The Effect of Adding Midazolam to Propofol Intravenous Sedation to Suppress Gag Reflex During Dental Treatment

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We retrospectively investigated the efficacy and safety of propofol administration alone and in combination with midazolam for gag reflex suppression during dental treatment under intravenous sedation. We included 56 patients with an overactive gag reflex who were to undergo dental treatment under intravenous sedation. They were divided into propofol (P group, $n = 22$) and midazolam with propofol (MP group, $n = 34$) groups. The P group received propofol alone, while the MP group received midazolam (0.04 mg/kg) prior to target-controlled infusion (TCI) of propofol (titrated for adequate sedation). The patients' anesthetic records were evaluated for vital sign changes, adverse cardiovascular or respiratory event frequency, the number of forced treatment interruptions, and the TCI-predicted cerebral propofol concentration at gag reflex suppression (posterior tongue stimulation with a dental mirror). No significant differences were observed between the 2 groups preoperatively. There were no cases of forced interruptions or significant respiratory compromise in either group. Cardiovascular adverse event frequency was lower in the MP group than in the P group (all $p < .05$). Our results suggest that propofol, when combined with midazolam, minimized cardiovascular effects compared with propofol alone when used to suppress the gag reflex in patients during dental treatment under intravenous sedation.

Key Words: Propofol; Midazolam; Gag reflex; Intravenous sedation; Dental treatment.

Dental treatment often involves uncomfortable procedures that require adequate sedation. Intravenous midazolam and propofol have long been used to induce appropriate sedation during dental treatment. In particular, propofol is used in patients with a severe gag reflex.^{1,2} Midazolam is a fast-acting benzodiazepine with a short elimination half-life. It exhibits sedative, anxiolytic, hypnotic, and anterograde amnesic properties.³ In addition, flumazenil, a benzodiazepine antagonist, can be used to treat a midazolam overdose. Propofol was more recently developed and is an ultra-short-acting intravenous anesthetic agent that rapidly induces sleep and exhibits a short recovery period.⁴ Propofol has a shorter half-life and a faster recovery time compared with

midazolam. It generally provides adequate anxiolytic effects in phobic dental patients and can effectively inhibit the gag reflex at lesser sedation levels compared with midazolam. However, pain at the infusion site is common after propofol administration; moreover, there is no propofol antagonist.^{5–8} Propofol is administered in Japan only by dental anesthesiologists with a targeted-controlled infusion (TCI) system to achieve a pertinent level of sedation in patients undergoing dental procedures.^{9–11} Some studies examining propofol use during endoscopic procedures have shown more serious cardiovascular and respiratory complications with propofol use than with midazolam use. Therefore, we speculated that sedation induced with a combination of propofol and midazolam may be safer and more effective than sedation induced with either drug alone.^{12,13}

To the best of our knowledge, few studies have compared safety and efficacy between propofol administration alone and propofol administration in combination with intravenous midazolam for adequate sedation during dental treatment.¹⁴ The endpoint of the present study was to determine if one method was superior in patients with an overactive gag reflex.

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Accordingly, we retrospectively reviewed vital sign changes, the adverse event frequency, the number of forced treatment interruptions, and the TCI-predicted cerebral propofol concentration between patients who received propofol alone and those who received propofol in combination with midazolam for gag reflex suppression during dental treatment under intravenous sedation.

METHODS

This study was performed at Tsurumi University Dental Hospital (Yokohama, Japan). All subjects provided written informed consent to participate in the study. The requirement for ethical approval was waived because of the retrospective study design.

Study Subjects

Individuals identified as having an overactive gag reflex requiring sedation and scheduled to undergo similar dental procedures from May 2015 to March 2016 at Tsurumi University Dental Hospital (Yokohama, Japan) were considered for inclusion. Sedation was induced and monitored by departmental dental anesthesiologists in all patients. Patients younger than 16 years of age, those older than 90 years of age, and those with American Society of Anesthesiologists class III–V were excluded. In all patients, 2% lidocaine with 1 : 80,000 adrenaline was used for local anesthesia during dental treatment.

Sedation Anesthesia and Gag Reflex Evaluation

The included patients were divided into a propofol only (P) group and a midazolam with propofol (MP) group. The P group patients received TCI of propofol for the induction and maintenance of an appropriate level of anesthesia. The MP group patients first received an intravenous bolus of midazolam (0.04 mg/kg), which was followed by TCI of propofol after 3 minutes.¹⁵ The initial propofol target concentration was set at 0.6 µg/mL. The gag reflex was evaluated by inserting a dental mirror into the oral cavity and stimulating the posterior tongue every 5 minutes with the TCI-predicted cerebral propofol concentration increased by 0.2 µg/mL until the gag reflex was suppressed. All patients received oxygen via a nasal cannula at a rate of 2 L/min. The modified Observer's Assessment of Alertness/Sedation scale¹⁶ (Table 1) did not exceed a score of 2, which indicates

Table 1. Scoring System for the Modified Observer's Assessment of Alertness/Sedation Scale

<i>Response</i>	<i>Score</i>
Responds rapidly to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1

deep sedation (ie, patient is responsive after mild prodding or shaking). The score was evaluated every 5 minutes.

