Place of Nitrous Oxide in Neuroanesthesia: Still a Valuable Drug

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Nitrous oxide (N₂O) has been used as anesthetic drug since 1863. Its introduction to clinical anesthesia was surrounded by controversy (1). During its history of nearly 130 years of clinical use it has outlived many inhalation anesthetic drugs such as ether, cyclopropane chloroform, fluoroxyne, trichloroethylene, and methoxyflurane, to name a few. This longevity of N₂O is attributed to some of its physical properties such as noninflammability, low solubility, and relative inertness and odorlessness. These characteristics, combined with low cost, compared with other currently available inhalation anesthetic drugs, make N₂O a valuable tool in an anesthesiologist's armamentarium. It can provide a rapid induction of anesthesia with minimal cardiovascular depression and a quick emergence from general anesthesia. It is true that N₂O was introduced and well accepted in clinical practice without rigorous testing for side effects and toxicity, which modern inhalation anesthetic drugs have to undergo before being approved by the Food and Drug Administration. Recent methodological advances in drug testing have revealed that indeed, N₂O is neither as inert nor totally free of toxicity as was once believed. This has led to some controversy about the appropriateness of its continued use in clinical anesthesia (2-4).

One subset of surgical patient population, in which nitrous-narcotic or balanced anesthesia had traditionally been highly recommended, is patient with intracranial pathology, undergoing craniotomy. In recent years, several clinical investigation of effects of N₂O on cerebral blood flow (CBF) intracranial pressure (ICP), cerebrospinal fluid (CSF) dynamics, sensory evoked potentials (SEPs), and pneumocephalus have been published. Results of these studies have raised the question: Should we continue to use N₂O in neuroanesthesia? To answer this question, one first needs to examine the principles on which anesthetic management of patients with intracranial pathology should be based. Broadly speaking, these principles are as follows.

1. Prevent a rise of ICP during induction, because many of these patients have decreased intracranial compliance.
2. Provide a "shrunken brain" to facilitate surgical exposure, thus avoiding undue pressure during retraction, which may result in ischemic injury of underlying vital brain structures.
3. If electrophysiological monitoring (electroencephalogram/SEPs/facial nerve recordings) is being used, an anesthetic technique that causes the least interference with monitoring should be used.
4. Rapid emergence—thus allowing adequate neurological evaluation in the immediate postoperative period. It also allows early detection of neurological deterioration in the recovery room.

Next, one can make a decision about the place of N₂O in achieving these goals in clinical practice based on the current knowledge of the effects of N₂O in comparison to alternative choices. For the sake of brevity we will concentrate on published clinical studies only.
RISE IN ICP

Cerebral Blood Flow

Although it is common knowledge that inhalation anesthetic drugs increase cerebral blood flow in a dose-dependent manner, published literature on comparative effects of inhalation anesthetic drugs on CBF in humans is limited to only a few studies. The most frequently quoted clinical study of comparative effects of inhalation anesthetic agents was done by Murphy et al.* The data from this study were presented at the annual meeting of the American Society of Anesthesiologists in 1974 and they were published in abstract form only. Despite the fact that this study is quoted in every textbook of anesthesia and that the data were flashed as a slide in almost all lectures on the subject of anesthetic agents and cerebral blood flow, I have not been able to find these data published in a peer-reviewed journal as a full-length article with details of methodology and statistical analysis. Despite these limitations, Murphy et al. showed that in paralyzed, mechanically ventilated, normocapnic volunteers, 0.5–0.6 minimum alveolar concentration (MAC) of the three inhalation anesthetic agents (halothane, enflurane, isoflurane) studied affected the CBF similarly. Differences became apparent as the dose was increased from 0.5 to 1.75 MAC. At 1.1 MAC the increase in CBF was least with isoflurane. It should be emphasized that N₂O was not included in this study; therefore, comparative effect of N₂O cannot be evaluated. We recently studied the effect of N₂O on CBF in spontaneously breathing, normocapnic, awake volunteers (5) and documented that CBF increased in a dose-dependent manner (25% N₂O = 14% increase and 50% N₂O = 37% increase) with inhalation of N₂O. One reason why Murphy et al. could not study the effect of N₂O on CBF may be that N₂O is an incomplete anesthetic drug; thus, it is unacceptable to use N₂O alone in paralyzed volunteers. For the same reason N₂O should not be used as the only anesthetic agent in clinical practice (neurosurgical or otherwise) and is commonly supplemented with either intravenous drugs (barbiturate, narcotic, and benzodiazepine drugs) or low-dose (0.25–0.5 MAC) inhalation anesthetic agents. Wollman et al. (6) have indeed shown that when used in such a manner in paralyzed and ventilated volunteers, there was no increase in CBF. Therefore, it should be emphasized that our findings of increase in CBF with 25–50% N₂O in spontaneously breathing humans should caution the practitioner against using N₂O anaesthesia to supplement, say, regional anesthesia in spontaneously breathing patients with compromised intracranial compliance (closed head injury). These findings do not suggest that N₂O should always be excluded from balanced anesthesia for patients undergoing craniotomy.

