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CLINICAL RESEARCH

Comparison of palonosetron-dexamethasone and ondansetron-dexamethasone for prevention of postoperative nausea and vomiting in middle ear surgery: a randomized clinical trial

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KEYWORDS
Dexamethasone;
Middle ear surgery;
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Postoperative nausea and vomiting

Abstract

Background: Postoperative nausea and vomiting is the second most common complaint in the postoperative period after pain. The incidence of postoperative nausea and vomiting was 60–80% in middle ear surgeries in the absence of antiemetic prophylaxis. Because of this high incidence of postoperative nausea and vomiting, we aimed to assess the effect of palonosetron-dexamethasone and ondansetron-dexamethasone combination for the prevention of postoperative nausea and vomiting in patients of middle ear surgery.

Methods: Sixty-four patients, scheduled for middle ear surgery, were randomized into two groups to receive the palonosetron-dexamethasone and ondansetron-dexamethasone combination intravenously before induction of anesthesia. Anesthesia technique was standardized in all patients. Postoperatively, the incidences and severity of nausea and vomiting, the requirement of rescue antiemetic, side effects and patient satisfaction score were recorded.

Results: Demographics were similar in the study groups. The incidence difference of nausea was statistically significant between groups O and P at a time interval of 2–6 hours only ($p = 0.026$). The incidence and severity of vomiting were not statistically significant between groups O and P during the whole study period. The overall incidence of postoperative nausea and vomiting (0–24 hours postoperatively) was 37.5% in group O and 9.4% in group P ($p = 0.016$). Absolute risk reduction with palonosetron–dexamethasone was 28%, the relative risk reduction was 75%, and the number-needed-to-treat was 4. The patient's satisfaction score was higher in group P than group O ($p = 0.016$). The frequency of rescue medication was more common in group O than in group P patients ($p = 0.026$).

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Conclusion: The combination of palonosetron-dexamethasone is superior to ondansetron-dexamethasone for the prevention of postoperative nausea and vomiting after middle ear surgeries.

PALAVRAS-CHAVE
Dextametasona;
Cirurgia do ouvido médio;
Palonosetrona;
Ondansetrona;
Náusea e vômito no pós-operatório

Comparação entre palonosetrona-dexametasona e ondansetrona-dexametasona na prevenção de náuseas e vômitos no pós-operatório de cirurgia do ouvido médio: estudo clínico randomizado

Resumo

Justificativa: Náusea e vômito no pós-operatório é a segunda queixa pós-operatória mais frequente após a dor. Sem profilaxia antiemética, a incidência de náusea e vômito no pós-operatório foi de 60–80% após cirurgia do ouvido médio. Dada a alta incidência relatada de náusea e vômito no pós-operatório, nosso objetivo foi avaliar o efeito da combinação de palonosetrona-dexametasona e ondansetrona-dexametasona na prevenção de náusea e vômito no pós-operatório em pacientes submetidos a cirurgia do ouvido médio.

Método: Sessenta e quatro pacientes programados para cirurgia de ouvido médio foram aleatoriamente divididos em dois grupos. Um recebeu a combinação de palonosetrona-dexametasona (grupo P) e o outro ondansetrona-dexametasona (grupo O) por via intravenosa antes da indução anestésica. A técnica anestésica foi padronizada em todos os pacientes. No pós-operatório, foram registradas incidência e gravidade das náuseas e vômitos, necessidade de antiemético de resgate, efeitos colaterais e índice de satisfação dos pacientes.

Resultados: As características demográficas foram semelhantes nos grupos estudados. A diferença na incidência de náusea foi estatisticamente significante entre os grupos O e P apenas no intervalo de tempo entre 2 e 6 horas ($p = 0,026$). A incidência e gravidade de vômito não foram estatisticamente significantes entre os grupos O e P durante todo o período do estudo. A incidência geral de náusea e vômito no pós-operatório (0–24 horas de pós-operatório) foi de 37,5% no grupo O e de 9,4% no grupo P ($p = 0,016$). A combinação palonosetrona-dexametasona associou-se com redução do risco absoluto de 28%, redução do risco relativo de 75%, e o número necessário para tratar foi 4. O escore de satisfação do paciente foi maior no grupo P ($p = 0,016$). A frequência da medicação de resgate foi mais comum no grupo O ($p = 0,026$).

Conclusão: A combinação de palonosetrona-dexametasona é superior à ondansetrona-dexametasona na prevenção da náusea e vômito no pós-operatório após cirurgia de ouvido médio.

