



Complications caused by nitrous oxide in dental sedation

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The first clinical application of nitrous oxide (N₂O) was in 1844, by an American dentist named Horace Wells who used it to control pain during tooth extraction. Since then, N₂O has shared a 170-year history with modern dental anesthesia. N₂O, an odorless and colorless gas, is very appealing as a sedative owing to its anxiolytic, analgesic, and amnesic properties, rapid onset and recovery, and, in particular, needle-free application. Numerous studies have reported that N₂O can be used safely and effectively as a procedural sedation and analgesia (PSA) agent. However, N₂O can lead to the irreversible inactivation of vitamin B₁₂, which is essential for humans; although rare, this can be fatal in some patients.

Keywords: Conscious Sedation; Nitrous Oxide; Vitamin B₁₂ Deficiency.



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INTRODUCTION

Many patients experience dental fear and anxiety (DFA), which imposes a significant level of stress in dentists who must treat such patients [1-3]. While there are various non-pharmacological methods for dealing with DFA, these methods may not be effective in patients with severe DFA; therefore, pharmacological approaches including sedation and general anesthesia (GA) may be unavoidable in treating some patients [4]. Although there is very little difference in the prevalence of DFA between adults and children [1,2], adults are able to avoid their DFA by canceling or delaying their own dental appointments, whereas children often do not have such options. Moreover, children are often unable to repress their expression of fear, which may manifest as excessive

crying and/or physical struggle. These reasons led to the early adoption of sedation in pediatric dentistry. According to a survey of the members of International Association of Paediatric Dentistry (IAPD) and European Academy of Paediatric Dentistry (EAPD), the pharmacological method most often used for behavioral control was GA (52%), followed by N₂O-only sedation (46%) and oral sedation (44%) [5]. The objective of this review was to investigate the properties of N₂O as a PSA agent and identify the adverse events (AEs) associated with N₂O.

N₂O FOR PROCEDURAL SEDATION AND ANALGESIA

Since its initial introduction in 1844 by an American dentist named Horace Wells for pain control during tooth

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extraction, N₂O has been widely used in dentistry to control the pain and distress in patients [6]. N₂O is an odorless and colorless gas with anxiolytic, analgesic, and amnesic properties, along with rapid onset and recovery, which represent the ideal characteristics of a sedative [6,7]. Moreover, as a major advantage of using N₂O is the mitigation of needle phobia [7], it is therefore commonly to achieve PSA in pediatric patients. In particular, N₂O is used for simple venipuncture [8], with Pasarón and colleagues [9] reporting that 98% of patients who underwent PSA by N₂O did not even remember the injection. In other words, patients who are sedated by the inhalation of N₂O through a mask are not only very receptive to being injected by a needle owing to the anxiolytic and analgesic effects of N₂O (often being completely unaware of needling itself), but they may also not remember the injection. Undoubtedly, these characteristics of N₂O make it a very appealing sedative for patients who have a significant phobia of needles. However, PSA with N₂O alone may not provide a sufficient analgesic effect in procedures that can cause severe pain, such as fracture reduction or foreign body removal [10].

In many countries, including the US, Australia, and France, there have been reports on the safe use of N₂O as a PSA agent, where it is also used in diverse areas, including dentistry, radiology, orthopedics, and the emergency department (ED) [9,11-15]. Unlike Korea, N₂O can be used in the US and France without a dentist, doctor, or anesthesiologist present [11,14,16]; naturally, nurses who can perform N₂O sedation are registered nurses who have completed N₂O certification courses [17].

There have been many studies in France on the safety and efficacy of N₂O as a PSA agent [14,15,18,19]. However, because the use of N₂O in France is based on a 50% N₂O/O₂ premix one-bottle system [14], those

studies from France were excluded in this review owing to the potential for slight differences to the two-bottle system used in Korea.

There is a risk of diffusion hypoxia after cessation of N₂O [20], which may be minimized by using O₂ together with N₂O where 100% O₂ is supplied after cessation of N₂O [21]. Moreover, the N₂O inhalation sedation unit most widely used today (MDM, Matrx, NY, USA) has a minimum O₂ concentration setting of 25%-30% and has an O₂ fail-safe system, in which the unit automatically shuts off the supply of N₂O when the oxygen pressure drops below a certain preset level [22]. Although there is no specific formula or a general rule for how long 100% O₂ should be supplied after cessation of N₂O, longer sedation times typically requires a longer time to remove the sedative effect [22]. Some studies have reported no difference in recovery under room air versus 100% O₂ supply [23]. However, a 2010 study by Zier et al. [24] reported that three out of six atypical AEs were associated with apnea/O₂ desaturation after recovery under room air when patients were supplied with 100% O₂ for 2-3 minutes after cessation of N₂O. Meanwhile, Malamed [22] reported that 100% O₂ should be supplied for at least 3-5 minutes for the complete elimination of N₂O from the body, after which the patient should be re-evaluated to determine whether additional 100% O₂ should be supplied.

