

# Changes in Intra-cerebral Oxygenation During Intravenous and Inhalational Sedation: A Original Research

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## ABSTRACT

**Background:** Although sedatives such as midazolam or nitrous oxide (N<sub>2</sub>O) are administered to dental patients, the effects of these drugs on intra-cerebral oxygenation are not well-known. **Aims:** We investigated the effects of intravenous midazolam or inhalational N<sub>2</sub>O on intra-cerebral oxygenation using near-infrared spectroscopy. **Setting and Design:** University hospital, prospective. **Materials and Methods:** During intravenous sedation, volunteers received supplemental oxygen through nasal cannula at 3 L/min for 10 min (control group). Midazolam (0.05 mg/kg) was then injected intravenously with flumazenil (20 mg) injected 30 min later. In the inhalational sedation study, volunteers lay quietly for 10 min receiving 100% oxygen, then received N<sub>2</sub>O via nasal mask at concentrations of 10%, 20%, and 25% for 5 min; 30% for 20 min; and supplemental oxygen at 100% for 15 min after N<sub>2</sub>O was discontinued. **Statistical Analysis:** Intra-group comparisons were made using one-way analysis of variance for repeated measures followed by Dunnett's test for multiple comparisons. Differences were considered statistically significant at  $P < 0.05$ . **Results:** During intravenous sedation, oxyhemoglobin increased 10 min after midazolam administration, and total hemoglobin increased slightly until 20 min after flumazenil administration, followed by a decrease. During inhalational sedation, oxyhemoglobin increased until 5 min after starting N<sub>2</sub>O, and total hemoglobin increased until 5 min after starting N<sub>2</sub>O, followed by a decrease. **Conclusions:** Midazolam and N<sub>2</sub>O influenced intra-cerebral oxygenation during intravenous or inhalational sedation. Cerebral blood flow increased with intravenous sedation when midazolam was administered once at a dose of 0.05 mg/kg and with inhalational sedation when N<sub>2</sub>O was supplied at a concentration of 25-30%.

**Key words:** Inhalational sedation, intra-cerebral oxygenation, intravenous sedation, oxyhemoglobin, total hemoglobin

## INTRODUCTION

Intravenous or inhalational sedation can be necessary in dental treatment and oral and maxillofacial

surgery for patients with dental phobia, gag reflex, hypertension, and other factors.<sup>[1-3]</sup> Although dentists and dental anesthetists often administer sedatives such as midazolam or nitrous oxide (N<sub>2</sub>O), the effects of these drugs on intra-cerebral oxygenation are not well-known. Benzodiazepines generally, and midazolam and N<sub>2</sub>O, specifically, reduce cerebral blood flow by decreasing cerebral oxygen metabolism when these drugs have been studied in several conditions.<sup>[4,5]</sup> The doses of intravenous midazolam used for dental sedation are low compared with general anesthesia. Therefore, we studied whether the dose

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of midazolam during intravenous sedation or the concentration of N<sub>2</sub>O during inhalational sedation for dental treatment decreases cerebral blood flow and affects cerebral oxygenation similar to results seen in general anesthesia, using non-invasive near-infrared spectroscopy (NIRS).<sup>[6,7]</sup>

## MATERIALS AND METHODS

This observational study was approved by the ethic committee of Iwate Medical University and met the guidelines of the Helsinki Declaration of 1975, as amended in 2000.

Eight healthy volunteers were ranged in age from 25-35 years, with a statistical height of  $168.2 \pm 2.1$  cm and weight of  $65.8 \pm 8.0$  kg. All volunteers received both intravenous midazolam sedation and inhalational N<sub>2</sub>O sedation. The observations were performed on different days.

### Protocol

#### Intravenous sedation

Volunteers received supplemental oxygen (O<sub>2</sub>) via nasal cannula at a flow rate of 3 L/min for 10 min (control). Midazolam (0.05 mg/kg) was then injected intravenously, and flumazenil (20 mg) was injected 30 min later. A modified Observer's Assessment of Alertness/Sedation (OAA/S) scale score of 3 ("responds only after name is called loudly and/or repeatedly")<sup>[4]</sup> was the end point for the midazolam titration. We monitored non-invasive blood pressure (BP) with tonometry, and pulse rate and blood oxygen saturation (SpO<sub>2</sub>) every minute. We monitored changes in oxyHb, deoxyHb, total Hb, and cyt with a near-infrared oxygen monitor (NIRO 500®, Hamamatsu Photonics, Hamamatsu, Japan) every 30 s. The NIRO sensor was placed on opposite sides of the forehead before starting the procedure. "The optodes of the NIRO were placed on the forehead with tape. The NIRO sensors were covered with crepe bandage wrapped around there head. The NIRO measured the changes in parameters from a baseline that was set at zero at the start of measurement"<sup>[8]</sup> and a baseline measurements were made for 1 or 2 min.

