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Nitrous Oxide in Neuroanesthesia

Tried and True or Toxin?

NITROUS oxide is a funny gas. It got off to a less than auspicious start when Horace Wells was humiliated by boos and jeers when he administered it for surgery the first time at Massachusetts General Hospital (Boston, Massachusetts) on January 18, 1845, and his patient, having the mask removed too soon, cried out with pain. It is implicated in a litany of well-known problems even today: nausea and vomiting, increased pressure in air-containing closed spaces, neurologic deficits in B_{12}-deficient patients, hyperhomocysteinemia (associated with cardiovascular disease and dementia), surgical wound infection,[1] and possibly neurodegeneration in neonates.[2] Adding to its problems, nitrous oxide is also a drug of abuse and destroys the ozone layer. However, nitrous oxide is the only anesthetic drug that has been used continuously and, arguably, safely in clinical anesthesia for 162 yr. Contemporary anesthesiologists either love it or hate it, and perhaps no group is more polarized about it than neuroanesthesiologists. Nitrous oxide increases cerebral metabolic rate, blood flow, and intracranial pressure and, in animals, exacerbates ischemic neurologic injury, all theoretically undesirable effects in the setting of intracranial neurosurgery. Fueled by this information, the debate simmers, albeit largely uninformed by data on how nitrous oxide affects neurologic outcomes in humans—which brings us to the work of McGregor *et al.*[3] in this issue of the Journal. These investigators studied short- and long-term gross neurologic and subtle neuropsychological outcomes in 1,000 subarachnoid hemorrhage patients as a function of whether they received nitrous oxide intraoperatively during craniotomy for intracranial aneurysm clipping. Low and behold, nitrous oxide did not make a difference in any of the primary outcomes.

McGregor *et al.*[3] capitalized on the wealth of information collected as part of the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST). The details of IHAST are presented elsewhere,[4] but a few things are important to mention here. IHAST enrolled 1,001 patients who had a subarachnoid hemorrhage and had intracranial surgery for aneurysm clipping. Such patients have a high incidence of neurologic deficits, which may occur intraoperatively due to brain retraction or temporary clipping of an intracranial artery. Outcomes were measured using a variety of well-established neurologic and neuropsychological tools. By design, IHAST excluded the most seriously neurologically injured subarachnoid hemorrhage patients (where the likelihood of improving outcome with any treatment is low and the ability to detect decline is limited), making it ideal for testing a potentially protective intervention (mild hypothermia) or, as in this case, a putatively harmful one.

But mining the IHAST database also has limitations. Like other IHAST spin-offs, this study conducted a *post hoc* analysis of the data. This retrospective approach is one of the study's main weaknesses. Another is that use of nitrous oxide was entirely at the discretion of the anesthesia team caring for the patient, so the patients were not randomized on the main variable in this study. This is important because the groups are unevenly distributed, with only 373 patients (37%) receiving nitrous oxide.[3] Moreover, use of nitrous oxide was uneven across participating centers; the majority used it in less than 25% or greater than 75% of the cases, suggesting strong institutional preferences and biases about nitrous oxide in this high-risk patient population.[3] Besides introducing potential bias, nonrandom allocation of patients may have rendered the study somewhat underpowered to detect small differences between the groups. Patients that received nitrous oxide also had lesser neurologic impairment at baseline but more often had a temporary clip placed and received putatively neuroprotective agents (in addition to hypothermia) intraoperatively.[3] These are potentially significant confounders that cloud some of the outcome trends, a point the authors recognize and discuss candidly. But no study, especially one of this magnitude, is perfect, and these imperfections do not undermine the validity of the study's principal conclusion: Nitrous oxide is unlikely to cause adverse neurologic or neuropsychological outcomes in neurosurgical patients at high risk for cerebral ischemia. If anything, the trend suggests nitrous oxide is associated with improved long-term outcome (patients who received nitrous oxide tended to have improved neurologic outcome 3 months after surgery and were more likely to be discharged to home,[3] certainly a meaningful outcome from the patient's perspective), but a larger study, with better matching of premorbid condition between the groups, would be needed to prove it. Because it is highly improbable such a study will ever be performed, the work of McGregor *et al.*[3] will likely be the

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final word on nitrous oxide as an anesthetic adjunct for neurosurgical procedures.

As such, McGregor *et al.*[3] may change attitudes about nitrous oxide, but we are doubtful the study will change clinical practice. This is because there is nothing in the data to compel neuroanesthesiologists who currently avoid nitrous oxide to adopt it. Statistically nonsignificant trends toward improved outcomes aside, there was no evidence for the neuroprotection observed in some animal studies and, conversely, no indication that using something else (*e.g.*, more volatile agent, opioids) in lieu of nitrous oxide was suboptimal. Nitrous oxide or no, it did not seem to matter. This may be precisely why nitrous oxide has held on for so long. It does something obviously "good" (analgesia, sedation) and, in the majority of patients, very little obviously, seriously— or objectively proven to be—"bad."

So, our fears about nitrous oxide causing adverse neurologic or neuropsychological outcomes in patients at risk for cerebral ischemia are probably unfounded. We cannot say that we are surprised; we use it regularly during craniotomies, to no obvious ill effect, and it is all too common for a well-done human trial to yield different results than the animal studies that led up to it. IHAST itself is an example of that, finding no protective benefit of mild hypothermia when available animal data suggested possible efficacy.[4] Among other things, this reinforces the need to exercise caution in extrapolating the current wave of animal studies about general anesthetic neurotoxicity to humans. But it also raises a troubling question. Does anything we do intraoperatively in terms of anesthetic choices and management— beyond the internist's admonition to "avoid hypoxia and hypotension"—matter in the long run? Some might point to inspired oxygen concentration (or nitrous oxide) and depth of anesthesia as examples of things that do, but these are still quite controversial.[1,5,6] In the setting of neurosurgery, hopes for mild hypothermia and pharmacologic brain protection have not materialized, and, as shown by McGregor *et al.*,[3] fears about nitrous oxide are unsubstantiated.

It is probably human nature to believe our interventions are either "good" or "bad." Sometimes, in some circumstances, they are simply indifferent. As unsatisfying as that may seem, we must not lose sight of a fundamental truth: If one needs surgery, anesthesia is good. How one achieves it is probably far less important than that it occurs. Nitrous oxide, like all of our anesthetic agents, is flawed and imperfect. But it has served us and our patients well for 162 yr; it is tried and true. Anytime a 162-yr-old drug performs in the symphony of care as well as a contemporary alternative, either it deserves respect or youth is getting us nowhere.

Deborah J. Culley, M.D.,* **Gregory Crosby, M.D.** Harvard Medical School and Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Boston, Massachusetts. *dculley@zeus.bwh.harvard.edu

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