Remifentanyl in Combination With Propofol Is Suitable for Use in the Dental Outpatient Setting

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Although several adjuncts to the general anesthetic propofol have been proposed, there is insufficient research identifying the ideal agent, and in what dosage, to combine with propofol in dental outpatient anesthesia. Here we examined the combination of remifentanyl or nitrous oxide and propofol in patients with severe dental avoidance undergoing dental treatment in the outpatient setting. Eighty patients were randomized to 4 groups and administered propofol/saline solution (PS; $n = 20$), propofol/remifentanyl 0.25 $\mu\text{g/kg/min}$ (PRe-0.25; $n = 20$), propofol/remifentanyl 0.125 $\mu\text{g/kg/min}$ (PRe-0.125; $n = 20$), or propofol/66% nitrous oxide (PN; $n = 20$). During anesthesia, the bispectral index value was kept between 40 and 60. Body movements and hemodynamic changes during anesthesia, emergence, and recovery as well as anesthetic cost were compared between the combinations. Body movements were observed in all patients administered PS but in no patients administered PRe-0.25, PRe-0.125, or PN. Postoperative nausea was observed in 5 patients (25%) administered PRe-0.25 and in 1 patient (5%) administered PN. Although both PRe-0.125 and PN were useful clinically, PRe-0.125 was the least expensive combination.

Key Words: Propofol; Remifentanyl; Ambulatory anesthesia; Dental anesthesia; Anesthetic cost.

Rapid onset, absence of complications (eg, nausea, vomiting, and delirium), lack of pain after treatment, patient satisfaction, and low cost are universal goals in outpatient anesthesia.¹ In a previous study on the recovery process after general anesthesia, we reported that although time to awakening was longer after general anesthesia with propofol alone than after anesthesia with sevoflurane alone, the total time for recovery did not differ.² Furthermore, although patient satisfaction after propofol anesthesia was superior to that after sevoflurane anesthesia, body movements and hemodynamic fluctuations were observed during anes-

thesia with propofol alone.² Previous reports have documented the usefulness of^{3–6} and problems associated with^{4,7} jointly administering an analgesic agent (eg, nitrous oxide,⁴ fentanyl, remifentanyl,^{3,6} or ketamine) during propofol anesthesia to reduce or prevent adverse events and hemodynamic fluctuations.^{4,5,7} However, few studies have examined the use of propofol in combination with an analgesic agent under mildly invasive surgical conditions such as dental treatment in the outpatient setting.

In this study, we evaluated patients with severe dental avoidance undergoing dental treatment in an outpatient setting. We studied body movements and hemodynamic changes during anesthesia, emergence, and recovery profiles as well as the costs of anesthesia for remifentanyl (0.125 or 0.25 $\mu\text{g/kg/min}$) or 66% nitrous oxide/oxygen in combination with propofol.

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METHODS

Patients

This study was approved by the Ethics Review Board of Tokyo Dental College Ethics Committee (approval No. 267). Eighty patients with severe dental avoidance, including those with dental phobia, gagging problems, or both, were enrolled in the study. All patients gave written informed consent to participate in the study. The patients were randomly assigned to 1 of 4 groups and administered propofol/saline solution (PS group; $n = 20$), propofol/remifentanyl 0.25 $\mu\text{g}/\text{kg}/\text{min}$ (PRe-0.25 group; $n = 20$), propofol/remifentanyl 0.125 $\mu\text{g}/\text{kg}/\text{min}$ (PRe-0.125 group; $n = 20$), or propofol/66% nitrous oxide (PN group; $n = 20$). All patients were classified as American Society of Anesthesiologists physical status 1 or 2. Patients were excluded if they had a prior history of alcohol or drug dependence or psychiatric disease or had undergone invasive treatments such as impacted tooth extraction.

Method of Anesthesia

Patients entered the outpatient treatment room without premedication where standard monitors were applied: electrocardiograph, noninvasive blood pressure, and peripheral oxygen saturation, as well as bispectral index (BIS). An intravenous line was established in the left cephalic vein, and acetated Ringer's solution was infused at 2 to 4 mL/kg/h. Anesthesia was induced with propofol (1% Diprivan injection kit, AstraZeneca, London, UK) by using a target controlled infusion pump (Terufusion TCI syringe pump TE-371, Terumo Corporation, Tokyo, Japan) set to a target effect-site concentration of 3.5 $\mu\text{g}/\text{mL}$ with oxygen inhalation at 6 L/min. Nasotracheal intubation was facilitated with 0.9 mg/kg rocuronium bromide (Eslax intravenous solution, Schering-Plough, Kenilworth, NJ). In the PN group, oxygen and nitrous oxide were delivered during maintenance of anesthesia at 1 and 2 L/min, respectively. In the other 3 groups, oxygen and air were delivered at 1 and 3 L/min, respectively. The propofol concentration was adjusted to keep the BIS value between 40 and 60. The rate of administration of remifentanyl via separate infusion pump and the inhalation concentration of nitrous oxide were fixed during treatment. Patients were artificially ventilated, and tidal volume and respiratory rate were adjusted to maintain the end-tidal carbon dioxide tension between 35 and 45 mm Hg. When body movements such as bucking or tremor in the hand or foot were observed during treatment, a bolus injection (0.2 mg/kg)

