Review Article

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# Complications caused by nitrous oxide in dental sedation

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The first clinical application of nitrous oxide ($N_2O$) was in 1844, by an American dentist named Horace Wells who used it to control pain during tooth extraction. Since then, $N_2O$ has shared a 170-year history with modern dental anesthesia. $N_2O$, an odorless and colorless gas, is very appealing as a sedative owing to its anxiolytic, analgesic, and amnestic properties, rapid onset and recovery, and, in particular, needle-free application. Numerous studies have reported that $N_2O$ can be used safely and effectively as a procedural sedation and analgesia (PSA) agent. However, $N_2O$ 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 $B_{12}$ Deficiency.



## 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 $N_2O$-only sedation (46%) and oral sedation (44%) [5]. The objective of this review was to investigate the properties of $N_2O$ as a PSA agent and identify the adverse events (AEs) associated with $N_2O$.

## $N_2O$ 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, $N_2O$ has been widely used in dentistry to control the pain and distress in patients [6]. $N_2O$ is an odorless and colorless gas with anxiolytic, analgesic, and amnestic properties, along with rapid onset and recovery, which represent the ideal characteristics of a sedative [6,7]. Moreover, as a major advantage of using $N_2O$ is the mitigation of needle phobia [7], it is therefore commonly to achieve PSA in pediatric patients. In particular, $N_2O$ is used for simple venipuncture [8], with Pasarón and colleagues [9] reporting that 98% of patients who underwent PSA by $N_2O$ did not even remember the injection. In other words, patients who are sedated by the inhalation of $N_2O$ through a mask are not only very receptive to being injected by a needle owing to the anxiolytic and analgesic effects of $N_2O$ (often being completely unaware of needling itself), but they may also not remember the injection. Undoubtedly, these characteristics of $N_2O$ make it a very appealing sedative for patients who have a significant phobia of needles. However, PSA with $N_2O$ 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 $N_2O$ 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, $N_2O$ can be used in the US and France without a dentist, doctor, or anesthesiologist present [11,14,16]; naturally, nurses who can perform $N_2O$ sedation are registered nurses who have completed $N_2O$ certification courses [17].

There have been many studies in France on the safety and efficacy of $N_2O$ as a PSA agent [14,15,18,19]. However, because the use of $N_2O$ in France is based on a 50% $N_2O/O_2$ 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 $N_2O$ [20], which may be minimized by using $O_2$ together with $N_2O$ where 100% $O_2$ is supplied after cessation of $N_2O$ [21]. Moreover, the $N_2O$ inhalation sedation unit most widely used today (MDM, Matrx, NY, USA) has a minimum $O_2$ concentration setting of 25%–30% and has an $O_2$ fail-safe system, in which the unit automatically shuts off the supply of $N_2O$ 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% $O_2$ should be supplied after cessation of $N_2O$, 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% $O_2$ supply [23]. However, a 2010 study by Zier et al. [24] reported that three out of six atypical AEs were associated with apnea/$O_2$ desaturation after recovery under room air when patients were supplied with 100% $O_2$ for 2–3 minutes after cessation of $N_2O$. Meanwhile, Malamed [22] reported that 100% $O_2$ should be supplied for at least 3–5 minutes for the complete elimination of $N_2O$ from the body, after which the patient should be re-evaluated to determine whether additional 100% $O_2$ should be supplied.

The most common AE associated with using PSA with $N_2O$ 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 | |
| | 12 years | 70% | Desaturation | 2.5 mg Morphine sulfate IV 1 hour before PSA |
| Zier et al. (2010) [24] | 2 years | 50% | Apnea >15 seconds (on return to room air) | Trisomy 21<br>After cessation of $N_2O$, 100% $O_2$ 3 min |
| | 16 months | 65-70% | Desaturation to 89% (on return to room air) | After cessation of $N_2O$, 100% $O_2$ 2 min |
| | 3 years | 70% | Unresponsive/desaturation to 89% (On return to room air) | After cessation of $N_2O$, 100% $O_2$ 3 min |
| | 2 months | 70% | Stridor | |
| Zier et al. (2010) [28] | 12 months | 1st: 70% for 4 min<br>2nd: 50% for 8 min<br>3rd: 65% | Tonic-clonic seizure for 3 min just after the 3rd administration | |
| | 2 years | 60% 9 min | Tonic-clonic seizure | One probable nonfebrile seizure history<br>After cessation of $N_2O$, during administration of 100% $O_2$ |
| | 17 months | 70% 4 min | Tonic-clonic seizure | Two febrile and one nonfebrile seizure history<br>Familial history for febrile seizures |

IV: Intravenous injection, PSA: Procedural sedation and analgesia, $N_2O$: nitrous oxide, $O_2$: 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 $N_2O$ 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 $N_2O$ supply [12].

