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REVIEW

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Nitrous oxide intoxication: systematic literature review and proposal of new diagnostic possibilities

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Abstract

Background: Nitrous oxide (N2O), also called "laughing gas," is the most commonly used inhalation anesthetic in dentistry. The N2O is no longer used, because of the long-term neurologic and cardiovascular sequelae. Due to its sedative and euphoric properties, N2O is often used for recreational use or in some erotic activities. Accidental deaths are mainly associated with the uses of N2O: death can occur from sudden cardiac arrhythmia or, most commonly, acute asphyxiation due to hypoxia. This paper aims to study the literature concerning deaths due to N2O intoxication and highlight pathological findings useful for diagnosis when the crime scene investigation does not reveal any evidence.

Materials and methods: The authors conducted the literature search by PubMed and Scopus databases, searching for articles from 1 January 1970 to 1 March 2020 using the key terms: "Nitrous oxide," "Laughing gas," "Hypoxic damage," "Nitrous oxide anesthesia," and "Nitrous oxide death."

Results and discussion: A total of 244 articles were collected. Only 26 articles were included in the systematic review. Most of the deaths from intoxication are due to asphyxiation; the diagnosis is often difficult and immunohistochemistry could be helpful. Nitrous oxide increases the intracellular adhesion molecule expression, E- and P-Selectin (markers of the early inflammatory response), and HIF-1 α (indicative of oxidative stress during ischemia-reperfusion).

Conclusion: The macroscopic and microscopic signs of N2O intoxication are non-specific, but N2O has been proven to cause hypoxic damage to the brain. The suspicion of the presence of the gas in the environment should guide the pathologist. Tissue analyzes provide important information; immunohistochemical stains can confirm hypoxic damage through the use of markers such as HIF-1 α, E-Selectin, and P-Selectin.

Keywords: Nitrous oxide, Laughing gas, Immunohistochemistry, Hypoxic damage, Nitrous oxide death, Forensic pathology, Forensic investigation, Autopsy

Background

Nitrous oxide (N2O), also called "laughing gas" (West 2014), was the most commonly used inhalation anesthetic in dentistry (Becker and Rosenberg 2008; Pichelin et al 2016). Nowadays, the safety and efficacy of nitrous oxide have been questioned (Leslie et al 2011; Baum et al 2012), mainly because of the long-term neurologic and cardiovascular sequelae (Brotzman et al 2018) so that, in anesthesia, N2O is no longer used. Nitrous oxide produces moderate analgesia at subanesthetic concentrations and anxiolytic effects (Turan et al 2015). Anesthetic effects are obtained at concentrations 50–67%, while higher levels can cause hypoventilation and then asphyxiation (Wren et al 1984).

Due to its sedative and euphoric properties, N2O is often used for recreational use (Kaar et al 2016; van

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Amsterdam et al 2015) or in some erotic activities (Gillman 1988). Accidental deaths are mainly associated with recreational uses of N2O: death can occur from sudden cardiac arrhythmia or, most commonly, acute asphyxiation due to hypoxia (Garakani et al 2016). In literature, there are rare reports of accidental inhalation at work or due to its incorrect administration to hospitalized patients during anesthesia (Poli et al 2010; Bonsu and Stead 1983).

Often, crime scene analysis identifies N2O asphyxia as a cause of death, while the autopsy, pivotal to the cause of death, is often not enough to find the guilty gas for asphyxiation (van Amsterdam et al 2015; DiMaio and Garriott 1978). Often autopsy findings are only generic signs of asphyxia (Prahlow and Byard 2011), but nothing suggests nitrous oxide intoxication. Hematoxylin-eosin (H&E) staining gives nonspecific results, while immunohistochemical can detect hypoxic damage markers.

This paper aims to study the literature concerning deaths due to N2O intoxication and highlight pathological findings useful for diagnosis when the crime scene investigation does not reveal any evidence. The diagnosis of N2O intoxication is complicated, and this paper tries to summarize the typical findings to help the forensic pathologist.

