Nitrous Oxide Withdrawal Reduces Intracranial Pressure in the Presence of Pneumocephalus

Stephen Skahen, M.D.,* Harvey M. Shapiro, M.D.,† John C. Drummond, M.D.,‡
Michael M. Todd, M.D.,§ Vladimir Zelman, M.D.¶

Nitrous oxide anesthesia has been implicated as contributing to the development of delayed tension pneumocephalus following surgery performed in the sitting position. The authors tested the hypothesis that withdrawal of nitrous oxide anesthesia administered during formation of an intracranial gas cavity would lead to a decrease in intracranial pressure (ICP) as N_2O diffuses from the cavity back into the blood. Ten halothane-anesthetized rabbits were prepared for measurement of supracortical ICP and arterial blood pressure (BP) and for intracranial volume alterations *via* a cisterna magna infusion catheter. Hyperventilation (Pa_{CO_2} = 28–30 mmHg) and mannitol were used to shrink the brain to accommodate intracranial infusion of either air or lactated Ringer's (LR) solution, which was used to elevate ICP to between 10–15 mmHg from a baseline ICP of 2.1 ± 2.5 mmHg over a period of 8 to 10 min. Following stabilization at an elevated ICP, inhalation of nitrous oxide (75%) was either initiated or withdrawn (if already present during the induced ICP increase) and the subsequent changes in mean ICP and BP were recorded. Following ICP elevation with LR to 10 ± 1 mmHg, initiation of 75% N_2O administration resulted in no change in ICP and modest increases ($P < 0.05$) in BP and cerebral perfusion pressure (CPP = BP − ICP) after 4 min. However, when ICP was raised (to 12 ± 3.5 mmHg) with intracranial air infusion, subsequent initiation of 75% N_2O inhalation caused an abrupt ICP increase to 22.3 ± 9 mmHg (from control $P < 0.001$). Withdrawal of N_2O after ICP had been elevated (15.2 ± 1.0 mmHg) by air infusion during N_2O administration caused an abrupt and significant ($P < 0.001$) decrease in ICP ranging to 5.0 ± 4.6 mmHg, accompanied by a modest BP decline. These results confirm that N_2O can diffuse back into the blood stream from a previously equilibrated intracranial gas cavity and lowers ICP when N_2O is eliminated from the inspired gases. These findings suggest that discontinuance of N_2O anesthesia after cranial–dural closure in patients who have a potential for developing significant pneumocephalus might reduce the potential for development of delayed tension pneumocephalus following craniectomy performed in the sitting position. (Key words: Neurosurgery. Nitrous oxide. Sitting position. Tension pneumocephalus.)

DURING MOST NEUROSURGICAL procedures performed with the patient in the sitting position, cerebrospinal fluid (CSF) is replaced by air with resultant formation of pneumocephalus.[1-3] The serious complication of tension pneumocephalus develops in only a relatively small number of these patients. Because of the recognized propensity for nitrous oxide to diffuse into intracranial air pockets, it has been suggested by some that N_2O be eliminated from anesthetic protocols for patients in the sitting position prior to closure of the dura in order to reduce the incidence of tension pneumocephalus.[3-10] Theoretically, the presence of an intracranial air–nitrous oxide mixture after craniectomy closure should lead to an intracranial pressure (ICP) reduction when N_2O is withdrawn from inspired gases, as the N_2O present in the gas pocket diffuses back into the blood.[11,12] This hypothesis was tested in anesthetized rabbits subjected to systematic administration and withdrawal of 75% N_2O in the presence of an experimentally induced intracranial air or fluid space-occupying mass.

Methods

Ten New Zealand White rabbits (3.0–3.5 kg, unselected for sex) were anesthetized with 4% halothane in oxygen. Following endotracheal intubation, the animals were ventilated with a Harvard respirator at a tidal volume and rate sufficient to produce hypocapnia (Pa_{CO_2} = 28–30 mmHg). Muscle relaxation was obtained with pancuronium bromide (0.1 $mg \cdot kg^{-1} \cdot h^{-1}$) given *via* a percutaneously inserted ear vein catheter, and the inspired halothane was reduced to 1.5% for performance of surgery. Bupivacaine (0.25%) was infiltrated locally prior to performing a femoral incision for cannulation of the femoral artery to provide continuous arterial pressure monitoring and intermittent sampling for blood gases.