Introduction

Post-Operative Nausea and Vomiting (PONV) is the second most common complaint in the post-operative period after pain. There are multiple factors responsible for the occurrence of PONV; these are a duration of surgery, the type of drugs used during anesthesia, the technique of anesthesia, age, sex and smoking habit.[1,2] Incidence of PONV was reported between 30–80% depending on the type of surgery and associated risk factors.[3,4] The incidence of PONV in middle ear surgeries ranges from 60% to 80%, in the absence of any antiemetic treatment.[5,6] High incidence of PONV significantly interferes with smooth emergence from anesthesia and markedly increases patient discomfort in the postoperative period.

Nowadays, 5-HT3 receptor antagonist is the first choice (laparoscopic, gynecologic, middle ear surgery etc.) because of its effectiveness, safety, and favorable side-effects profile as it lacks the sedative, dysphoric and extrapyramidal side effects of other drugs.[7,8] Ondansetron was the initial 5-HT3 receptor antagonist used clinically and its antiemetic efficacy is well established. It has a moderately short half-life of 3–5 hours.[9] Palonosetron has a special chemical structure; the interaction pattern with the 5-HT3 receptor is not quite the same as prior 5-HT3 receptor antagonists with extra allosteric site binding property.[10] Dexamethasone is an economical, long-acting antiemetic drug. It can enhance the effect of other antiemetics by different mechanisms like prostaglandin antagonism, the release of endorphins, and bradykinin reduction.[11]

According to the Consensus Guidelines for the Management of PONV, a combination of antiemetic medications is suggested as the most suitable regimen for patients with moderate to high risk of PONV.[12] Concerning the high incidence of PONV after middle ear surgery, and as there is no previous study to assess and compare the preventive effect of palonosetron-dexamethasone and ondansetron-dexamethasone combination on PONV, we aimed to compare the effect of palonosetron-dexamethasone and ondansetron-dexamethasone combination with PONV in patients of middle ear surgery.

Methods

After obtaining approval from the Institutional Ethical Committee and written informed consent from the patients, this prospective, double-blind, randomized study was conducted on 68 ASA I and II patients of either sex, age 20–60 years, undergoing middle ear surgery under general anesthesia. The study was enlisted at Clinical Trials.gov.www.ctri.nic.in (ref: CTRI/2017/03/007998). Patients with known sensitivity to the study drug, history of addiction or use of other antiemetic drugs, motion sickness, central and/or nervous system disorders, cardiovascular, history of psychiatric illness, pregnant and lactating women were excluded from the study.

The patients were randomly allotted with the assistance of a computer-generated randomized schedule using block randomization of variable block size was generated for two equal groups of 32 each.

Group O – Ondansetron 8 mg + dexamethasone 8 mg intravenously before induction of anesthesia.

Group P – Palonosetron 0.075 mg + dexamethasone 8 mg intravenously before induction of anesthesia.

An independent anesthesia registrar (SR), not involved in the study, prepared all study drugs based on randomization as per sealed opaque envelope. All the study drugs were taken in identical 5 mL syringes and diluted up to 5 mL with normal saline. The study drugs were administered slowly over 30 seconds just before the induction of anesthesia. Patients, anesthesiologists involved in intraoperative care, and investigator collecting data in the post-operative ward were unaware of the group allotment.

The anesthesia technique was standardized in all patients. In the operation room, monitoring was done with 5 lead electrocardiogram, pulse oximetry, noninvasive blood pressure, and capnography. All patients were premedicated with injected midazolam 0.03 mg.kg^{-1}. The induction of anesthesia was achieved with injected fentanyl 1.5 mcg.kg^{-1}, injected propofol 1.5–2.0 mg.kg^{-1} followed by injected vecuronium 0.1 mg.kg^{-1} body weight. Orotracheal intubation was completed with a cuffed endotracheal tube of appropriate size. Anesthesia was maintained with oxygen:nitrous oxide (O_2:N_2O; 40:60) which was substituted by air before closing the tympanic membrane, propofol infusion, and intermittent boluses of vecuronium and fentanyl as required. After surgery, neuromuscular blockade was reversed with neostigmine (40 mcg kg^{-1}) and glycopyrrolate (10 mcg kg^{-1}).

The primary outcome was the incidence and severity of nausea and vomiting experienced by each patient after surgery. This was recorded at the following three assessment periods: 0–2, 2–6, and 6–24 hours after surgery. Nausea was assessed using a visual analog scale (VAS: 0–10, 0 = no nausea and 10 = worst possible nausea). A score of more than 5 was considered severe, 5 was moderate and less than 5 was mild nausea. If the episodes of vomiting were more than two, it was considered as severe, two was moderate and less than two was mild. Rescue antiemetic, metoclopramide 10 mg intravenous (iv) was given for moderate and severe nausea or vomiting episodes.[13]

The secondary outcome was the requirement of rescue antiemetic and patient's satisfaction score. The requirement of rescue antiemetic during 0–2, 2–6 and 6–24 hours were recorded. The patient's satisfaction score was recorded after 24 hours of surgery by using 10 points verbal rating scale (VRS: 0 = not satisfied, 10 = fully satisfied). Any drug-related adverse effects like headache, dizziness, abdominal disturbances (constipation/diarrhea) and ECG changes were also recorded.

