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The effects of conscious sedation with nitrous oxide/oxygen on cognitive functions

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Background/aim: The aim of this study was to investigate the effects of conscious sedation with 40% nitrous oxide/oxygen (N_2O/O_2) on cognitive functions.

Materials and methods: Forty dental patients referred to the sedation unit at Gazi University Faculty of Dentistry Department of Oral and Maxillofacial Surgery received a combination of 40% N_2O/O_2 inhalation for conscious sedation. Psychometric tests were applied three times: before sedation, during sedation, and at the end of the recovery, for assessing cognitive functions.

Results: The results of this study showed that the 40% N_2O/O_2 combination impaired cognitive functions during the conscious sedation. Recovery of most of the cognitive functions occurred 15 min after sedation. However, in addition to the persistence of 'hypnotic effects' and 'sensations of isolation' during the recovery period, 'motor loss value' showed more cognitive impairment 15 min after sedation than before the sedation period, and, thus, the ability to execute fine motor skills was not totally recovered by then.

Conclusion: The results of this study could be crucial for informing patients about avoiding attentive activities soon after conscious sedation via 40% N_2O/O_2.

Key words: Cognitive symptoms, conscious sedation, nitrous oxide

1. Introduction

Conscious sedation is defined as 'a technique in which the use of a drug or drugs produces a state of depression of the central nervous system enabling treatment to be carried out, but during which verbal contact with the patient is maintained throughout the period of sedation' (1). Inhalation sedation using nitrous oxide/oxygen (N_2O/O_2) is one of the standard techniques for achieving conscious sedation (2).

Utilization of N_2O for conscious sedation is a widespread approach owing to its acceptable cardiovascular effects and the technique's several advantages at clinical concentrations (3,4). N_2O is a nonflammable, colorless, and virtually odorless gas with a faint, sweet smell (5). It provides a rapid onset of sedation with short duration of action and early recovery. The level of sedation can be easily altered or discontinued (6).

Conscious sedation via N_2O/O_2 is a reliable, efficient, and safe adjunct to local anesthesia for patients undergoing ambulatory oral surgery procedures and can be administrated safely and effectively by trained dental practitioners (7–9). However, the use of N_2O has not always been unproblematic or without controversy (10,11). Despite the widespread clinical use, nitrous oxide's cognitive effects are not completely understood. The aim of this study was to investigate the effects of conscious sedation via 40% N_2O/O_2 on cognitive functions in consideration of the recovery time and side effects.

2. Materials and methods

2.1. Patients

This study was approved by the local institutional review board (Ankara University Faculty of Medicine, Board of Assessment of Clinical Studies) and the General Directorate of Pharmaceuticals and Pharmacy of the Republic of Turkey's Ministry of Health. It was performed in accordance with the guidelines of the Declaration of Helsinki. The study included 40 healthy adult dental patients aged 22 to 31. All were classified as ASA I patients and showed a moderate level of anxiety (determined by Corah Dental Anxiety Scale) towards dental treatment (12,13). The patients were enrolled in the study after

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signing their written informed consent. Patients with a medical contraindication to the use of N_2O (persistence of closed/air-filled cavity, reduced consciousness of any origin, pregnancy, conditions making the application of the nasal mask difficult) were excluded. Sedation applications and cognitive assessments were performed by the same researchers.

2.2. Materials

The subjects received a 40% N_2O/O_2 combination inhalation via nasal mask for conscious sedation (AMS Relaxodent AMS Ltd, Ankara, Turkey). Vital functions that include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate (PR), and peripheral saturation of oxygen (SpO_2) values were monitored throughout the procedure. Psychometric tests that originated from the digit span subtest (DSS), digit symbol coding test (DSCT), Nelson hand reaction test (NHRT), and finger tapping test (FTT) were applied three times: before sedation (T_0), during sedation (T_1), and at the end of the recovery (T_2) for assessing cognitive functions. Three different test formats with the same difficulty level were constituted for the DSS and DSCT with the aim of prohibiting a memorizing effect.

Digit span subtest: This test serves to measure the subject's attention and working memory whereby the subject has to memorize and articulate increasing lengths of sequences of numbers read aloud by the experimenter in a specific order, i.e. in both the same and reverse order. Each sequence involves two trials; each correct response is awarded one point. High scores indicate better performances (14,15).