The most common AE associated with using PSA with N₂O is vomiting [9,12,13,24]. Burnweit et al. [25] reported that preoperative fasting is a cause of nausea and vomiting. In a retrospective review of 12 years of cases from a single institution, the rate of vomiting among patients who were asked to eat something light during 2 hours before the procedure was 0.7%, which was lower than the vomiting rates found in other studies (Table 1)

Table 1. Study of adverse events of nitrous oxide/oxygen procedural sedation and analgesia

Study	Country	Total number of patients	Nitrous oxide: oxygen ratio	Serious adverse events, %	Minor adverse events, %	Vomiting, %
Babl et al. (2008) [13]	Australia	762	Up to 70:30	0.3	8.3	5.7
Zier & Liu (2011) [12]	USA	7,802	Up to 70:30	0.14	5.0	2.2
Pasarón et al. (2015) [9]	USA	1,058	Up to 60:40	0	1.8	0.7

Table 2. Description of serious adverse events during nitrous oxide/oxygen procedural sedation and analgesia

Study	Patient's age	Percentage of nitrous oxide	Description of serious adverse events	Notes
Babl et al. (2015) [26]	16 months	70%	Laryngospasm	
Babl et al. (2008) [13]	11 years	70%	Stabbing central chest pain	2.5 mg Morphine sulfate IV 1 hour before PSA
Zier et al. (2010) [24]	12 years	70%	Desaturation	Trisomy 21
	2 years	50%	Apnea >15 seconds (on return to room air)	After cessation of N ₂ O, 100% O ₂ 3 min
	16 months	65-70%	Desaturation to 89% (on return to room air)	After cessation of N ₂ O, 100% O ₂ 2 min
	3 years	70%	Unresponsive/desaturation to 89% (On return to room air)	After cessation of N ₂ O, 100% O ₂ 3 min
	2 months	70%	Stridor	
Zier et al. (2010) [28]	12 months	1 st : 70% for 4 min 2 nd : 50% for 8 min 3 rd : 65%	Tonic-clonic seizure for 3 min just after the 3 rd administration	
	2 years	60% 9 min	Tonic-clonic seizure	One probable nonfebrile seizure history After cessation of N ₂ O, during administration of 100% O ₂
	17 months	70% 4 min	Tonic-clonic seizure	Two febrile and one nonfebrile seizure history Familial history for febrile seizures

IV: Intravenous injection, PSA: Procedural sedation and analgesia, N₂O: nitrous oxide, O₂: Oxygen, min: minutes.

[9]. In the study by Babl et al. [13], which required at least 2 hours of preoperative fasting, 5.7% presented with vomiting. In Zier & Liu's study 2.2% presented with vomiting [12]. In Zier & Liu's study, four hours of preoperative fasting was required for patient who underwent N₂O procedure during the first 4 months of the study; a light meal during the 4 hours before the procedure was advised for the 6 months; and no fasting-related requirement was given for the rest of the study period as the interim analysis on the first two periods revealed no difference in AE rates. In addition, this study also reported that frequency of minor AEs (MAEs) increased with longer treatment time or deeper sedation [9]. Meanwhile, Zier and Liu reported that the frequency of AEs increased with a longer duration of N₂O supply [12].

Recently, laryngospasm was reported after PSA with only N₂O/O₂ [26]. As laryngospasm does not occur under minimal or moderate sedation, only when the patient is under deep sedation or light GA [22], this indicated that 70% N₂O induced deep sedation, close to GA, for the patients in this case. Because drug reactions vary greatly between patients, N₂O (1 MAC = 105-107, MAC: minimal alveolar concentration) may induce deep sedation

in some patients, sufficient to cause laryngospasm [27]. Moreover, because dental treatments regions coincided with upper airway space, there is a high risk of airway irritation during dental treatment. Thus, reactions of a patient must be carefully observed to titrate the concentration of N₂O.

