Original Article

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Risk factors for postoperative nausea and vomiting in patients of orthognathic surgery according to the initial onset time: a cross-sectional study

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Background: A high incidence (40–73%) of postoperative nausea and vomiting (PONV) has been reported following orthognathic surgery, and various risk factors have been associated with it. Identifying PONV risk factors based on initial onset time will help establish preventive measures. This study aimed to identify factors that are significantly related to PONV based on the initial onset time after orthognathic surgery.

Methods: This study included 590 patients who underwent orthognathic surgery. Multivariate logistic regression analysis was performed to identify the risk factors that are significantly related to PONV. The objective variables were classified into three categories: no PONV, early PONV (initial onset time: 0–2 h after anesthesia), and late PONV (initial onset time: 2–24 h after anesthesia). The explanatory variables included relevant risk factors for PONV, as considered in previous studies.

Results: Total intravenous anesthesia with propofol was a significant depressant factor for early PONV (adjusted odds ratio [aOR] = 0.340, 95% confidence interval [CI] = 0.209–0.555) and late PONV (aOR = 0.535, 95% CI = 0.352–0.814). The administration of a combination of intraoperative antiemetics (vs. no administration) significantly reduced the risk of early PONV (aOR = 0.464, 95% CI = 0.230–0.961). Female sex and young age were significant risk factors for late PONV (aOR = 1.492, 95% CI = 1.170–1.925 and unit aOR = 1.033, 95% CI = 1.010–1.057, respectively).

Conclusion: We identified factors that are significantly related to PONV based on the initial onset time after orthognathic surgery. Total intravenous anesthesia with propofol significantly reduced the risk of PONV not only in the early period (0–2 h after anesthesia) but also in the late period (2–24 h after anesthesia).

Keywords: General Anesthesia; Logistic Models; Orthognathic Surgery; Postoperative Nausea and Vomiting; Risk Factors.

INTRODUCTION

Countermeasures to prevent postoperative nausea and vomiting (PONV) due to general anesthesia are crucial for promoting high-quality recovery and patient satisfaction after surgery. According to meta-analyses, PONV occurs in approximately 20–30% of surgical patients [1,2]. Importantly, many studies have attempted to determine the risk factors associated with PONV [1-6], and a high incidence of PONV (40–73%) has been reported following orthognathic surgery [7-10]. Previous

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studies have examined the risk factors for PONV in orthognathic surgery [9-15], including sex, age, surgery type, type of inhalational anesthetic, anesthesia time, fluid infusion volume, and administration of postoperative opioids. A study also compared the frequency of PONV occurrence according to different time periods and found a difference in frequency [16].

We hypothesized that factors that are significantly related to PONV based on the initial onset time will help elucidate the etiology of PONV and establish preventive measures in orthognathic surgery. However, to the best of our knowledge, no study has examined the risk factors associated with PONV based on the initial onset time in the field of oral surgery. Therefore, this observational study aimed to identify the factors that are significantly related to PONV according to the initial onset time in patients undergoing orthognathic surgery under general anesthesia.

METHODS

This cross-sectional study was conducted in accordance with the guidelines of the Declaration of Helsinki and reported per the STROBE Statement. Patients who underwent orthognathic surgery under general anesthesia performed by dental anesthesiologists at Hokkaido University Hospital between January 2007 and December 2019 were included in this study. The exclusion criteria were as follows: 1) patients with inadequate or a lack of nursing records and anesthesia summary for PONV within 24 h after anesthesia; 2) patients aged below 16 years; and 3) patients with an American Society of Anesthesiologists (ASA) physical status of III or higher. PONV was defined as nausea, vomiting, or both. Additionally, the presence or absence of PONV was determined by entries in the medical, anesthesia, and nursing records.

1. Evaluation points (Study endpoints)

The primary endpoints were factors significantly associated with the initial onset time of PONV (early: 0–2 h and late: 2–24 h after anesthesia), which are expressed as adjusted odds ratio (aOR) and 95% confidence interval (CI). The secondary endpoints were the incidence of PONV at 0–2, 2–24, and 0–24 h after anesthesia in the participants' reports.

