Original Article

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Managing general anesthesia for low invasive dental procedures while maintaining spontaneous respiration with low concentration remifentanil: a cross-sectional study

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Background: We assessed the relationship between patient age and remifentanil dosing rate in patients managed under general anesthesia with spontaneous breathing using low-dose remifentanil in sevoflurane.

Methods: The participants were patients with an American Society of Anesthesiologists Physical Status of 1 or 2 maintained under general anesthesia with low-dose remifentanil in 1.5-2.0% sevoflurane. The infusion rate of remifentanil was adjusted so that the spontaneous respiratory rate was half the rate prior to the induction of anesthesia, and γ^H (μg/kg/min) was defined as the infusion rate of remifentanil under stable conditions where the respiratory rate was half the rate prior to the induction of anesthesia for $\geq$ 15 minutes. The relationship between γ^H and patient age was analyzed statistically by Spearman's correlation analysis.

Results: During dental treatment under general anesthesia using low-dose remifentanil in sevoflurane, a significant correlation was detected between γ^H and patient age. The regression line of $y = -0.00079x + 0.066$ (y-axis; γ^H, x-axis; patient's age) was provided. The values of γ^H provide 0.064 μg/kg/min at 2 years and 0.0186 μg/kg/min at 60 years. Therefore, as age increases, the dosing rate exhibits a declining trend. Furthermore, in the dosing rate of remifentanil when the patient's respiratory rate was reduced by half from the preanesthetic respiratory rate, the dosing rate provided was around 0.88 mL/h in all ages if the remifentanil was diluted as 0.1 mg/mL. $EtCO_2$ showed 51.0 ± 5.7 mmHg, and SpO_2 was controlled within the normal range by this method. In addition, all dental treatments were performed without major problems, such as awakening and body movement during general anesthesia, and the post-anesthetic recovery process was stable.

Conclusion: General anesthesia with spontaneous breathing provides various advantages, and the present method is appropriate for minimally invasive procedures.

Keywords: Age; Minimally Invasive Surgical Procedures; Remifentanil; Sevoflurane; Spontaneous Respiration.

INTRODUCTION

Remifentanil is a widely used ultra-short-acting opioid analgesic that causes severe respiratory depression. However, low concentrations of remifentanil that are used under sedation with artificial ventilation in the ICU have been reported to improve respiratory patterns, reduce the workload on the respiratory muscles while maintaining spontaneous respiration [1], suppress stress hormone secretion, secure urine volume during perioperative management, and effectively prevent hyperglycemia [2].

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Furthermore, the coadministration of remifentanil with propofol at a dose of 0.05-0.1 μg/kg/min allowed for intravenous sedation while maintaining spontaneous respiration and was effective in suppressing an abnormal gag reflex [3].

Low concentrations of remifentanil are often used with sevoflurane [4,5,6] or propofol [7,8,9] to maintain general anesthesia under spontaneous respiration. Many previous case reports were limited to specific age groups, such as children [4,5,8,9] and adults [6,7], with no examination of the correlation between administration rates across all age groups (from infants to adults). Based on the above findings, we maintained general anesthesia in all age groups using a low concentration of remifentanil, at which the spontaneous respiration rate was half of the rate prior to the induction of anesthesia. Based on this large amount of data, we hypothesized that the maintenance dose of remifentanil at which the spontaneous respiration rate becomes half of the rate prior to the induction of anesthesia could be predicted at any age by obtaining a regression line for age and maintenance dose of remifentanil.

