Nitrous Oxide

Deep in the Zone of Uncertainty

THE question of whether or not nitrous oxide increases the risk of cardiovascular events after surgery has been around for some time. There is no doubt that nitrous oxide increases plasma homocysteine and is likely lead to endothelial dysfunction, both being associated with higher rates of myocardial infarction and stroke in nonsurgical settings. But is homocysteine an issue for anesthesiologists? Recent trials seem to have discounted the importance of hyperhomocysteinemia, and its correction with folate and other B-vitamins as a therapy to reduce myocardial infarction and stroke risk, in nonsurgical settings.

In this issue of the journal, Nagele *et al.*[1] report their results of a clinical trial investigating the effect of B-vitamins and *MTHFR* gene polymorphisms on nitrous oxide–induced cardiac events. The central premise of their study was that nitrous oxide may increase the risk of cardiac events because of its effect on folate metabolism and plasma homocysteine. This is a valid, well-argued concept, which could be very important, given the world-wide availability and use of nitrous oxide in anesthesia. In contrast, there is preliminary evidence suggesting that nitrous oxide may reduce the risk of persistent pain after surgery,[2] and some recent studies have failed to identify any increased risks with the use of nitrous oxide.[3–6] Other studies have reported mixed findings,[7,8] offering opportunities for both supporters and nonsupporters of nitrous oxide to support their case—in other words, uncertainty prevails.

"[The results of this study] might appear to lessen the likelihood that nitrous oxide–containing anesthesia leads to serious cardiovascular events. But the anesthesiology community is deep in the zone of uncertainty...."

The possibility that some individuals have genetically determined differences in a drug's therapeutic effects and side effects is a very active area of research. If some *MTHFR* gene polymorphisms were to be associated with greater risk of nitrous oxide–induced cardiac events, this information would be relevant when deciding on the anesthetic regimen for an individual patient. In contrast to their previous work,[9] Nagele *et al.* could not identify any relationship between *MTHFR* gene polymorphisms and increased level of postoperative plasma homocysteine. It seems that genetic influences, if they exist in anesthesia, are probably small, but this may not be so clear cut.

Nagele *et al.*[1] also found no evidence that either B-vitamins or *MTHFR* gene polymorphisms had any effect on postoperative cardiac events. Their findings could mean that no such effect exists or a true effect was missed because of inadequate study power, a nonideal study population that had high rates of B-vitamin and folate supplementaion and grain fortification in the community,[10] or an incorrect B-vitamin dosage regimen (dose, combination, or duration of treatment). Normal plasma concentrations of vitamin B_{12} and folate are 200–900 pg/ml and 2.7–17.0 ng/ml, respectively. Few, if any, patients enrolled in their study could

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be classified as vitamin deficient. The chosen dose in the active treatment group was 1 mg of vitamin B_{12} and 5 mg of folic acid before and after surgery. They were able to show that this led to increased plasma levels of these vitamins and blunting the increase in plasma homocysteine, but the latter was not completely suppressed when compared with the nonnitrous group, indicating that there was incomplete B-vitamin protection of the nitrous oxide effect. Vitamin B_6 (pyridoxine) and B_2 (riboflavin) may have offered additional protection, but were not used.[10] We know that a folate deficiency state can exist in the setting of normal folate levels, by a process known as methyl trapping.[11]

The primary endpoint of the study was the incidence of myocardial injury, which is defined by an increased level of cardiac troponin I within the first 72 h after surgery.[1] This is a valid and clinically useful endpoint. Increased troponin is associated with poorer long-term survival. But the study was not powered to reliably detect an effect on rates of myocardial infarction, stroke, or death. The study was designed to detect a 50% reduction in the rate of myocardial injury. It seems an unlikely proposition that *MTHFR* gene polymorphisms or vitamin supplementation could have such a dramatic effect. Lee's revised cardiac risk index suggests an expected rate of major cardiac complications of approximately 4% in this study cohort, for which a 30% reduction required a study sample size of more than 20,000 participants. Only 500 patients were studied. We thus cannot be certain whether or not *MTHFR* gene polymorphisms or vitamin supplementation have an effect on nitrous oxide–induced myocardial injury.

The inclusion of a third group, a near-contemporaneous control group that did not receive nitrous oxide, offers an opportunity to consider the direct effect of nitrous oxide on perioperative cardiac events. It must be stressed, however, that this third group was not randomly assigned and had some potentially important baseline differences that can affect cardiac risk when compared with the trial patients. There was a lower rate of study dropouts in the nonnitrous oxide group, suggesting that anesthesiologists were worried about nitrous oxide–induced adverse effects in the patients excluded from this control group. That is, there was confounding by indication (due to lower risk status or severity of illness in those given nitrous oxide),[12] a bias that can also explain some of the previous "negative" nitrous oxide studies.[3,4,6,7] Confounding can be overcome in large randomized trials.

Intriguingly, the incidence of myocardial infarction was 6.0% in the placebo group and 2.8% in the B-vitamin group, 15 *versus* 7 events, risk ratio 2.14, $P = 0.09$.[1] In addition, there were three deaths in the placebo group and none in the B-vitamin group up to 30 days after surgery; rates of cardiovascular events were similarly increased, 10.0 *versus* 6.4%, respectively. Although not statistically significant, these data indicate that nitrous oxide without B-vitamin supplementation could possibly increase the risk of cardiovascular events and death. Other studies, mostly *post hoc* analyses of large randomized trials, provide some evidence to support such a view.[2,8]

Much of the concern regarding nitrous oxide has stemmed from the secondary findings of the ENIGMA trial,[13] for which I was the leading author. A single positive study usually cannot provide sufficient evidence to justify a change in practice and secondary analysis of clinical trials should be treated with particular caution. We had thus tempered our conclusions, noting that further study was required, but until such information was available for the routine use of nitrous oxide in adult patients undergoing major surgery should be questioned.[13]

Anesthesiologists are trained to mitigate risk, but the challenge of a difficult case or unexpected emergency is ever-present. There are times when decisive action is required and a need for rapid and clear communication, intervention, and reassessment. We are taught to be certain of our knowledge, skills, and judgments. Our patients and colleagues seem to want this from us. But certainty can mislead us and our patients.[14] Decision-making in medicine is nearly always based on inadequate information, where the evidence exists on a continuum, and its critical appraisel is frequently subjective and biased. Doctors are very poor at acknowledging their own uncertainty.[14]

Uncritical acceptance of studies that support one's view, and rejection of those that don't—confirmation bias—help to maintain a sense of certainty. This perhaps explains why many doctors feel uncomfortable acknowledging uncertainty when offered an opportunity to contribute to a multicenter randomized trial. Equipoise is lost, weakening any opportunity to cooperate in the trial and to eventually advance our knowledge base.

Nagele *et al.*[1] have conducted a very good study that deserves our attention. It might appear to lessen the likelihood that nitrous oxide–containing anesthesia leads to serious cardiovascular events. But the anesthesiology community is deep in the zone of uncertainty, and this reality needs to be acknowledged. The only solution to this dilemma is to conduct rigorous, definitive, large trials. The ENIGMA-II trial,[15] investigating outcomes of nitrous oxide in 7,000 patients undergoing major surgery, is expected to report its findings later this year.

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