In addition, other serious AEs (SAEs), including stabbing central chest pain, O₂ desaturation, apnea > 15 seconds, stridor, and tonic-clonic seizure have been reported (Table 2); these SAEs occurred when a high concentration of N₂O, from over 50% to nearly 70%, was used [13,24,26,28]. The 2011 survey of 311 members of IAPD and EAPD reported one case of N₂O-related death, but did not give specific details [5].

VITAMIN B₁₂ INACTIVATION BY N₂O

N₂O may cause irreversible inactivation of vitamin B₁₂ [29], an essential nutrient that acts as a cofactor in the folate and methionine cycles in humans [30]. However, because the human body is unable to synthesize vitamin B₁₂, it must be obtained through the consumption of foods of animal origin [31].

Vitamin B₁₂ deficiency may cause megaloblastic anemia in the peripheral blood and bone marrow, subacute combined degeneration (SCD) of the spinal cord, polyneuropathy, optic nerve injury, glossitis, dementia, thrombosis, and/or infertility [31-34]. In children, the possibility of Vitamin B₁₂ deficiency should be carefully monitored as it can impair the development of the brain and the overall growth, which may lead to permanent disabilities [35,36].

Vitamin B₁₂ deficiency may be caused by various factors, including genetic factors such as 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency, impaired vitamin B₁₂ absorption (observed in pernicious anemia, inflammatory bowel diseases such as Crohn's disease, a history of partial/total gastrectomy or ileal resection, gastric subacidity, and the use of metformin), insufficient dietary consumption of vitamin B₁₂ (in vegetarians/vegans, or infants breastfed by mothers with vitamin B₁₂ deficiency), as well as repeated occupational

or recreational exposure to N₂O [31,37-39].

However, when vitamin B₁₂ deficiency is subclinical, such patients may appear to be healthy and consequently classified as ASA class I without any suspicion; indeed, they may even have a previous history of uneventful N₂O anesthesia or sedation [40]. Caution should be taken as the use of N₂O on such patients may result in fatal outcomes [40].

The first case of hematological changes as a result of prolonged N₂O use was a report by Goilmsen in 1955 [41]. At the time of the report, prolonged N₂O use was not identified as the cause; this was subsequently determined by Lassen et al. in 1956 [42]. In this study, GA, which included the use of N₂O, for the treatment of tetanus, was performed over several days and severe bone marrow depression was found 4-17 days after the use of N₂O [42]. Since then, there have been numerous case reports of N₂O toxicity (Table 3) [32,37,40,43-48]. Symptoms appeared from after 2 days to even after 2

Table 3. Summary of case studies on nitrous oxide toxicity

Study	Patient's age	Concentration and duration of exposure to N ₂ O	Time of onset of symptoms	History or undiagnosed disease	Treatment	Consequences
Lassen et al. (1956) [42]	10 years	14 days	14 th day	—	—	—
	11 years	12 days	6-10 th day	—	—	—
	15 years	17-18 days	17-18 th day	—	—	Mortality (on 29 th day)
	53 years	16 days	16 th day	—	—	Mortality (on 16 th day)
Koblin and Biebuyck (1986) [43]	25 years	1 st : 90 min, 1980, Mar. 2 nd : 1982, Apr.	2 months later	Ileal resection for Crohn's disease	Cyanocobalamin injection	Reversible
	58 years	90 min	6 weeks later	Pernicious anemia	Cyanocobalamin injection	Reversible
Hadzic et al. (1995) [44]	47 years	70% for 8 hours	6 weeks later	Pernicious anemia	Cobalamin injection	Reversible
Rosener and Dichgans (1996) [45]	50 years	66% for 2 hours	4 weeks later	Vegetarian diet	Cyanocobalamin injection	Reversible
McNeely et al. (2000) [37]	6 months	—	2 weeks later	Breast feeding vegetarian mother	Vitamin B ₁₂ supplementation	Developmental delay
Ilniczky et al. (2002) [32]	52 years	—	1 week later	Macrocytic, hyperchromic anemia with decreased serum levels of vitamin B ₁₂	IM injection of vitamin B ₁₂	Reversible
	57 years	—	2 months later	Borderline anemia with decreased serum levels of vitamin B ₁₂	IM injection of vitamin B ₁₂	Reversible
Selzer et al. (2003) [40]	3 months	1 st : 60% for 45 min 2 nd : 60% for 270 min (4 days after 1 st anesthesia)	25 days after 2 nd anesthesia	MTHFR deficiency	—	Mortality (46 days after 2 nd anesthesia)

(Continued to the next page)