2. Evaluation methods for the primary endpoint

Objective variables were classified into three categories: no PONV, early PONV (initial onset time 0–2 h after anesthesia), and late PONV (initial onset time 2–24 h after anesthesia).

The explanatory variables were factors considered relevant in previous investigations [1-6, 9-15]. Patient-specific factors included age, sex, and presence/absence of smoking. Anesthesia-related factors included anesthetic maintenance (total intravenous anesthesia [TIVA] with propofol or general anesthesia with volatile inhalation anesthetics), intraoperative fluid infusion volume, intraoperative fentanyl dose, and the number of intraoperative antiemetic types used (0, 1, and 2 or more). Antiemetics included droperidol, dexamethasone, and metoclopramid. Surgery-related factors included surgery time, blood loss, and surgery type (LeFort I osteotomy in combination with sagittal split ramus osteotomy [SSRO], either LeFort I osteotomy or SSRO alone, or other surgeries including surgical-assisted rapid palatal expansion and genioplasty). In our hospital, it is standard to treat postoperative pain with both intravenous and oral nonsteroidal anti-inflammatory analgesics, as well as acetaminophen. Thus, analgesic opioids were not used for postoperative pain control and excluded from the explanatory variables.

3. Evaluation methods for the secondary endpoints

A comparison of the incidence of PONV at 0–2 h and 2–24 h after anesthesia, including the overlap, was performed.

4. Statistical analyses

Multivariate logistic regression analysis was performed

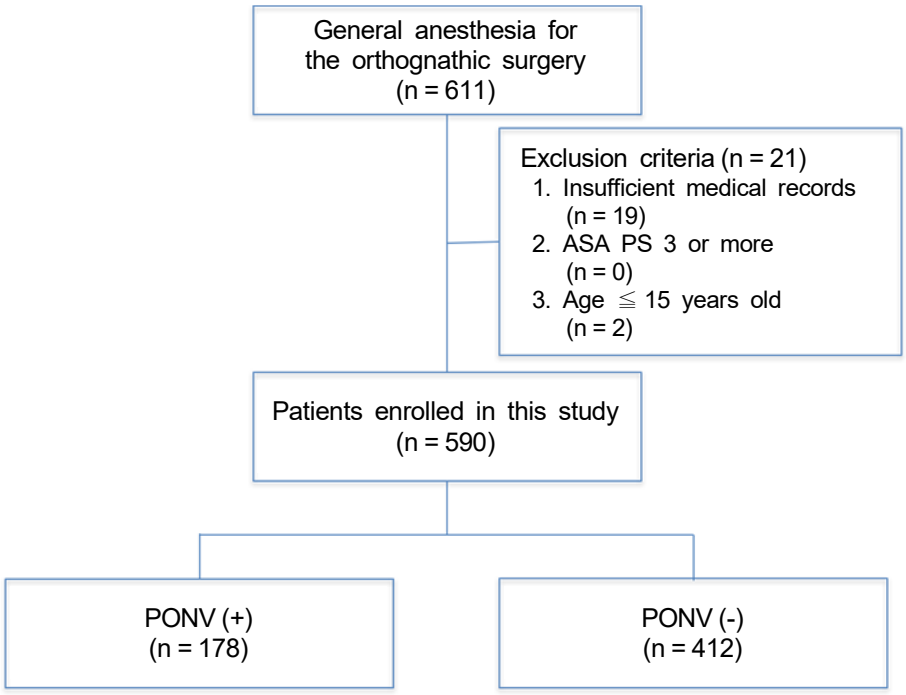

Fig. 1. Study flow diagram. ASA PS, American Society of Anesthesiologists physical status; n, number; PONV, postoperative nausea and vomiting.

to identify factors significantly related to PONV. The Mann–Whitney U test was conducted to compare continuous variables between the presence and absence of PONV, and Fisher's exact test was performed for categorical variables. A test for ratio difference was performed to compare the incidence of early and late PONV.

All calculations were performed using a statistical software (JMPTM Pro14, SAS Institute Inc., Cary, NC, USA). A P value < 0.05 was considered statistically significant. Categorical variables are presented as n (%). Continuous data are expressed as mean (standard deviation) when normally distributed or as median with first and third quartiles when not normally distributed.