Materials and methods

Search strategy

The authors conducted the systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline (Page et al 2021). The quality assessment of this study was evaluated using the Checklist for Systematic Reviews and Research Syntheses recommended by the Joanna Briggs Institute (JBI).

The authors conducted the literature search by PubMed and Scopus databases. We searched for articles from 1 January 1970 to 1 March 2020 using the key terms: "Nitrous oxide," "Laughing gas," "Hypoxic damage," "Nitrous oxide anesthesia," and "Nitrous oxide death." The methodology of the search strategy is presented in Fig. 1.

Inclusion and exclusion criteria

Inclusion criteria were articles in English, case report; case series; original article; and death related to the N2O assumption. Exclusion criteria were by title, abstract, or full text; non-English language reports, abstract, poster, proceedings, and cases not involving the direct toxic effect of N2O; and death not directly related to the N2O assumption.

Methodological evaluation

The researchers independently reviewed those documents whose title or abstract appeared to be relevant and selected those which analyzed the nitrous oxide damage and nitrous oxide death, analyzing the reference of each paper also. The results are summarized in Table 1.

Result

A total of 244 articles were collected, removing 98 duplicates. The authors analyzed the rest of the pertinent articles. Twenty-six articles were included in the systematic review, and 120 articles were excluded and summarized in Fig. 1. The authors collected the following features from case reports: the number of cases, macroscopic findings, histological findings, toxicological findings (samples, analysis techniques, results), crime scene investigation or anamnesis of the patient, and modality of the death.

Discussion

Even if nitrous oxide (N2O) was the most commonly used inhalation anesthetic in dentistry, emergency centers, and ambulatory surgery centers (Becker and Rosenberg 2008; Pichelin et al 2016), its safety and efficacy in recent years have been questioned (Leslie et al 2011; Baum et al 2012) because of the long-term neurologic and cardiovascular sequelae (Brotzman et al 2018).

Nowadays, alternative substances, such as induction hypnotics, opioids, muscle relaxants, or volatile anesthetics, make nitrous oxide outdated (Prahlow and Byard 2011; Jahn and Berendes 2005). Nitrous oxide is an *N*-methyl-D-aspartate (NMDA)-antagonist drug (Grundmann et al 1998).

N2O produces moderate analgesia at subanesthetic concentrations and an anxiolytic effect (Turan et al 2015). However, the gas has adverse effects, documented, for example, in patients undergoing anesthesia and personnel exposed to work (Trevisan and Gori 1990; Yagiela 1991; Korttila et al 1978). The administration of nitrous oxide is associated with hypoventilation (Wren et al 1984).

The ENIGMA-I and ENIGMA-II studies (Evaluation of Nitrous Oxide in the Gas Mixture for Anesthesia) assessed the outcomes of the perioperative patient, providing information on the link between the use of N2O and patient morbidity and mortality (Myles et al. 2007; Myles et al 2009) and its neurotoxicity (Savage and Ma 2014).

In adults, nitrous oxide increases cerebral blood flow and the cerebral metabolic rate of oxygen, reducing cerebral autoregulation (Iacopino et al 2003; Kaisti et al 2003). In children, middle cerebral artery blood flow

