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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]

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

changes than primarily a nitrous oxide effect.[33] A more recent study however showed that this combination has no direct neurotoxic effect.[34] The effects seen in animal studies may therefore be related to other components of the anaesthetic management of these animals. Pragmatically, the realities of animal studies preclude the detailed metabolic, haemodynamic, and respiratory management given to human patients. In addition, the timing and duration of anaesthetic exposure in animal models may not correlate with, and probably far exceeds, clinical anaesthetic exposure.[35 36] Finally, despite the controversy generated by animal studies, and recent concerns regarding an association between anaesthesia and learning disabilities, no human clinical trials have linked nitrous oxide exposure specifically to adverse neurodevelopmental outcomes.[37]

Nitrous oxide has been linked to postoperative cognitive dysfunction in elderly rats.[38 39] Current human data suggest that the aetiology is multifactorial, including varied risk factors such as the neuroinflammatory response to surgery, environmental factors, and sleep disturbances, with little evidence to suggest a role for nitrous oxide.[40–42]

Contemporary neuroanaesthesia teaching often suggests that nitrous oxide adversely affects intracranial dynamics, with increased cerebral metabolic rate (CMR), cerebral blood flow (CBF), cerebral blood volume (CBV) and intracranial pressure (ICP), and also impaired autoregulation; with recommendations that its use be avoided in the neurologically 'at risk' patient. An evidence-based approach shows that the reality is more complex.[43]

While some studies show an increase in CBF, others report no significant effect.[44–51] CBF effects may depend on which hypnotic is co-administered with nitrous oxide, for example, no change in CBF is seen with desflurane.[49] The findings with propofol are inconsistent, but a number of studies report no effect.[48 50 51] The effect with sevoflurane seems to be concentration dependent.[52]

Effects on autoregulation are also inconsistent. The addition of nitrous oxide to propofol anaesthesia does not seem to impair autoregulation.[51] The effect with sevoflurane is concentration dependent, with nitrous oxide impairing autoregulation when added to 1 minimum alveolar concentration (MAC) sevoflurane, but not when added to 1.5 MAC sevoflurane.[52] These findings suggest that the maintenance hypnotic exerts more effect on cerebral haemodynamics than nitrous oxide itself.

Early animal data suggested nitrous oxide increased cerebral metabolic activity.[53 54] Based on these data, it made sense to avoid nitrous oxide in the neurologically at risk patient. This metabolic effect is however complex. While nitrous oxide does not in fact increase global cerebral metabolic rate in humans, it may alter the regional distribution of metabolic activity.[46] The global effect on human cerebral metabolic rate may be dependent on depth of anaesthesia and the agent co-administered with nitrous oxide.[47 55] Nitrous oxide increased CMR during propofol-induced electrical silence, but it did not increase CMR when added to clinically relevant concentrations of isoflurane.[47 55] In non-surgical volunteers, CMR was however higher with an equi-MAC combination of nitrous oxide and isoflurane than with isoflurane alone.[47] However, the cerebral metabolic effect of nitrous oxide in patients exposed to surgical stimuli may be reduced if it is used to achieve an appropriate level of hypnosis and analgesia, an 'optimal anaesthetic fit' hypothesis.[56 57] It is perhaps time to re-evaluate the role of nitrous oxide in this context, as is being done with ketamine, another NMDA antagonist.[58]

Another factor to consider is carbon dioxide reactivity. While some studies report a reduction in carbon dioxide reactivity when nitrous oxide is co-administered with a volatile anaesthetic agent, this appears most significant at high concentrations of the volatile agent.[59 60] During clinical use, carbon dioxide reactivity is largely maintained and any potential adverse effects on cerebral haemodynamics could be countered by an appropriate use of mild hypocapnia.[61–65]

The common theme in the examples above is that the effects of nitrous on intracranial dynamics are highly dependent on the anaesthetic milieu. Adverse effects are seen when nitrous oxide is added to other agents to achieve deep anaesthesia, >1.5 MAC, or when subjects are too lightly anaesthetized. Both these extremes are inappropriate and minimal effects are seen when nitrous oxide is used to achieve an appropriate depth of anaesthesia.

Are we even looking at the correct parameters when it comes to the effect of nitrous oxide on intracranial dynamics though? A study by Hancock and Nathanson raises interesting questions in this regard.[66] Conceptually, most anaesthetists are comfortable that cerebral perfusion pressure (CPP) is the difference between mean arterial pressure (MAP) and ICP or central venous pressure (CVP). This, however, ignores the influence of vascular tone, which may well be the primary determinant of downstream pressure in many patients. The interaction between ICP, CVP, and vascular tone can be represented by the zero flow pressure (ZFP), which is the MAP at which CBF ceases. Hancock and Nathanson showed that nitrous oxide reduces the ZFP and increases the CPP. This implies that, although nitrous oxide-induced vasodilation increases CBV, the effect on ZFP dominates and results in a net increase in CPP. This study was done on subjects without intracranial pathology and so cannot be simply extrapolated to the neurologically at risk patient, but it does offer an interesting alternative approach to traditional views on intracranial dynamics and provides a basis for future research.