All parameters were continuously recorded using a PowerLab 4/25T data acquisition system (AD Instruments, Bella Vista, Australia). Changes in oxyHb, deoxyHb, total Hb, and cyt values are expressed as

the mean value for each 10 min. The value for each parameter before sedation (control) was compared with that 10, 20, and 30 min after administration of midazolam, and 10, 20, 30, 40, and 50 min after administration of flumazenil.

#### Inhalational sedation

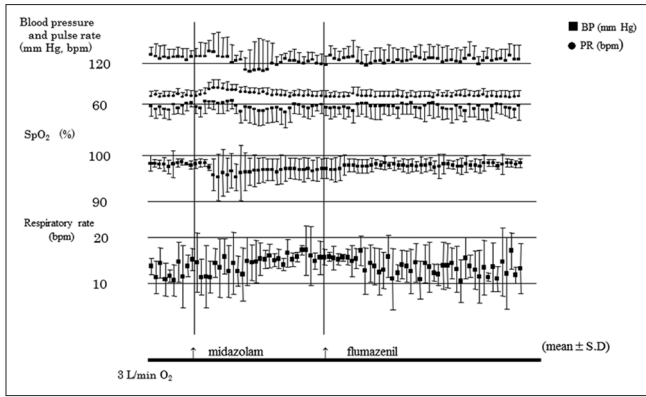
Volunteers received supplemental oxygen via nasal mask at a flow rate of 6 L/min for 10 min. After laying quietly for 10 min receiving 100% oxygen, they received supplemental N<sub>2</sub>O via nasal mask at concentrations of 10%, 20%, and 25% for 5 min, and 30% for 20 min; and supplemental oxygen at 100% for 15 min after supplemental N<sub>2</sub>O was discontinued. An OAA/S scale score of 4 ("lethargic response to name spoken in normal tone") was the end point for the titration of the N<sub>2</sub>O supplementation. We monitored non-invasive BP, pulse rate, and SpO<sub>2</sub> every 2.5 min. We monitored changes in oxyHb, deoxyHb, total Hb, and cyt with the NIRO 500® near-infrared oxygen monitor (Hamamatsu Photonics) every 30 s. As for midazolam sedation, the NIRO measured changes in the parameters and baseline measurements were made for 1 or 2 min.

NIRS was continuously recorded using a PowerLab 4/25T data acquisition system (AD Instruments), as for intravenous sedation. Changes in oxyHb, deoxyHb, total Hb, and cyt values are expressed as the mean value at 2.5 min intervals. The value of each parameter 10 min before supplying N<sub>2</sub>O (control) was compared with: Values 5 min before delivering the N<sub>2</sub>O; during N<sub>2</sub>O delivery at 10%, 20%, and 25%; 5, 10, 15, and 20 min after N<sub>2</sub>O delivery at 30%; and 5, 10, and 15 min after discontinuing N<sub>2</sub>O delivery.

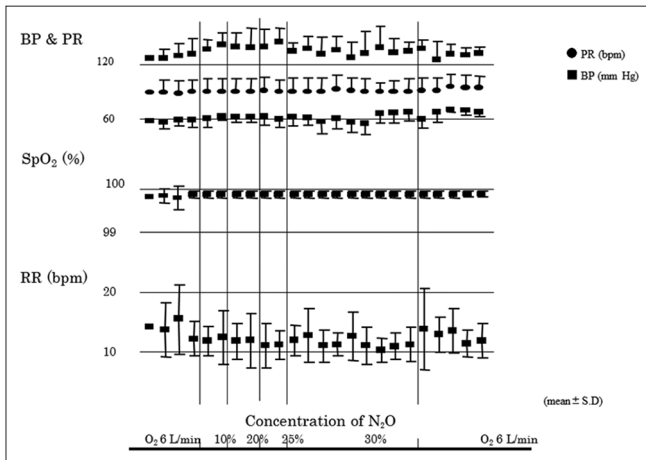
Values are presented as mean  $\pm$  standard deviation. Intra-group comparisons were made using one-way analysis of variance for repeated measures followed by Dunnett's test for multiple comparisons. Differences were considered statistically significant at  $P < 0.05$ .

