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REVIEW ARTICLES

Nitrous oxide: are we still in equipoise? A qualitative review of current controversies

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Editor's key points

- The role of nitrous oxide in routine anaesthesia practice has been questioned.
- This review provides a balance of arguments in favour and against the use of nitrous oxide.
- The authors conclude that nitrous oxide should remain an option in contemporary anaesthesia.

Summary. This review considers the current position of nitrous oxide in anaesthetic practice and balances potential beneficial and disadvantageous effects. The classic adverse characteristics of nitrous oxide, such as diffusion hypoxia, expansion of gas-filled spaces, and postoperative nausea and vomiting, are often cited as reasons to avoid this old drug. Recent concerns regarding neurotoxicity, adverse cardiovascular outcomes, and wound complications have further hardened many practitioners against nitrous oxide. New evidence and underpinning mechanistic data, however, suggest potential beneficial effects on the central nervous system, cardiovascular system, and acute and chronic pain. While we await the outcome of large studies including ENIGMA-II, many clinicians have already decided against this agent. The authors argue that this abandonment may be premature.

Clinical Trial Registration. None required.

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In recent years, isolated concerns regarding the safety profile of nitrous oxide have grown into a chorus of criticism. Increasingly, modern anaesthetists view nitrous oxide as an anachronism; a relic from the 'bad old days' of anaesthesia. It is therefore reasonable to ask whether there is a role for nitrous oxide in modern anaesthetic practice. The answer to this question requires a two-pronged approach: first, does nitrous oxide have a unique selling proposition that warrants its specific use and, secondly, does its side-effect profile justify continued use?

Nitrous oxide has several advantages. Its physicochemical properties, especially its relatively low solubility in blood, allow for rapid, reliable changes in depth of anaesthesia/analgesia and rapid recovery. Its molecular mechanism of action, as predominantly an *N*-methyl-D-aspartate (NMDA) receptor antagonist, differs from the majority of our conventional anaesthetic agents which are predominantly gamma-aminobutyric acid (GABA) agonists. This review highlights its analgesic effects, potential to reduce awareness, role in neuroprotection, and haemodynamic effects.

Pragmatically, nitrous oxide is an agent with which we are familiar, easy to use, and easy to monitor: all advantages in real-world anaesthesia. Nitrous oxide has been used for more than 150 yr without leaving an obvious trail of death and destruction in its wake. It is thus clearly safe for most patients.[1]

Outstanding questions are whether subtle adverse effects have been missed over the years, and if there are specific vulnerable populations? We discuss potential effects on acute and chronic pain, neurological and cardiovascular outcomes, and wound infection as these remain controversial and are the focus of current research. Certain characteristics of nitrous oxide, including expansion of gas-filled cavities, the second-gas effect, diffusion hypoxia, and its propensity to postoperative nausea and vomiting, are well known and are therefore not the focus of this review.

Pain

The acute analgesic effect of nitrous oxide is used as a component of balanced anaesthesia. The magnitude of this effect is however unclear. Given the pharmacokinetic profile of nitrous oxide, a relevant comparison is with remifentanil where 66–70% nitrous oxide is equivalent to remifentanil 0.085–0.17 $\mu g\ kg^{-1}\ min^{-1}$, or a whole-blood concentration of 2 $ng\ ml^{-1}$.[2 3] The analgesic effect of nitrous oxide may be smaller when co-administered with GABAergic agents; however, these studies used either animal models or sub-anaesthetic concentrations of sevoflurane and nitrous oxide.[4–6]

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Nitrous oxide may reduce postoperative pain when compared with remifentanil and attenuate remifentanil-induced hyperalgesia.[7–9] Nitrous oxide may also have utility in the prevention and treatment of chronic pain syndromes. In a follow-up study of participants in the ENIGMA trial, nitrous oxide use was associated with a significant reduction in chronic postsurgical pain which was maintained after multivariate analysis.[10 11] Although the methodology was not robust (telephonic survey), this requires further investigation. The findings are biologically plausible though, because even a single exposure to nitrous oxide results in a prolonged reduction in pain hypersensitivity in an animal model of peripheral neuropathy.[12]

Prevention of anaesthetic awareness

The amnestic and analgesic effects of nitrous oxide have a similar dose–response profile, and there are sound pharmacokinetic and pharmacodynamic reasons for it to decrease anaesthetic awareness.[13] Hopkins[13] suggests that the number need to treat (NNT) to prevent awareness with nitrous oxide compares favourably with monitoring with bispectral index (BIS). Tramer and colleagues[14] reported an NNT of 46 with nitrous oxide, whereas Myles and colleagues[15] reported an NNT of 138 with BIS monitoring in high-risk patients. In contrast, ENIGMA reported two cases with awareness, both in the nitrous oxide group.[10] Currently then, the effectiveness of nitrous oxide as a tool to prevent anaesthetic awareness remains controversial although it is an attractive proposition.[16]

