

# Recreational nitrous oxide and thrombotic events: a case series

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## ABSTRACT

**Background** The study aimed to elucidate the prevalence of nitrous oxide (N2O) usage in patients with unexplained venous thromboembolism (VTE), highlighting the potential association with hyperhomocysteinaemia (HHcy).

**Methods** We conducted a retrospective study at the Royal London Hospital, examining cases of N2O-related VTE from March to August 2023. Among 50 patients identified, four (8%) had recent unprovoked VTE. Patient data were collected based on N2O ambulatory emergency care pathway admissions.

**Results** Among the 50 patients identified, four (8%) had recent or concurrent VTE. Three were male (75%), with an ethnic distribution of 50% Asian or Asian British and 50% Black or Black British. Patients were distributed across quintiles of the index of multiple deprivation. All had actual or functional vitamin B12 deficiency.

**Discussion** The association between N2O use and VTE requires further investigation, though a plausible mechanism involving HHcy has been proposed. Clinicians should be vigilant for VTE in N2O users, especially those presenting with unexplained symptoms. VTE prophylaxis may be worth considering, particularly if continued exposure to nitrous oxide is anticipated.

**Conclusion** N2O misuse may increase the risk of VTE, warranting attention from healthcare providers. Further research is needed to elucidate this association and inform preventive strategies. Public awareness about the risks of N2O remains essential.

## INTRODUCTION

An association between recreational N2O use and neurological sequelae, including subacute combined degeneration of the spinal cord (SACD) and neuropathy, has been well documented. The link between venous thromboembolism (VTE) and N2O is less well defined. Hyperhomocysteinaemia (HHcy) can be caused by nitrous oxide use and may explain an increased VTE risk. While conclusive evidence is sought, clinicians should be vigilant for VTE in N2O users. Our objective was to investigate the prevalence of VTE occurrence in nitrous oxide users among patients admitted to the Royal London Hospital from March to August 2023,

specifically those with a confirmed diagnosis of unprovoked VTE.

Here, we describe two cases (out of four in total) for illustrative reasons at East London Hospital in which VTE occurred, with and without SACD, in the context of regular nitrous oxide use.

## CASE 1

A patient in their early 30s, presented in August 2023 with dizziness, loss of coordination and severe headache following consumption of alcohol and nitrous oxide, around 6–8 cylinders over a weekend (1 cylinder=70 small canisters×8g). During the examination, left-beating nystagmus on lateral gaze was noted, but apart from this, there were no other remarkable clinical findings. Blood tests showed the following: vitamin B12 332 ng/L (normal range:197–1000 ng/L; the patient reported having vitamin B12 injections privately while taking N2O to avoid complications), methylmalonic acid (MMA) 0.16 umol/L (normal range: 0–0.28 umol/L) and unremarkable clotting profile. The medical team advised the discontinuation of recreational drugs and alcohol. The patient was discharged without brain imaging.

In September 2023, the patient returned with a persistent headache. An MRI scan revealed a subacute cerebral venous sinus thrombosis (CVST) without parenchymal damage. A CT venogram confirmed the presence of thrombosis in the right transverse and sigmoid sinuses. The patient was promptly initiated on low-molecular-weight heparin enoxaparin (100 mg BD). Abstinence from N2O caused significant improvement as the patient's neurological symptoms resolved.

The medical and family history did not reveal any additional risk factors for VTE. The patient had been using nitrous oxide since 2020, initially consuming one box of



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small canisters (1 box=24 small canisters × 8 g) occasionally. The consumption gradually increased and reached a peak of 5–6 cylinders every 3 weeks by 2023.

## CASE 2

A patient in their early 30s was admitted to the hospital in March 2023 with bilateral leg paresthesia, shortness of breath and left-sided chest discomfort. The patient was diagnosed with extensive bilateral pulmonary embolism (PE) with right ventricular strain and left leg deep vein thrombosis (DVT), proven with computed tomography pulmonary angiogram (CTPA) and ultrasound (US) Doppler, respectively. Thrombolysis with alteplase was given in the intensive care unit, and the patient was later discharged with a 6-month course of rivaroxaban.

The patient had been using nitrous oxide since 2019, starting with 4–5 boxes of small canisters once or twice a week, increasing to 2–4 cylinders per month by June 2022 and 8 cylinders per month by January 2023. The patient became abstinent from N<sub>2</sub>O by June 2023. Other potential VTE risk factors were young paternal stroke and smoking (one cigarette per day for 10 years).