With the rabbit in the sphinx position, its head was secured in a stereotaxic frame to permit positioning of supracortical subdural and cisterna magna intracranial catheters for ICP monitoring and injection or withdrawal of air or fluid. The subdural catheter (PE 90) was placed through a burr hole over the right hemisphere and a wa-

tertight seal was achieved with Eastman-910® cement. Cisterna magna catheterization was accomplished with a butterfly needle (23-gauge) connected via a stopcock to a syringe infusion pump. ICP was measured from the supracortical CSF catheter, and the cisterna magna catheter was used to inject or withdraw lactated Ringer's (LR) solution or air. All transducers were zeroed to mid-head level to permit calculation of cerebral perfusion pressure (CPP = blood pressure (BP) − ICP). Esophageal temperature was maintained at 37° C via a servocontrolled infrared lamp.

Mannitol was then administered (1 g · kg⁻¹) to decrease brain volume and expand the potential CSF space. Following a 45-min stabilization period at 1% inspired halothane concentration, baseline physiologic measurements were performed and included: BP, subdural ICP, and blood gases.

Each rabbit was then exposed to three sequentially imposed conditions consisting of inhalation or withdrawal of nitrous oxide (75%) in the presence of ICP elevations induced with either the infusion of LR or air into the cisterna magna. Observations were made at the following steps: Step I, ICP elevated to 10 ± 1 mmHg by LR infusion followed by nitrous oxide administration; Step II, ICP elevated to 12.5 ± 5 mmHg with infusion of air followed by nitrous oxide administration; and Step III, ICP elevated to 15 ± 1 mmHg by infusion of air during a stabilized administration of nitrous oxide and followed by withdrawal of N₂O.

Intracranial gas and liquid infusions were accomplished with a Harvard syringe infusion pump after demonstration of catheter communication with the CSF space. Pressures were obtained from the polygraph record at 1-min intervals, between 1 min prior to and for 5 min following a change in N₂O administration. Each step in the study did not commence until the ICP drift was less than −1 mmHg · min⁻¹ with the infusion pump turned off and gas tight stopcocks controlling each catheter closed. Table 1 indicates the infusate and infusion times for each of the three sequential steps. For each step, a gas or liquid volume was infused intracranially for 8–10 min and then N₂O was either added or removed from the breathing circuit and ICP was observed for 5 min. Between each step both catheters were opened to atmospheric pressure at the same supracortical level to permit return to baseline ICP and 15 min was allowed for stabilization. A skull x-ray, obtained in one animal, demonstrated intracranial air located over the parietal portion of the cerebral hemisphere in proximity to the supracortical ICP measurement catheter. Paired t tests were used to determine statistical significance (tables 1 and 2), and multiple comparisons were performed using analysis of variance for repeated measurements and the Bonferonni correction for the unpaired t statistic (fig. 1).[13,14]

TABLE 1. Pump Volume (ml) and Infusion Time at Each Step prior to Changing N₂O

	Infusate	Volume (ml)	Time (min)
Step I	Liquid	0.8 ± 0.5	8.8 ± 4.9
Step II	Air	0.8 ± 0.3	8.4 ± 3.2
Step III	Air	0.4 ± 0.4	10.6 ± 4.8

Mean ± SD.
No difference among infused volumes and infusion times; $P > 0.05$.

Results

Arterial blood gas status immediately prior to administration or withdrawal of nitrous oxide is indicated in table 2. There were no differences among these variables at any step, with the exception of Pa_{O_2}, which reflected presence or absence of nitrous oxide in the inspired gases.

Figure 1 summarizes the alterations in ICP, BP, and CPP occurring prior to and after the administration or withdrawal of 75% nitrous oxide at elevated ICPs obtained either by intracranial infusion of LR or air. In Step I the administration of nitrous oxide after LR elevation of ICP caused no significant change in ICP, a modest mean BP elevation of approximately 7 mmHg at 5 min, and a similar increase in CPP ($P < 0.05$). With Step II, following infusion of intracranial air to raise ICP, introduction of nitrous oxide caused an abrupt and significant ($P < 0.01$) 6 mmHg ICP elevation after 2 min, which continued to increase until a total ICP gain of about 10 mmHg ensued after 5 min of N₂O administration. This was accompanied by no significant change in BP or CPP. In Step III, withdrawal of nitrous oxide in the presence of an elevated ICP due to air infusion led to a significant ($P < 0.01$) 7 mmHg ICP reduction within 2 min, with a net ICP decrease of 9 mmHg at 5 min. There was no change in CPP, and the BP decreased slightly 2 min after N₂O was discontinued in Step III.