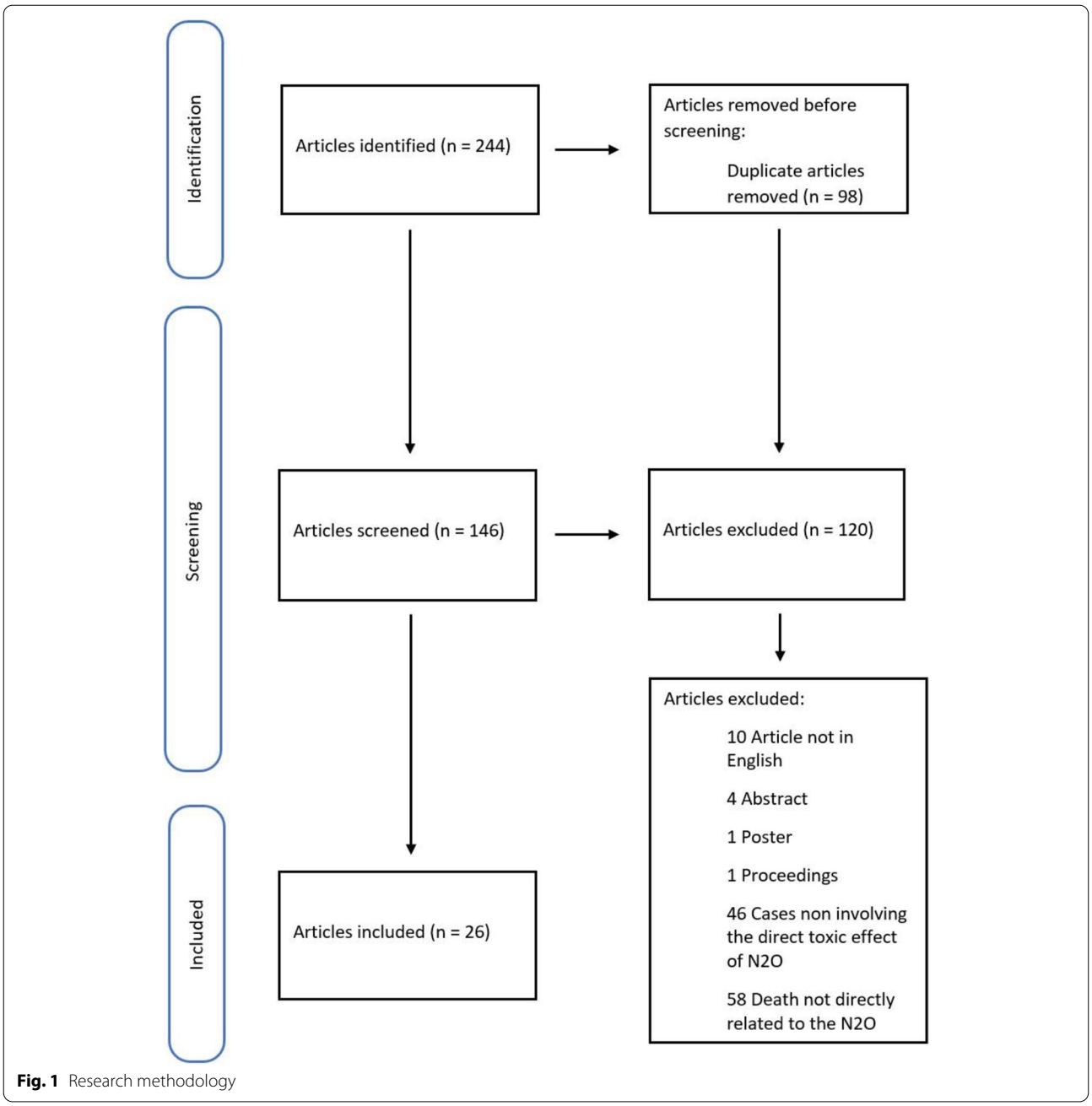

Fig. 1 Research methodology

and cerebral vasoreactivity vary depending on volatile or intravenous anesthetics (Karsli et al 2003; Myles et al. 2007; Wilson-Smith, Karsli, Luginbuehl, Bissonnette, 2003).

Other evidence shows that N2O administration is associated with post-operative cardiac problems (Leslie et al 2011; Kawamura et al 1980; Myles et al. 2007), including myocardial infarction (Leslie et al 2011), due to elevated homocysteine levels (Myles et al 2008), but not with stroke (Ko et al 2014; Zhang et al 2017). However, the ENIGMA-II trial and long-term follow-up suggest that N2O administration in non-cardiac surgical patients (with known or suspected cardiovascular disease) is safe (Myles et al 2014; Leslie et al 2015). The use of N2O increases the risk of surgical-site infection (Fleischmann et al 2005).