With these contradictory underpinnings are there any clinical data that integrate these results? Good surgical conditions have been reported with the use of nitrous oxide-based regimes in brain tumour surgery despite many of these patients having a significant mass effect before operation.[67 68] More recently Singh and colleagues[69] reported on a comparison between a nitrous oxide–isoflurane regime and an isoflurane-only regime for supratentorial tumour surgery. Although this was only a small pilot study, they found no differences in surgical conditions and intraoperative or postoperative complications between the groups, and the nitrous oxide group had more stable haemodynamics and lower analgesic and neuromuscular blocking agent requirements.

From a practical point of view, the effect of nitrous oxide on intracranial dynamics appears more benign than is often claimed. Holistically, the relative haemodynamic stability of anaesthetic techniques including nitrous oxide may be advantageous. In the neurologically at risk patient, avoiding secondary insults, such as hypotension, may be more important to the patient than any specific choice of hypnotic.

Finally, two additional matters of relevance from a neurosurgical point of view need to be addressed: these both relate to the ability of nitrous oxide to expand gas-filled spaces.

In head-injured or neurosurgical patients, nitrous oxide may theoretically convert a pneumocephalus into a tension pneumocephalus. There appears, however, to be no difference in the volume of intracranial gas post-craniotomy in patients who have received nitrous oxide *vs* those who have had a nitrous-free anaesthetic.[70] In fact it has been reported that patients who received nitrous oxide during dural closure had lower ICPs than those who did not receive nitrous oxide.[71] It appears that the rapid washout of nitrous oxide may actually decrease the pneumocephalus and that the risk of tension pneumocephalus with nitrous oxide is overstated.

Also of concern here is the risk that nitrous oxide may expand venous air emboli (VAE). The timeframe involved is in all likelihood too short to have any clinically significant effect though. In support of this, Losasso and colleagues[72] found no evidence that nitrous oxide increased the risk, volume, or clinical consequences of VAE. Although it is not rational then to omit nitrous oxide-based solely on the fear of a VAE, it is still prudent to stop its administration if an air embolus is suspected.

Cardiovascular effects

The cardiovascular effects of nitrous oxide have generated much discussion since the publication of the original ENIGMA trial and a subsequent *post hoc* secondary analysis of long-term morbidity and mortality.[10 73] ENIGMA demonstrated a trend to a lower risk of myocardial infarction in the nitrous oxide-free group [adjusted OR=0.58 (95% CI: 0.22–1.50; P=0.26)]. The long-term follow-up, over a median of 3.5 yr, further demonstrated a statistically significant increase in the risk of myocardial infarction in patients exposed to nitrous oxide [adjusted OR 1.59 (95% CI: 1.01–2.51; P=0.04)]; however, 17% of patients were lost to follow-up. Nevertheless, these data have raised serious concerns and have generated a clear hypothesis that is currently being tested in the ENIGMA-II study.[74]

Should we then avoid the use of nitrous oxide in those with cardiovascular risk factors?

Given the statistical equipoise in ENIGMA, the next question is whether a sound biological basis exists for increased cardiovascular risk caused by nitrous oxide? Nitrous oxide inactivates vitamin B_{12}, inhibiting methionine synthase, preventing the conversion of homocysteine to methionine, and resulting in elevation of plasma homocysteine levels. Hyperhomocysteinaemia in turn creates a milieu for acute coronary syndrome via endothelial dysfunction and prothrombotic effects. However, the cardiovascular risk posed by chronically elevated homocysteine levels (that is the basis for our acute concerns) is being questioned. Recent studies have questioned whether this association truly exists and even if it does, if it is causal, or merely an association, as recent studies using folate/B-vitamins to reduce homocysteine levels failed to reduce cardiovascular adverse events.[75–77]