The sample size was estimated using a two-sided significance level. The reported incidence of PONV is 70% in middle ear surgery.[5,6] We assumed that the incidence of PONV would be reduced from 70% to 30% in groups O and P after drug treatment. For this reduction following therapy, one would need to include 25 patients in each group for the results to be significant (with $\alpha = 0.05$ and $\beta = 0.20$ [80% power]). We enrolled 32 patients in each group to account for 20% potential dropouts or protocol violations.

Statistical analysis was performed using the Graph pad prism 7.0 statistical software. Patient characteristics data were analyzed with the Student *t*-test for continuous variables and Chi-Square test for categorical variables. The incidence and severity of discomfort (mild, moderate, and severe) of postoperative nausea and vomiting between groups were analyzed by Fisher's exact test. Patient satisfaction score was analyzed by the Mann-Whitney test. A *p*-value of < 0.05 is considered statistically significant.

Results

A total of 68 patients were assessed for eligibility, out of which 64 patients were included in the study after randomization and all 64 patients completed the study. Four patients were excluded on account of the patient's refusal to participate (2) and a history of preoperative opioid consumption (2) (Fig. 1).

Demographics were similar in study groups (Table 1). The incidence of nausea was statistically significant between groups O and P at the time interval 2–6 hours only ($p = 0.026$). The severity of nausea was not statistically significant between the two groups during the whole study period (Table 2). The incidence of nausea was 34.4% in group O and 9.4% in group P 24 hours postoperatively ($p = 0.032$). The incidence and severity of vomiting were not statistically significant between groups O and P during the study period (Table 3). The incidence of vomiting was 18.8% in group O and 9.4% in group P 24 hours postoperatively ($p = 0.474$).

The overall incidence of PONV (0–24 hours postoperatively) was 37.5% in group O and 9.4% in group P ($p = 0.016$) (Table 4). The absolute risk reduction with palonosetron-

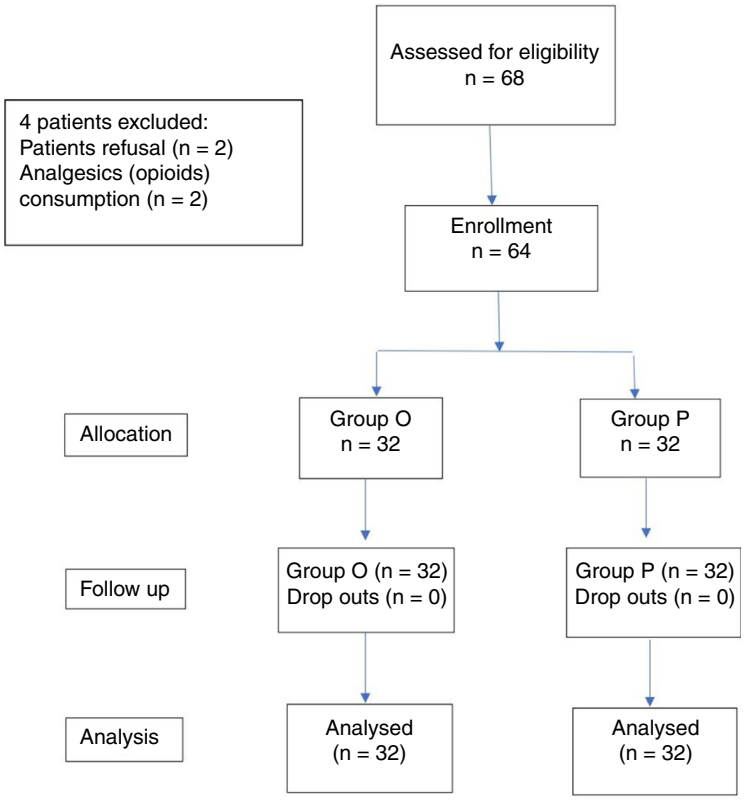

Figure 1 CONSORT flow diagram.

Table 1 Demographic data.