Hypocapnia

The second intervention anesthesiologists most commonly resort to for lowering raised ICP and thus improving intracranial compliance is to induce hypocapnia with mechanical hyperventilation. Hypocapnia reduces CBF and hence ICP. It has been shown that CO₂ reactivity of CBF is better preserved under nitrous-narcotic anesthesia as compared with inhalation anesthesia in both human (7) and feline (8) models.

CSF

Another component of ICP is the volume of CSF. At present the published information dealing with the effects of anesthetic agents on production and absorption of CSF is limited to a canine model only. However, no increase in CSF production occurs in dogs when N₂O is added to enflurane (9).

SHRUNKEN BRAIN

Providing satisfactory operating conditions for the neurosurgeon is the ultimate goal of a well-conducted anesthetic for intracranial surgery. A necessary component is to reduce the size of the brain. This is accomplished by administration of osmotic diuretic drugs, inducing hypocapnia and using an anesthetic technique that causes the least increases in CBF and brain swelling. There are no clinical data suggesting that the choice of one inhalation anesthetic agent over others in low doses makes any difference. From and co-workers (10) have recently conducted a well-designed, prospective, double-blind, comparative study of alfentanil,

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fentanyl, and sufentanil supplementation of N₂O anesthesia for patients undergoing craniotomy. They found no clinically significant differences in terms of brain swelling, rate of emergence from anesthesia, or final outcome. This observation is contrary to the drug company’s claims of several advantages, including a rapid emergence and absence of renarcotization phenomenon, with newer (and more expensive) narcotic drugs (alfentanil and sufentanil), nor did this study support the findings of animal experiments showing increases in CBF and ICP with alfentanil and sufentanil. Are we likely to find similar results if four currently used inhalation anesthetic agents (N₂O, halothane, enflurane, and isoflurane) were to be studied in a similar manner? It seems reasonable that we do not make any claims of one inhalation anesthetic drug being superior (or inferior) to others until such a clinical study is done.

ANESTHETIC DRUGS AND ELECTROPHYSIOLOGIC MONITORING

Advances in computer technology have resulted in an increased use of intraoperative SEP monitoring in patients undergoing intracranial, spinal cord, or vertebral column surgery. In the early 1980s it was commonly recommended that patients undergoing this monitoring be anesthetized using nitrous-narcotic anesthesia (11), because early experience at Cleveland Clinic (12) had shown that administration of halothane attenuated posterior tibial nerve evoked potentials beyond recognition. Subsequent studies (13–16) have shown that administration of other inhalation anesthetic agents in concentrations between 0.5 and 1 MAC is compatible with adequate SEP monitoring. Comparative effect of N₂O and halogenated anesthetic drugs is difficult to evaluate because in most of these studies (13–15) inhalation anesthetic drugs were studied along with 60% N₂O in oxygen. Thus, let us resolve that intraoperative evoked potential monitoring is feasible with a nitrous narcotic techniques as well as with a combination of N₂O and low-dose inhalation anesthetic technique. It seems that posterior tibial nerve potentials are affected by halothane to a greater extent (15) than median nerve potentials are (14).

INTRACRANIAL AIR

The blood gas solubility coefficient of N₂O is 30 times that of nitrogen. Therefore, the number of N₂O molecules given up by the blood to the air within a cavity far exceeds the number of nitrogen and oxygen molecules absorbed, within a few minutes. In a closed cavity such as cerebral ventricles or cranial vault, this results in a marked rise in pressure, resulting in compression and distortion of important brain structures. It had been long appreciated by anesthesiologists (from the “ancient” days of pneumoencephalography) that in patients who required general anesthesia within 48 h after a pneumoencephalogram, administration of N₂O should be avoided. Currently, pneumoencephalography as a diagnostic test has virtually been abandoned in favor of computerized tomography (CT) and magnetic resonance imaging. However, there are many case reports of pneumocephalus in sitting position craniotomies (17,19). This information should warn a prudent anesthesiologist that the possibility of intracranial air exists in all patients after a craniotomy and N₂O should not be administered if such a patient comes either for a reexploration or other extracranial surgical procedure, just as it should be avoided in all trauma victims in whom the presence of pneumothorax has not been ruled out. Pandit et al. (20) reported intracranial air to be present (on CT scan) for as long as 1 week after craniotomy. They also noticed that if N₂O is used throughout surgery (craniotomy) in the sitting position, then ICP after closure of the dura does not rise. However, there is a dramatic rise in ICP after dural closure if N₂O is not used during craniotomy and is added only after the dura is closed. Therefore, one should be cautious in switching the anesthetic drug toward the end of a craniotomy to achieve rapid emergence. However, use of N₂O for maintenance of anesthesia is not absolutely contraindicated. Actually, it can be argued that the presence of N₂O in the intracranial air cavity will facilitate a quicker absorption than if it were filled with air alone. However, this phenomenon has not been studied systematically.