METHODS

This was a cross-sectional study (case series). The participants included patients who had been treated in the previous 5 years (2015-2020) at our university and affiliated clinics for whom dental treatment while maintaining consciousness was difficult due to dental phobia, abnormal gag reflex, intellectual disability, or refusal of treatment (in the case of children), and those classified as grades 1-2 according to the American Society of Anesthesiologists Physical Status (ASA-PS) classification system. General anesthesia was maintained with spontaneous breathing using low concentrations of remifentanil and 1.5–2.0% sevoflurane alone. Patients undergoing highly invasive surgeries, such as those involving the jawbone, were excluded from the study. The participants were limited to those who underwent conservative treatment, prosthetic treatment, or simple extraction under general anesthesia. For procedures accompanied by pain, infiltration anesthesia was administered as required. This study was approved by the Ethics Committee of Ohu University (approval number: 186). The informed consent, which was approved by this Committee, was obtained from all participants in this study. The authors declare no conflicts of interest.

A total of 200 patients were included in this study. General anesthesia was induced in all 200 patients at an oxygen rate of 2 L/min, nitrous oxide rate of 4 L/min, and sevoflurane at 5% and maintained using sevoflurane at 1.0-1.5% following endotracheal intubation. At the same time, the administration of remifentanil, which was adjusted to a dosing rate of 0.01-0.1 μg/kg/min, was started. Around 20-40 minutes later, when the spontaneous respiration rate decreased by ~30% compared with that prior to the induction of anesthesia, administration of nitrous oxide was discontinued, and only oxygen was administered at 6 L/min, whereas sevoflurane was increased by 1.5-2.0% and maintained at that value. Thereafter, the infusion rate was adjusted such that γ^H was the infusion rate of remifentanil (μg/kg/min) at which the spontaneous respiration rate was half of the rate prior to the induction of anesthesia and remained stable for ≥ 15 minutes. A 2 mg vial of remifentanil was diluted with 20 mL of physiological saline and continuously administered with a syringe pump to a dose of 0.1 mg/mL. The volume of fluid that was administered was in the range–40-60 mL/h. The infusion rate of remifentanil was calculated based on actual body weight for patients with a body mass index (BMI) of ≤ 25 kg/m^2 and standard body weight for patients with a BMI of ≥ 25 kg/m^2. Pain treatment procedures were performed under local anesthesia; however, patients with obvious fluctuations in heart rate, blood pressure, and respiration were excluded because local anesthesia was not successfully administered. The respiratory rate prior to the induction of anesthesia (RRcont), (γ^H), the respiratory rate at which the infusion rate was stable (RRremi), the amount of carbon dioxide in exhaled air

Table 1. Subjects background

Subjects number	200
Sex (M / F)	101 / 99
Age (yr)	29.2 ± 20.3 (3-62)
Body height (cm)	145.1 ± 23.0 (87-182)
Body weight (kg)	44.4 ± 21.1 (13-105)
ASA -PS	1 or 2

mean ± SD (Min − Max).
ASA-PS, The American Society of Anesthesiologists Physical Status. F, female; M, male. Other data during spontaneous general anesthesia.

Table 2. Other data during spontaneous general anesthesia

RRcont (breath/min)	18.9 ± 4.1 (12-30)
γ^H (μg/kg/min)	0.042 ± 0.019 (0.016-0.093)
RRremi (breath/min)	8.3 ± 2.8 (4-18)
$EtCO_2$ (mmHg)	51.0 ± 5.7 (36-63)
SpO_2 (%)	99.4 ± 0.8 (96-100)

mean ± SD (Min − Max).
RRcont, The respiratory rate prior to the induction of anesthesia; γ^H, The remifentanil dosing rate that reduced preanesthesia spontaneous respiratory rate by half; RRremi, The respiratory rate at which the infusion rate was stable; $EtCO_2$, End tidal CO_2; SpO_2, Saturation of percutaneous oxygen.

($EtCO_2$), and oxygen saturation (SpO_2) were measured. The Spearman's correlation test was performed to statistically analyze the relationship between patients' γ^H and age. For the multivariate analysis, multiple regression analysis with the dosing rate of remifentanil at half of the preanesthetic respiratory rate (mL/h at 0.1 mg/mL) was used as the dependent variable. Variable selection was based on the forced input method. Data were analyzed using IBM SPSS version 29 for Windows (IBM, Armonk, NY, USA). Statistical significance was set at $P < 0.05$.