## RESULTS

Changes in invasive BP, SpO<sub>2</sub>, and pulse rate during sedation are shown in Figure 1 for intravenous sedation and Figure 2 for inhalational sedation. BP, SpO<sub>2</sub>, and pulse rate remained stable during both intravenous and inhalational sedation. During intravenous sedation Figure 3, the maximum oxyHb value occurred 10 min after midazolam administration ( $1.7 \pm 3.1$  nmol/L;  $n = 8$  measurements). OxyHb increased 10 min

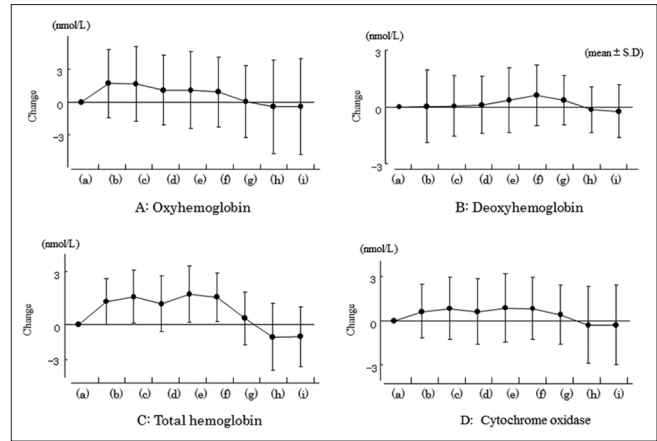


**Figure 1:** Changes in blood pressure (BP), pulse rate, SpO<sub>2</sub>, and respiratory rate during intravenous sedation. Blood pressure, SpO<sub>2</sub>, and pulse rate remained stable during intravenous sedation. BP: blood pressure; HR (bpm): heart rate (breaths per minute); RR (bpm): respiratory rate (breaths per minute); SpO<sub>2</sub>: hemoglobin oxygen saturation



**Figure 2:** Changes in blood pressure (BP), pulse rate, SpO<sub>2</sub>, and respiratory rate during inhalational sedation. Blood pressure, SpO<sub>2</sub>, and pulse rate remained stable during inhalational sedation. BP: Blood pressure; HR (bpm): Heart rate (breaths per minute); RR (bpm): Respiratory rate (breaths per minute); SpO<sub>2</sub>: Hemoglobin oxygen saturation; N<sub>2</sub>O: Nitrous oxide

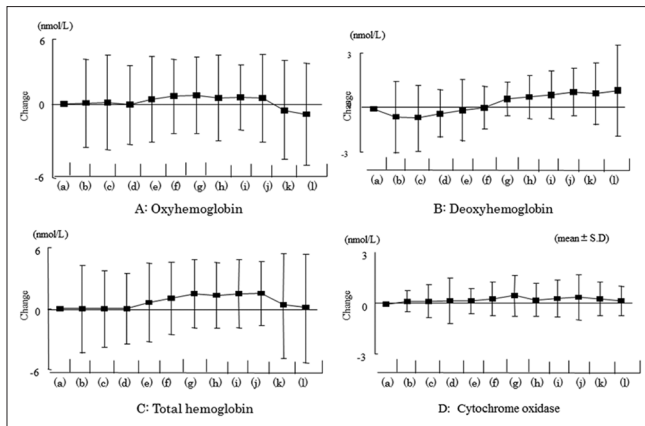
after midazolam administration, followed by a slight decrease to 50 min after flumazenil administration ( $-0.5 \pm 4.4$  nmol/L; n = 8 measurements). The maximum deoxyHb level occurred 20 min after flumazenil administration ( $0.6 \pm 1.6$  nmol/L; n = 8 measurements), increasing slightly until 20 min after flumazenil administration, followed by a decrease to  $0.6 \pm 1.6$  nmol/L (n = 8 measurements). Maximum total-Hb value occurred 10 min after flumazenil administration ( $1.7 \pm 1.7$  nmol/L; n = 8 measurements), increasing slightly until 20 min after flumazenil administration, followed by a decrease to  $-0.7 \pm 1.2$  nmol/L (n = 8 measurements). The maximum cyt value occurred 10 min after flumazenil administration ( $0.9 \pm 1.7$  nmol/L; n = 8 measurements), increasing slightly until 10 min



**Figure 3:** Changes in intra-cerebral oxygenation during intravenous sedation. (a) Before sedation (control); time after administration of midazolam: (b) 10 min (c): 20 min, and (d): 30 min; time after administration of flumazenil: (e) 10 min, (f) 20 min, (g) 30 min, (h) 40 min; and (i) 50 min. The maximum oxyHb value occurred 10 min after midazolam administration followed by a slight decrease to 50 min after flumazenil administration. The maximum deoxyHb value occurred 20 min after midazolam administration and values increased slightly until 20 min after flumazenil administration followed by a decrease. The maximum total Hb value occurred 10 min after midazolam administration then increased slightly until 20 min after flumazenil administration followed by a decrease. The maximum cyt value occurred 20 min after midazolam administration then increased slightly until 20 min after flumazenil administration followed by a decrease

after flumazenil administration, followed by a decrease to  $-0.3 \pm 1.4$  nmol/L (n = 8 measurements).