RAPID EMERGENCE

Nothing makes a neurosurgeon appreciate an anesthesiologist more than having a patient who can respond to verbal commands immediately after the surgical procedure is finished. It can be argued that with easy availability of a CT scan to rule out the presence of intracranial blood and/or swelling, the
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need to have an “awake” patient is not as pressing an issue as it used to be in the past. There is no question that having an “awake” patient at the end of a craniotomy will save a lot of time and expense, not to mention the tension the surgical team goes through while awaiting the results of diagnostic studies. Most anesthesiologists will agree that emergence from a N₂O-based anesthetic is quicker than that with pure inhalation anesthetic drugs. When combined with judicious use of narcotic drugs along with 60–70% N₂O, patients wake up tolerating the endotracheal tube without bouts of vigorous coughing during emergence from general anesthesia.

CONCLUSION

Most anesthesiologists will agree that none of the four inhalation anesthetic drugs (N₂O, halothane, enflurane, and isoflurane) currently in clinical use, if used alone, is suitable for anesthesia for craniotomy. If we consider that ED₉₅ of inhalation anesthetic drugs is 1.3 MAC, then N₂O alone is an incomplete anesthetic drug and all halogenated anesthetic drugs, if used in 1.3 MAC dose, do not satisfy the basic four prerequisites of neuroanesthesia (prevention of rise in CBF, ICP, brain swelling, interference with electrophysiologic monitoring, and rapid emergence) previously outlined.

This is the reason why the concept of “balanced” anesthesia is popular in the management of neurosurgical patients. How one “balances” different drugs is a matter of personal preference rather than a rationale based on outcome. Theoretically, our choices are combinations of (a) 0.5–0.7 MAC of halogenated anesthetic supplemented by narcotic analgesic drugs (equivalent to 0.6–0.8 MAC dose), i.e., no nitrous technique; (b) combination of 0.5–0.7 MAC of halogenated anesthetic drug and 0.5–0.6 MAC of N₂O; and (c) N₂O 0.5–0.7 MAC supplemented with narcotic analgesic drugs (equivalent of 0.25 MAC) and either benzodiazepine drugs or 0.25 MAC of inhalation anesthetic agents (for amnesia).

With technique (a), when combined with hypocapnia, three of four basic principles of neuroanesthesia are attainable. Emergence from anesthesia may not be as quick as desired. A higher dose of narcotic drugs (compared with technique (c)) can result in prolonged ventilatory depression in the postoperative period, thus prolonging the time of elimination of inhalation agents. Technique (b) has not really been tested in terms of effects on CBF, brain swelling, and ICP in humans. Is the effect of 1 MAC of halogenated anesthetic drug the same as that of 0.5 MAC halogenated anesthetic drug plus 0.5 MAC of N₂O? Is it more or less? If it is more, then technique (b) should not be used. If it is less or even the same, then technique (b) still has an advantage over technique (a) in terms of quicker emergence, but then that establishes that N₂O still has a place in neuroanesthesia. Technique (c) has been used for a long time in clinical practice. A large number of craniotomies have been done using this technique with satisfactory results. Should we discard it? Why? Just because newer anesthetic agents are available should not be a reason to discard an “old faithful.” Newer drugs should be welcome additions to our armamentarium for the few situations in which N₂O may be contraindicated, i.e., patients with pneumothorax, pneumocephalus, or those requiring high FiO₂. We should not necessarily regard them as dictating exclusion of N₂O.

To summarize my point of view (supported by long-term use and existing literature), N₂O has been used in neuroanesthesia for a longer time than any other inhalation anesthetic drug. It has withstood the test of time. It has a remarkable property of quick induction and emergence and lack of ventilatory depression in the postoperative period—all highly desirable features in neurosurgical patients. Most of its toxic effects have been documented either in experimental animals or with chronic exposure (health care workers), not in patients undergoing anesthesia. However, in light of these studies one should be cautious and avoid its use in subsets of patients with chronic anemia, chronic pulmonary disease (need for higher FiO₂), and air-filled cavities including recent craniotomy. In the majority of patients, N₂O is a valuable drug in neuroanesthesia, and its use should be continued until we have data showing that the choice of one anesthetic over others makes a difference in outcome.

REFERENCES


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