RESULTS

Fig. 1 shows a flow diagram of the study. We obtained the records of 611 patients who underwent orthognathic surgery. Of these, 590 patients that did not meet the exclusion criteria were included in the study; of the 21 patients that met the exclusion criteria, 19 patients had insufficient medical records and 2 patients were aged below 16 years. There were no patients with ASA physical status III or higher.

There were significant differences in sex, age, weight, height, and the type of anesthetic maintenance between patients with and without PONV (univariate analysis) (Table 1). Regarding the type of surgery, SSRO accounted for > 50%, and LeFort I osteotomy in combination with SSRO accounted for > 30% of the surgeries. Additionally, > 90% of the patients were maintained with propofol TIVA. Owing to the high partial correlation coefficient, which exceeded 0.7, indicating multicollinearity, we excluded surgery time from the multivariate logistic regression analysis.

Table 2 presents the factors significantly associated with early and late PONV. Factors that were significantly related to early PONV (0–2 h after anesthesia) included propofol TIVA (vs. volatile inhalation anesthetics, which decreased the risk of PONV) and the administration of a combination of intraoperative antiemetic (vs. no administration, which decreased the risk of PONV). The

Table 1. Characteristics of patients, anesthesia and surgery

Variable (unit)	Total (n = 590)	PONV (+) (n = 178)	PONV (−) (n = 412)	P-values
Sex				
Male	196 (33.2)	41 (23)	155 (37.6)	< 0.001
Female	394 (66.8)	137 (77)	257 (62.4)	
Age (years)	25 (20–33)	22 (20–30)	25 (21–34)	0.001
Weight (kg)	55.2 (49.7–64.0)	54.2 (48.0–61.8)	56.0 (50.0–65.6)	0.004
Height (cm)	164 (9)	162 (8)	165 (9)	< 0.001
Smoking status	81 (13.7)	18 (10.1)	63 (15.3)	0.117
Nonsmoking status	509 (86.3)	160 (89.9)	349 (84.7)	
Surgery time (min)	237 (189–382)	246 (192–396)	233 (186–377)	0.216
Type of surgery				
Le fort I osteotomy + SSRO	187 (31.7)	65 (36.5)	122 (29.6)	
Le fort I osteotomy	6 (1)	3 (1.7)	3 (0.7)	0.065
SSRO	306 (51.9)	91 (51.1)	215 (52.2)	
Others*	91 (15.4)	19 (10.7)	72 (17.5)	
Anesthesia time (min)	312 (262–474)	319 (269–485)	309 (259–463)	0.149
Anesthetic maintenance				
Volatile anesthetic	48 (8)	25 (14)	23 (5.6)	< 0.001
TIVA	542 (92)	153 (86)	389 (94.4)	
Number of intraoperative antiemetic types used				
0	19 (3.2)	6 (3.3)	13 (3.2)	0.818
1	50 (8.5)	17 (9.6)	33 (8)	
2 or more	521 (88.3)	155 (87.1)	366 (88.8)	

Values are presented as mean (standard deviation) or median (25–75% (interquartile) for continuous variables and number (%) for nominal variables.
min, minutes; PONV, postoperative nausea and vomiting; SSRO, sagittal split ramus osteotomy; TIVA, total intravenous anesthesia
Others* : SARPE (surgical assisted rapid palatal expansion) and genioplasty

Table 2. Adjusted odds ratios of risk factors for early/ late PONV: multivariate logistic regression analysis