of the paralytic rocuronium bromide was administered. When the mean blood pressure dropped to 50 mm Hg or less, patients received a bolus of 4 mg ephedrine hydrochloride as needed. Lidocaine hydrochloride solution containing 1:80,000 epinephrine was used for local anesthesia during dental procedures such as caries treatment, pulp extirpation, and tooth extraction. An intravenous injection of 50 mg flurbiprofen axetil was administered at the completion of anesthesia. Extubation was performed after confirming the return of spontaneous respiration, reaction to verbal commands, and appearance of the deglutition reflex.

Observation Periods and Measurements

The study period was divided into 4 observation periods: maintenance, emergence, recovery, and follow-up after discharge. The maintenance period was set as the period from induction of anesthesia to cessation of propofol administration. Body movements such as bucking or tremor in the hand or foot, number of rocuronium bromide administrations, and total dosage of propofol were recorded during this period. During this maintenance period, changes in blood pressure and heart rate over time were also observed. Systolic blood pressure, diastolic blood pressure, mean blood pressure, and heart rate at the time of entry into the treatment room were set as the preanesthesia values. Observations were made at 45 and 90 minutes after intubation, at the completion of anesthesia, and immediately before extubation.

The emergence period was set as the period from cessation of anesthetic drug administration to extubation. Time to return of spontaneous respiration, time to BIS value at 75, time to eye opening, and time to extubation were recorded during this period.⁸

The recovery period was set as the period from extubation to discharge. Time to ambulation and time to discharge were recorded. The Aldrete score⁹ and modified Post-Anesthesia Discharge Scoring System score¹⁰ were recorded every 5 minutes, and ambulatory tests were carried out when each of the scores was 9 or greater. Patients were discharged in accordance with the discharge scoring system for home readiness described by Chung et al.¹⁰

For the follow-up period after discharge, inquiries were made by telephone about the patient's general condition 24 hours after anesthesia on the basis of a postgeneral anesthesia checklist given to the patient at the time of discharge. Occurrences and frequency of postoperative nausea and vomiting were recorded.

Anesthetic cost was estimated by summing the cost for each anesthetic on the basis of the amounts administered

Table 1. Patient Characteristics*

	PS	PRe-0.25	PRe-0.125	PN
Number	20	20	20	20
Age, y	31.9 (8.3)	32.3 (7.3)	35.2 (10.5)	35.6 (8.9)
Gender, male:female	11:9	11:9	11:9	10:10
Height, cm	163.3 (6.8)	163.1 (6.8)	162.8 (9.6)	164.8 (10.1)
Weight, kg	58.0 (13.6)	57.5 (10.6)	61.2 (15.8)	62.1 (16.6)
Body mass index, kg/m ²	21.4 (4.1)	21.3 (3.5)	22.5 (4.5)	22.3 (4.0)
Duration of treatment, min	241.1 (39.1)	243.6 (57.5)	247.5 (73.0)	257.6 (66.2)
Duration of anesthesia, min	282.9 (37.8)	282.7 (57.4)	286.1 (75.9)	300.1 (75.8)
Number of treated teeth [under local anesthesia]	9.4 (1.2) [4.5 (1.3)]	9.2 (1.3) [4.4 (1.1)]	9.2 (1.2) [4.3 (1.3)]	8.9 (1.9) [4.0 (1.4)]

* No significant differences in patient background among the 4 groups. Values are mean (SD). PS indicates propofol/saline solution; PRe-0.25, propofol/0.25 µg/kg/min remifentanyl; PRe-0.125, propofol/0.125 µg/kg/min remifentanyl; and PN, propofol/66% nitrous oxide.

and reported in US dollars per kilogram bodyweight per hour of anesthesia.