During inhalational sedation Figure 4 the maximum oxyHb value occurred 10 min after supplying N<sub>2</sub>O at a concentration of 30% ( $0.72 \pm 3.3$  nmol/L; n = 8 measurements), then increased until 5 min after beginning N<sub>2</sub>O, followed by a decrease to  $0.9 \pm 4.4$  nmol/L (n = 8 measurements). The minimum deoxyHb value occurred when N<sub>2</sub>O was begun at a concentration of 10% ( $-0.4 \pm 1.4$  nmol/L; n = 8 measurements) with the maximum value occurring 15 min after initiating N<sub>2</sub>O. DeoxyHb values then decreased until delivering N<sub>2</sub>O at 10%, followed by an increase to  $0.8 \pm 1.9$  nmol/L (n = 8 measurements). Total-Hb maximum value occurred 10 min after beginning N<sub>2</sub>O ( $1.4 \pm 3.0$  nmol/L (n = 8 measurements), then increased until 5 min after beginning N<sub>2</sub>O delivery, followed by a decrease to  $0.1 \pm 5.2$  nmol/L (n = 8 measurements). The maximum cyt value occurred 10 min after the beginning N<sub>2</sub>O ( $0.3 \pm 1.1$  nmol/L; n = 8 measurements) and increased until 5 min after beginning N<sub>2</sub>O delivery followed by a decrease to  $0.2 \pm 0.7$  nmol/L (n = 8 measurements). There was no significant difference between the groups.



**Figure 4:** Changes in intra-cerebral oxygenation during inhalational sedation. (a) 10 min before delivering nitrous oxide ( $N_2O$ ) (control) and (b) 5 min before delivering  $N_2O$ ; (c) during  $N_2O$  delivery at: 10%, (d) 20%, and (e) 25%; time after beginning  $N_2O$  at 30%: (f) 5 min, (g) 10 min, (h) 15 min, and (i) 20 min; (j) 5 min after discontinuing  $N_2O$  followed by supplementation with 100% oxygen and (k) 10 min after discontinuing  $N_2O$  followed by supplementation with 100% oxygen. The maximum oxyHb value occurred 10 min after beginning  $N_2O$  delivery at 30%, then increased until 5 min after discontinuing  $N_2O$  followed by a decrease. The minimum deoxyHb value occurred during delivery of  $N_2O$  at 10% and the maximum value occurred 15 min after beginning  $N_2O$  delivery at 30%. DeoxyHb values decreased until the  $N_2O$  was delivered at 10%, followed by an increase. Total Hb reached a maximum value 10 min after beginning  $N_2O$  delivery at 30%, then increased until 5 min after discontinuing  $N_2O$  delivery, followed by a decrease. The cyt maximum value occurred 10 min after beginning  $N_2O$  delivery and increased until 5 min after discontinuing  $N_2O$ , followed by a decrease

## DISCUSSION

Our results showed that intravenous midazolam and inhalational  $N_2O$  influenced intra-cerebral oxygenation.

During intravenous sedation, there was an increase in oxyHb and total-Hb and a slight increase in deoxyHb 10 min after administration of midazolam to 20 min after administration, followed by a decrease. These changes indicated increased cerebral blood flow because oxyHb and total Hb increased simultaneously. Benzodiazepines, including midazolam, decrease cerebral blood flow through a decrease in cerebral oxygen metabolism.<sup>[9]</sup> It was suggested that steady-state cerebral blood flow decreased with midazolam sedation when 0.5 mg midazolam was administered, with an additional bolus dose of 0.5 mg administered every 2 min after OAA/S assessment until an OAA/S scale score of 3 was reached.<sup>[4]</sup> We administered midazolam only once, in this study. Midazolam is usually administered at an initial and single dose of 0.05 mg/kg to reach an OAA/S scale score of 3, but for dental treatment, this score indicates light or

moderate sedation.<sup>[4,10,11]</sup> Clinically, the OAA/S scale score needs to be 2-3 (moderate or deep sedation) for dental treatment or oral and maxillofacial surgery. Our data may have been inconsistent with previous studies<sup>[4,9]</sup> because of different methods of midazolam administration. Our results suggested that midazolam influenced intra-cerebral oxygenation because oxyHb, deoxyHb, total Hb, and cyt all increased after midazolam administration followed by a decrease after flumazenil.