Discussion

To some degree pneumocephalus probably complicates most intracranial surgical procedures, especially those that entail large amounts of CSF loss. Usually, pneumocephalus is not of clinical significance and resolves over a period

TABLE 2. Arterial Blood Gas Status*

	Step I	Step II	Step III
Pa_{CO_2} (mmHg)	30.4 ± 4.2	30.3 ± 5.1	28.0 ± 3.3
Pa_{O_2} (mmHg)	363 ± 103	299 ± 167	113 ± 33†
pH_a	7.43 ± 0.09	7.45 ± 0.06	7.39 ± 0.06

Mean ± SD.
* Determined just prior to starting or stopping N₂O anesthesia. Step I taken as control condition.
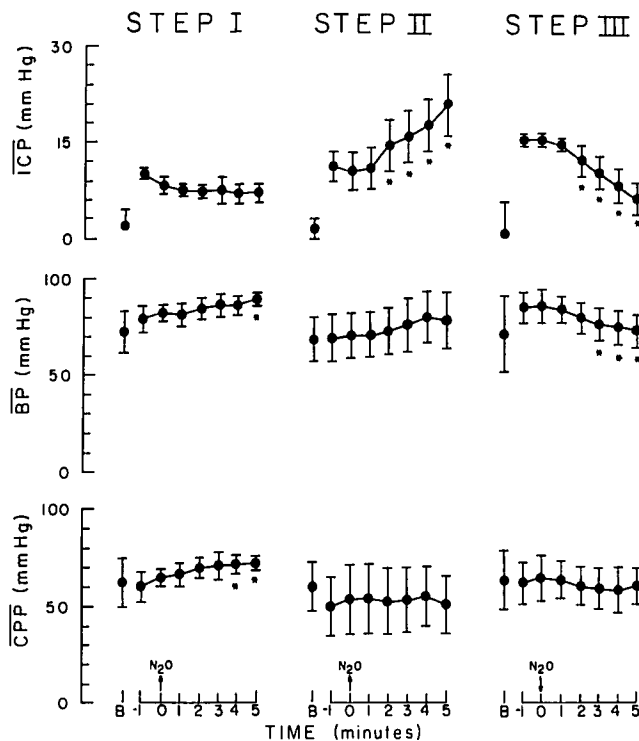† $P < 0.001$ compared with Step I or Step II.

FIG. 1. Mean (±SD) intracranial pressure (ICP), arterial blood pressure (BP), and cerebral perfusion pressure (CPP) alterations following elevation of ICP with either fluid (Step I) of air (Steps II and III) followed by administration of N_2O (↑) or withdrawal of N_2O (↓) in halothane-anesthetized rabbits (see text for details of protocol). Baseline (B) values are indicated by the nonconnected point at the beginning of each step. The infusion pump elevating ICP was turned off at zero time. Asterisks indicate $P < 0.01$.

of days to weeks. Occasionally, intracranial hypertension develops in association with pneumocephalus leading to the syndrome of tension pneumocephalus, which can present as delayed recovery from anesthesia, diminished level of consciousness with or without focal neurologic signs, and/or death due to intracranial hypertension. This diagnosis may be considered while patients are still in the postanesthesia recovery room. Tension pneumocephalus has been described in the absence of exposure to nitrous oxide, and the role of this anesthetic in the genesis of this syndrome remains controversial.[15]

In an attempt to clarify some of the issues concerning the use of nitrous oxide during sitting-position neurosurgical procedures, we developed a laboratory model for pneumocephalus in the rabbit. In this model several steps were introduced to control for certain variables. Step I, consisting of introducing nitrous oxide after elevating ICP with LR, was employed to detect possible ICP-elevating effects of nitrous oxide due to its ability to increase cerebral blood flow (CBF).[16] In our halothane-anesthetized rabbits this effect appears to be negligible, as the ICP did not increase with nitrous oxide administration. Lack of an ICP elevation in our experimental circumstance may

be due to the already present cerebrovasodilator action of halothane, which may attenuate further N_2O vasodilator effects on CBF.[17] It could also be due in part to the downward drift of ICP, which is inherent in models employing intracranial volume infusions to raise ICP. In our preparation downward ICP drift was less than 1 $mmHg \cdot min^{-1}$ immediately after the infusion pump was stopped and is progressively attenuated thereafter (unpublished observations). Thus major CBF and cerebral blood volume changes as reflected by the ICP probably do not occur due to nitrous oxide administration in our model.