When nitrous oxide has been used for prolonged periods as a sedative and analgesic causes bone marrow depression, ataxia, weakness, impotence, and loss

Table 1 Qualitative and quantitative data resulted from the literature review. *NR* not reported

Case report	No. of cases	Clinical/ macroscopic findings	Histological findings	Toxicological samples	Toxicological technique	Toxicological results	Crime scene/ anamnesis	Modality
Mehta 1974	1	Cyanosis, respiratory arrest	NR	NR	NR	NR	Anesthesia induced venously, then deepened with pure N2O for six breaths	Anestesiologucal accident
	1	Extremely pale	NR	NR	NR	NR	Dental anestesia with 75% N2O	Anesthesiological accident
Mody 1975	1	Cyanosis, respiratory arrest	NR	NR	NR	NR	Dental anestesia with 75% N2O	Anesthesiological accident
DiMaio and Garriott 1978	4	Acute visceral congestion	NR	Blood, lung air	HSGC	8.97 ml/dl in blood; 4.8, 9.3, 4. 6 in the blood; in lung air 13.6 %, 12.3 %, and 22.7 %	N2O tank connected to a rubber tube held in the mouth; open tank of N2O in a car	Recreational use
LiPuma et al 1982	2	Pneumomediastinum, sore throat, neck swelling, bilateral emphysema of the neck and supraclavicular regions hoarseness., injected pharynx, dried exudation at the corners of both eyes	NR	NR	NR	NR	Many cartridges of N2O inhaled few hours before	Recreational use
Duncan and Moore 1984	4	Cyanosis	NR	NR	NR	NR	Anesthesia machine failure, cross connection	Anesthesiological accident
Fraunfelder 1988	1	N R	NR	NR	NR	NR	Plastic bag over victim's head and a canister pf N2O	Recreational use
Leadbeatter 1988	1	NR	NR	Blood, urine, and air in cylinders	NR	Traces of N2O in blood	Anesthesiological machine with 95% N2O and 5% O_2	Autoerotical activities
Chadly et al 1989	1	Heavy and edematous lungs, abundant congestion, multiorgan congestion	Contraction bands in myocardial fibers, multiviscer congestion	NR	NR	NR	Anesthesiological machine in an operating theater	Suicide
Wagner et al 1992	5	Lung congestion	NR	Blood and air in the left mainstem bronchus	NR	Positive for N2O	Plastic garbage bag close around the head with a belt and a N2O cartridge in the bag	NR

Table 1 (continued)

Case report	No. of cases	Clinical/ macroscopic findings	Histological findings	Toxicological samples	Toxicological technique	Toxicological results	Crime scene/ anamnesis	Modality
Gowitt and Hanzlick 1992	1	Decomposition	NR	NR	NR	Negative for N2O	Head covered with a plastic bag and a N2O tank nearby	Autoerotical activities
Prahlow and Lantz 1994	1	NR	NR	Blood and lungs	NR	35 ug/mL in blood, 45 ug/mL in lungs	Head covered with a plastic bag and a N2O tank in another room	Recreational use
Winek et al 1995	1	Cyanosis, congestion, and edema of tracheal mucosa, lung tissue, and bronchi	Acute cerebral edema and hyperemia, spongy degeneration and vacuolation of the myelin sheath, scattered axonal swelling	Hearth blood, lungs, bile, urine	HSGC	All samples were positive	Plastic mask on the face connected to a N2O cylinder	Recreational use
Hwang et al 1996	1	Frostbite on the left cheek	NR	NR	NR	NR	N2O sniffed directly from a cylinder in contact with the left cheek	Recreational use
Shields et al 2005	1	NR	NR	NR	NR	NR	A plastic bag encircled the victim's head connected by a tube to a N2O canister	Authoerothical activities accident
Herff et al 2007	6	Respiratory arrest	NR	NR	NR	NR	Oxigen pipeline connecten to N2O tank	Anesthesiological accident
Poli et al 2010	8	Decomposition	NR	Air from the stomach (buried), from trachea (not buried); blood, urine, liver, bile, kidney, fat, brain	HSGC/ECD	5.28-83.63 g/m3 (air)	Cross connection between O2 and N2O lines in a hospital	Anesthesiological accident
Potocka-Banas et al 2011	1	Lung edema	Cerebral edema, acute anoxic lesions of the myocardium	NR	GC, LC e GC.MS	Negative for exogenous organic compounds	Man found with a lot o whipped cream canisters and a professional anesthesia machine	Recreational use
Bäckström et al 2015	2	Cyanosis, congestion of inner organs	NR	NR	NR	Negative for alcohol and illicit drugs	Modified gas mask connected to a whipped cream pump on the face; gas mask connected to a N2O cylinder	Authoerotical activities accident

