Dexamethasone and Ondansetron Combined Decreases Postoperative Nausea and Vomiting in Orthognathic Surgery Compared With Dexamethasone Alone: A Prospective Randomized Controlled Trial

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Objective: This study aimed to compare the efficacy of dexamethasone alone and dexamethasone-ondansetron combined for preventing postoperative nausea and vomiting (PONV) in patients undergoing orthognathic surgery.
Methods: Patients scheduled to undergo mandibular orthognathic surgery who were 18 to 50 years of age and American Society of Anesthesiologists physical status I or II were enrolled. Dexamethasone 6.6 mg was administered after intubation, followed by either ondansetron 4 mg (group DO) or saline placebo (group D) 15 minutes before the end of surgery. Nausea severity was assessed at 3 times postoperatively (immediately after the end of anesthesia, 2 hours later, and 24 hours later) using a 11-point numeric rating scale (NRS). If a patient complained of postoperative nausea or vomited, the NRS score was reevaluated. If the NRS score was 3 or higher, intravenous metoclopramide 10 mg was administered for PONV rescue. Assessed data included nausea NRS scores, vomiting, metoclopramide use, and other patient demographics.
Results: Mean nausea NRS scores at 2 hours were significantly lower in group DO vs group D (0.3 vs 2.1; $P = .003$), but differences in vomiting rates were not significant ($P > .05$). PONV rescue rates with metoclopramide were lower overall and at 2 hours later in group DO ($P < .001$).
Conclusion: Dexamethasone combined with ondansetron was more effective in preventing early postoperative nausea and reducing need for PONV rescue than dexamethasone alone for patients undergoing orthognathic surgery.

Key Words: Ondansetron; Dexamethasone; Postoperative nausea and vomiting (PONV); Metoclopramide; Orthognathic surgery.

One of the most common complications after general anesthesia is postoperative nausea and vomiting (PONV). Orthognathic surgery is considered to be a surgical procedure with a high risk of developing PONV due to the large number of young women undergoing the procedure and the potential for bleeding that can be swallowed.[1] The incidence of PONV in oral and maxillofacial surgery ranges from 21% to 46%; however, it is reported to be even higher in orthognathic surgery, ranging from 43% to 72%.[2] There are also reports stating that vomiting is the postoperative complication patients most prefer to avoid[3] and that PONV leads to reduced patient satisfaction.[4] In addition, orthognathic surgery increases the risk of airway obstruction and aspiration pneumonia should emesis occur due to intermaxillary fixation that is often in place postoperatively, making prevention and treatment of PONV even more important. At our hospital, dexamethasone is routinely administered prior to the start of orthognathic surgery due to its anti-inflammatory[5] and antiemetic effects. However, approximately 60% of patients still develop PONV with dexamethasone alone.

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Ondansetron, a serotonin (5-HT3) receptor antagonist, is considered the gold standard for managing PONV due to its efficacy and safety.[6] Furthermore, for patients with several PONV risk factors, prophylaxis with multiple antiemetics that act on different receptors is recommended.[6] There is strong evidence for combined administration of ondansetron and dexamethasone,[6] which has been shown to be more effective than either agent alone.[7] However, no studies have been conducted to date examining the efficacy of dexamethasone and ondansetron combined to prevent PONV in orthognathic surgery.

Because ondansetron has been available for clinical use in Japan only since August 2021, the primary objective of this study was to compare the efficacy of dexamethasone alone vs dexamethasone and ondansetron together for PONV prevention in patients undergoing orthognathic surgery. Secondary study objectives included assessing for differences between the study groups regarding known PONV risk factors and need for PONV rescue.

METHODS

This prospective randomized controlled study was approved by the Ethical Review Committee of Tokyo Dental College (approval number 1099) and registered with the University Hospital Medical Information Network (registration number UMIN000047706). The participants were healthy patients 18 to 50 years of age, American Society of Anesthesiologists physical status (ASA-PS) I or II, scheduled to undergo bilateral sagittal split ramus osteotomy (SSRO) or genioplasty at Tokyo Dental College Suidobashi Hospital, and from whom a written informed consent was obtained in advance. Exclusion criteria included patients undergoing emergency surgery or with contraindications to ondansetron or dexamethasone.