Step II in our protocol was introduced in order to test the ability of our model to reveal ICP elevations known to occur when nitrous oxide anesthesia is administered in the presence of a sealed intracranial pocket of air.[11] The expected abrupt ICP increase after nitrous oxide was administered confirms model validity in this respect. Step III was designed to simulate the clinical circumstance wherein intracranial air accumulates during an anesthetic in which N_2O is given. Withdrawal of N_2O in this situation simulates the clinical circumstance in which N_2O anesthesia is maintained until dural and cranial closure is completed. The abrupt decrease in ICP following discontinuation of nitrous oxide confirms our hypothesis that delayed removal of this anesthetic should reduce the incidence of tension pneumocephalus.

Clinically, a number of intraoperative factors can contribute to the development of delayed tension pneumocephalus. Those factors that act to either decrease brain volume or promote CSF drainage out of the cranial cavity can contribute to the development of delayed tension pneumocephalus. They can include hyperventilation, gravity reduction of cerebral venous volume, osmotic diuretics, release of noncommunicating hydrocephalus, and suctioning of CSF.[18] When these occur in a patient in the sitting position, air enters the cranial cavity and may percolate to the highest point over the hemispheres. This condition has been likened to the phenomenon that occurs with an "inverted pop bottle."[3,19] The presence of a nitrous oxide anesthetic may increase the rate at which an intracranial gas volume expands in this situation. However, the final intracranial gas volume depends more on the degree of brain shrinkage and CSF loss as long as the system remains open or can be vented to the atmosphere through the surgical site. At closure intracranial tension should therefore be at ambient pressure. Postoperatively, with resumption of the supine position, the processes leading to brain shrinkage and CSF loss are reversed, and reexpansion of the brain along with accumulation of CSF volume may generate the high ICP associated with tension pneumocephalus as the gas pocket now serves as a space-occupying lesion. Any process that can reduce the volume of intracranial gas remaining after dural closure will create more potential space to accommodate postoperative brain

and CSF volume increases, thus buffering ICP elevation. We believe that our experiment indicates that delayed removal of nitrous oxide from anesthetic gases that have equilibrated with the intracranial pneumatocele actually accomplishes this desired goal.

Much of the confusion surrounding the use of nitrous oxide when intracranial air accumulation is possible can be resolved by consideration of the prior content of the gas cavity, the conditions under which it has accumulated, and whether or not the dura and skull are closed. It has been clearly demonstrated that nitrous oxide introduction in the presence of a preexisting, sealed intracranial air pocket and closed cranial vault can result in an abrupt and severe elevation in ICP.[12] Our study indicates that when the intracranial gas cavity has equilibrated with inspired N₂O anesthesia, removal of nitrous oxide results in a fall in ICP. Similar results with a corresponding time frame have been described that explored this question in a canine model.[12] Because the incidence of intraoperative tension pneumocephalus, as evidenced by acute brain swelling, appears to be relatively low, we suggest that, more often than not, N₂O is in equilibration with the supratentorial pneumocephalus that accumulates during posterior fossa neurosurgery with the patient in the sitting position. Several case studies of surgery performed on patients in the supine and lateral positions implicate N₂O in the genesis of tension pneumocephalus.[20,21] Under these conditions (absent the "inverted pop-bottle" mechanism) intracranial air collections might not have time to equilibrate with N₂O prior to dural closure. Also, in these cases the circumstances regarding the actual existence of high pressures within the pneumocephalus are poorly defined, although the existence of large intracranial gas pockets acting as space-occupying lesions was demonstrated. When the possibility for introduction of intracranial air *via* a ventriculostomy or shunt device exists, acute intraoperative tension pneumocephalus can develop due to the presence of N₂O anesthesia.[2,10,22] Because the conditions leading to N₂O–air pocket equilibration at ambient atmospheric pressure may not always exist, withdrawal of N₂O prior to dural closure should be considered whenever acute intraoperative brain swelling occurs.