Table 3. Continued

Study	Patient's age	Concentration and duration of exposure to N ₂ O	Time of onset of symptoms	History or undiagnosed disease	Treatment	Consequences
Lacassie et al. (2006) [46]	52 years	1 st : 50% for 200 min for 2 nd : 50%, 105 min (8 weeks after 1 st anesthesia)	2 weeks after 1 st anesthesia	Polymorphism of MTHFR	Vitamin B ₁₂ and folic acid supplementation	Reversible
Singer et al. (2008) [47]	27 years	—	2 months later	Pernicious anemia	IM injection of vitamin B ₁₂	Reversible
Renard et al. (2009) [48]	46 years	—	2 days later	Borderline anemia	IM injection of vitamin B ₁₂	Reversible

Min: minutes, IM: Intramuscular, MTHFR: 5,10-Methylenetetrahydrofolate Reductase.

months, with the initial symptoms including symmetric paresthesia or numbness in the limbs, which gradually spread to the trunk to cause gait unsteadiness. In most patients, the injection or oral supplements of vitamin B₁₂ may be effective to alleviate the symptoms, but sensory impairment and other sequelae may persist. In particular, N₂O toxicity may be fatal in pediatric patients who are still in a developmental stage [37,40].

Previously, reports on N₂O toxicity have been related to GA, recreational abuse, and occupational exposure [49-53]. However, the important factor was not whether N₂O was used for GA or PSA, but the degree of exposure to N₂O: that is, the concentration of N₂O used and how long and often the patient was exposed to N₂O were important [54-56]. In addition, as mentioned above, patients with diagnosed or undiagnosed vitamin B₁₂ deficiency may experience symptoms from a single exposure to N₂O. Even in those patients with no signs of vitamin B₁₂ deficiency, repeated occupational exposure or recreational abuse may place them at high-risk of N₂O toxicity.

N₂O interferes with the process of transformation from homocysteine and methionine through the inactivation of vitamin B₁₂; consequently, it causes elevation of the plasma homocysteine concentration [57]. In 2008, Nagele et al. [58] reported that exposure to 66% N₂O for over 4 hours resulted in a significant increase in postoperative plasma homocysteine concentration levels, whereas in 2013, Hakimoglu et al. [59] reported that postoperative plasma homocysteine concentration level was significantly higher when the duration of GA with 60% N₂O was > 3 hours than when it was < 3 hours. Amos et

al. [60] reported that megaloblastic bone-marrow change occurred in patients who underwent GA with N₂O for ≥ 2 hours, which was affected more by the general condition of the patient than the length of N₂O exposure. Moreover, in the deoxyuridine (dU) suppression test for the assessment of abnormalities in DNA synthesis, all 15 patients who did not undergo GA with N₂O showed normal results, whereas 39 of 42 patients who underwent GA with N₂O showed abnormal results, and this difference was detected for patients who were exposed to N₂O for a minimum of 1 hour.

It is not simple for experts to recognize and diagnose vitamin B₁₂ deficiency in a clinical setting [31]. However, since patients with vitamin B₁₂ deficiency sometimes present with neurological symptoms or anemia and as over 98% of them have increased serum methylmalonic acid and total homocysteine levels, a preoperative evaluation of these parameters may be helpful for the identification of patients at risk of N₂O toxicity.

Although there are differences in prevalence based on ethnicity, the number of patients with risk factors for N₂O toxicity is a low proportion of the total population [61]. Indeed, relevant information often goes unmentioned in contraindications for PSA with N₂O. Nevertheless, based on cases reported from time to time, this factor should not be underestimated. If screening is possible prior to PSA, the use of a suitable alternative sedative would be preferable. Moreover, if related symptoms occur after PSA with N₂O, early detection and appropriate treatment may reverse such symptoms. Therefore, it is necessary to provide an introduction and warnings about possible initial symptoms to patients who may not have been screened.

CONCLUSION

Since the introduction of clinical anesthesiology, N₂O has been used for sedation and analgesia, and it remains a popular option. The rate of SAEs after PSA with only N₂O is low (0–0.3%), with vomiting being the most common AE. Cases of laryngospasm after a high-dose of N₂O have been reported, and even a few cases of death. Furthermore, in patients who are repeatedly exposed to N₂O or have vitamin B₁₂ deficiency, various neurological symptoms may result from N₂O-induced vitamin B₁₂ inactivation. In summary, while sedation with N₂O rarely presents with SAEs, further investigation on understanding of N₂O-related AEs and their triggers may prove to be beneficial towards patients with greater risk.

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