Table 1 (continued)

Case report	No. of cases	Clinical/ macroscopic findings	Histological findings	Toxicological samples	Toxicological technique	Toxicological results	Crime scene/ anamnesis	Modality
Giuliani et al 2015	1	NR	NR	Brain, lung, peripheral blood	HS-GC-MS	47 µm/g in the brain 27 µm/g in the lung, 370 microgr/g in the blood	NR	NR
Lin and Bause 2017	1	NR	NR	NR	NR	NR	The dentist found with tube detached from the inhaler, held in the left hand, and held tightly between the teeth. The tube was connected to an N2O cylinder	Anesthesiological accident/suicide
Lee et al 2017	1	Cianosis	NR	NR	NR	NR	Death after dental anesthesia, % of O_2 administrated not reported	Anesthesiological accident
Leth and Astrup 2017	1	Severe lung stasis and edema, cyanosis, dark lividity	NR	Lung and brain	HGCMS	NR	Plastic bag on the face filled with N2O from a cartridge for whipped cream dispenders	Suicide

of sphincter control similar to the polyneuropathy seen with chronic vitamin B12 deficiency (Campdesuner et al 2020).

Nitrous oxide inactivates vitamin B12, affecting the synthesis of the critical amino acid methionine from its homocysteine precursor, preventing the deoxyribonucleic acid synthesis (DNA) (Deacon et al 1980; Blackburn et al 1977), leading in some cases to demyelinating myelopathy (Sleeman et al 2016; Kang et al 2019).

Psychiatric disorders also have been reported (Garakani et al 2014), such as analgesia, depersonalization, derealization, dizziness, euphoria, sound distortion (Weimann 2003), depression, hypomania, and paranoid psychosis (Wong et al 2014).

The Diagnostic and Statistical Manual (DSM) did not consider inhalants a distinct class of drug substances until DSM-V (Diagnostic and statistical manual of mental disorders, 2013).

Nitrous oxide is now a commonly used recreational drug in the general population, especially between adolescents and young adults, with 6.1% of 16–24-year-olds admitting use in the previous year (HSCIC 2013). The most recent data, in 2013, reported a lifetime N2O use of 4.7% total (ages 12–17 years: 6%; ages 18–25 years: 4.4%; ages 26 years and over: 5.3%) (National Survey on Drug Use and Health 2016).

In the literature, there are case reports concerning deaths associated with the recreational use of N2O due to its pleasant euphoric effects. Generally, there is an accidental death due to the asphyxial effect of the gas; in fact, the deceased often put his head inside a bag to inhale the substance (Kaar et al 2016).

For inhalation, an aerosol container is often used, such as the tool for whipping cream (hence the street name for the drug is "whippits") or inflating balloons (Sleeman et al 2016). In literature, there are many cases of suicide caused by suffocation from covering the face with household plastic wrap, combined with nitrous oxide inhalation (Leth and Astrup 2017; Madentzoglou et al 2013), although compared to other methods of suicide it is uncommon (Byard and Heath 2019).