Statistical Analysis

Repeated-measures analysis of variance and Dunnett's test were used for intragroup comparisons of hemodynamic fluctuations at various times. The $M \times n \chi^2$ test was used to compare occurrence frequencies of nausea and vomiting. An independent analysis of variance and the Student–Newman–Keuls test were used to compare other measurements between groups. $P < .05$ was considered statistically significant. The target sample size in this study was 20 patients per group because 18 was deemed sufficient for detecting differences with a power of 0.8 from our previous study.²

RESULTS

There were no significant differences in patient characteristics among the 4 groups (Table 1).

During anesthesia, all patients in the PS group developed body movements such as bucking or tremor in the hand or foot. In contrast, none of the patients in the other 3 groups developed such movements (Table 2).

Table 2. Body Movements During Anesthesia†

	PS	PRe-0.25	PRe-0.125	PN
Number of cases with body movements	20	0	0	0
Number of rocuronium bromide doses	6.4 (2.0)	0*	0*	0*
Total dose of rocuronium bromide, mg [mg/kg]	72.5 ± 2.4 [1.3 ± 0.4]	0 [0]	0 [0]	0 [0]
Propofol used, mg/kg/h	9.0 (1.4)	7.1 (1.0)*	7.1 (0.6)*	7.5 (1.0)*

† Body movements were seen in the PS group during the procedure. Values are mean (SD). PS indicates propofol/saline solution; PRe-0.25, propofol/0.25 µg/kg/min remifentanyl; PRe-0.125, propofol/0.125 µg/kg/min remifentanyl; and PN, propofol/66% nitrous oxide.

* $P < .05$ versus group PS.

Furthermore, the number of doses of rocuronium bromide administered was significantly higher in the PS group than in the other 3 groups ($P < .05$; Table 2).

Systolic blood pressure, mean arterial pressure, diastolic blood pressure, and heart rate were significantly lower at 45 and at 90 minutes after intubation and at completion of anesthesia than during the preanesthesia period in the PRe-0.25, PRe-0.125, and PN groups (Table 3). In contrast, no significant changes were observed in the PS group in any of the hemodynamic parameters at any of the time points examined (Table 3). Ephedrine hydrochloride was not administered to any of the patients.

In the emergence period, time to return of spontaneous respiration was significantly longer in the PRe-0.25 and PRe-0.125 groups than in the PS and PN groups. No significant differences were observed among the 4 groups in time to BIS value at 75, time to eye opening, or time to extubation (Table 4).

In the recovery period, no significant differences were observed in the time to ambulation or time to discharge among the 4 groups (Table 5).

Five patients (25%) reported postoperative nausea within 24 h after anesthesia in the PRe-0.125 group. This number was significantly more ($P < .05$) than in the other 3 groups (Table 5). No other complications were reported in any of the groups following discharge.

Table 3. Hemodynamic Parameters During Anesthesia†

	<i>Preanesthesia</i>	<i>45 Min After Intubation</i>	<i>90 Min After Intubation</i>	<i>Completion of Anesthesia</i>	<i>Directly Before Extubation</i>
SBP					
PS	128.3 (24.0)	121.3 (14.6)	116.4 (17.0)	117.7 (17.8)	118.8 (16.8)
PRe-0.25	122.8 (22.2)	83.3 (8.7)*	85.9 (7.8)*	95.5 (18.0)*	114.7 (14.6)
PRe-0.125	131.7 (21.9)	87.0 (11.3)*	87.3 (7.8)*	91.5 (13.6)*	122.9 (15.3)
PN	119.4 (19.0)	98.1 (15.2)*	94.1 (12.0)*	100.4 (11.6)*	111.4 (20.6)
MAP					
PS	95.6 (18.1)	91.6 (11.8)	91.9 (13.2)	88.4 (15.2)	88.4 (14.1)
PRe-0.25	91.8 (19.0)	60.9 (6.1)*,**	61.1 (5.2)*,**	69.7 (12.9)*	87.1 (12.5)*
PRe-0.125	98.4 (19.2)	62.5 (8.1)*,**	61.7 (7.6)*,**	64.8 (10.5)*,**	79.7 (12.9)*
PN	88.5 (12.9)	71.8 (13.0)*	71.4 (12.8)*	72.5 (9.0)*	81.8 (16.6)*
DBP					
PS	79.1 (15.8)	76.7 (11.3)	70.8 (10.5)	70.7 (14.7)	72.2 (13.9)
PRe-0.25	76.4 (17.5)	49.7 (5.7)*	50.0 (5.0)*	56.7 (11.8)*	73.3 (12.4)
PRe-0.125	81.4 (18.2)	50.5 (8.7)*	49.2 (9.0)*	51.6 (9.6)*	64.0 (13.9)
PN	73.7 (11.3)	58.7 (12.3)*	56.4 (9.8)*	59.3 (8.3)*	69.9 (15.1)
HR					
PS	94.4 (19.3)	98.4 (16.5)	92.0 (16.6)	87.2 (12.2)	86.0 (13.0)
PRe-0.25	87.3 (17.5)	62.2 (9.8)*	56.0 (7.6)*	62.8 (17.4)*	81.2 (14.4)
PRe-0.125	87.5 (18.4)	64.7 (10.0)*	58.1 (10.6)*	57.3 (9.8)*	82.8 (15.4)
PN	86.9 (19.1)	75.6 (10.4)*	70.6 (9.8)*	69.6 (11.8)*	87.0 (17.1)