There are, however, a number of concerns with this attractive paradigm. First, there is a significant variation in the reported magnitude and time-scale of the postoperative increase in plasma homocysteine. Badner and colleagues described a 22% increase in the post-anaesthesia care unit and a 48% increase at 48 h after operation in one trial, and a 74% increase after operation in an earlier trial; Myles and colleagues reported a 45% increase within 24 h; and Nagele and colleagues reported a 228% increase within the first few hours after operation, which returned to baseline by 24 h.[78–81] In addition, Nagele and colleagues showed that the magnitude of the increase varied from 14 to 567% amongst different individuals.[81] The rapid increase raises questions as to whether this is really the direct effect of a reduction in methionine synthase activity or whether there is another mechanism at play. The swift return to preoperative levels leads one to question whether this could really explain the effects on long-term cardiovascular events. Elevations in plasma homocysteine from preoperative levels are also seen after operation in patients not exposed to nitrous oxide.[82] The inter-individual variability raises questions as to what other risk factors are involved. Duration of nitrous exposure seems significant, vitamin B_{12} and folate deficiency may play a role, and genetic polymorphisms may be relevant: at present, we have insufficient data to properly explain this variability.[81 83–85]

Perhaps the most powerful risk factor for postoperative hyperhomocysteinaemia is ASA III or IV status.[85] Hyperhomocysteinaemia increased the risk of major postoperative complications, independent of nitrous oxide use. Does this imply that homocysteine levels are simply a marker of cardiovascular risk and that any effect of nitrous oxide may serve to unmask an underlying risk? Certainly there is no easily discernible linear cause and effect between nitrous oxide use and cardiac risk.

While Myles and colleagues reported that nitrous oxide exposure was associated with both an increase in homocysteine and a reduction in flow-mediated vasodilation (a marker of endothelial dysfunction) and while others have reported a direct association between homocysteine exposure and endothelial dysfunction, the clinical significance is uncertain.[80 86] Badner and colleagues, for example, reported that nitrous oxide increased the risk of postoperative ischaemia in patients undergoing carotid endarterectomy.[78] There was an increase in the number of patients with ischaemia, the number of episodes of ischaemia, and the number of episodes of >30 min duration. However, the number of patients with total ischaemia of >2 h was not significantly increased. Again, it is difficult to interpret the clinical impact of these findings as clinical outcomes were not reported and it is currently unclear what duration of ischaemia is associated with

adverse clinical outcomes. In contrast, Kozmary and colleagues[87] had previously found a trend towards a reduction in intra- and postoperative myocardial ischaemia/infarction in patients undergoing carotid surgery who received nitrous oxide.

In terms of recent clinical data, a subgroup analysis of the General Anaesthetic vs Local Anaesthetic for carotid surgery (GALA) trial showed no association between nitrous oxide and an increased risk of the composite primary endpoint of stroke, death, or myocardial infarction within 30 days of carotid endarterectomy.[88] Furthermore, a *post hoc* subanalysis of the Perioperative Ischemic Evaluation (POISE) study trial showed no increase in adverse cardiovascular events in the nitrous oxide group and a recent large retrospective cohort analysis showed no difference in cardiac complications between those who received nitrous oxide and those who did not.[1 89] The presence and clinical significance of acute effects of nitrous oxide on endothelial function and adverse cardiovascular events thus remain unclear.

Might the excess cardiovascular risk implied by ENIGMA then be because of confounding factors? In ENIGMA, the median volatile anaesthetic concentration was 0.87 MAC in the N_2O-free group and 0.67 MAC in the N_2O group, while in Badner and colleagues' study the comparison was 0.48% fractional end-tidal (F_{et}) isoflurane in the N_2O group *vs* 0.67% F_{et} isoflurane in the nitrous oxide-free group.[10 78] The ENIGMA trial used 70% nitrous oxide, whereas Badner and colleagues' study used >50% nitrous oxide. Thus, the nitrous oxide groups in both studies have a greater depth of anaesthesia, as quantified by total MAC fraction, than the nitrous oxide-free groups. Might the greater depth of anaesthesia experienced by patients given nitrous oxide account for the adverse cardiovascular events reported in both sets of patients?[90]

While the association between nitrous oxide, homocysteine, and acute coronary syndromes remains a matter of debate, can we hedge our bets and 'play it safe' but still use nitrous oxide? Vitamin B_{12} and folate supplementation has been investigated with conflicting results. Badner and colleagues showed that oral supplementation for a week before operation prevented nitrous oxide-associated increases in homocysteine levels, but Rao and colleagues[82] failed to show an effect with a single i.v. dose in the pre-anaesthetic holding area.[91] Thus, further work needs to be done to define the optimal dose, duration, and timing of this therapy and to evaluate its clinical efficacy. It may also prove impractical clinically.