What is the effect of nitrous oxide on commonly used depth of anaesthesia monitors? NMDA receptor antagonists, such as ketamine, xenon, and nitrous oxide, suppress the cortical electroencephalogram less than GABAergic agents, so BIS and spectral entropy are relatively insensitive to nitrous oxide.[17] Although the magnitude of this effect is controversial, using these monitors to titrate a nitrous oxide-based anaesthetic may result in an inappropriately deep anaesthetic, potentially leading to morbidity or mortality.[18] Failure to take this into account or to prevent or control for differences in depth of anaesthesia may explain some of the adverse outcomes seen in recent studies, such as the ENIGMA trial.[10]

Adverse neurological effects

Potential adverse neurological effects include myelinopathies, neurotoxicity/hypoxic-ischaemic injury, neurodevelopment disturbances, postoperative cognitive dysfunction, and alterations in intracranial dynamics.

Myelinopathies, such as sub-acute combined degeneration of the cord (SACD) feature prominently on most anaesthetic trainees list of nitrous oxide-related complications. While there is a sound biochemical basis for nitrous oxide to induce myelinopathy, this complication is limited to case reports and usually involves prolonged exposure, either occupationally or as a result of nitrous oxide abuse, that exceeds clinical anaesthetic exposure.[19–22] However, patients with untreated vitamin B_{12} or folate deficiency may be at some risk from medical exposure, as are patients with genetic disorders such as methylene tetrahydrofolate reductase deficiency.[23–25] As SACD is a potentially devastating complication if undiagnosed and untreated, patients with risk factors, such as untreated B_{12} deficiency, should receive appropriate treatment with B-vitamins, or nitrous oxide should be avoided.

Does nitrous oxide cause direct cerebral neurotoxicity or potentiate hypoxic-ischaemic injury? Animal studies are contradictory. Rat studies have shown worsening of ischaemic injury and direct neurotoxic changes. The former, however, was only seen with total ischaemia and not partial ischaemia, the latter only with hyperbaric exposure, was short-lived, and was prevented by co-administration with a GABAergic agent such as a volatile anaesthetic, as occurs in clinical anaesthesia.[26 27] These effects are thus inconsistent and do not reflect real-world scenarios. In addition, nitrous oxide may in fact have a neuroprotective effect via the reduction of NMDA-induced glutamate excitoxicity, and in support of this animal studies have reported a smaller cortical infarct volume in ischaemic stroke with the use of nitrous oxide.[28]

So, while the animal data muddy the water, are there any human data to guide us? Unfortunately, there is little good-quality evidence that focuses primarily on this issue. The Intraoperative Hypothermia in Aneurysm Surgery Trial (IHAST) randomized 1001 patients undergoing cerebral aneurysm clipping to either of mild hypothermia or normothermia.[29] A *post hoc* analysis by McGregor and colleagues[30] found no difference in early or late neurological deficits between those who had received nitrous oxide and those who had not. More patients in the nitrous oxide group were however able to be discharged home. In an additional *post hoc* analysis, Pasternak and colleagues[31] evaluated only the subgroup of patients who had temporary aneurysm clipping, a neurologically high-risk group. While the nitrous oxide group in this analysis had an increased risk of delayed ischaemic neurological deficit, an 'early' adverse neurological outcome, there was a lower risk of impairment on neuropsychological testing at 3 months, and a greater chance of being discharged home. While there are many methodological concerns and confounding factors when it comes to using *post hoc* analyses of a trial of hypothermia to answer questions regarding anaesthetic management, this is the best clinical evidence that we have in this regard. IHAST reflects real-world anaesthetic practice and is of a magnitude and quality that is unlikely to be repeated specifically to examine the role of nitrous oxide in this context. Finally, by conducting separate analyses on both the whole cohort and those who had temporary aneurysm clipping the use of nitrous oxide in patients at both 'standard' and 'high' risk of cerebral ischaemia was evaluated. The best clinical evidence, therefore, suggests that nitrous oxide is safe to use in patients at risk of cerebral ischaemic injury.

Concerns have been raised about possible adverse neurodevelopmental effects of nitrous oxide. NMDA receptor antagonists have been associated with widespread neuronal apoptosis in rat pups.[32] However, with respect to nitrous oxide, this has been demonstrated when nitrous oxide was used in combination with isoflurane and may have reflected more an exacerbation of isoflurane-induced neurodegenerative

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