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 mg/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 mg/mL. The variables measured included the bispectral index (BIS) value, tidal volume (VT), percutaneous arterial oxygen saturation (SpO2), respiratory rate (RR), end-tidal carbon dioxide tension (ETCO2), estimated ES propofol concentration, and minute volume.

Results: BIS value, VT, SpO2, and ETCO2 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 SpO2, RR, and ETCO2 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 SpO2 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. Intravenous sedation facilitates treatment of dental patients, such as those with phobia and those with special needs, by relieving their fear and anxiety. Propofol, which has a short context-sensitive half-life and allows rapid emergence, and midazolam, which has good anxiolytic and amnesic effects, 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, enable the use of lower doses than when either is used alone, 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 ef-
fect, 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), 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 Dur-
ing midazolam sedation, RR increases to compensate
for decreased VT12 and peaks 2 to 3 minutes after mid-
azolam 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 intrave-
nous sedation with propofol alone, 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 ses-
sions. 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 partici-
pants 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, percuta-
neous arterial oxygen saturation (SpO2), RR, end-tidal
carbon dioxide tension (ETCO2), 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 concentra-
tion 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) simul-
taneously with the start of continuous infusion of
propofol through a TCI pump with the target ES con-
centration 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’ pre-
liminary study.

In the 2 groups, measurements were taken every 10
seconds over a 10-minute period after sedative
administration. SpO2, ETCO2, 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 ETCO2 sampling. VT was measured by the anes-
thesia 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, SpO2, RR, and ETCO2 relative to the
respective control values were calculated at each mea-
surement 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 po-
wer analysis of VT and RR (α = 0.05, β = 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 multi-
ple 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) partici-
ated 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
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