	Group O (n = 32)	Group P (n = 32)
Mean age (year)	37.41 ± 13.17	38.84 ± 12.26
Male/Female	18/14	15/17
Weight (kg)	53.97 ± 7.93	55.28 ± 8.44
Type of surgery		
Timpanopasty/Mastoidectomy	21/11	23/9
Duration of surgery (min)	74.53 ± 18.64	79.22 ± 19.18
Intraoperative Fentanyl	92.50 ± 12.44	94.84 ± 13.53

Data are presented as either mean values ± SD or by absolute numbers.

Table 2 Incidence and severity of nausea.

Time interval	**0–2 h**		**2–6 h**		**6–24 h**	
Groups	O	P	O	P	O	P
n	32	32	32	32	32	32
Nausea						
No	28 (87.5)	30 (93.8)	24 (75)	31 (96.9)	30 (93.8)	31 (96.9)
Yes	4 (12.5)	2 (6.2)	8 (25)	1 (3.1)	2 (6.2)	1 (3.1)
p-value (Incidence)	0.672		0.026*		1.0	
Relative risk (95% CI)	1.38 (0.74–2.6)		2.03 (1.39–2.98)		1.36 (0.58–3.14)	
Mild (VAS < 5)	1 (25)	1 (50)	4 (50)	1 (100)	1 (50)	1 (100)
Moderate (VAS = 5)	2 (50)	1 (50)	2 (25)	0	1 (50)	0
Severe (VAS > 5)	1 (25)	0	2 (25)	0	0	0
p-value (Severity)	0.392		0.638		1.0	

Data are presented as absolute frequency (percentage).

Table 3 Incidence and severity of vomiting.

Time interval	0–2 h		2–6 h		6–24 h	
Groups	O	P	O	P	O	P
n	32	32	32	32	32	32
Vomiting						
No	29 (90.7)	30 (93.8)	28 (87.5)	30 (93.8)	31 (96.9)	32 (100)
Yes	3 (9.3)	2 (6.2)	4 (12.5)	2 (6.2)	1 (3.1)	0
p-value (Incidence)	1.0		0.672		1.0	
Relative risk (95% CI)	1.22 (0.57–2.61)		1.38 (0.74–2.58)		2.03 (1.58–2.61)	
Mild (episode <2)	2 (66.7)	2 (100)	2 (50)	2 (100)	1 (100)	0
Moderate (episode = 2)	1 (33.3)	0	2 (50)	0	0	0
Severe (episode >2)	0	0	0	0	0	0
p-value (Severity)	1.0		1.0		1.0	

Table 4 Incidence of postoperative nausea and vomiting 0–24 h.

	Group O	Group P	*p*-value	Relative risk (95% CI)
Nausea incidence				
No	21 (65.6)	29 (90.6)	0.032*	1.87 (1.22–2.86)
Yes	11 (34.4)	3 (9.4)		
Vomiting incidence				
No	26 (81.2)	29 (90.6)	0.474	1.41 (0.83–2.42)
Yes	6 (18.8)	3 (9.4)		
PONV incidence				
No	20 (62.5)	29 (90.6)	0.016*	1.96 (1.29–2.99)
Yes	12 (37.5)	3 (9.4)		

Data are presented as absolute frequency (percentage).

Table 5 Satisfaction score and rescue antiemetics.

	Group O	Group P	*p*-value
Satisfaction score	84.06 ± 10.43	90.31 ± 8.61	0.016*
Rescue antiemetics	8 (25)	1 (3)	0.026*

Data are presented as either mean values ± SD or by absolute numbers (percentage).

dexamethasone was 28%, the relative risk reduction was 75%, and the number-needed-to-treat was 4.

The patient's satisfaction score was higher in group P than in group O ($p = 0.016$). The frequency of rescue medication (metoclopramide) was more in patients from group O than in the ones from group P with *p*-value of 0.026 (Table 5). There is no significant difference regarding the incidence of adverse effects between the groups.

Discussion

Postoperative Nausea and Vomiting (PONV) is a troublesome experience after general anesthesia and surgery, with an incidence ranging between 20–80% among different surgeries. Middle ear surgery (tympanoplasty or mastoidectomy) is associated with a higher incidence of PONV (60–80%)[5,6] warranting the use of prophylactic anti-emetics. The etiology of PONV after middle ear surgery is multifactorial in origin and depends on age, sex, history of motion sickness and/or previous PONV, duration of surgery, type of drugs and technique used for anesthesia and postoperative pain. In the middle ear surgery, due to stimulation of the labyrinth, PONV usually persists for up to 24 hours after anesthesia.