The free software G-power was used to calculate the sample size. In the t-test for Spearman's correlation, the effect size, alpha error probability, and power were set to 0.25, 0.05, and 0.95, respectively. The total sample size and power were 197 and 0.950, respectively. For the F-tests of the linear multiple regression, the effect size, alpha error probability, power, and number of predictors were set to 0.15, 0.05, 0.95, and two, respectively. The total sample size and power were 107 and 0.952, respectively. Therefore, the sample size of this study was confirmed to be sufficient.

RESULTS

Data from 286 patients were analyzed in this study. Fifteen patients were excluded because anesthesia-related agents other than sevoflurane, nitrous oxide, and remifentanil were administered during general anesthesia. Thirty-three patients were excluded because their respiratory and circulatory conditions could not be stabilized for more than 15 min, the treatment time was too short, or the effect of local anesthesia was insufficient. Thirty-eight patients were excluded because the data of γ^H or BMI data were outside the box-and-whisker plot of the initial data. Therefore, 86 patients were excluded from the study, and quality data from 200 patients were evaluated.

Participants' backgrounds are listed in Table 1. The mean age of the patients was 29.2 (± 20.3 SD) years, ranging from 3 years 2 months to 62 years. The mean body weight was 44.4 (± 21.1 SD) kg, ranging from 13 kg to 105 kg. In all patients who were included in this study, general anesthesia was maintained with spontaneous respiration using a low-concentration remifentanil infusion, which allowed dental treatment without any major problems, such as intraoperative awakening or body movement. No postoperative abnormalities or problems were observed in any patient after regaining consciousness. The data obtained during spontaneous general anesthesia are shown in Table 2. The SpO_2 level during the maintenance of general anesthesia under spontaneous respiration with low concentration remifentanil varied between 96% and 100%, and the mean $EtCO_2$ was 51.0 mmHg (± 5.7 SD).

The Spearman's correlation test with age on the x-axis and γ^H expressed as μg/kg/min on the y-axis (Fig. 1) revealed a significant negative correlation between the two variables ($r_S = 0.82$, $P = 2.1^{-49}$), and a regression line of $y = -0.00079x + 0.066$ was obtained. The γ^H corresponding to the age of 2 years was 0.064 μg/kg/min, as shown by the regression line and that corresponding

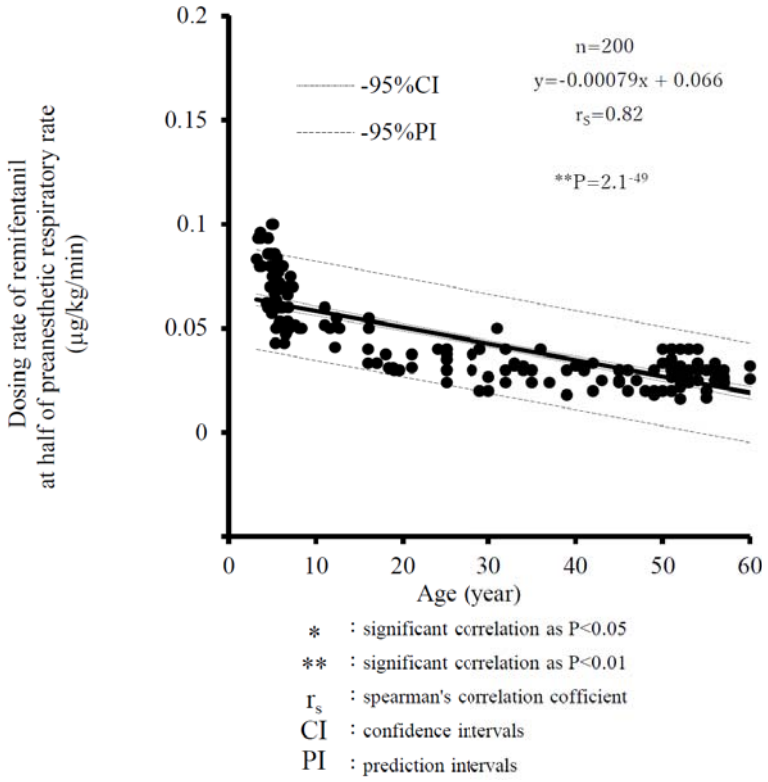

Fig. 1. Relationship between age and dosing rate of remifentanil (μg/kg/min)