Digit symbol coding test: This is one of the oldest and best established psychological tests that assesses visual acuity, motor coordination and, speed (15). In this test, digits from 1 to 9 were each assigned a respective symbol, which the subjects had to match. Then they were given a series of random digits next to which the subjects had to write the corresponding symbols within 90 s (16). For the current protocol 2 min are given for testing time. During the data assessment for DSCT, symbols that were coded formless and untidy by subjects were considered an indication of the impairment of fine motor functions and termed as 'motor loss value'.

Nelson hand reaction test: In this measure of motor coordination and reaction time, the subject is asked to grab a ruler that contains numbers on its surface. Subjects must put their hand on the appropriate position and must use their thumb and index finger to grab the ruler. The number between the fingers represents the score. Low scores indicate better performances (17). For the current protocol 10 trials with the dominant hand were recorded.

Finger tapping test: In order to test fine motor speed, subjects are to tap a lever with the index finger of each hand, in 10-s intervals. The test records how many times the subjects can fulfill this task. For the current protocol five trials with the dominant hand were recorded (14,18).

2.3. Procedure

The patients were instructed not to consume food or drink 4 h before the procedure. Consumption of caffeine-containing drinks was restricted to only one cup of tea or coffee at breakfast on the test day. Tobacco was not permitted 2 h before the onset of the procedures on the test day. The subjects were instructed not to consume any alcohol or medication before the start of the test session until the end of the session.

Vital functions that include SBP, DBP, PR, and SpO_2 values were monitored throughout the session and recorded at the time T_0, T_1, T_2, and before discharge of patient (T_3). The level of consciousness, color of skin, and subjective and side effects experienced by subjects were evaluated. Hemodynamic values and side effects were recorded at the time T_0, T_1, T_2, and T_3.

The subjects were settled in a dental chair in the sedation room. Psychometric tests were performed and baseline cognitive values were obtained (T_0). The nasal mask was attached to the patient and the machine adjusted to administer 100% O_2 at an appropriate flow rate (5 L/m). Three minutes later, the subjects were given 10% N_2O and were informed that they may experience light-headedness, tingling of the hands and feet, suffusion of warmth, and changes in visual or auditory sensation (19). The N_2O level was increased gradually (10% per min) up to a level of 40% N_2O and 60% O_2. The N_2O level was maintained at 40% (5 L/m). Verbal contact was maintained all the time to maintain the subjects' confidence and cooperation. The cognitive assessment did not begin until 3 min of continuous inhalation of 40% N_2O. Psychometric tests were performed at the end of this time (T_1), and cognitive values during the sedation period were obtained. After the completion of the cognitive assessment, N_2O flow was turned off incrementally, and 100% O_2 was administered for 3 min before the nasal mask was removed. Fifteen minutes after mask removal, psychometric tests were applied a third time (T_2) and cognitive values representing the estimated recovery time were obtained. Sedation procedures were accomplished in all cases without encountering any serious complications. The whole planned procedure took approximately 40 minutes to perform for each subject. After the completion of the procedure, subjects were observed for 30 minutes and subsequently, they were discharged with postoperative instructions.

2.4. Statistical analyses

Statistical analyses were performed with SPSS Version 17.0 (SPSS Inc., Chicago, IL, USA). The results are presented as mean, standard deviation, minimum–maximum, and number [mean ± SD, (min–max), n (%)]. P-values < 0.05 were considered statistically significant.

The Kolmogorov–Smirnov test was used to evaluate distributions of measurable parameters. Intergroup statistical analyses were performed using one-way ANOVA and Tukey's test. Side effects and DSCT - motor loss values were analyzed using the chi-squared test or Fisher's exact chi-squared test.

3. Results

The characteristics of the subjects are presented in Table 1. Hemodynamic parameters that include SBP, DBP, PR, and SpO_2 are shown in Table 2. SBP was significantly higher (P = 0.005) during the sedation period compared to the baseline. Other hemodynamic parameters were similar.

The effects of N_2O on cognitive performance are presented in Table 3. Cognitive performance was impaired significantly at T_1 compared to T_0 for both tests (P < 0.0001). Cognitive values at T_2 (15 min after cessation of N_2O) indicated a high level of cognitive functions compared with T_0 and were statistically significant for DSCT, NHRT, and FTT (P values respectively: P = 0.001, P = 0.002, P = 0.019). Motor loss values in the DSCT are shown in Table 4. Motor loss values showed more cognitive impairment at T_1 and T_2 compared with T_0 (P < 0.0001).