The patients were randomly allocated to either the dexamethasone group (group D) or the dexamethasone-ondansetron group (group DO) using a computer by a dentist anesthesiologist not participating in the study. All patients received dexamethasone 6.6 mg immediately after anesthesia induction, and no additional doses were given thereafter. The study drugs, the experimental drug (ondansetron 4 mg) and the control/placebo (saline), were prepared by a dentist anesthesiologist not participating in the study. Both were prepared by drawing 2 mL of each into 2.5-mL syringes wrapped with tape to obscure the syringe contents. Postoperative evaluations were performed by a dentist anesthesiologist blinded to participant study group assignment.

All participants received intubated general anesthesia according to the following protocol. After arrival at the operating room (OR) and starting standard anesthetic monitoring (noninvasive blood pressure, percutaneous oxygen saturation, electrocardiography, and capnography), peripheral intravenous (IV) access was established, and a continuous infusion of remifentanil 0.5 μg/kg/min was initiated. An IV bolus of propofol 2 mg/kg was administered for induction of general anesthesia, and nasotracheal intubation was performed after neuromuscular paralysis was obtained with rocuronium 0.6 mg/kg. Following successful intubation and placement of a throat pack, an IV bolus of dexamethasone 6.6 mg was administered. The surgical procedure was started after delivery of local anesthesia 2% lidocaine with 1:80,000 epinephrine using infiltration anesthesia and inferior alveolar nerve blocks. General anesthesia was maintained with sevoflurane 1.2%, oxygen 1 L/min, and air 2 L/min along with a remifentanil infusion. Remifentanil infusion rates were started at 0.2 μg/kg/min and adjusted accordingly ±0.05 μg/kg/min every 5 minutes depending on changes in systolic blood pressure (±20%) as compared with the previous values 5 minutes prior.

Approximately 20 minutes before the end of surgery, an IV bolus of fentanyl 2 μg/kg was administered, and approximately 15 minutes before the end of surgery, either the ondansetron 4 mg or the saline placebo was administered, depending on the group assignment. Following completion of the surgery, the degree of neuromuscular paralysis was assessed using a train-of-four monitor, and sugammadex 2 to 4 mg/kg was administered as needed. Patients were extubated awake after sufficient spontaneous ventilation and responsiveness to verbal commands were confirmed.

Nausea severity as rated by patients was assessed at 3 times: immediately after the end of anesthesia (right before leaving the OR), 2 hours later, and 24 hours later, using an 11-point numeric rating scale (NRS; 0, no nausea; 10, maximum imaginable nausea). Any episodes of vomiting were also recorded along with the timing. Whenever a patient complained of nausea or vomited, the NRS was again evaluated, and IV metoclopramide 10 mg was administered if the NRS score was 3 or higher whenever a patient complained of nausea or vomited.[8] Metoclopramide was administered up to twice daily. If metoclopramide was administered, the timing and frequency were documented. Acetaminophen and loxoprofen were used for postoperative analgesia.

NRS scores were compared between the 2 groups using the maximum value recorded for each of the 3 time periods. If there were no complaints of nausea or vomiting, the NRS scores recorded immediately after the end of anesthesia, 2 hours later, and 24 hours later were used for each period respectively.

Additional study data gathered included patient demographics (age, sex, body weight, body mass index, ASA-PS, smoking history, history of PONV or motion sickness) and surgical/anesthetic factors (surgery type, operation time, anesthesia time, total local anesthetic dose, total remifentanil dose, total intraoperative fentanyl dose, blood loss, infusion volume, postoperative opioid use (fentanyl), and metoclopramide use (timing and frequency of administration).

Figure. CONSORT Flowchart

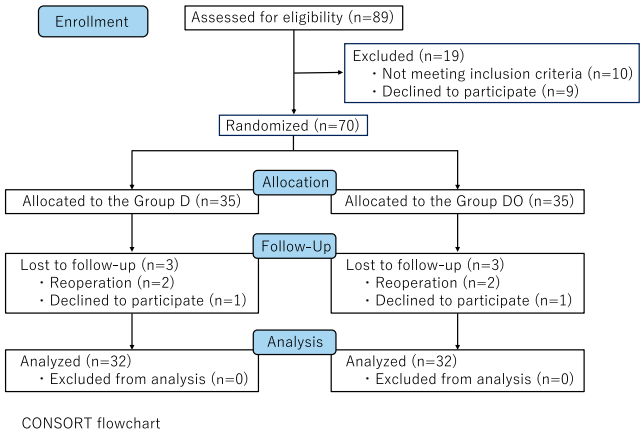

Illustration of the process used to select patients for study inclusion.