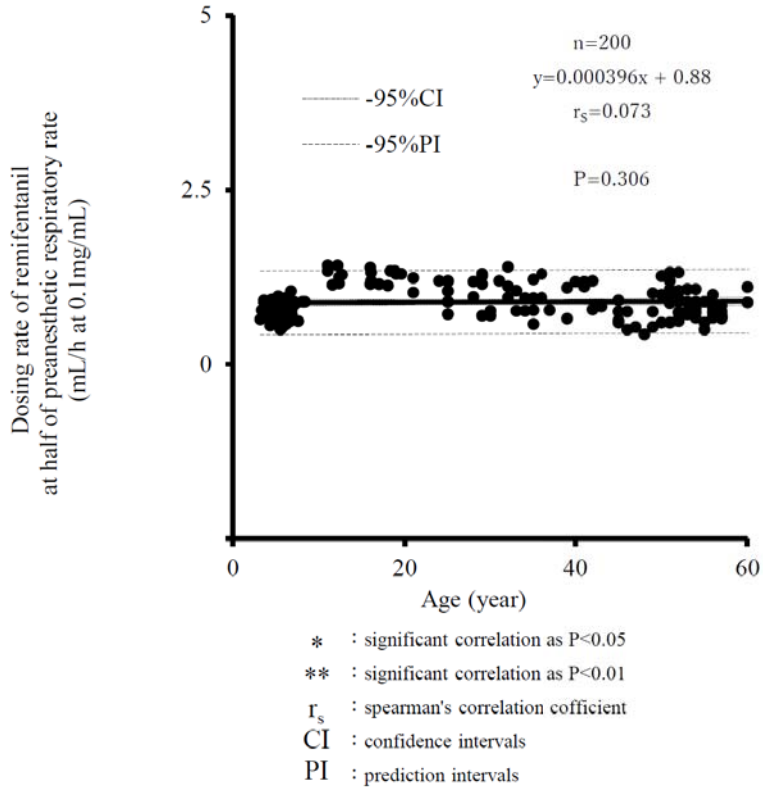

Fig. 2. Relationship between age and dosing rate of remifentanil (mL/h at 0.1mg/mL)

Table 3. Multiple regression analysis on dosing rate of remifentanil (mL/h at 0.1 mg/mL)

	β	P value	95%CI	
			Lower	Upper
Age	-0.101	0.164	< 0.001	< 0.001
Sex	-0.025	0.729	-0.082	0.058

Dependent variable was dosing rate of remifentanil at half of preanesthetic respiratory rate (mL/h at 0.1 mg/mL). β, standardized partial regression coefficient; CI, confidence interval.

to 60 years was 0.0186 μg/kg/min. This demonstrates that the remifentanil dosing rate decreases with increasing age.

Moreover, when the infusion rate of remifentanil diluted to 0.1 mg/mL was changed to mL/h, γ^H was used as the vertical axis and the patient's age was used as the horizontal axis. Spearman's correlation analysis (Fig. 2) showed no increasing or decreasing changes. Therefore, there was no significant correlation between γ^H expressed in mL/h and patient age (r_S = 0.073, P = 0.306). The obtained regression line of y = 0.000396x + 0.88 showed that γ^H expressed as mL/h did not increase or decrease with age and that γ^H was around 0.88 mL/h at any age (Fig. 2).