Patients with a high risk of PONV needs a combination of antiemetic drugs, with a different mechanism of action to provide better prophylaxis and less side effects of each drug. In our study, we used 5-HT3 receptor antagonists (ondansetron or palonosetron) and dexamethasone combination because various authors confirm the effectiveness of this combination is superior to other combinations or monotherapy in a different type of surgery. Desai et al.[14] confirmed the superiority of dexamethasone and ondansetron combination than ramosetron alone for the prevention of PONV after middle ear surgeries. A combination of granisetron and dexamethasone was more efficient than each drug alone for the prevention of PONV after middle ear surgery as observed by Fujii et al.[15] Chatterjee and colleagues also reported the same results in investigations of the influence of palonosetron and dexamethasone on PONV. They found the lower incidence of PONV in combination therapy than using each drug individually. The incidence declined from 56% to 23% by the use of this combination.[16] This suggests that dexametha-

sone may be used as a component of combined prophylaxis in addition to 5-HT3 receptor antagonist for the control of PONV in high-risk patients.

In our study, we used ondansetron 8 mg or palonosetron 0.075 mg with a combination of dexamethasone 8 mg because various authors suggested that these are the most effective doses of a drug. Kovac et al.[17] also suggested that palonosetron in a dose of 0.075 mg was the most effective dose for the prevention of PONV after comparing three different doses of palonosetron. Sekhavat et al.[18] confirmed that prophylactic 8 mg dexamethasone is effectively reducing PONV. Single-dose ondansetron 8 mg was found to be efficient in reducing PONV compared to 4 mg in patients undergoing laparoscopic cholecystectomy.[19] The timing of prophylactic antiemetic administration is also important. Dexamethasone is found to be more effective when given at the induction of anesthesia,[20] so we have given these combinations before induction of anesthesia. Our results confirm that the palonosetron-dexamethasone combination is superior to ondansetron-dexamethasone combination for preventing PONV in middle ear surgery. This is because of the long duration of action and 30 times higher binding affinity for the 5-HT3 receptor subtype of palonosetron comparison to ondansetron. Furthermore, palonosetron also exhibits antinauseatic property which is in contrast to other 5-HT3 blockers.

Sharma S et al.[21] compared palonosetron (1 mcg.kg^{-1}) with ondansetron (0.1 mg.kg^{-1}) for the prevention of PONV in middle ear surgery and observed that the incidence of PONV was 66% in ondansetron group and 30% in palonosetron group in the first 24 hours. In our study, the incidence of PONV was 37.5% in the ondansetron-dexamethasone group and 9.4% in the palonosetron-dexamethasone group. The decrease incidence of PONV in our study may be caused by of the addition of dexamethasone to both groups and avoidance of sevoflurane during maintenance of anesthesia. Dexamethasone aggravates the effect of other antiemetics by various mechanisms like prostaglandin antagonism, release of endorphins and bradykinin reduction. Apfel et al.[22] also revealed that the utilization of inhalational anesthetics with nitrous oxide should be considered as a leading cause of early PONV.

In our study, we selected metoclopramide as a rescue antiemetic in patients who complained of PONV, as its mechanism of action is different from the study drugs. The requirement of rescue antiemetic was higher in group O (25%) than in group P (3%). The patient's satisfaction was higher in group P than in group O because of palonosetron drug control PONV up to 24 hours. Both palonosetron and ondansetron are known to have non-serious adverse effects like headache, constipation, dizziness, and prolongation of QTc interval.

In our study, we compared the most effective doses of palonosetron and ondansetron, without information of equipotent dosages of these medications, so some level of abstract mistake is inescapable in the evaluation of PONV. The postoperative analgesia and antibiotic were kept indistinguishable in all cases, yet they were not actually indistinguishable in all cases. We also did not evaluate the baseline incidence of PONV by the inclusion of a placebo group because it would be unethical to withhold prophylactic antiemetic drugs in middle ear surgery, where the incidence of PONV is high. We also did not measure the biochemical parameters of PONV such as C-reactive protein, aldehydes, and ketones. The incidence of PONV and antiemetic effects of study drugs beyond 24 hours could not be studied because of our study design (Fig. 1). Our study population was limited to ASA physical status I and II. We could exclude ASA physical status III (and beyond) patients in perspective on an ethical issue just as restrictions emerging because of fixed intraoperative sedative strategy.

Conclusion

Our study has shown that palonosetron-dexamethasone is more effective in the prevention of PONV with superior antiemetic efficacy in the first 24 hours compared to ondansetron-dexamethasone with decreased incidence of nausea, decreased requirement of rescue antiemetics and better patient satisfaction. Therefore, we recommend a combination of palonosetron-dexamethasone for prophylaxis for PONV in middle ear surgeries.

Conflicts of interest

The authors declare no conflicts of interest.

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