Recently, laryngospasm was reported after PSA with only $N_2O/O_2$ [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% $N_2O$ induced deep sedation, close to GA, for the patients in this case. Because drug reactions vary greatly between patients, $N_2O$ (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 coincied 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 $N_2O$.

In addition, other serious AEs (SAEs), including stabbing central chest pain, $O_2$ desaturation, apnea > 15 seconds, stridor, and tonic-clonic seizure have been reported (Table 2); these SAEs occurred when a high concentration of $N_2O$, 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 $N_2O$-related death, but did not give specific details [5].

## VITAMIN $B_{12}$ INACTIVATION BY $N_2O$

$N_2O$ may cause irreversible inactivation of vitamin $B_{12}$ [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 $B_{12}$, it must be obtained through the consumption of foods of animal origin [31].

Vitamin $B_{12}$ 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 $B_{12}$ 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 $B_{12}$ deficiency may be caused by various factors, including genetic factors such as 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency, impaired vitamin $B_{12}$ 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 $B_{12}$ (in vegetarians/vegans, or infants breastfed by mothers with vitamin $B_{12}$ deficiency), as well as repeated occupational or recreational exposure to $N_2O$ [31,37-39].

However, when vitamin $B_{12}$ 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 $N_2O$ anesthesia or sedation [40]. Caution should be taken as the use of $N_2O$ on such patients may result in fatal outcomes [40].

The first case of hematological changes as a result of prolonged $N_2O$ use was a report by Goilmsen in 1955 [41]. At the time of the report, prolonged $N_2O$ 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 $N_2O$, for the treatment of tetanus, was performed over several days and severe bone marrow depression was found 4-17 days after the use of $N_2O$ [42]. Since then, there have been numerous case reports of $N_2O$ 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 $N_2O$ | 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 $N_2O$ | Time of onset of symptoms | History or undiagnosed disease | Treatment | Consequences |
|---|---|---|---|---|---|---|
| Lacassie et al. (2006) [46] | 52 years | 1st: 50% for 200 min for 2nd: 50%, 105 min (8 weeks after 1st anesthesia) | 2 weeks after 1st 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 $B_{12}$ may be effective to alleviate the symptoms, but sensory impairment and other sequelae may persist. In particular, $N_2O$ toxicity may be fatal in pediatric patients who are still in a developmental stage [37,40].

Previously, reports on $N_2O$ toxicity have been related to GA, recreational abuse, and occupational exposure [49-53]. However, the important factor was not whether $N_2O$ was used for GA or PSA, but the degree of exposure to $N_2O$: that is, the concentration of $N_2O$ used and how long and often the patient was exposed to $N_2O$ were important [54-56]. In addition, as mentioned above, patients with diagnosed or undiagnosed vitamin $B_{12}$ deficiency may experience symptoms from a single exposure to $N_2O$. Even in those patients with no signs of vitamin $B_{12}$ deficiency, repeated occupational exposure or recreational abuse may place them at high-risk of $N_2O$ toxicity.

$N_2O$ interferes with the process of transformation from homocysteine and methionine through the inactivation of vitamin $B_{12}$; consequently, it causes elevation of the plasma homocysteine concentration [57]. In 2008, Nagele et al. [58] reported that exposure to 66% $N_2O$ 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% $N_2O$ 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 $N_2O$ for $\geq$ 2 hours, which was affected more by the general condition of the patient than the length of $N_2O$ 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 $N_2O$ showed normal results, whereas 39 of 42 patients who underwent GA with $N_2O$ showed abnormal results, and this difference was detected for patients who were exposed to $N_2O$ for a minimum of 1 hour.

It is not simple for experts to recognize and diagnose vitamin $B_{12}$ deficiency in a clinical setting [31]. However, since patients with vitamin $B_{12}$ 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 $N_2O$ toxicity.

Although there are differences in prevalence based on ethnicity, the number of patients with risk factors for $N_2O$ toxicity is a low proportion of the total population [61]. Indeed, relevant information often goes unmentioned in contraindications for PSA with $N_2O$. 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 $N_2O$, 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, $N_2O$ has been used for sedation and analgesia, and it remains a popular option. The rate of SAEs after PSA with only $N_2O$ is low (0–0.3%), with vomiting being the most common AE. Cases of laryngospasm after a high-dose of $N_2O$ have been reported, and even a few cases of death. Furthermore, in patients who are repeatedly exposed to $N_2O$ or have vitamin $B_{12}$ deficiency, various neurological symptoms may result from $N_2O$-induced vitamin $B_{12}$ inactivation. In summary, while sedation with $N_2O$ rarely presents with SAEs, further investigation on understanding of $N_2O$-related AEs and their triggers may prove to be beneficial towards patients with greater risk.

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