† Hemodynamic parameters during the procedure were significantly lower than the control. Values are mean (SD). PS indicates propofol/saline solution; PRe-0.25, propofol/0.25 µg/kg/min remifentanyl; PRe-0.125, propofol/0.125 µg/kg/min remifentanyl; PN, propofol/66% nitrous oxide; SBP, systolic blood pressure; MAP, mean arterial pressure; DBP, diastolic blood pressure; and HR, heart rate.

* $P < .05$ versus control; ** $P < .05$ versus group PN.

Total anesthetic cost was lowest in the PRe-0.125 group (Table 6).

DISCUSSION

In this study of patients with severe dental avoidance undergoing dental treatment in the outpatient setting, we compared the effects of different combinations of the general anesthetic propofol with an analgesic (0.25 or 0.125 µg/kg/min remifentanyl, or nitrous oxide) on body movements and hemodynamic changes during anesthesia, emergence, and recovery as well as on the overall anesthetic costs.

Body movements were observed during anesthesia in all patients administered PS, and rocuronium bromide was administered in all cases. In contrast, no body

movements were observed during anesthesia in patients administered PRe (0.25 or 0.125 µg/kg/min) or PN. Propofol increases inhibitory neurotransmission via gamma-aminobutyric acid receptors to produce a hypnotic action without analgesia. Remifentanyl is a µ-receptor agonist that has an analgesic effect comparable to that of fentanyl.¹¹ Nitrous oxide inhibits the function of N-methyl-D-aspartic acid receptors¹² and activates α_{2B} adrenoceptors to produce an analgesic effect.¹³ It is therefore likely that the suppression of propofol-induced body movements observed in the present study with the addition of adjunct agents was due to the analgesic actions of remifentanyl and nitrous oxide inducing an increased depth of anesthesia that was not reflected in the BIS values.^{14–16}

Remifentanyl is known to decrease heart rate and blood pressure through vagotonic and sympatholytic

Table 4. Emergence Profile†

	<i>PS</i>	<i>PRe-0.25</i>	<i>PRe-0.125</i>	<i>PN</i>
Spontaneous respiration, s	255.3 (154.1)	660.8 (358.4)*	647.8 (149.9)*	326.7 (235.9)
BIS ≥ 75, s	634.4 (345.7)	757.9 (344.2)	751.9 (193.7)	744.9 (464.5)
Eye opening, s	670.2 (325.0)	862.7 (430.2)	778.1 (302.2)	825.5 (395.8)
Extubation, s	817.0 (326.2)	1094.8 (475.8)	1010.8 (313.0)	1002.8 (459.6)

† The time to the appearance of spontaneous breathing was significantly longer in the PRe-0.25 group and PRe-0.125 group than in the PS group and PN group. Values are the mean (SD). PS indicates propofol/saline solution; PRe-0.25, propofol/0.25 µg/kg/min remifentanyl; PRe-0.125, propofol/0.125 µg/kg/min remifentanyl; and PN, propofol/66% nitrous oxide.

* $P < .05$ versus group PS and PN.

Table 5. Recovery Profiles*

	PS	PRe-0.25	PRe-0.125	PN	Statistics
Time to ambulation, min	43.7 (12.5)	51.4 (24.3)	44.3 (16.6)	49.6 (48.7)	ns
Discharge time, min	193.9 (44.7)	198.2 (47.3)	161.5 (40.6)	169.2 (70.1)	ns
Incidence of nausea, <i>n</i>	0	5	0	1	<i>P</i> < .05

* No significant difference was found among the 4 groups in the time to ambulation, the discharge time, or patient satisfaction. Postoperative nausea was observed in 5 cases (25%) in the PRe-0.25 group. Values are mean (SD). PS indicates propofol/saline solution; PRe-0.25, propofol/0.25 µg/kg/min remifentanyl; PRe-0.125, propofol/0.125 µg/kg/min remifentanyl; and PN, propofol/66% nitrous oxide.

