstalk.

Palonosetron's pharmacologic properties may lessen the need for combination therapy, which is often necessary for PONV prevention in high-risk patients.

**Kovac et al.** showed found, when compared to a placebo, palonosetron 0.075 mg significantly decreased PONV up to 72 hours following surgery. **[17]** In their dose-ranging investigation, they discovered that 0.075 mg of palonosetron was the optimal dosage. Furthermore, in high-risk women undergoing fentanyl-based intravenous PCA, in the first 48 hours after lap surgery, palonosetron 0.075 mg prevented PONV better than ondansetron 4 mg and ramosetron 0.3 mg.

Our investigation revealed that full responders, 130 were more in palonosetron group than in ondansetron and dexamethasone combination. While the incidence of PONV was decreased with palonosetron, the two groups' rates of headache and vertigo remained comparable of patients undergoing caesarean section and this is in accordance with the Comparative analysis of dexamethasone and palonosetron coupled and ramosetron **by Narayanappa et.al. [14]**

This clearly indicates that as prophylaxis palonosetron alone is better than dexamethasone and ondansetron combination to the under spinal anesthesia, manage nauseous vomiting during an elective cesarean surgery.

## CONCLUSION

Based on the findings and analyses of the current investigation, it may be deduced that, administration of pre-emptive intravenous 0.075mg palonosetron reduces the incidence of nausea and vomiting during surgery and consumption of antiemetics in female patients having an elective cesarean surgery under spinal anaesthesia compared to pre- emptive use of combination of 6mg ondansetron and 8mg dexamethasone.

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