Adverse Events

The heart rate, electrocardiography findings, oxygen saturation, and blood pressure were recorded before, during, and after anesthesia administration. These parameters were recorded every 5 minutes throughout the procedure. If oxygen saturation, as measured using a pulse oximeter (BP-608 Evolution III, OMRON COLIN Co, Ltd, Tokyo, Japan), decreased below 90% during treatment, the subject was considered to have experienced a major adverse event. Marked changes in the blood pressure (>20% of the baseline value) or pulse rate (>50% of the baseline value) after induction were also regarded as major adverse events. We also recorded the number of cases in which treatment required discontinuation (ie, the number of forced interruptions).

Statistical Analysis

Data are presented as means ± standard deviations where applicable. The statistical significance of differences between the P and MP groups was evaluated using Fisher exact test for categorical variables and Student's *t* test for normally distributed continuous variables. All statistical analyses were performed using GraphPad Prism software (version 6, GraphPad Software Inc, La Jolla, Calif). Statistical significance was defined as *p* < .05.

RESULTS

The study included 56 subjects (17–70 years of age; mean age, 41.9 ± 13.9 years; 35 men, 21 women), including 22 in the P group and 34 in the MP group. There were no significant differences between groups with regard to age, sex, body weight, height, body mass

Table 2. Characteristics of Patients Who Received Propofol Alone (P Group) and in Combination With Midazolam (MP Group) to Prevent the Gag Reflex During Dental Treatment Under Intravenous Sedation*

	P Group (n = 22)	MP Group (n = 34)	p Value
Age, y	37.9 ± 14.1	44.6 ± 13.7	.060
Sex, male : female	16 : 6	19 : 15	.161
Height, cm	168.7 ± 5.3	163.7 ± 9.8	.062
Weight, kg	61.3 ± 10.4	63.7 ± 14.5	.250
BMI, kg/m ²	21.4 ± 2.7	23.7 ± 5.3	.070
Vital signs before induction			
SBP, mm Hg	134.5 ± 17.5	129.9 ± 18.8	.180
DBP, mm Hg	82.6 ± 11.4	78.9 ± 14.7	.164
Pulse rate, bpm	80.8 ± 16.6	83.8 ± 12.7	.220
SpO ₂ , %	98.0 ± 1.2	97.9 ± 1.2	.294
Time to treatment from induction, min	14.1 ± 6.7	11.9 ± 11.8	.099
Amount of local anesthetic, mL	2.1 ± 1.3 (12/22 cases)	2.7 ± 1.8 (18/34 cases)	.135 (.562)
Treatment time, min	48.5 ± 21.4	55.1 ± 23.8	.143
Recovery time, min	21.1 ± 10.0	18.1 ± 11.1	.153

* Fisher exact test was used for categorical variables and Student's *t* test for normally distributed continuous variables. Data are presented as means ± standard deviations. BMI indicates body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; SpO₂, oxygen saturation.

index, preoperative cardiorespiratory parameters, time to treatment from induction, amount of local anesthetic, treatment time, or recovery time (Table 2). The Observer's Assessment of Alertness/Sedation scores before gag reflex evaluations were similar in both groups ($p = .257$). There were no cases of forced interruptions. The TCI-predicted cerebral concentration of propofol required for gag reflex suppression was significantly lower in the MP group ($1.07 \pm 0.09 \mu\text{g/mL}$) than in the P group ($1.67 \pm 0.11 \mu\text{g/mL}$, $p = .0002$; Figure).

Frequency of Adverse Events

The heart rate, electrocardiography findings, oxygen saturation, and blood pressure were stable in all patients before the induction of sedation. No major adverse events associated with oxygen saturation occurred in either group, and the number of patients with respiratory depression was not significantly different between groups. Marked blood pressure changes ($>20\%$) after drug administration were more common in the P group ($n = 7$) than in the MP group ($n = 2$, $p = .014$). This was also true for large changes ($>50\%$) in the pulse rate (P group: $n = 5$, MP group: $n = 0$; $p = .007$; Table 3). None of these adverse events required intervention.

