Comparison of Changes in Respiratory Dynamics Immediately After the Start of Propofol Sedation With or Without Midazolam

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Purpose: The aim of this study was to compare changes in respiratory dynamics starting immediately after administration of propofol alone or a combination of propofol and midazolam.

Materials and Methods: Twenty-seven healthy adult volunteers participated in a randomized crossover study of undergoing sedation with propofol alone (P group) or with a combination of propofol and midazolam (PM group). In the P group, continuous infusion of propofol through a target-controlled infusion (TCI) pump was started with the target effect site (ES) concentration set at 1.2 μg/mL. In the PM group, participants received a bolus administration of midazolam 0.02 mg/kg simultaneously with the start of continuous infusion of propofol through a TCI pump with the target ES concentration set at 0.8 μg/mL. The variables measured included the bispectral index (BIS) value, tidal volume (VT), percutaneous arterial oxygen saturation (SpO_2), respiratory rate (RR), end-tidal carbon dioxide tension ($ETCO_2$), estimated ES propofol concentration, and minute volume.

Results: BIS value, VT, SpO_2, and $ETCO_2$ decreased after sedative administration in the 2 groups. RR increased in the 2 groups. These changes occurred sooner in the PM group than in the P group. The ratio of change in VT to change in BIS value decreased in the 2 groups and was markedly smaller in the PM group than in the P group. Ratios of changes in SpO_2, RR, and $ETCO_2$ to change in BIS value increased in the 2 groups and were larger in the PM group than in the P group.

Conclusion: Changes in respiratory dynamics occurred sooner in the PM group than in the P group. In the PM group, although VT began to decrease before the change in BIS value, the increase in RR caused the rate of decrease in SpO_2 to be smaller than the rate of decrease in BIS value.

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Intravenous sedation facilitates treatment of dental patients, such as those with phobia and those with special needs, by relieving their fear and anxiety.[1-3] Propofol, which has a short context-sensitive half-life and allows rapid emergence,[4-6] and midazolam, which has good anxiolytic and amnesic effects,[3-5] are frequently used as sedatives. Although these drugs are usually used alone, propofol and midazolam often are used together to ensure more secure and stable sedation,[4,7] enable the use of lower doses than when either is used alone,[1,4,7] and decrease recollection of vascular pain during

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propofol administration by the amnesic effect of midazolam.[3]

Propofol and midazolam exert a sedative effect. At the same time, they have a respiratory-depressant effect[5,8]; thus, respiratory monitoring is important for intravenous sedation during dental treatment.[9] Previous studies have shown that tidal volume (VT) decreases during propofol sedation, leading to an increase in respiratory rate (RR),[10] whereas others have found no change in RR.[5] Hypoxic response has been found to be depressed by half when the effect site (ES) concentration of propofol is 0.6 μg/mL.[11] During midazolam sedation, RR increases to compensate for decreased VT[12] and peaks 2 to 3 minutes after midazolam administration.[13] During intravenous sedation with a combination of propofol and midazolam, the blood concentration of propofol has been found to be approximately 25% higher than that during intravenous sedation with propofol alone,[7] suggesting that the combined use of propofol and midazolam could cause greater respiratory depression compared with the use of propofol or midazolam alone. Therefore, this study compared changes in respiratory dynamics starting immediately after administration of propofol alone or a combination of propofol and midazolam.

Materials and Methods

This study was approved by the ethics committee of Tokyo Dental College (Tokyo, Japan; approval number 586). All procedures were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant. Healthy adult volunteers classified as having American Society of Anesthesiologists physical status 1 participated in a randomized crossover study and underwent sedation with propofol alone (P group) or with a combination of propofol and midazolam (PM group). There was an interval of at least 2 days between the 2 study sessions. Participants were prohibited from drinking for 2 hours before the start of the experiment. Smokers, participants with respiratory disorders, those with an allergy to the drugs used, and those taking regular medication were excluded from the study.

Participants were placed in the supine position in a dental chair in a quiet room. A 24-gauge catheter was inserted into the left dorsal hand vein or the cephalic vein, and acetated Ringer solution was infused at a rate of 1 mL/kg per hour. Participants were supplied air at a total flow of 8 L/minute through a face mask that was attached tightly with a head band to prevent any leakage.[12] The face mask was connected to an anesthesia machine (Fabius Tiro, Dräger, Tokyo, Japan) through an anesthesia circuit. To ensure that participants maintained stable breathing, variables were measured 5 minutes after the start of inhalation and used as control values. The variables measured included the bispectral index (BIS) value, VT, percutaneous arterial oxygen saturation (SpO_2), RR, end-tidal carbon dioxide tension ($ETCO_2$), and estimated ES propofol concentration. Minute volume (MV) was calculated as RR × VT. After control measurement, in the P group, continuous infusion of propofol (1% Diprivan, Astellas, Osaka, Japan) through a target-controlled infusion (TCI) pump (TE-371, Terumo, Tokyo, Japan) was started with the target ES concentration set at 1.2 μg/mL. In the PM group, participants received a bolus administration of midazolam 0.02 mg/kg (Dormicum, Astellas, Tokyo, Japan) simultaneously with the start of continuous infusion of propofol through a TCI pump with the target ES concentration set at 0.8 μg/mL. These doses of sedatives in the 2 groups were determined based on doses that resulted in a BIS value of 70 to 80 in the authors' preliminary study.

In the 2 groups, measurements were taken every 10 seconds over a 10-minute period after sedative administration. SpO_2, $ETCO_2$, and RR were measured using a Capnostream 20P monitor (Covidien, Tokyo, Japan). A FilterLine Vitaline H Set (Covidien) sampling tube attached to the inside of the face mask was used for $ETCO_2$ sampling. VT was measured by the anesthesia machine. BIS value was measured using a BIS monitor (A-2000, 3.23, XP platform, Aspect Medical Systems, Newton, MA). The averages of measured values were calculated every 20 seconds based on the value at the time of measurement and those taken 10 seconds before and after. To compare change in BIS value with changes in respiratory dynamics, changes in BIS value, VT, SpO_2, RR, and $ETCO_2$ relative to the respective control values were calculated at each measurement point, and the percentage of change in objective variables divided by the percentage of change in BIS value was compared for each variable.

The sample size was determined by performing power analysis of VT and RR ($\alpha = 0.05$, $\beta = 0.2$) using data from the preliminary study, which showed that at least 24 and 14 participants were required, respectively. GraphPad PRISM 6.01 (GraphPad Software, La Jolla, CA) was used for statistical analysis. Two-way repeated measures analysis of variance was used for intragroup comparisons, and the Dunnett test was used for multiple comparisons. Paired *t* test was used for intergroup comparisons. In all comparisons, *P* values less than .05 were regarded as significant.

Results

Twenty-seven individuals (7 men, 20 women) participated in this study. The age, height, and weight for participants were 25.1 ± 2.9 years (22 to 33 yr), 162.0 ± 8.2 cm (150 to 179 cm), and 54.2 ± 8.5 kg