Table 3 shows the results of multiple regression analysis with the dosing rate of remifentanil (mL/h at 0.1 mg/mL) as the dependent variable. Age and sex were not significant independent variables for the dosing rate of remifentanil at half the pre-anesthetic respiratory rate.

DISCUSSION

The regression equation y = − 0.00079x+0.066 (x-axis: age, y-axis: γ^H in μg/kg/min) enabled us to calculate γ^H in μg/kg/min, which was best adjusted for the patient's age. Minimally invasive procedures, such as dental procedures, can be performed by maintaining anesthesia with the respiratory rate controlled at approximately half of that at preanesthetic levels. Moreover, when using remifentanil, diluted to 0.1 mg/mL, the initial dosing rate was approximately 0.88 mL/h for all age groups. The dose for continuous infusion is usually expressed as μg/kg/min per body weight. However, when administering drugs to patients, the diluent is placed on a syringe pump, and the dose is set to mL/h. Remifentanil is usually administered continuously as a 0.1 mg/mL dilution using a syringe pump. Therefore, it is interesting that the remifentanil infusion rate, which reduces the spontaneous respiration rate to half that before induction of anesthesia, can be achieved regardless of age or physique by simply setting the syringe pump to about 0.88 mL/h. Furthermore, by making small adjustments according to the degree of the patient's respiratory depression, anesthesia can be maintained with the respiratory rate controlled at approximately half of the preanesthetic respiratory rate. This maintenance method is also effective during the final stage of the procedure to reinduce spontaneous breathing in the patient; however, stabilization of the spontaneous respiratory rate after changing the dosing rate may require approximately 20-40 min.

Compared with general anesthesia with positive pressure ventilation, the maintenance of spontaneous ventilation is associated with a lesser degree of decreased venous return and unequal ventilation perfusion ratio [10,11]. Furthermore, as reported by Osaka et al. [12], the presence of spontaneous ventilation or $EtCO_2$ values during spontaneous ventilation under general anesthesia provides valuable data regarding the depth of general anesthesia or the state of invasion. Numerous studies have recommended anesthetic management under spontaneous respiration to maintain pulmonary blood flow in patients with pulmonary hypertension. Patients with pulmonary hypertension managed with regional anesthesia and propofol-ketamine without aggravation of hemodynamics through spontaneous respiration [13], and patients managed with sevoflurane and ketamine without elevation of pulmonary vascular resistance during general anesthesia by preserving spontaneous respiration [14] were reportedly successfully managed with adequate pulmonary blood flow. Based on these findings, spontaneous ventilation during general anesthesia may have several advantages.

Our findings showed that increased age was associated

with a gradual decrease in the remifentanil dosing rate that is required to reduce the spontaneous respiration rate to half of the preanesthetic respiratory rate (γ^H). Peacock et al. [7] varied the remifentanil and propofol infusion rates and reported adequate spontaneous respiration in 88% of the study's 64 participants who were aged 18-65 years by remifentanil of 0.026-0.053 μg/kg/min. Barker et al. [8] also examined the relationship between age and remifentanil dose rate as associated with the occurrence of spontaneous respiration in propofol-remifentanil anesthesia. According to their study, spontaneous breathing occurred when remifentanil was administered at 0.192 μg/kg/min for children aged 0.5-3 years, 0.095 μg/kg/min for children aged 3-6 years, and 0.075 μg/kg/min for children aged 6-9 years, which is generally consistent with our results for patients aged 3 years old and over. Furthermore, in a study of 32 children aged 2-7 years undergoing conservative dental treatment, Ansermino et al. [4] reported that for general anesthesia combined with the coadministration of remifentanil and sevoflurane, the mean dosing rate before the disappearance of spontaneous breathing was 0.127 μg/kg/min. These results are also consistent with ours, in which we determined the dosing rate of remifentanil that would reduce the spontaneous respiration rate to half of the preanesthetic respiratory rate.