Side effects that occurred during the sessions were divided into 14 groups (Table 5). Side effects including hypnotic effects, sensation of isolation, euphoric effects, perioral numbness, tinnitus, and dizziness were significantly high during the sedation period (T_1) compared with the baseline period (T_0) (respectively P < 0.0001, P < 0.0001, P < 0.0001, P < 0.0001, P = 0.005, P < 0.0001). Hypnotic effects and sensation of isolation were still significantly high during the recovery period (T_2) compared with the baseline period (T_0) (respectively P = 0.001, P < 0.0001).

Table 1. Subject's characteristics.

Age (years)	25.15 ± 2.17 (22–31)
Sex (male/female)	20/20
Body weight (kg)	68.10 ± 14.60 (46–110)
Height (cm)	172.03 ± 9.99 (155–193)
BMI	22.75 ± 2.84 (18.3–32.5)
Duration of sedation procedure (min)	23.30 ± 3.81 (17–35)

Data are presented as mean ± SD (min–max) or number of subjects
BMI, body mass index

Table 2. Time-dependent hemodynamic parameters of the patients.

	T_0 (n = 40)	T_1 (n = 40)	T_2 (n = 40)	T_3 (n = 40)	**P
SBP (mmHg)	116.98 ± 11.00 (95–140)	120.93 ± 10.85* (94–148)	116.85 ± 8.79 (101–137)	117.28 ± 10.06 (98–137)	0.049
DBP (mmHg)	77.13 ± 6.45 (64–91)	76.98 ± 9.79 (55–96)	77.70 ± 8.47 (55–94)	77.23 ± 8.40 (59–101)	0.982
PR (pulse/min)	77.05 ± 8.21 (58–94)	76.18 ± 9.85 (52–103)	75.63 ± 9.02 (56–97)	74.83 ± 8.90 (58–98)	0.731
SpO_2	98.58 ± 0.68 (97–99)	98.78 ± 0.62 (96–99)	98.65 ± 0.58 (97–99)	98.58 ± 0.64 (97–99)	0.442

Data are presented as mean ± SD (min–max)
**P < 0.05 Multiple comparison (one-way ANOVA)
*P < 0.05 Compared with baseline

Table 3. The effects of N_2O on cognitive performance measures.

	T_0 (n = 40)	T_1 (n = 40)	T_2 (n = 40)	**P
DSS	17.95 ± 4.30 (11–27)	15.03 ± 4.14* (9–24)	18.78 ± 3.71& (12–26)	P < 0.0001
DSCT	77.23 ± 13.39 (49–106)	68.48 ± 13.50* (36–95)	81.33 ± 12.70*,& (45–113)	P < 0.0001
NHRT	13.78 ± 2.77 (7.30–18.40)	16.99 ± 4.64* (4.70–26.90)	12.55 ± 2.43*,& (5.30–17.50)	P < 0.0001
FTT	350.30 ± 48.80 (246–466)	331.78 ± 48.67* (237–502)	361.85 ± 53.10*,& (280–551)	P = 0.029

Data are presented as mean ± SD (min–max)
**P < 0.05 Multiple comparison (one-way ANOVA)
*P < 0.05, Compared with T_0
&P < 0.05, Compared with T_1

Table 4. Motor loss values in DSCT.

	T_0 (n = 40)	T_1 (n = 40)	T_2 (n = 40)	**P
0	27 (67.5)	7 (17.5)	7 (17.5)	$\chi^2 = 49.842$ P < 0.0001
1	10 (25)	7 (17.5)	6 (15)	
2	-	4 (10)	9 (22.5)	
3	-	6 (15)	4 (10)	
4	2 (5)	6 (15)	4 (10)	
5	-	3 (7.5)	1 (2.5)	
6	1 (2.5)	3 (7.5)	2 (5)	
7	-	3 (7.5)	4 (10)	
8	-	1 (2.5)	2 (5)	
9	-	-	-	
10	-	-	-	
11	-	-	1 (2.5)	

Data presented as [n (%)]
**P < 0.05 Multiple comparison (chi-squared or Fisher's exact chi-squared)

4. Discussion

It is well documented that N_2O at the dosages routinely used for dental procedures affects cognitive functions such as psychomotor performances, attention, memory, reaction time, and facial recognition tasks (20–23). The common impression is that N_2O at analgesic dosage levels such as in routine dental procedures acutely impairs cognitive functions, but within 5 min most of these functions were recovered completely, and by 20 min all of them (22).