Variable (unit)	Early PONV (0–2 h)				Late PONV (2–24 h)			
	aOR	Unit aOR	95% CI	P-values	aOR	Unit aOR	95% CI	P-values
Sex								
Female vs. male	1.424		0.956–2.198	0.093	1.492		1.170–1.925	0.002
Age (year decrease)		1.021	0.985–1.062	0.280		1.033	1.010–1.057	0.005
Nonsmoking status vs. smoking status	1.485		0.869–2.886	0.188	1.267		0.920–1.800	0.164
Blood loss (ml)		1.000	0.999–1.002	0.642		1.000	0.999–1.001	0.190
Surgery type (vs. others*)								
Le fort I osteotomy + SSRO	0.797		0.300–2.278	0.652	0.911		0.471–1.802	
Le fort I osteotomy	2.800		0.260–15.837	0.286	1.951		0.385–8.571	
SSRO	0.826		0.381–2.059	0.643	1.331		0.746–2.475	
Anesthetic maintenance								
TIVA vs. volatile anesthetic	0.340		0.209–0.555	<.001	0.535		0.352–0.814	0.003
Number of intraoperative antiemetic types used (vs. 0)								
1	1.245		0.540–2.660	0.582	2.191		1.013–6.312	0.069
2 or more	0.464		0.230–0.961	0.034	0.934		0.469–2.604	0.866
Fentanyl usage per unit weight during anesthesia (μg/kg)		1.047	0.913–1.199	0.510		1.077	0.996–1.165	0.063
Fluid infusion volume per unit weight during anesthesia (ml/kg)								
≧ 25 vs. < 25	1.012		0.634–1.588	0.959	1.169		0.895–1.526	0.250

aOR, adjusted odds ratio; CI, confidence intervals; h, hour; PONV, postoperative nausea and vomiting; SSRO, sagittal split ramus osteotomy; TIVA, total intravenous anesthesia.
Others* : SARPE (surgical assisted rapid palatal expansion) and genioplasty

factors that were significantly associated with late PONV (2–24 h after anesthesia) were female sex (vs. male, which increased the risk of PONV), young age (the younger the age, the higher the risk of PONV), and propofol TIVA

(vs. volatile inhalation anesthetics, which decreased the risk of PONV).

The incidence of PONV overall (0–24 h after anesthesia) was 30.2% (178/590 patients), of which the incidence of late PONV (28.0%, 165/590 patients) was significantly higher than that of early PONV (6.8%, 40/590 patients) ($P < 0.001$). There were 27 patients that overlapped with both early and late PONV.

DISCUSSION

To summarize the key results, the factors that were significantly related to early PONV (0–2 h after anesthesia) were propofol TIVA and the administration of a combination of intraoperative antiemetics (vs. no administration). Moreover, the factors that were significantly related to late PONV (2–24 h after anesthesia) were female sex, young age, and propofol TIVA.

Propofol TIVA significantly reduced the risk of PONV not only at 0–2 h but also at 2–24 h after anesthesia. The duration of the PONV-suppressing effect of propofol has been discussed in various studies [16, 17-22]. We compared our study with studies [17-20] analogous to ours, excluded any confounding factors by multiple logistic regression analysis or randomized controlled trials (RCTs), and subdivided the time into 0–2 and 2–24 h after anesthesia. Similar to our findings, some studies have shown that propofol TIVA significantly reduces the risk of PONV not only in the early period but also in the late period [17,18], while others have only observed the effect in the early period [19,20]. Some studies have reported the PONV suppression effect of propofol, such as RCTs, showing an effect of up to 6 h [16,21] and another study showing an effect of up to 4 h [22]; however, the categorization of PONV based on the onset time varied from that of our study. Interestingly, propofol has been observed to suppress PONV, regardless of plasma concentration [23,24]. As the onset time in our study included only two categories, 0–2 h and 2–24 h, it is necessary to investigate with a further detailed categorization of the onset time in the future.

The administration of a combination of intraoperative antiemetics significantly reduced the risk of early PONV but did not reduce the risk of late PONV. In the late period after anesthesia, the imbalance between the plasma half-life of antiemetics and timing of administration may explain this finding. Droperidol is often administered mid-surgery to prevent the occurrence of side effects of QT prolongation after exiting the operating room. Furthermore, a study by Apfel et al. [25] found that the antiemetic property of a single bolus dose of droperidol is short-lived because of its short (approximately 2 h) plasma half-life. Similarly, dexamethasone, which has an antiemetic effect in addition to its anti-inflammatory effect, is often administered early in surgery. Due to its plasma half-life of approximately 4–5 h, its effectiveness may not extend into the late period after anesthesia. Hence, further investigation should be performed to determine whether additional administration in the early postoperative period can maintain the dexamethasone concentration for the effective prevention of PONV.

