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The effect of nitrous oxide inhalation on the hypotensive response to propofol: a randomized controlled trial

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Objective. Decrease in arterial blood pressure is a prominent adverse reaction during propofol (Disoprivan; AstraZeneca K.K., Osaka, Japan) sedation. The purpose of this prospective randomized study was to explore the effects of nitrous oxide (N_2O) on the hypotensive response during propofol sedation.

Study design. Twenty-six healthy volunteers received intravenous sedation with propofol alone (group P, $n = 13$) or a combined technique using 20% N_2O and propofol (group N + P, $n = 13$). Propofol was administered by a target-controlled infusion system to attain and maintain a plasma propofol concentration of 1.5 μg/mL. Hemodynamic and autonomic parameters were measured.

Results. Mean arterial pressure decreased in both groups, the hypotensive response in group N + P being significantly smaller than in group P. Reduction in the low-frequency power of systolic blood pressure variability, indicative of sympathetic nervous activity, was also smaller in group N + P than in group P.

Conclusions. Addition of N_2O to propofol sedation can attenuate the hypotensive effect of propofol. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;■:e1-e8)

Propofol (Disoprivan; AstraZeneca K.K., Osaka, Japan) is one of the most commonly used sedative agents for intravenous sedation during dental procedures. The short context-sensitive half-time and effect site equilibration time of propofol allow both administration of a continuous infusion of propofol and titration of the drug dose that provides a desired level of sedation and rapid recovery without residual sedation after the infusion is terminated.[1] However, propofol has some adverse effects, the most prominent of these being respiratory compromise and a decrease in arterial blood pressure.[2] Ebert[3] reported that although moderate to deep sedation with propofol does not clinically compromise respiration, it does substantially reduce blood pressure. There are some clinical reports on the occurrence of hypotension during sedation with propofol,[4-6] as well as during induction of general anesthesia. The decreases in arterial blood pressure are often accompanied by reduction in cardiac output and systemic vascular resistance, which are primarily due to inhibition of sympathetic nervous activity.[2,7] Baroreceptor reflex control of heart rate (HR) may also be depressed by sedative doses of propofol.[7] These adverse responses are likely to occur in a dose-dependent manner.

When propofol is used alone, relatively large doses may be required to achieve adequate patient comfort, resulting in hypotension. Therefore, if other sedative agents are added to propofol, the resultant decrease in dosage of propofol may be helpful in decreasing the frequency of hypotension. Amornyotin et al.[4] reported that a combination sedation technique of propofol, fentanyl, and midazolam caused profound reduction in blood pressure during endoscopic gastrostomy. Cohen et al.[8] also reported that propofol combined with small doses of midazolam and meperidine caused a drop in blood pressure of 20 mm Hg or more in 41% patients. Therefore, the combination of propofol and opioids/benzodiazepines is not likely to beneficially influence the reduction in blood pressure.

On the other hand, nitrous oxide (N_2O) inhalation sedation is considered to be safe during dental procedures. N_2O inhalation sedation only produces light

Statement of Clinical Relevance

Nitrous oxide (N_2O) added to propofol can enhance the hypnotic effect and attenuate its hypotensive effect. The combination technique of N_2O and propofol is a useful method of sedation.

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sedation with relatively stable cardiovascular effects at the typically used clinical concentrations. However, some studies have shown that brief exposure to 40% N_2O produces an augmentation in baseline sympathetic nervous activity.[9,10] Sellgren et al.[11] showed that N_2O was associated with increased sympathetic activity, which was counteracted by isoflurane in a dose-related fashion. Ebert[9] has stated that increased sympathetic nerve activity by N_2O might be partially responsible for the relatively stable cardiovascular effects observed when N_2O is administered in conjunction with other inhalational agents. These findings suggest that N_2O and propofol have opposite effects on sympathetic outflow.

We hypothesized that the sympathomimetic effect of N_2O might weaken the impact of the sympathoinhibitory effect of propofol, leading to stable hemodynamics. Therefore, we designed this study to investigate whether N_2O inhalation combined with intravenous sedation with propofol can reduce the occurrence of hypotension and improve the quality of sedation.