Use of ICP monitoring or drains to permit venting of gas or fluids should be considered whenever a large intracranial cavity (filled with gas or fluid) has been created intraoperatively and the potential for significant postoperative brain expansion and/or swelling is high. Early discontinuation of nitrous oxide from anesthetic protocols prior to dural and cranial closure is not indicated in most cases, and maintenance of N₂O in the anesthetic protocol until the end of the case has the advantages of reducing intracranial gas volume as well as promoting early arousal and neurologic evaluation of patients who are in the sitting position when surgery is performed.

References

1. Dandy WE: Pneumocephalus (intracranial pneumatocele or aerocele). Arch Surg 12:949–982, 1926
2. Grundy BL, Spetzler RF: Subdural pneumocephalus resulting from drainage of cerebrospinal fluid during craniotomy. ANESTHESIOLOGY 52:269–271, 1980
3. Lecunda G, Cabezudo JM, Areitio E, Vaguero J, Gilsamz F: Subdural tension pneumocephalus after posterior fossa operation: Is the inverted bottle phenomenon the only causative factor? Surg Neurol 15:303–305, 1980
4. Kitahata LM, Katz JD: Tension pneumocephalus after posterior fossa cranitomy, a complication of the sitting position. ANESTHESIOLOGY 44:448–450, 1976
5. Hulett WB, Laing JW: Tension pneumocephalus and the sitting position. ANESTHESIOLOGY 45:578, 1976
6. Wolf S, Albin M: Anesthetic management of pneumocephalus. ANESTHESIOLOGY 53:521, 1980
7. Thiagarajah S, Frost EAM, Singh T, Shulman K: Cardiac arrest associated with tension pneumocephalus. ANESTHESIOLOGY 56:73–75, 1982
8. Toung T, Donham RT, Lehner A, Alano J, Campbell J: Tension pneumocephalus after posterior fossa craniotomy report of four additional cases and review of postoperative pneumocephalus. Neurosurgery 12:164–166, 1983
9. Artru AA: Nitrous oxide plays a direct role in the development of tension pneumocephalus intraoperatively. ANESTHESIOLOGY 57:59–61, 1982
10. Frost EAM: Central nervous system effects of nitrous oxide, Nitrous Oxide/N₂O. Edited by Eger EI. New York, Elsevier, 1985, p 170
11. Saidman LJ, Eger EI: Change in cerebrospinal fluid pressure during pneumoencephalography under nitrous oxide anesthesia. ANESTHESIOLOGY 26:67–72, 1965
12. Friedman GA, Norfleet EA, Bedford RF: Discontinuance of nitrous oxide does not prevent tension pneumocephalus. Anesth Analg 60:57–58, 1981
13. Dixon WJ. BMDP Statistical Software. Berkley, University of California Press, 1981
14. Glantz SA: Primer of Biostatistics. New York, MacGraw-Hill, 1981
15. McL Black P, Davis JM, Kjellberg RN, Davis KR: Tension pneumocephalus of the cranial space. Neurosurgery 5:368–370, 1979
16. Pelligrino DA, Miletich DJ, Hoffman WE, Albrecht RF: Nitrous oxide markedly increases cerebral cortical metabolic rate and blood flow in the goat. ANESTHESIOLOGY 60:405–412, 1984
17. Shapiro HM: Anesthesia effects upon cerebral blood flow-metabolism, electroencephalogram, and evoked potentials, Anesthesia. Edited by Miller RD. New York, Churchill-Livingstone, 1985, pp 1249–1287
18. MacGillivray RG: Pneumocephalus as a complication of posterior fossa surgery in the sitting position. Anaesthesia 37:722–725, 1982
19. Lunsford LD, Maroon JC, Sheptar PE, Albin MS: Subdural tension pneumocephalus. Report of two cases. J Neurosurg 50:525–527, 1979
20. Raggio JF, Fleischer AS, Sung YF, Hoffman JC: Expanding pneumocephalus due to nitrous oxide anesthesia: Case report. Neurosurgery 4:261–263, 1979
21. Mallamo JT, Hubbard RB: Expansion of an air-filled subdural space during nitrous oxide anesthesia. Radiology 115:369–372, 1975
22. Drummond JC: Tension pneumocephalus and intermittent drainage of ventricular CSF (letter). ANESTHESIOLOGY 60:609–610, 1984