Then, in July 2023, the patient presented with recurrent falls and reduced mobility. On examination, ataxia, lower limb weakness, diminished reflexes and sensory loss to the knees bilaterally and preserved upper limb function were found, and the cranial nerves were intact. Vitamin B<sub>12</sub> level was low (174 ng/L); thus, the patient was started on vitamin B<sub>12</sub> injections in the ambulatory care department (before testing homocysteine (Hcy) or MMA, hence, these results were not available). An MRI scan of the spine revealed hyperintense posterior cervical cord signal change, consistent with SACD. The signs and symptoms have been improving with treatment.

## METHODS

We encountered four clinical cases that occurred between March and August 2023 at the Royal London Hospital. Patients were referred from the emergency department, urgent treatment centre, and general practice on the ambulatory emergency care nitrous oxide pathway. Therefore, they are likely to represent only a proportion of patients seen with N<sub>2</sub>O-related VTE during this period. Inclusion criteria included individuals coded with nitrous oxide misuse and VTE within the specified timeframe, who exhibited confirmed VTE on imaging and lacked any identifiable provoking factor for the VTE. Exclusion criteria for provoked VTE were determined in accordance with the guidelines outlined by the National Institute for Health and Care Excellence (NICE).<sup>1</sup> Moreover, patients referred on the pathway in February and discussed later in March were also excluded.

## RESULTS

Between March and August 2023, our pathway for N<sub>2</sub>O-related neurological events encountered 53 patients who were discussed at N<sub>2</sub>O multidisciplinary team meetings. Among these 53 patients, 3 were referred on the pathway in February, resulting in a total of 50 patients included in this study. Among these 50 patients, four (~8%) had recent or concurrent VTE, and we describe two in this article for illustrative purposes. The majority of patients were male (n=3, 75%), and the ethnic distribution among the cohort was 50% Asian or Asian British and 50% Black or Black British.

Stratifying by the index of multiple deprivation, 25% fell within quintiles 1–2, 25% in 3–4, 25% in 5–6 and another 25% in the 7–8 range (with 0% in 9–10). The patients were diagnosed with PE (n=1, 25%), PE and DVT (n=2, 50%) and CVST (n=1, 25%). The patients presented with actual or functional vitamin B<sub>12</sub> deficiency. Study constraints prevented the acquisition of all results during patient presentation, with one patient displaying elevated levels of MMA (1.29 μmol/L), Hcy (110.2 μmol/L) and D-dimer (3.34 mg/L).

## DISCUSSION

According to the Office for National Statistics, in 2012–2013 among 16–24-year-olds nitrous oxide use was 6.1%, reaching a peak of 9.0% in 2016–2017. Between 2017 and 2020, the prevalence remained relatively stable between 8.7–8.8%. The first report after the first year of the covid pandemic, 2021–2022, noted that nitrous oxide use had reduced significantly to 3.9%.<sup>2</sup> The Crime Survey in England and Wales is likely to underestimate use as it was a government-run, in-person survey of households.

Several studies, including three meta-analyses, showed an association between elevated homocysteine levels and the increased risk for the occurrence of venous thrombosis.<sup>3</sup> The relative risk has been estimated to be 2–3 times higher compared with people with normal homocysteine levels.<sup>3</sup> Separately, a study in the Netherlands reported 326 cases of recreational use of N<sub>2</sub>O between January 2015 and May 2021. Of these, 17 (5%) patients presented with thrombotic events.<sup>4</sup>

Myeloneuropathy, including SACD, is already a recognised consequence of recreational nitrous oxide use.<sup>5,6</sup> While there have been occasional reports of an association between nitrous oxide use and VTE, the association is currently under-recognised, despite a plausible mechanism.<sup>4,6,7</sup> These patients frequently seek neurologists' attention due to toxic myeloneuropathy resulting from functional B<sub>12</sub> deficiency. Chronic nitrous oxide misuse leads to reduced vitamin B<sub>12</sub> levels and inhibits methionine synthase, resulting in higher homocysteine levels, which in turn may cause thrombotic events.<sup>4,8,9</sup> Reduced mobility due to nitrous oxide-related myeloneuropathy and quantity of nitrous oxide misuse could also contribute to VTE. As such, VTE prophylaxis may be

worth considering, particularly if continued exposure to nitrous oxide is anticipated.

