

## Is It Time to Retire High-concentration Nitrous Oxide?

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DURING the past decade, anesthesiologists have increasingly recognized that the effects of anesthesia reach beyond the postanesthesia care unit. Researchers have extended their vision beyond studies of pain and postoperative nausea and vomiting in the postanesthesia care unit (still important outcomes) to studies of the impact of anesthesia on a broad range of postoperative outcomes, including cardiac complications and surgical wound infection. Myles *et al.*,<sup>1</sup> in this issue of ANESTHESIOLOGY, report an outstanding, large (2,050 patients), multicenter, pragmatic randomized controlled trial of the effect of intraoperative gas selection on a wide range of postoperative complications. Patients undergoing major surgery were randomly assigned to receive 80% oxygen with 20% nitrogen *versus* 30% oxygen with 70% nitrous oxide intraoperatively. Patients assigned to the high inspired oxygen-nitrous oxide avoidance group had fewer major postoperative complications and less frequent severe postoperative nausea and vomiting, and were more rapidly discharged from the intensive care unit, although hospital stay did not differ between groups. The authors conclude, "The routine use of nitrous oxide in patients undergoing major surgery should be questioned." An alternative conclusion would be that the routine use of high inspired oxygen (which precludes high inspired nitrous oxide) in patients undergoing major surgery should become routine.

A number of well-designed randomized controlled trials have demonstrated outcome benefits of maintaining intraoperative normothermia, including reduced blood loss in hip arthroplasty,<sup>2</sup> reduced surgical site infection in colon surgery,<sup>3,4</sup> and reduced cardiac morbidity and

mortality in patients undergoing vascular surgery.<sup>5</sup> Perioperative administration of  $\beta$  blockers<sup>6</sup> or clonidine<sup>7</sup> reduces cardiac morbidity and mortality in patients at risk for coronary artery disease undergoing noncardiac surgery. Although most of these studies have not been repeated, and controversy remains about their generalizability, the results have rapidly been adopted in clinical guidelines and by regulatory (Joint Council on Accreditation of Healthcare Organizations) and insurance (Centers for Medicare and Medicaid Services) agencies.

Two large, well-designed randomized controlled trials in colon surgery<sup>3,4</sup> showed a 40-50% reduction in surgical site infection in patients given 80% inspired oxygen intraoperatively and for a period of time postoperatively. Conflicting data from another small, "real-world" randomized trial<sup>8</sup> have limited rapid clinical adoption. The current study by Myles *et al.*<sup>1</sup> may help to accelerate that process.

Another reason for slower clinical adoption of high inspired oxygen is the concern of many anesthesiologists that it could cause oxygen toxicity or increased atelectasis. Oxygen toxicity is not a risk in the short term (less than days), and therefore is not pertinent in the operating room. Some degree of atelectasis is inevitable in all patients undergoing major surgery. Akca *et al.*<sup>9</sup> demonstrated similar degrees of atelectasis in colon surgery patients randomly assigned to 80% *versus* 30% oxygen (balance nitrogen) intraoperatively. Myles *et al.* found that high inspired nitrous oxide caused more atelectasis than high inspired oxygen. Therefore, these issues should not limit the use of high inspired oxygen.

The authors of the current study intended to examine the value of avoidance of nitrous oxide in reducing postoperative complications. The difficulty in designing such a study is that you cannot change the concentration of nitrous oxide without replacing the gas with another, such as nitrogen, oxygen, or helium. The nitrous oxide avoidance group also received 80% oxygen, previously suggested to be of benefit in preventing surgical site infection and postoperative nausea and vomiting, whereas the 70% nitrous oxide group received only 30% oxygen. Therefore, it is impossible to determine whether the beneficial effects reported resulted from high inspired oxygen, avoiding nitrous oxide, or a combination of the two. Fleischmann *et al.*<sup>10</sup> found no difference in surgical site infection rate when comparing 70% nitrogen-30% oxygen *versus* 70% nitrous oxide-30% oxygen as the intraoperative gas mixture, but did not include an 80% oxygen group. These results suggest

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that avoidance of nitrous oxide may be less important than high inspired oxygen.

In the end, it may not matter to clinicians whether the benefits found in the study by Myles *et al.* resulted from avoidance of nitrous oxide or administration of high inspired oxygen, because administration of high inspired oxygen by necessity requires avoidance of 70% nitrous oxide. There is certainly plentiful evidence that nitrous oxide use is associated with an increased incidence of postoperative nausea and vomiting.<sup>11</sup> Conversely, a randomized controlled trial in colon surgery patients demonstrated that high inspired oxygen reduced postoperative nausea and vomiting,<sup>12</sup> suggesting that the reduced incidence in the study by Myles *et al.* could also result from high inspired oxygen. A number of other potential adverse effects of nitrous oxide have been reported in the literature, although their clinical relevance is not clear.<sup>11</sup> There is some evidence for lack of harm from nitrous oxide (the study by Fleischmann *et al.*<sup>10</sup>), but there is little evidence for benefit. Myles *et al.* add a compelling argument for eliminating nitrous oxide use in patients undergoing major surgery by showing potential harm from nitrous oxide (whether directly or through reducing the capacity to provide a high inspired oxygen concentration).

As a practical matter, especially with the introduction of new anesthetic agents in recent years, it is relatively easy to exclude nitrous oxide—or to include high inspired oxygen—in one's practice. Nitrous oxide is certainly useful for inhalation inductions in children, as well as for analgesia in laboring parturients or in patients having dental procedures. It is preferred by many anesthesiologists because of its reputation for providing a "smoother landing"—although this is not substantiated by scientific evidence. On the other hand, nitrous oxide avoidance is standard practice in patients in whom nitrous oxide is contraindicated, as is the case with pneumothorax or bowel distention, for example.

Would eliminating nitrous oxide use or adopting routine use of high inspired oxygen in major surgery in response to this article represent making a change based on too little evidence? Possibly. There are certainly shortcomings in the study, including lack of standardization of potential confounding factors such as timing and choice of prophylactic antibiotic administration and maintenance of normothermia. On the other hand, in such a large study, the confounders should have similar impact in each group. Anesthesiologists had the option to "cross over" based on personal preference or patient circum-

stances. This happened a small percentage of the time. Because it is such a large study, these crossovers seem not to have had much impact. In any case, the study is a pragmatic one, and such crossovers are likely to happen in real clinical practice as well. Therefore, this article gives a result that likely has meaning not just in a carefully controlled group of patients, but in the large variety of patients presenting for major surgery.

This study is not the last word on nitrous oxide, but it is an important one that is likely to have a major impact on clinical practice in anesthesia. I personally stopped using nitrous oxide nearly a decade ago because of previous trials demonstrating the importance of high tissue oxygen in preventing wound complications. I am pleased to have added justification for residents who challenge me to provide evidence to support my clinical practice.

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