We also calculated the number of PONV risk factors according to the Apfel score[9]: female sex, nonsmoker, history of PONV and motion sickness, and postoperative opioid use.

Statistical Analysis

In a previous study,[10] the incidence of PONV 2 hours after recovery from anesthesia was 20% in the dexamethasone group and 4% in the dexamethasone-ondansetron group. Based on that study, an a priori power analysis was performed with G * Power (version 3.1.9.6, Heinrich Hein University). A sample size of 50 total participants was calculated based on the effect size of 0.4 using a significance level of 5% and a power of 80%.

Statistical analyses were performed using SPSS software (version 28, IBM). Categorical data were presented as numbers and were analyzed using χ^2 or Fisher exact test. Continuous data were presented as mean ± SD and were analyzed using Student *t* test. NRS scores were expressed as mean ± SD and analyzed using Mann-Whitney *U* test due to the skewed distribution of the data. A *P* value $<.05$ was considered significant.

RESULTS

A total of 89 patients were recruited for participation in this study, and none met the stated exclusion criteria. However, 21 patients failed to meet inclusion criteria and were excluded (10 were under 18 years of age and 11 did not consent to study participation). Another 4 patients underwent reoperation within 24 hours and were also excluded. Therefore, a total of 64 patients completed the study, with 32 participants in each group (Figure).

There were no significant differences noted between the study groups in terms of patient demographics or surgical/anesthetic factors (Table 1). No patients in either group received fentanyl postoperatively for analgesia.

The mean nausea NRS scores at 2 hours were significantly higher for group D (2.1 ± 2.3) vs group DO (0.3 ± 1.1; $P = .003$; Table 2). Although the mean nausea NRS scores were higher in the other 2 time periods for group D vs group DO, the differences lacked statistical significance ($P > .05$). Similarly, the total numbers of patients who vomited overall and at each of the 3 postoperative times were higher for group D vs group DO, but those differences all lacked significance ($P > .05$; Table 3).

Table 1. Patient Demographics and Surgical/Anesthetic Factors

	Group D (n = *32*)	*Group DO* (n = *32*)	*P value*
Patient demographics			
Age, mean (SD), y	26 (6)	29 (9)	.15
Sex, male/female, No.	13/19	14/18	.80
Body weight, mean (SD), kg	58 (8)	59 (12)	.54
Body mass index, mean (SD), kg/m^2	21 (3)	22 (2)	.70
ASA-PS, I/II, No.	27/5	24/8	.53
Smoking history, y/n, No.	11/21	6/26	.25
History of PONV or motion sickness, y/n, No.	11/21	13/19	.80
Surgical/anesthetic factors			
Surgery type, SSRO/genioplasty, No.	21/11	24/8	.58
Operation time, mean (SD), min	137 (30)	147 (40)	.24
Anesthesia time, mean (SD), min	185 (31)	198 (43)	.17
Total local anesthetic dose, mean (SD), mL	19 (3)	20 (4)	.28
Total remifentanil dose, mean (SD), mg	1.8 (0.5)	1.9 (4.6)	.57
Total intraoperative fentanyl dose, mean (SD), μg	145 (30)	115 (20)	.83
Blood loss during surgery, mean (SD), mL	112 (100)	81 (79)	.19
Total infusion volume, mean (SD), mL	1070 (197)	1165 (242)	.09
Postoperative opioid use, y/n, No.	0/32	0/32	1.00

Abbreviations: ASA-PS, American Society of Anesthesiologists physical status; PONV, postoperative nausea and vomiting; SSRO, sagittal split ramus osteotomy.

Table 2. Mean Postoperative Nausea NRS Scores

NRS evaluation periods	*Group D (n = 32)*	*Group DO (n = 32)*	*P value*
Immediately after anesthesia, mean (SD)	1.0 (1.7)	0.3 (0.8)	.20
2 h later, mean (SD)	2.1 (2.3)	0.3 (1.1)	.003*
24 h later, mean (SD)	0.8 (2.0)	0.2 (0.8)	.40

Abbreviation: NRS, numeric rating scale.
* $P < .05$.