N2O does not cause major respiratory depression but will inhibit the normal physiological response to hypoxia at high concentrations (> 50%) due to oxygen depletion (Jay 2008; Wagner et al 1992; Winek et al 1995; Giuliani et al 2015).

The complications of acute nitrous oxide abuse are hypoxia, aspiration, cardiac arrhythmias, seizures, trauma, and pneumomediastinum (Randhawa and Bodenham 2016; Potocka-Banas et al. 2016). There are also rare reports of accidental inhalation at work or incorrect administration to hospitalized patients during anesthesia (Poli et al 2010; Bonsu and Stead 1983). Poli et al. in Poli et al 2010 reported a series of eight N2O intoxications during O_2 administration in a new Cardiovascular Intensive Care Unit (ICU) in a public hospital caused by the erroneous replacement of O_2 with N2O in the gas system.

The toxicological studies conducted with head-space gas chromatography (Giuliani et al 2015) found abnormal amounts of N2O in all tissue (blood, urine, liver, bile, kidney, fat, and brain), highlighting that the presence of N2O could be revealed even 31 days after death.

Also, Herff et al. (Herff et al 2007) described 6 cases of nitrous oxide-related death during anesthesia due to misconnected oxygen and nitrous oxide pipelines.

In hospitals, deaths by N2O-induced asphyxia are generally caused by malfunctioning or poorly manufactured equipment (cross-connection between N2O and O_2 lines) and machines or by incorrect usage. Several authors reported anesthesia machine failures, human errors, and even a case in which there was a displacement of a repainted O_2 cylinder (Cooper et al 2002; Wicker and Smith 2006; Duncan and Moore 1984; Poli et al 2010).

Lebourdais reports the case of a 6-year-old girl who died during anesthesia because the N2O and O_2 tubes had been cross-connected (LeBourdais 1974). A similar event occurred in a British hospital in the 70, causing two deaths (Duncan and Moore 1984). In Italy, eight people died because of N2O asphyxiation caused by cross-connection (Poli et al 2010). There were also cases of stolen or "antique" anesthesia equipment used for recreational/autoerotic inhalation of N2O (Potocka-Banas et al 2011).

Other authors described nitrous oxide-related death (Lebourdais 1974) during pediatric dental anesthesia conducted with N2O (Duncan and Moore 1984; Lee et al 2017; Lee et al 2013; Mortazavi 2017). When a victim dies in such circumstances, the crime scene analysis allows for identifying N2O asphyxia as the cause of death (DiMaio and Garriott 1978; Randhawa and Bodenham 2016). Police often find tanks, whipped cream canisters, N2O cartridges, and professional or self-made anesthesia equipment (Potocka-Banas et al 2011; Bäckström et al 2015).

Generally, autopsy only shows generic signs of asphyxia, such as cyanosis, conjunctival petechiae, visceral congestion, and lung and brain edema (Prahlow and Byard 2011), but nothing leading directly to nitrous oxide intoxication.

Histopathological examinations with standard hematoxylin-eosin (H&E) staining are not helpful because they cannot identify specific characteristics of N2O-induced asphyxia. They can only confirm the suspicion of multiorgan hypoxic damage (contraction bands in the myocardium [Leadbeatter et al 1989], vacuolation of brain cells [Van Reempts 1984]).

Courville (Courville 1964) found damage in the globus pallidus and the parieto-occipital region, describing its evolution from acute to chronic phase. Generic signs of cerebral injury (such as petechiae in subcortical white matter) characterized the first days after the hypoxic action of nitrous oxide. These signs quickly develop into focal and laminar necrosis, with neuronal loss and gliosis.

Clinically, in people surviving the acute phase of intoxication, N2O asphyxia leads to post-hypoxic brain damage, with hyperpyrexia, convulsions, and vision difficulties (Brierley 1966). These signs are attributable to an ischemia-reperfusion damage, in which the main target is the endothelium.