Shen et al. [5] found that for general anesthesia with spontaneous breathing in children in whom remifentanil at a mean dosing rate of 0.036 μg/kg/min was co-administered with sevoflurane, the mean $EtCO_2$ was 53 mmHg. Moreover, compared with general anesthesia with sevoflurane alone, the time to awakening was 9 min shorter, and the incidence of post-extubation airway obstruction was significantly lower. Hu et al. [6] reported that the administration of general anesthesia with spontaneous breathing in adults who were co-administered remifentanil at a mean dosing rate of 0.028 μg/kg/min with sevoflurane resulted in a mean $EtCO_2$ of 52 mmHg, a shorter time to awakening (4 min shorter than that in general anesthesia with sevoflurane alone), and a significantly lower incidence of post-extubation airway obstruction. Furthermore, Shen et al. [9] reported that for tracheal foreign object removal in 65 children under general anesthesia with propofol-remifentanil and spontaneous breathing, the mean $EtCO_2$ was 59 mmHg but was safely controlled. As indicated by the above reports, $EtCO_2$ tends to be higher in general anesthesia with spontaneous breathing using a low concentration of remifentanil; however, $EtCO_2$ of 53 ± 6 mmHg can be safely managed based on the concepts of permissive hypercapnia [15,16]. Therefore, general anesthesia with spontaneous ventilation using low concentrations of remifentanil that is co-administered with sevoflurane is considered a safe method that shortens the time to awakening and is associated with a low incidence of post-extubation airway obstruction. In contrast, conscious intubation is recommended to secure the airways in patients with difficult intubation. Appropriate sedation and preservation of spontaneous breathing are the principles of conscious intubation [17]. Among these, opioids such as remifentanil are often used to alleviate pain [18,19]. However, excessive opioid administration can easily stop spontaneous respiration. Therefore, controlling the administration rate is important to preserve spontaneous respiration. The administration rates of remifentanil in these studies were within the ranges specified in this report. In addition, the age-adjusted rate shown in this study would be useful for setting an appropriate opioid administration rate to preserve spontaneous breathing.

Nevertheless, a higher concentration of remifentanil is required for some procedures, such as highly invasive surgeries, making management with spontaneous ventilation impossible. Therefore, this method of maintaining general anesthesia using a low concentration of remifentanil that preserves spontaneous ventilation is considered feasible for minimally invasive procedures, such as dental treatments, which can be performed without inducing pain, as local anesthesia induces a sufficient response.

Multiple regression analysis adjusted for sex also showed that the dosing rate of remifentanil at half the preanesthetic respiratory rate was not correlated with age. BMI was not used as an independent variable because

the dosing rate of remifentanil in obese patients was calculated from the standard body weight based on a BMI of 22 kg/m^2, which was not associated with the actual BMI. Moreover, this regression equation is only an estimate for setting the dosing rate, and the precise concentration or dosing rate must be adjusted for each patient according to the individual responses to sevoflurane or remifentanil. There are various cases of clinical general anesthesia, and it is hoped that this report will be of some help in cases where the preservation of spontaneous breathing is advantageous.

In conclusion, in minimally invasive procedures, such as dental procedures, anesthesia can be maintained by the administration at a dosing rate of − 0.00079 × patient age + 0.066 μg/kg/min with 1.5-2.0% sevoflurane to reduce and control the spontaneous respiratory rate to approximately half of the preanesthetic respiratory rate after approximately 20-40 min. The administration of remifentanil solution diluted to 0.1 mg/mL at approximately 0.88 mL/h allows anesthesia to be maintained while reducing the spontaneous respiratory rate to approximately half of the preanesthetic respiratory rate after approximately 20-40 min in patients of all age groups. Because general anesthesia under spontaneous ventilation has many advantages, our method is a promising and effective means of administering anesthesia in minimally invasive procedures.

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Fumihiko Suzuki: Data curation, Formal analysis
Hiroyoshi Kawaai: Supervision
Shinya Yamazaki: Conceptualization, Supervision, Writing - review & editing

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