Uncovering the underlying risk factors within Asian or Asian British and Black or Black British groups could provide crucial insights for targeted preventive measures and interventions, ultimately improving our understanding of thrombotic events and optimising healthcare strategies for an at-risk population. This phenomenon could stem from underlying genetic, nutritional or dietary predispositions to neurological damage.<sup>5,6</sup> Additionally, it could be influenced by circumstances leading to its usage. The current understanding does not clarify whether various ethnic groups exhibit varying susceptibility to this issue based on their B12 status and metabolism.

Limited data availability currently impedes comprehensive examination of the relationship between nitrous oxide and VTE. Elevated homocysteine is a mediator of thrombotic processes, through effects on endothelial dysfunction, platelet activation and impaired fibrinolysis.<sup>10</sup> Patients with HHcy have an elevated risk of VTE (DVT, PE and CVST), with a relative increase of 2.5–2.95 times compared with normal levels of homocysteine.<sup>11,12</sup> HHcy also increases the likelihood of recurrent VTE.<sup>7,13</sup>

Elevated homocysteine levels can occur for reasons other than B12 deficiency, and while it is a more sensitive marker of functional B12 deficiency, it is less specific than MMA.<sup>14</sup> Its routine measurement also poses practical challenges in some healthcare settings (it needs to be transported on ice). MMA is a more specific and less sensitive marker for B12 deficiency, and its measurement was incorporated in recent management guidelines.<sup>5</sup>

Immediate discontinuation of nitrous oxide, coupled with vitamin B12 supplementation, forms the basis of management for the neurological sequelae of nitrous oxide use.<sup>6,14</sup> Treatment with IM B12 alone without abstinence from nitrous oxide may be ineffective at preventing neurological disorders.<sup>5</sup> Thromboprophylaxis measures should be considered, and a high index of suspicion of VTE should be maintained in individuals with a history of N<sub>2</sub>O exposure who are immobile for whatever reason. Additionally, integrating physiotherapy and mobilisation into the treatment regimen is vital for optimising patient recovery.<sup>15</sup>

Individuals managing large retail and online supply chains should be aware of the intended use of compressed gas, particularly nitrous oxide. Monitoring nitrous oxide usage in commercial kitchens is manageable, but questions arise about its actual purpose when sold through retail outlets. In the UK, criminal sanctions for nitrous oxide possession were reinforced on November 8, 2023. While Australian regulations exist, their effectiveness is debatable. To tackle potential misuse, there is a need for restrictions on non-legitimate sales, reducing availability, including from online vendors. Despite widespread littering associated with nitrous oxide, there is currently no mechanism to monitor its environmental impact. While there is no substantive evidence linking nitrous oxide to criminal activities, addressing environmental

concerns is crucial. Nitrous oxide has numerous legitimate uses, and a consultation with industry and academia is vital to avoid disproportionate burdens on these uses.<sup>2</sup>

The study faces limitations due to a small sample size, raising concerns about the generalisability of findings. While the report describes a plausible connection between nitrous oxide exposure and unexplained VTE in young adults, it lacks a thorough investigation into the biological mechanisms linking nitrous oxide to VTE.

Recent nitrous oxide use in the presented cases highlights a potential new concern for recreational users and an important alert for clinicians managing these patients. In each of the cases, a pattern of increasing nitrous oxide use over time was observed, which is consistent with our general observations when managing this patient group.

## CONCLUSION

A liability towards VTE driven by nitrous oxide misuse highlights an understudied and under-recognised danger. While the neurological consequences have been widely publicised, the potential link between nitrous oxide and VTE requires urgent further research, although there is a prior mechanism for an association (ie, driven by HHcy).

Clinicians (neurologists and acute medical staff) must be vigilant to thrombosis and myeloneuropathy due to recreational nitrous use occurring separately, sequentially or concurrently, and we should enquire about nitrous oxide use in young people with otherwise unexplained VTE. Raising awareness and public education about the harms of nitrous oxide remain of paramount importance.

## Key points

- ⇒ A potential association between venous thromboembolism and nitrous oxide use is currently under-recognised but likely to be encountered by neurologists and acute medical staff treating this patient group.
- ⇒ This association requires urgent further research, but challenges in undertaking this based on current coding practices and exposure measurement are anticipated.
- ⇒ Identification and management of thrombotic events should be incorporated into treatment guidance for nitrous oxide cases presenting to healthcare settings.

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