For dental outpatients undergoing conscious sedation, recovery from sedation must be sufficient to allow a safe discharge home (24). As a general approach, after 10–15 min following the N_2O/O_2 sedation the patient is usually fit to be discharged (6). We hypothesized that cognitive impairment could persist for 15 min after conscious sedation via 40% N_2O/O_2 inhalation. We aim to reconsider discharge requirements and instructions for patients after N_2O sedation.

Armstrong et al. (21) reported that 15% N_2O impairs attention and psychomotor performance. Thompson et al. (25) reported that 25% N_2O does not significantly impair higher cognitive tasks, and, thus, patients can resume normal activities in the postoperative period and so there is no need for an escort to accompany them.

Table 5. Side effects.

	T_0 (n = 40)	T_1 (n = 40)	T_2 (n = 40)	T_3 (n = 40)	**P
Euphoric effects	0/40	34 (85)/6(15)*	2 (5)/38(95)	0/40	χ^2 = 115.090 P < 0.0001
Hypnotic effects	0/40	13 (32.5)/27(67.5)*	10 (25)/29(75)*	2(5)/38(95)	χ^2 = 22.139 P < 0.0001
Sensation of isolation	0/40	38 (95)/2(5)*	11 (27.5)/29(72.5)*	3(7.5)/37(92.5)	χ^2=93.207 P < 0.0001
Perioral numbness	0/40	18 (45)/22(55)*	3 (7.5)/37(92.5)	0/40	χ^2 = 48.839 P < 0.0001
Tinnitus	0/40	8 (20)/32(80)*	0/40	0/40	χ^2 = 25.263 P < 0.0001
Rise of pressure in ear	0/40	3(7.5)/37(92.5)	0/40	0/40	χ^2 = 6.747 P = 0.080
Subjective effects related to attention/perceive	0/40	4 (10)/36(90)	0/40	1(2.5)/39(97.5)	χ^2 = 8.870 P = 0.065
Mild headache	0/40	1(2.5)/39(97.5)	2(5)/38(95)	2(5)/38(95)	χ^2 = 2.271 P = 0.518
Dizziness	0/40	12 (30)/28(70)*	0/40	0/40	χ^2 = 38.919 P < 0.0001
Objective symptoms (slowing of conversation, reducing of eye movements)	0/40	4 (10)/36(90)	0/40	0/40	χ^2 = 8.492 P = 0.055
Palpitation	0/40	2 (5)/38(95)	0/40	0/40	χ^2 = 5.522 P = 0.132
Nausea	0/40	2 (5)/38(95)	2(5)/38(95)	2(5)/38(95)	χ^2 = 2.078 P = 0.556
Being cold	0/40	0/40	3(7.5)/37(92.5)	0/40	χ^2 = 6.747 P = 0.080
Other symptoms	0/40	3(7.5)/37(92.5)	0/40	1(2.5)/39(97.5)	χ^2 = 6.154 P = 0.104

Data are presented as [n (%)]

**P < 0.05 Multiple comparison (chi-square or Fisher's exact chi-square)

*P < 0.05 Comparing with baseline

N_2O had a significant effect on reaction time and facial recognition tasks at dosages ranging from 30% to 55% in a previous study (22). Zacny et al. (26) reported that psychomotor recovery from N_2O was rapid and completed 5 min after the inhalation period. Ayer and Getter (27) reported that psychomotor impairment accruing from the use of N_2O (range from 35% to 40%) during dental treatment was completely recovered after 20 min.

Lichtor et al. (28) reported that during 20% and 40% N_2O inhalation subjects had mood and psychomotor effects based on the questionnaire, visual analogue scale, and psychomotor tests. One hour after the cessation of inhalation, these effects were not significant. Their study suggests that the long-term effects of N_2O are not significant, and after 1 h there is no evidence for abstaining from normal activities.

The results of this study showed that a 40% N_2O/O_2 combination impaired cognitive functions during conscious sedation; however, the recovery of most of the cognitive functions occurred 15 min after sedation. In the meantime, motor loss value was indicated by coding symbols formless and untidy in the DSCT; the result of this value showed more cognitive impairment 15 min after sedation than before the sedation period. Thus, the ability to execute fine motor skills was not totally recovered at this time. Side effects including hypnotic effects and sensation of isolation continue 15 min after sedation, supporting the findings of loss of ability to perform fine motor skills.

The result of this study could be crucial for giving information to the patients about avoiding attentive activities soon after conscious sedation via N_2O/O_2. In our opinion, written postoperative instructions that indicate avoiding tasks that require attention, precision, and fine motor skills after N_2O sedation should be mandatory.

