New Evidence of Enhanced Safety of Nitrous Oxide in General Anesthesia

Nitrous oxide has been used in anesthetic practice for nearly 170 years, longer than any other anesthetic agent. It has withstood the test of time despite its critics. In the pioneering days of anesthesia, nitrous oxide general anesthesia, using the primary and secondary saturation technique described by Dr Fred Clement, was by far best suited for ambulatory office dental surgery compared to diethyl ether and chloroform. Induction of ether anesthesia was slow and unpleasant, its recovery was prolonged, and it was explosive. Chloroform induction was somewhat more pleasant and faster than ether, but recovery was still slow and sudden cardiac arrest due to its cardiac arrhythmogenicity made it considerably less popular compared to nitrous oxide and ether in the United States. Of course the major problems with nitrous oxide were its lack of anesthetic potency and its minimal ability to provide skeletal muscle relaxation. Although the induction of general anesthesia with 100% nitrous oxide and maintenance of unconsciousness with the addition of only low concentrations of oxygen would be far below the modern standard of care, the mortality rates associated with the other anesthetic agents available at that time were at least as high as that associated with nitrous oxide general anesthesia.

Ultimately, as anesthetic skills and techniques improved and newer anesthetic agents were developed, the use of the hypoxic nitrous oxide anesthetic technique in the dental office became outdated. However, in the latter half of the 20th century, Dr Harry Langa revived the use of nitrous oxide in the dental office by using it along with 20% to 30% oxygen as an analgesic, often as a substitute for local anesthetic. Patients were technically conscious, highly analgesic, and well oxygenated, but the high concentrations of nitrous oxide produced a significant percentage of patients with nausea, vomiting, and hallucinations. The Langa nitrous oxide analgesia technique was ultimately modified to what became known as nitrous oxide–oxygen conscious sedation and is currently known as nitrous oxide–oxygen minimal sedation. With this technique, the nitrous oxide is typically carefully titrated to a concentration of 50% or less in combination with oxygen and is used primarily for its sedative and anxiolytic effects rather than for its analgesic effects. With this modern use, operative analgesia is primarily dependent on the local anesthetic, while the nitrous oxide alleviates the anxiety associated

with the local anesthetic injection and the dental procedure.

Nitrous oxide has also been used in combination with other sedative or anesthetic agents to produce moderate or deep sedation and general anesthesia. The addition of nitrous oxide decreases the amount of these other agents needed to maintain an adequate level of sedation or anesthesia; it can therefore increase the speed of induction and recovery because it enters and leaves the brain so quickly compared to the other drugs that are given with it.

Nitrous oxide, however, has not been without its detractors. Young investigators, eager to publish scientific articles with statistically significant differences, have designed research projects to demonstrate the increased side effects of nitrous oxide. The majority of articles showing increased rates of nausea and other side effects were designed to utilize a standard sedation or anesthetic technique plus either 70% nitrous oxide or 70% nitrogen. The increased incidence of nausea at this high nitrous oxide concentration following sedation or general anesthesia is not surprising, particularly for those dentists who have had experience with the Langa high-dose nitrous oxide analgesia technique. Clearly, those of us using nitrous oxide in concentrations at 50% or less know that nausea at these concentrations is a rare event. Certainly nitrous oxide can, for instance, increase gastrointestinal pressure if the patient has an acute bowel obstruction, but in healthy dental patients receiving 50% nitrous oxide, any increase in gastrointestinal gaseous pressure would probably be much less than if the patient were to eat a plate of delicious Mexican refried beans. Any drug whose dose is pushed to the limit will have an increased incidence of adverse side effects. One can only imagine the statistically significant incidence of gastrointestinal side effects of a 1-week course of 10 g of amoxicillin administered orally 4 times per day compared to a placebo.

Recently, an Australian research study known as ENIGMA-I involved a randomized trial of 2050 patients undergoing noncardiac surgery with general anesthesia lasting more than 2 hours that included either 70% nitrous oxide in 30% oxygen or 80% oxygen in 20% nitrogen (not exactly a fair comparison). Patient records were studied over a period of 30 days. The administration of 70% nitrous oxide was associated with a slightly increased risk of myocardial infarction compared to general anesthesia with 80% oxygen and no nitrous oxide, although a cause-and-effect relationship was not established.

In a long-term follow-up study of ENIGMA-I patients over a median time of 3.5 years, the administration of 70% nitrous oxide versus 80% oxygen was associated with a small increase in the long-term risk of myocardial infarction, but not of death or stroke. The deficiencies noted in the ENIGMA-I trial to determine the exact relationship between nitrous oxide administration and serious long-term adverse outcomes will require confirmation by an appropriately designed large randomized controlled trial, namely ENIGMA-II, which is currently ongoing. In ENIGMA-II, 7000 patients at risk for coronary artery disease undergoing major noncardiac surgery will be given a general anesthetic that includes either 70% nitrous oxide with 30% oxygen or 70% nitrogen with 30% oxygen. While this study still utilizes a high dose of nitrous oxide compared to nitrogen, at least the percentage of oxygen in both groups will remain constant at 30%. Perhaps the outcomes of this study will further enlighten us on the risk, if any, of cardiovascular complications associated with high-dose nitrous oxide, but its results may still not apply to nitrous oxide–oxygen minimal sedation using dental office concentrations of 50% or less for minimally invasive dental surgery.

In an even more recent study¹ involving more than 20,000 patients at the Cleveland Clinic, Turan et al concluded that adding nitrous oxide to the general anesthetic for noncardiac surgery of greater than 2 hours' duration does not increase the rate of complications and death and might even decrease the risk. The results suggested that there was a significant reduction (one third lower) in the risk of death after surgery that included nitrous oxide in the anesthetic compared to those whose anesthetic did not include nitrous oxide. There was also a significant decrease in the complication rates, including a 40% reduction in the risk of major pulmonary complications in the nitrous oxide group. Unfortunately, the percentage of nitrous oxide administered was variable, but the authors indicated that it was

approximately 55% based on the common Cleveland Clinic practice.

While no single study will ever prove or disprove the ultimate safety of nitrous oxide, reports of its demise are premature. In fact, based on the Cleveland Clinic studies, nitrous oxide may once again become as popular in medical anesthesia practice and in our dental training programs, as it has remained popular in dentistry. It is my hope that research projects will be designed in the future, not only to discover the side effects of 70% nitrous oxide but also the side effects, if any, of nitrous oxide in a concentration of 50% or less, which is so commonly used in dentistry. Dentistry therefore needs to do its own research to justify its ability to provide its own sedation and anesthesia care with the agents that may be perhaps uniquely suitable to the dental office. Somehow, dental anesthesia departments, chaired by board-certified dentist anesthesiologist graduates of 3-year dental anesthesia residencies accredited by the Commission on Dental Accreditation, need to be created in every dental school if this quintessential research will ever be accomplished. Otherwise, our choices of what sedative and anesthetic drugs can be administered and who can administer them may be limited by what medical anesthesia researchers determine is statistically most suitable for anesthesia care for major noncardiac surgical cases administered by medical anesthesiologists in the hospital operating room.

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1. Turan A, Mascha EJ, You J, et al. The association between nitrous oxide and postoperative mortality and morbidity after noncardiac surgery. *Anesth Analg*. 2013 May;116(5):1026–1033.