There were no significant differences between the 2 groups regarding the number of PONV risk factors based on the Apfel score: female sex, nonsmoker, history of PONV/motion sickness, and postoperative opioid use ($P = .97$; Table 4).

The total number of patients who received metoclopramide postoperatively was significantly higher in group D (19 patients; 59%) vs group DO (3 patients; 9%; $P < .001$; Table 5). Similarly, group D had significantly more patients who received metoclopramide at 2 hours later compared with group DO (14 patients vs 1 patient, respectively; $P < .001$), and the number of patients who received metoclopramide twice was significantly higher in group D (5 patients) vs group DO (0 patients; $P = .03$; Table 5). Differences between the study groups regarding metoclopramide use immediately after anesthesia and 24 hours later lacked significance.

DISCUSSION

The primary objective of this study was to determine the efficacy of dexamethasone and ondansetron in combination vs dexamethasone alone for the prevention of PONV in patients undergoing orthognathic surgery. The results of this study showed that mean nausea NRS scores at 2 hours were significantly lower in group DO vs group D. Group DO also had fewer patients for whom metoclopramide was administered as a rescue agent for PONV. However, there was no difference in vomiting between group DO and group D. These results indicate that the dexamethasone-ondansetron combination is more effective than dexamethasone alone in preventing early postoperative nausea (at 2 hours) and reducing the need for PONV rescue after orthognathic surgery.

Table 3. Vomiting Rates

	Group D (n = 32)	*Group DO (n = 32)*	*P value*
Total who vomited, No. (%)	4 (11)	1 (3)	.18
Immediately after anesthesia, No. (%)	1 (3)	0 (0)	1.00
2 hours later, No. (%)	2 (6)	1 (3)	.12
24 hours later, No. (%)	1 (3)	0 (0)	1.00

Table 4. Number of PONV Risk Factors According to Apfel Score[a]

No. of Risk Factors	*Group D (n = 32)*	*Group DO (n = 32)*	*P value*
0	6	3	.97
1	9	10	
2	9	11	
3	8	8	
4	0	0	

Abbreviation: PONV, postoperative nausea and vomiting.
[a] Risk factors consisted of female sex, nonsmoking status, history of PONV or motion sickness, and postoperative opioid use.

The Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting based on an international panel of experts under the auspices of the American Society of Enhanced Recovery and Society for Ambulatory Anesthesia list the following risk factors for PONV: female sex, high-risk surgery, volatile anesthetic and nitrous oxide use, history of PONV/motion sickness, nonsmoking status, duration of anesthesia, younger age, postoperative opioid use, and general vs regional anesthesia use.[6] These risk factors can be generally subclassified into patient, surgical, and anesthetic factors. Prevention of PONV requires a comprehensive examination of these risk factors in each case and development of appropriate preventive PONV strategies tailored to the patient's individual risk level.

The Apfel score was used to calculate the total score of 4 risk factors (female sex, smoking status, history of PONV/motion sickness, and postoperative opioid use) for patients within this study,[9] and 55 of the 64 patients were found to have one or more of these PONV risk factors.

Surgical factors in this study would include surgery time and high-risk surgery type (ie, orthognathic surgery). Surgeries lasting more than 60 minutes are considered risk factors for PONV.[6] In addition, the incidence of PONV in orthognathic surgery has been reported to be approximately 43% to 72%,[2] making it high risk for PONV. In a study by Olaondo et al,[10] the incidence of PONV 2 hours after gynecological surgery was lower in the combined dexamethasone-ondansetron group than in the dexamethasone alone group, a finding similar to the present study. Like orthognathic surgery, gynecological surgery is considered to have a high incidence of PONV,[6] and the combined administration of dexamethasone-ondansetron was shown to be highly effective in preventing PONV in these high-risk surgeries.