effects.¹⁷ In the present study, decreases in blood pressure and heart rate of approximately 30% were observed in the PRe-0.25 and PRe-0.125 groups. This is similar to the results of previous reports indicating that hemodynamic inhibition by remifentanyl is dose independent.¹⁸

In contrast, nitrous oxide has been shown to produce hemodynamic activation via a sympathomimetic effect.¹⁹ However, in the present study, hemodynamic parameters were suppressed rather than activated in the PN group. This suggests that in addition to promoting hemodynamic stability by inhibiting noxious stimuli, nitrous oxide also prevented hemodynamic fluctuations by producing an increased depth of anesthesia not reflected in the BIS values.^{14–16} In the present study, ephedrine hydrochloride did not need to be administered to any of the patients because the severity of hemodynamic depression was not clinically relevant.

Spontaneous respiration returned more quickly in the PS and PN groups than in the PRe groups. However, the longer time to return in the PRe groups was not clinically relevant because the recovery profiles were comparable in all 4 groups. The advantages of using a combination of propofol and remifentanyl for outpatient anesthesia are well known. Milne et al⁶ reported a dose-dependent decrease in propofol requirement with increasing remifentanyl concentration. Brady et al³ reported that propofol in combination with remifentanyl is more cost effective and results in earlier discharge from hospital. Similarly, in the present study, concomitant use of

remifentanyl was propofol sparing and times to discharge were comparable to those of the PS and PN groups.

The nausea and vomiting associated with opioids is due to stimulation of central dopamine type 2 (D2) receptors, which in turn stimulates the vomiting center of the brain in the medulla oblongata.²⁰ Nausea and vomiting occur less often with remifentanyl than with fentanyl.²¹ Propofol has been reported to reduce postoperative nausea and vomiting via an antiemetic action mediated by antagonism of D2 receptor mechanisms.⁵ In the present study, no nausea was reported in the PRe-0.125 group, presumably because the opposing pharmacologic actions of remifentanyl and propofol were balanced. In contrast, postoperative nausea was reported by 5 patients (25%) in the PRe-0.25 group, indicating that remifentanyl-induced nausea may be dose dependent. Nitrous oxide also has an emetic action,²² which propofol administration is reported to counteract.^{23,24} In the present study, no cases of vomiting and 1 case (5%) of nausea were seen in the PN group, consistent with previous reports.^{23,24}

In the present study, propofol-induced body movements were suppressed by administration of PRe-0.125 or PN without affecting the emergence and recovery profiles of propofol. The level of respiratory and hemodynamic depression observed with the combinations assessed did not necessitate the administration of ephedrine hydrochloride. PRe-0.125 was the least expensive of the combinations assessed. Although the clinical effects of PN were comparable with those of

Table 6. Anesthetic Cost†

	PS	PRe-0.25	PRe-0.125	PN
Propofol, US dollar/kg/h	0.32 (0.05)	0.25 (0.04)*	0.25 (0.02)*	0.26 (0.04)*
Additional rocuronium bromide, US dollar/kg/h	0.037 (0.02)	—	—	—
Remifentanyl, US dollar/kg/h	—	0.15	0.07	—
Nitrous oxide, US dollar/kg/h	—	—	—	0.14
Total, US dollar/kg/h	0.37 (0.06)**	0.41 (0.04)*,**	0.33 (0.02)	0.40 (0.04)*,**

† The anesthetic cost was lowest for the PRe-0.125 group. Values are mean (SD). 1 US dollar = 123 Japanese Yen. PS indicates propofol/saline solution; PRe-0.25, propofol/0.25 µg/kg/min remifentanyl; PRe-0.125, propofol/0.125 µg/kg/min remifentanyl; and PN, propofol/66% nitrous oxide. 2015.7.29 Official rate: 1 US dollar = 123 Japanese Yen. Propofol: 500 mg/2208 Japanese Yen = 18.0 US dollar. Remifentanyl: 2 mg/6011 Japanese Yen = 48.9 US dollar. Rocuronium bromide: 50 mg/2500 Japanese Yen = 20.3 US dollar. Nitrous oxide: 1L/9 Japanese Yen = 0.07 US dollar.

* *P* < .05 versus group PS; ** *P* < .05 versus group PRe-0.125.

PRE-0.125, nitrous oxide may be an environmental pollutant.^{25,26}

In conclusion, of the combinations assessed in the present study, we recommend the combination of propofol and 0.125 µg/kg/min remifentanyl for general anesthesia in patients with severe dental avoidance undergoing dental treatment in the outpatient setting.

Conflict of Interest

None declared.

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