During inhalational sedation, oxyHb, and total Hb increased with a slight increase in deoxyHb when delivering  $N_2O$  at a concentration of 25% to 5 min after beginning delivery. These changes indicated increased cerebral blood flow given that the oxyHb and total Hb values increased simultaneously. In previous reports, cerebral blood flow increased significantly in response to the substitution of 60%  $N_2O$  for nitrogen during halothane anesthesia,<sup>[5]</sup> and oxyHb and total Hb increased gradually after additional supplementation with 50%  $N_2O$ .<sup>[12]</sup> Our results are consistent with previous studies.<sup>[5,12]</sup> We increased the concentration of  $N_2O$  in gradations to 30% because  $N_2O$  is usually delivered at a concentration of 25-30% to reach an OAA/S scale score of 4 (“lethargic response to name spoken in normal tone”)<sup>[4]</sup> for dental treatment, oral, and maxillofacial surgery. Our results suggested that  $N_2O$  influenced intra-cerebral oxygenation given that both oxyHb and total Hb increased after supplementation, followed by a decrease after discontinuing the  $N_2O$ .

One of the limitations of our study was the small sample size ( $n = 16$ ), which may have been insufficient to reach statistical significance. However, we believe that the data provide accurate and reliable information on intra-cerebral oxygenation during intravenous and inhalational sedation and are clinically useful for anesthesia management.

## CONCLUSION

Intravenous midazolam and inhalational  $N_2O$  influence intra-cerebral oxygenation. Our results suggested that cerebral blood flow increased with midazolam sedation when midazolam was administered once at a rate of 0.05 mg/kg and during inhalational sedation with  $N_2O$  at a concentration of 25-30%. It is prudent to know the expected changes in intracerebral oxygenation during intravenous and inhalational sedation when managing dental anesthesia.

## REFERENCES

1. Matsuura H. Systemic complications and their management during dental treatment. *Int Dent J* 1989;39:113-21.
2. Kubota Y. Research of systemic complications during dental treatment – a review of 30 year footsteps in department of dental anesthesiology. *Kokubyo Gakkai Zasshi* 1994;61:197-206.
3. Win NN, Kohase H, Miyamoto T, Umino M. Decreased bispectral index as an indicator of syncope before hypotension and bradycardia in two patients with needle phobia. *Br J Anaesth* 2003;91:749-52.
4. Ogawa Y, Iwasaki K, Aoki K, Gokan D, Hirose N, Kato J, *et al.* The different effects of midazolam and propofol sedation on dynamic cerebral autoregulation. *Anesth Analg* 2010;111:1279-84.
5. Sakabe T, Kuramoto T, Kumagai S, Takeshita H. Cerebral responses to the addition of nitrous oxide to halothane in man. *Br J Anaesth* 1976;48:957-62.
6. Owen-Reece H, Elwell CE, Harkness W, Goldstone J, Delpy DT, Wyatt JS, *et al.* Use of near infrared spectroscopy to estimate cerebral blood flow in conscious and anaesthetized adult subjects. *Br J Anaesth* 1996;76:43-8.
7. Lovell AT, Owen-Reece H, Elwell CE, Smith M, Goldstone JC. Continuous measurement of cerebral oxygenation by near infrared spectroscopy during induction of anesthesia. *Anesth Analg* 1999;88:554-8.
8. Satoh K, Chikuda M, Joh S. Hemodynamic changes after infiltration of local anesthetic into the neck skin in radical neck dissection. *Glob J Res A* 2015;4:108-10.
9. Wolff J. Cerebrovascular and metabolic effects of midazolam and flumazenil. *Acta Anaesthesiol Scand Suppl* 1990;92:75-7.
10. Sleight JW, Andrzejowski J, Steyn-Ross A, Steyn-Ross M. The bispectral index: a measure of depth of sleep? *Anesth Analg* 1999;88:659-61.
11. Ibrahim AE, Taraday JK, Kharasch ED. Bispectral index monitoring during sedation with sevoflurane, midazolam, and propofol. *Anesthesiology* 2001;95:1151-9.
12. Kitaguchi K, Ohsumi H, Kuro M, Nakajima T, Hayashi Y. Effects of sevoflurane on cerebral circulation and metabolism in patients with ischemic cerebrovascular disease. *Anesthesiology* 1993;79:704-9.

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