METHODS

This study was registered with the UMIN Clinical Trials Registry that is acceptable to the International Committee of Medical Journal Editors (UMIN000009728; Effect of combination of intravenous propofol and inhaled nitrous oxide: a randomized clinical trial) and was financially supported by our department (Department of Dental Anesthesiology, Osaka University Graduate School of Dentistry, Osaka, Japan). It was performed in accordance with the guidelines of the Declaration of Helsinki. After approval from the Institutional Review Board and Ethical Committee of Osaka University Dental Hospital (H22-E38), written informed consent was obtained between June 2011 and February 2012 from 26 healthy adult volunteers, aged 29-42 years, to participate in this study. A history of cardiovascular disease, hypertension, and respiratory disease was considered criteria for exclusion from the study. The volunteers were asked not to consume alcohol or caffeinated beverages 24 h before each study day and not to have any food or drinks within 4 h before the study. Each study was scheduled to start at about 4 PM in the operating room. In this way, all interventions were made at similar times on each day, and the effects of circadian fluctuations were minimized.

Study protocol

A peripheral 22-G catheter was inserted into the left forearm for propofol infusion. A comfortably fitting face mask was applied to all subjects. They breathed 100% oxygen delivered at 8 L/min into a semiclosed circle system.

Twenty-six healthy volunteers were assessed for eligibility and, using a computer-generated randomized sequence, were allocated in a single-blinded fashion (subjects were blinded) to one of the following 2 groups:

(1) Group N + P ($n = 13$): propofol was administered by a target-controlled infusion (TCI) system (TE-371, Terumo, Tokyo, Japan) to attain and maintain a plasma propofol concentration of 1.5 μg/mL. At the same time, N_2O was given via a face mask and was titrated to 10%, the dose being increased in increments of 5% every 6 min up to a maximum concentration of 20%.
(2) Group P ($n = 13$): propofol was administered in the same way as in group N + P. A mixture of oxygen and air was given via a face mask. The fraction of inspired oxygen was adjusted to coincide with that of group N + P during each corresponding period.

Monitoring and measurements

Continuous electrocardiogram (ECG), intermittent automated noninvasive blood pressure, HR, and arterial oxygen saturation (SpO_2) were monitored (IntelliVue MP50, Philips, Amsterdam, The Netherlands) throughout the study. Respiratory rate (RR) and end-tidal carbon dioxide and N_2O concentrations were also continuously measured with mass spectrometry. A bispectral index (BIS) sensor probe was placed on the subject's forehead and connected to the BIS monitor to assess the level of sedation. To evaluate left ventricular function during the study, noninvasive impedance cardiograms (CIC-1000, Sorba Medical Systems, Milwaukee, WI, USA) were recorded. Cardiac output was measured every 20 s using a computer-interfaced impedance device. Cardiac index (CI) and total peripheral resistance (TPR) were calculated using a CIC-1000. Radial artery pressure waveforms were continuously measured by a tonometric system sphygmomanometer (BP-608, Omron-Cholin Co. Ltd., Tokyo, Japan). ECG and blood pressure waveforms were digitized at 1000 Hz for analysis by the software, and the artifact-free, digitized signals were stored on a personal computer for later analysis. Fast peaks of R waves on the ECG were detected and used for R−R interval measurements. The peak values of systolic blood pressure for each cardiac cycle were also obtained. Data on the R−R interval and systolic blood pressure were analyzed using commercially available software (MemCalc/Tonam2C, GMS, Tokyo, Japan), where 2 frequency bands were automatically separated as follows: a low frequency (LF) band (between 0.04 and 0.15 Hz) and a high frequency (HF) band (between 0.15 and 0.4 Hz). The LF band of systolic blood pressure (SBP-LF) is a good marker of sympathetic activity in peripheral vessels.[12,13] The HF band of HR variability (HR-HF), on the other hand, coincides with the respiratory frequency and primarily