In cases of ischemia-reperfusion damage, there is the recruitment of leukocytes, which interact with endothelial cells. The regulation of the expression of cell adhesion molecules (CAM), such as the intracellular adhesion molecule 1 (ICAM-1), the vascular cell adhesion molecule 1 (VCAM-1), and E-selectin, affects this process. Indeed, E- and P-selectin are markers of the early inflammatory response (McEver 2015), and tumor necrosis factor α (TNF-α) increases the intracellular adhesion molecule expression (Jang et al 2021). Inhalation anesthetics (such as nitrous oxide) do not affect TNF-α induced E-selectin expression (Weber et al 2008). The primary effector of the hypoxic response is the transcription factor hypoxia-inducible factor 1-alpha (HIF-1 α) (Conde et al 2012; Li et al 2019); it is an early marker of cellular hypoxia (Jiang et al 1997; Semenza 2012; Feng et al 2021; Harrison et al 2018; Muciaccia et al 2016). HIF-1 α is expressed on pulmonary vessels in subjects who died of asphyxia (Cecchi et al 2014), such as E-Selectin in the lungs and brain (Ider et al 2022; Huang et al 2000; Novoyatleva et al 2019). All the evidence found in literature and resumed in the present manuscript are summarized in Table 2. Actually, it is very difficult to find all these elements in a crime scene, so this table could serve as a guideline for the forensic pathologist approaching a case of suspected poisoning by N2O.

Table 2 Summarized the evidence found in cases of N2O intoxication

Unknown death	
Crime scene investigation	Presence of N2O cylinder on site connected to a tube, or whipped canister, or plastic bag. Anamnesis of recent anesthesia.
Autoptic examination	Cyanosis, conjunctival petechiae, visceral congestion, and pulmonary edema. Exclusion of traumatic lesions.
Histological examination	Cerebral edema, widespread stasis, contraction bands in the myocardium. Exclusion of hemorrhage or other traumatic evidence.
Immunohistochemical examination	Positivity of ischemia-reperfusion markers indicative of hypoxia.
Toxicological examination	Finding of N2O in blood and urine. Exclusion of other causes of intoxication (alcohol, drugs, etc)

Conclusions

N2O deaths are rare, most of the time accidental, rarely suicidal. The macroscopic and microscopic signs of N2O intoxication are non-specific, but N2O has been proven to cause hypoxic damage to the brain. The suspicion of the presence of the gas in the environment should guide the pathologist.

The autopsy evidence is cyanosis, visceral congestion, and pulmonary edema. In histology, cerebral edema, widespread stasis, and non-specific cardiac signs (such as the contraction band of the myocardium) are typical. In the cases analyzed in the literature, toxicological analysis is not always performed (only 10 out of 23); often, the diagnosis is possible with the data of the inspection, that is, to find on the spot a plastic bag or whipped cream canister connected to an N2O pump or through the study of anesthesia machines. In 8 cases, death was due to an accident during anesthesia; in 11 cases, nitrous oxide is used for recreational or autoerotic purposes, and only in 2 cases for suicidal purposes. In cases where there is no circumstantial evidence of N2O exposure, it can be challenging to identify the cause of death. Tissue analyzes provide important information: through hematoxylin-eosin, it is possible to appreciate some indicative signs of asphyxiation, such as the rarefaction of Purkinje cells of the cerebellum or vacuolation of brain cells. Immunohistochemical stains can confirm hypoxic damage through the use of markers such as HIF-1 α, E-selectin, and P-selectin. Unfortunately, there is no real indicative marker of N2O asphyxia, but the forensic pathologist could consider using immunohistochemical methods to guide the diagnosis of death.

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S.D.S. analyzed the selected databases to provide the literature review. L.C. wrote the manuscript in consultation with S.D.S.; L.C. supervised the study. The authors have read and agreed to the published version of the final manuscript.

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Declarations

Ethics approval and consent to participate

All procedures performed in the study were in accordance with the ethical standards of the institution and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent for publication

Informed consent was obtained from the relatives.

Competing interests

The authors declare that they have no competing interests.

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