One of the vomiting-inducing pathways associated with the emetic center located in the parvicellular reticular formation includes an afferent pathway from the pharynx and gastrointestinal tract [26]. In the pharynx, the pathway by which inflammation spreads to the pterygomandibular space, lateral pharyngeal space, carotid sheath (including the vagus nerve), and retropharyngeal space has been well documented [27-29]. Additionally, when blood is ingested, iron irritates the gastric mucosa [30]. Therefore, factors for PONV induction associated with the combination of LeFort I osteotomy and SSRO or SSRO alone may cause surgical stimulation, bleeding, postoperative edema in the pharynx or surrounding soft tissues, and postoperative swallowing of blood [10,31,32].

In this study, we aimed to determine the relationship between factors of orthognathic surgical origin and PONV by examining PONV-related factors based on the initial onset time and surgery type. However, we did not

identify any significant surgical factors associated with PONV.

Female sex was significantly associated with increased PONV 2–24 h after anesthesia (aOR = 1.492), which is consistent with a previous systematic review [1]. However, from the perspective of the initial onset time, it is unclear why female sex was a significant factor associated with only late PONV in this study.

Young age was also found to be a significant risk factor for PONV 2–24 h after anesthesia (unit aOR = 1.033). This result is consistent with those of previous similar studies [33-35]. However, from the perspective of initial onset time, it is unclear why young age was a significant factor associated with only late PONV in this study.

The incidence of PONV in our study (30.2%), wherein > 90% of the patients were anesthetized with TIVA, was lower than that reported in previous studies (40–73%) [7-10], wherein the patients were anesthetized with volatile inhalational anesthetics in orthognathic surgery. Hence, the application of TIVA management in orthognathic surgery was shown to lower PONV incidence. Additionally, prophylactic administration of a combination of antiemetics in > 80% of the patients in this study could also have been responsible for the low incidence of PONV. These findings are consistent with the recommendations of multimodal antiemetics in the latest guidelines [2]. However, compared with the incidence of PONV in patients anesthetized with TIVA without limiting surgical areas (13.3% in a meta-analysis [36]), the incidence of PONV in this study (28.2%, 153/542 patients) was higher, and the incidence of PONV in the late period was significantly higher (> four times) than that in the early period. These results are consistent with the factor analysis results of TIVA and the administration of a combination of intraoperative antiemetics in this study. Therefore, countermeasures focusing on the late period may be necessary to prevent PONV after orthognathic surgery.

The present study has some limitations. First, the type, dose, and timing of antiemetic use during anesthesia were at the discretion of each dental anesthesiologist and was a confounding factor that resulted in a selection bias. Second, we did not distinguish nausea from vomiting, which are both physiologically distinct with different underlying mechanisms. Nausea is a subjective sensation requiring the activation of neural pathways, while vomiting is a complex reflex under the control of two functionally distinct medullary centers: the vomiting center and the chemoreceptor trigger zone [37]. These differ in time course [37], incidence [13,21,37], and patient perception [38] and may affect patient satisfaction. Third, the medical records did not include a history of PONV or motion sickness. Therefore, this information could not be included as an explanatory variable. According to the guidelines for the management of PONV [2], a history of PONV or motion sickness is an important risk factor in adults with a high odds ratio, second only to sex, high-risk surgery, and the use of volatile inhalation anesthetics. In future studies, these limitations should be considered. Finally, in Japan, the insurance coverage for ondansetron for PONV was not approved until August 2021. Therefore, ondansetron was not used within the timeframe of this study. The active use of ondansetron could have altered the results of this study. Additionally, the results of the present study may not be applicable to the general population because this study was limited to one oral surgery institution.

In summary, we identified factors significantly related to PONV, based on the initial onset time after orthognathic surgery. Total intravenous anesthesia with propofol significantly reduced the risk of PONV not only in the early period (0–2 h) but also in the late period (2–24 h).

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Keiji Hashimoto: Data curation, Writing - review & editing
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