In many areas of medical services 40% N_2O has been used with a great degree of safety (28). In dental practice, criteria such as the patient's sensitivity to the agent and the clinician's expectation of the sedation could cause remarkable variations, but the average concentration of N_2O needed for conscious sedation is 40% (29). In consideration of previous studies, we performed sedation sessions at the ratio of 40% N_2O to 60% O_2.

Faulks et al. (30) reported that sedation with 50% N_2O/O_2 for outpatient dental treatment of patients with intellectual disability was safe and effective; during 605 sedation sessions no serious side effects were observed and minor side effects (such as nausea, vomiting, sweating, headache) occurred in 10.1% of the sessions. In terms of a 10-year retrospective study, it has been reported that the use of N_2O/O_2 sedation provides reliable conscious sedation in the pediatric outpatient population; the nausea and vomiting rate was 1.5% (4).

Hennequin et al. (8) reported remarkable treatment success, patient cooperation, dentist satisfaction, and rare minor side effects in conscious sedation by using 50% N_2O in O_2 (Kalinox) by trained dental practitioners. The most frequently reported side effects were behavioral (euphoria, hyperexcitability), vagal (sweating, pallor, vertigo), and digestive disorders (nausea, vomiting) respectively in 5.3%, 4.4%, and 2.8% of the sessions. In consideration of the technique's safety and effectiveness, the authors recommended using it in complex dental treatments such as oral surgery. Abdullah et al. (31) reported side effects during sedation with N_2O/O_2: dizziness, paraesthesia of fingers, nausea, bradycardia, and headache respectively in 20%, 20%, 10%, 10%, and 5% of cases. Another review article reported that minor side effects such as nausea and vomiting occur in 4%–10% of cases (32).

In the present study, side effects that include hypnotic effects, sensation of isolation, euphoric effects, perioral numbness, tinnitus, and dizziness were significantly high during the sedation period compared with the period before sedation. Hypnotic effects and sensation of isolation were still significantly high during the recovery period. Nausea was determined during the sedation period and recovery period and before discharge in 5% of cases. That result was not statistically significant. Vomiting was not monitored in any case.

The data presented in this study only apply to N_2O given alone. Further studies are warranted for patients who have inhaled N_2O for longer periods or included the concurrent use of other sedative agents. Studies that include tests with high sensitivity and selectivity that assess cognitive functions and fine motor skills over a longer period after recovery time would be beneficial.

References

1. Allen M, Thompson S. An equivalence study comparing nitrous oxide and oxygen with low-dose sevoflurane and oxygen as inhalation sedation agents in dentistry for adults. Br Dent J 2014; 217: E18.
2. Craig DC, Wildsmith JAW. Conscious sedation for dentistry: an update. Br Dent J 2007; 203: 603-631.
3. Yokoe C, Hanamoto H, Boku A, Sugimura M, Morimoto Y, Kudo C, Niwa H. The effect of nitrous oxide inhalation on the hypotensive response to propofol: a randomized controlled trial. Oral Surg Oral Med Oral Pathol Oral Radiol 2014; 118: 166-173.
4. Hulland SA, Freilich MM, Sàndor GK. Nitrous oxide-oxygen or oral midazolam for pediatric outpatient sedation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002; 93: 643-646.
5. Ogle OE, Hertz MB. Anxiety control in the dental patient. Dent Clin North Am 2012; 56: 1-16.
6. Girdler NM, Hill CM, Wilson KE. Clinical Sedation in Dentistry. 1st ed. Chichester, West Sussex, UK: Wiley-Blackwell; 2009.
7. Berge TI. Acceptance and side effects of nitrous oxide oxygen sedation for oral surgical procedures. Acta Odontol Scand 1999; 57: 201-206.
8. Hennequin M, Collado V, Faulks D, Koscielny S, Onody P, Nicolas E. A clinical trial of efficacy and safety of inhalation sedation with a 50% nitrous oxide/oxygen premix (Kalinox™) in general practice. Clin Oral Investig 2012; 16: 633-642.
9. Hierons RJ, Dorman ML, Wilson K, Averley P, Girdler N. Investigation of inhalational conscious sedation as a tool for reducing anxiety in adults undergoing exodontia. Br Dent J 2012; 213: E9.
10. Vetter TR, McGwin Jr G. Comparing apples to oranges: just say no to N_2O? Anesth Analg 2013; 116: 959-961.
11. Lockwood AJ, Yang YF. Nitrous oxide inhalation anaesthesia in the presence of intraocular gas can cause irreversible blindness. Br Dent J 2008; 204: 247-248.
12. Corah NL. Development of a dental anxiety scale. J Den Res 1969; 48: 596.
13. Dailey YM, Humphris GM, Lennon MA. The use of dental anxiety questionnaires: a survey of a group of UK dental practitioners. Br Dent J 2001; 190: 450-453.