Anesthetic factors in this study correspond to sevoflurane (ie, volatile anesthetics) and opioids (remifentanil and fentanyl), which were used to maintain general anesthesia. Notably, fentanyl was not used for postoperative analgesia for any patients in this study. Volatile anesthetics are

Table 5. PONV Rescue With Metoclopramide

	Group D (n = 32)	*Group DO (n = 32)*	*P value*
Total who received metoclopramide, No. (%)	19 (59)	3 (9)	<.001*
Immediately after anesthesia, No. (%)	5 (16)	1 (3)	.10
2 hours later, No. (%)	14 (44)	1 (3)	<.001*
24 hours later, No. (%)	5 (16)	1 (3)	.10
Total who received metoclopramide 2 times, No. (%)	5 (16)	0 (0)	.03*

* $P < .05$.

considered a risk factor for early PONV (within 2 hours after surgery).[11]

Based on the above, the patients in this study had multiple risk factors for PONV. Because neurotransmitters such as serotonin, dopamine, histamine, acetylcholine, and neurokinin are associated with PONV,[12] prophylaxis with multiple drugs targeting different receptors is recommended, especially given that most of our patients had at least one PONV risk factor. There is high evidence of efficacy for the combined administration of ondansetron (a selective 5-HT3 serotonin receptor antagonist) and dexamethasone.[6] Selective 5-HT3 antagonists are thought to inhibit emesis by acting on serotonin receptors in the chemoreceptor trigger zone (CTZ) and afferent vagus nerve fibers located in the area postrema. Meanwhile, the mechanism of PONV prophylaxis by dexamethasone remains unknown, although animal studies suggest that it exerts antiemetic effects centrally by activating glucocorticoid receptors in the nucleus of the solitary tract of the medulla.[13] The results of this study indicate that PONV prophylaxis using combined dexamethasone-ondansetron may be more effective than dexamethasone alone in high-risk cases with a combination of patient, surgical, and anesthetic factors. However, because the number of patients who vomited in both groups in this study was small, the prophylactic effect of the dexamethasone-ondansetron combination on postoperative vomiting could not be determined.

If a patient who received ondansetron prophylactically complains of PONV within 6 hours of ondansetron administration, it is recommended that an antiemetic other than a 5-HT3 antagonist be used for PONV rescue.[14] Metoclopramide, administered as a rescue agent in this study, exerts its antiemetic effects by antagonizing dopamine (D2) receptors within the CTZ. We believe it would be appropriate to use metoclopramide, which acts on a receptor different from the 5-HT3 receptor, but further research is needed on the optimal antiemetic for this situation.

Although this study focused on bilateral SSRO or genioplasty, it has been suggested that among orthognathic surgeries, 2-jaw surgeries (eg Le Fort I osteotomy + SSRO) have the highest incidence of PONV, likely due to increased bleeding risks, and further PONV countermeasures should be taken for those cases in addition to the use of total IV anesthesia.[15] Future studies are needed to investigate the effect of combined dexamethasone-ondansetron administration on PONV prophylaxis in 2-jaw surgery osteotomies.

Previously, due to the limited availability of antiemetics in Japan, our institution had been using droperidol. Droperidol is thought to inhibit PONV by blocking dopamine receptors, which can cause extrapyramidal side effects like acute dystonia and Parkinsonism in rare cases. The incidence of such complications is estimated to approximate 0.2%,[16] and the frequency may be even higher among younger individuals due to their higher risk of sensitivity to droperidol. In fact, we experienced a case of extrapyramidal symptoms that were probably caused by droperidol after orthognathic surgery in a young patient who was not part of this study.[17] Although extrapyramidal symptoms caused by ondansetron have been reported, the drug is considered quite safe as the incidence of such complications is exceedingly rare.[18] In orthognathic surgery, which is often performed on relatively young patients, PONV prophylaxis with dexamethasone and ondansetron combined may prevent complications such as extrapyramidal symptoms that can occur with D2-receptor antagonists like droperidol.

This study has several limitations. First, due to the small sample size in this study, there were no significant differences for mean nausea NRS scores other than at 2 hours or for vomiting rates. Increasing the sample size may lead to different results in those areas, which should be considered in the future. Second, the study subjects were young and healthy patients (ASA-PS I or II). Therefore, it is unclear whether similar results can be obtained in patients with generalized health issues, older adults, and patients with other medical conditions.

CONCLUSION

The combined use of dexamethasone and ondansetron was shown to be more effective in preventing early postoperative nausea (at 2 hours) and reducing the need for PONV rescue than dexamethasone alone in patients undergoing orthognathic surgery. Antiemetic use should be tailored to the individual patient along with a PONV rescue plan that includes the use of antiemetics targeting different receptors.

DISCLOSURE

None of the authors have any relevant financial relationship(s) with a commercial interest.

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