DISCUSSION

The gag reflex is induced by adverse stimulation of the posterior oral cavity/tongue or pharyngeal area¹⁷ and is

a normal response that prevents foreign object entry into the pharynx, larynx, or trachea.¹⁸ However, this reflex can hinder the performance of dental procedures and cause patients to avoid dental treatment because of gagging-related discomfort. Factors that contribute to the gag reflex are divided into psychological and somatogenic categories.¹⁹ Psychological factors include visual, auditory, and olfactory stimulation,²⁰ and somatogenic factors include anatomical abnormalities in the oropharynx and neural hypersensitivities.¹⁸ In a previous study, radiographic investigation of the gag reflex revealed no correlation between its severity and

Concentration of propofol required alone and in combination with midazolam for gag reflex suppression during dental treatment under intravenous sedation. Data are presented as means ± standard deviations. * $p = .0002$ between the propofol (P) and midazolam plus propofol (MP) groups

Table 3. Frequency of Adverse Events in Patients Who Received Propofol Alone (P Group) and in Combination With Midazolam (MP Group) to Prevent the Gag Reflex During Dental Treatment Under Intravenous Sedation†

	<i>P Group</i> (<i>n</i> = 22)	<i>MP Group</i> (<i>n</i> = 34)	<i>p Value</i>
Respiratory depression			
SpO ₂ <90%	0	0	1.000
Cardiovascular changes			
BP (>20 mm Hg change)	7 (31.8%)	2 (5.9%)	.014*
Pulse rate (>50% change)	5 (22.4%)	0	.007*

† Values are presented as number (%). BP indicates blood pressure; SpO₂, oxygen saturation.

* *p* < .05.

morphological differences. It was therefore presumed that variations in vagal nerve innervation or sensitivity were the most likely somatogenic factor.²¹ It remains uncertain whether an overactive gag reflex is associated with sex differences, although a severe gag reflex is reportedly more common in men.²²

Various sedative agents have long been used during dental treatment in patients with a gag reflex. Nitrous oxide inhalation sedation can also help control the gag reflex^{23–25} via its effects on N-methyl-D aspartate receptors.²⁶ In addition, subanesthetic doses of ketamine, which also affect N-methyl-D aspartate receptors, can reduce the gag reflex during endoscopy performed under propofol sedation.²⁷ However, ketamine also increases salivary secretions, which can interfere with dental procedures.

It is known that propofol can suppress the gag reflex at doses lighter than those required for general anesthesia.²⁸ In the current study, we investigated the TCI-predicted cerebral concentration of propofol required for suppression of the gag reflex against a relatively strong gag stimulus (stimulation of the posterior tongue with a dental mirror). Therefore, the required predicted cerebral propofol concentration was higher than that in previous reports, where a weaker gag stimulus was used.²⁹ In our department, we generally use this technique to confirm suppression of the gag reflex in those with an overactive reflex.

In the present study, patients who received combined midazolam and propofol sedation exhibited significantly fewer cardiovascular adverse events with smaller hemodynamic changes compared with those sedated with propofol alone. A previous study demonstrated that intravenous conscious sedation with propofol versus midazolam differed with regard to changes in the heart rate and heart rate variability, with midazolam showing more sympathetic activation than propofol, during the sedation and recovery periods.³⁰

Furthermore, propofol is associated with a higher incidence of cardiovascular and respiratory complications (eg, hypotension, bradycardia, and respiratory depression) compared with other sedatives.³¹ In the present study, the predicted cerebral concentration of propofol required to suppress the gag reflex was lower in the MP group (1.07 ± 0.09 µg/mL) than in the P group (1.67 ± 0.11 µg/mL). This TCI dose was estimated to be an infusion rate of approximately 2 mg/kg/h (33 µg/kg/min) and 3.3 mg/kg/h (55 µg/kg/min) in the MP and P groups, respectively.³² This was probably because the use of a combination of midazolam with propofol produced additive effects and necessitated lower doses of propofol, which may have decreased the incidence of adverse effects associated with the use of a larger dose of propofol.³³ Furthermore, our results support those of the previous study reporting that the combined use of propofol and intravenous midazolam maximized the therapeutic effects of each drug alone.^{34,35}

Our study has several limitations. Because of its retrospective design, a potential bias cannot be completely excluded. Moreover, our sample size of 56 subjects was relatively small, and our data were obtained from a single hospital. Therefore, it may not be possible to generalize our results to patients at other centers. Larger, multicenter, randomized trials are needed to confirm our findings. In addition, patients with psychological disorders or chronic benzodiazepine use were not excluded from the study. Several patients were already taking one or more benzodiazepines preoperatively, and this may have skewed the results. Finally, the relationship between gagging severity and its management in the field of dentistry has been previously studied, with the authors finding that the effects of molar area examination on the gag reflex are indicative of gagging severity and play a key role in treatment selection.²² We perform gag reflex tests before all treatment procedures, including the injection of local anesthesia, to determine gag reflex severity. The actual degree of gag reflex severity was not evaluated or considered in our data analysis, and we believe that this should be considered in future studies.

In conclusion, the findings of the present study suggest that the cardiovascular effects of the combined use of intravenous midazolam administered prior to propofol sedation are milder than those when propofol alone is used to suppress the gag reflex in patients with an overactive gag reflex during dental treatment. Further prospective studies are necessary to determine the ideal sedative technique for suppression of the gag reflex during dental procedures.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest relevant to the content of this report.

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