14. Munro CA, Longmire CF, Drye LT, Martin BK, Frangakis CE, Meinert CL, Mintzer JE, Porsteinsson AP, Rabins PV, Rosenberg PB et al. Cognitive outcomes after sertaline treatment in patients with depression of Alzheimer disease. Am J Geriatr Psychiatry 2012; 20: 1036-1044.

15. Kaufman AS, Lichtenberger EO. Assessing Adolescent and Adult Intelligence. 3rd ed. Hoboken, New Jersey, USA: Wiley; 2006.

16. Tiplady B, Bowness E, Stien L, Drummond G. Selective effects of clonidine and temazepam on attention and memory. J Psychopharmacol 2005; 19: 259-265.

17. Johnson BL, Nelson JK. Practical Measurements for Evaluation in Physical Education. 4th ed. Minneapolis, MN, USA: Burgess Publishing; 1986.

18. Reitan RM, Wolfson D. The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation. Tucson, AZ, USA: Neoropsychology Press; 1985.

19. Skelly M, Craig D. Sedation for dental procedures. Anaesth Intensive Care 2005; 6: 255-257.

20. Block RI, Ghoneim MM, Hinrichs JV, Kumar V, Pathak D. Effects of a subanaesthetic concentration of nitrous oxide on memory and subjective experience: Influence of assessment procedures and types of stimuli. Hum Psychopharmacol Clin Exp 1988; 3: 257-265.

21. Armstrong PJ, Morton C, Sinclair W, Tiplady B. Effects of nitrous oxide on psychological performance. A dose-response study using inhalation of concentrations up to 15%. Psychopharmacology 1995; 117: 486-490.

22. Norton JC, Roth GI, Matheny JL, Falace DA, O'Reilly JE. The effect of nitrous oxide and age on psychological and psychomotor performance. Anesth Prog 1984; 31: 64-69.

23. Duarte R, McNeill A, Drummond G, Tiplady B. Comparison of the sedative, cognitive and analgesic effects of nitrous oxide, sevoflurane and ethanol. Br J Anaesth 2008; 100: 203-210.

24. Takarada T, Kawahara M, Irifune M, Endo C, Shimizu Y, Maeoka K, Tanaka C, Katayama S. Clinical recovery time from conscious sedation for dental outpatients. Anesth Prog 2002; 49: 124-127.

25. Thompson JM, Neave N, Moss MC, Scholey AB, Wesnes K, Girdler NM. Cognitive properties of sedation agents: comparison of the effects of nitrous oxide and midazolam on memory and mood. Br Dent J 1999; 187: 557-562.

26. Zacny JP, Sparacino G, Hoffmann P, Martin R, Lichtor JL. The subjective, behavioral and cognitive effects of subanesthetic concentrations of isoflurane and nitrous oxide in healthy volunteers. Psychopharmacology 1994; 114: 409-416.

27. Ayer WA, Getter L. Psychomotor responses to nitrous oxide-oxygen sedation during dental treatment. Anesth Prog 1974; 21: 71-73.

28. Lichtor JL, Lane BS, Zimmerman MB. Residual sleepiness after N_2O sedation: a randomized control trial [ISRCTN88442975]. BMC Anesthesiol 2004; 4: 5.

29. Jastak JT, Donaldson D. Nitrous oxide. Anesth Prog 1991; 38: 142-153.

30. Faulks D, Hennequin M, Albecker-Grappe S, Manière MC, Tardieu C, Berthet A, Wolikow M, Droz D, Koscielny S, Onody P. Sedation with 50% nitrous oxide/oxygen for outpatient dental treatment in individuals with intellectual disability. Dev Med Child Neurol 2007; 49: 621-625.

31. Abdullah WA, Sheta SA, Nooh NS. Inhaled methoxyflurane (Penthrox) sedation for third molar extraction: a comparison to nitrous oxide sedation. Aust Dent J 2011; 56: 296-301.

32. Berge TI. Nitrous oxide in dental surgery. Best Pract Res Cl Anaesthesiol 2001; 15: 477-489.