While most of the recent debate on the cardiovascular effects of nitrous oxide has focused on the issues raised above, are we ignoring 'low-tech' factors that have real-world benefits? The haemodynamic stability of nitrous oxide is an example. While nitrous oxide may have a direct myocardial-depressant effect, via the reduction in calcium release from the sarcoplasmic reticulum, this is generally counteracted by indirect sympathetic stimulation; the net effect being minimal cardiovascular depression.[92] In support of this, Fernandes and colleagues reported stable arterial pressure despite a greater functional depth of anaesthesia when nitrous oxide was added to sevoflurane in patients undergoing laparoscopic cholecystectomy; Inada and colleagues showed a trend towards a reduced heart rate and increased MAP when 0.65 MAC nitrous oxide was substituted for equi-MAC concentrations of isoflurane or sevoflurane; and Shiga and colleagues showed that 70% nitrous oxide caused little cardiovascular depression when added to clinically applicable target concentrations of propofol.[93–95] The clinical implication is that the anaesthetist at the 'coal-face' can use nitrous oxide to facilitate the balancing act of achieving an adequate depth of anaesthesia while maintaining haemodynamic stability without excessive use of inotropes/vasopressors. This may be particularly useful in the elderly, those on cardiovascular-depressant drugs (e.g. calcium channel blockers), and those with cardiovascular disease. While there is no evidence for an outcome benefit in this regard, we know that sustained intraoperative hypotension increases the risk of perioperative adverse cardiovascular events.[96] Unfortunately, the patients who would most benefit from the enhanced haemodynamic stability are a similar group that may be at increased risk of the 'homocysteine-related' adverse cardiac effects of nitrous oxide. How we tease out the competing influences and effects remains a major challenge for future research. ENIGMA-II may provide some answers.[74]

Finally, some lesser-known facets of the nitrous oxide–cardiovascular interaction warrant further exploration. Nitrous oxide, when administered as an adjunct to isoflurane anaesthesia, attenuated the vascular hyporeactivity seen after haemorrhagic shock.[97] This implies that our anaesthetic choice may affect postoperative cardiovascular function and, as vasomotor dysfunction is central to the development of organ dysfunction and death, potentially influence perioperative outcome.

Wound infection

While there are multiple potential mechanisms by which nitrous oxide may impair immune function and wound healing the clinical effect on wound infection is uncertain. ENIGMA highlighted a significant increase in wound infection in patients exposed to nitrous oxide.[10] However, previous research, with wound infection as the primary outcome, showed no increase in the risk of wound infection in the nitrous oxide group.[98] A large retrospective cohort analysis also showed no difference in wound disruption, and infectious complication in general, between the nitrous oxide and nitrous oxide-free groups.[1] Recent data on the subject suggest that nitrous oxide increases deoxyribonucleic acid damage which may predispose patients to a higher risk of wound infection.[99] These conflicting data highlight the enigma of nitrous oxide: after 150 yr of use we are left with more questions than answers, even regarding as 'simple' a complication as wound infection. It also highlights the conundrums that underpin the entire article: are there specific benefits to the use of nitrous oxide, and if so, can we identify specific groups in which these benefits outweigh the risks or identify strategies to mitigate these risks?

This review has focused on the most current and controversial issues around the use of nitrous oxide, issues that would be either 'deal breakers' or 'unique selling propositions' for many anaesthetists. There are of course a multitude of other considerations that may influence the individual practitioner or institution. These are beyond the scope of the review, but include clinical considerations such as the influence of nitrous oxide on postoperative nausea and vomiting; the impact of which requires careful consideration of available evidence including the compensatory effects of multi-modal anti-emetic prophylaxis.[14 100] There are also complex economic considerations, with nitrous oxide not necessarily reducing healthcare costs, as is often claimed by its proponents.[101] Finally, we must consider the environmental impact of our anaesthetic choices. While the contribution of nitrous oxide used for anaesthesia may be low, a recent review on the environment impact of anaesthetic gases is thought provoking.[102 103]

Conclusion

Nitrous oxide should remain an option in contemporary anaesthesia. There are potential advantages in pain control and prevention, reduction of awareness with recall, and use in neurologically and cardiovascularly 'at risk' patients. With respect to its side-effect profile, recent data suggest that nitrous oxide is safe (and possibly beneficial) in an unselected heterogenous patient population.[1] In addition, certain conventional concerns have been addressed (e.g. post-craniotomy pneumocephalus) or appear less of an issue than previously thought (e.g. intracranial dynamics). New concerns regarding matters such as neurotoxicity and adverse cardiovascular events have however emerged. Thus, while anaesthetists can rest assured that they are, in general, not doing their patients an injustice with the use of nitrous oxide, it remains incumbent upon the practitioner to utilize the data presented above, and any new data (e.g. ENIGMA-II), to evaluate the risk–benefit profile for the individual patient and make the use of nitrous oxide as safe as possible.

Authors' contributions

K.d.V.: conception and design of article, drafting and revising article, approval of final manuscript. J.R.S.: conception and design of article, drafting and revising article, approval of final manuscript.

Declaration of interest

None declared.

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