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The Use of Intraoperative Nitrous Oxide Leads to Postoperative Increases in Plasma Homocysteine

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Hyperhomocysteinemia is an independent risk factor for coronary artery and cerebrovascular disease, but its significance in the perioperative period is unknown. Nitrous oxide inhibits methionine synthase, which aids in the conversion of homocysteine to methionine. In this prospective, controlled, randomized study, we determined the effect of intraoperative nitrous oxide exposure on postoperative plasma homocysteine concentrations. Twenty ASA physical status I–III patients, aged >18 yr, presenting for elective craniotomy, were randomized to receive general anesthesia with or without nitrous oxide (inspired nitrous oxide >50%). Plasma was sampled before the induction of anesthesia, on arrival in the postanesthesia care unit (PACU) after discontinuation of nitrous oxide, and 24 h after induction. There was a significant increase (22.6 ± 11.4 vs 13.0 ± 4.7 μmol/L; $P = 0.0038$ for postoperative versus preinduction values) in plasma homocysteine concentrations in the nitrous oxide group on arrival in the PACU and for 24 h. In the nonnitrous oxide group, mean plasma homocysteine concentrations did not change (9.5 ± 1.9 vs 9.8 ± 1.6 μmol/L; $P = 0.86$ for postoperative versus preinduction values). The change in plasma homocysteine concentrations in the nitrous oxide group was significantly different from that in the nonnitrous group ($P = 0.0031$). We conclude that the use of intraoperative nitrous oxide leads to significant increases in perioperative plasma homocysteine concentrations. **Implications:** Short-term exposure to nitrous oxide led to significant increases in plasma homocysteine. Further investigations are required to determine the clinical significance of this change.

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Long-term increases in total plasma homocysteine concentrations are an independent risk factor for coronary artery and cerebrovascular disease (1,2). This occurs in 1%–2% of the general population, but in approximately 30% of patients with vascular disease (1,2). Affected individuals have increased basal homocysteine concentrations, as well as abnormal responses to methionine loading. Any significance of such changes in the perioperative period is unknown.

Nitrous oxide inhibits methionine synthase, which aids in the conversion of homocysteine to methionine, potentially leading to megaloblastic anemia (4). That nitrous oxide also increases homocysteine concentrations has been shown both in lymphocyte cell cultures (5) and human liver biopsy samples (6). Although studies investigating the effect of intraoperative nitrous oxide exposure on postoperative plasma homocysteine concentrations noted increases postoperatively, they were either uncontrolled (7) or nonrandomized (8). Finally, postoperative myocardial infarctions occur with a peak incidence on the first postoperative night (9). Because postoperative nitrous oxide-induced homocysteine increases could therefore be temporally implicated in the development of postoperative myocardial infarctions, we thought that these findings should be confirmed in a prospective, controlled, and randomized study.

Methods

After obtaining institutional ethics review board approval and written, informed consent, 20 ASA physical status I–III patients, aged >18 yr, presenting for elective craniotomy, were randomized to receive general anesthesia with or without nitrous oxide. Patients were excluded if they had received an anesthetic within 30 days before their scheduled surgery, if they had a family history or medical history of hyperhomocysteinemia, if they were currently taking medications known to affect plasma homocysteine (vitamins B_{12} and B_6, folic acid, D-penicillamine, methotrexate, azauradine, isoniazid, cycloserine, phenelzine or procarbazine), or if they were vitamin B_{12} or folate deficient, malnourished, or cirrhotic.

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Before the induction of anesthesia, a baseline blood sample was drawn. Anesthetic induction included IV propofol, a narcotic (fentanyl or sufentanil), and a nondepolarizing muscle relaxant. In the nitrous oxide group, anesthesia was maintained with an opioid (fentanyl or sufentanil), isoflurane, and nitrous oxide/oxygen (inspired nitrous oxide >50%). In the nonnitrous oxide group, anesthesia was maintained with opioid (fentanyl or sufentanil), isoflurane, and oxygen/air. Total opioid, in fentanyl equivalents (1 μg of sufentanil = 7 μg of fentanyl) (10), and estimated average inspired isoflurane concentrations were recorded. After completing the procedure, neuromuscular blockade was reversed. After emergence and tracheal extubation, the patient was monitored in standard fashion in the postanesthesia care unit (PACU).

Plasma samples were obtained before the induction of anesthesia, on arrival in the PACU, and 24 h after induction. Plasma homocysteine levels were determined by laboratory personnel blinded to treatment groups, using high-performance liquid chromatography as described elsewhere (11) but modified to include a short Novopack 5-cm C18 (5 μm) analytical column (Waters Inc., Mississauga, Ontario, Canada). This assay is sensitive to 5.0 μmol/L with interassay coefficient of variation of 6.8% at this concentration. Quality control was maintained with standards containing 50 μmol/L (n = 10, coefficient of variation 7.0%).

Statistical analysis of demographic and intraoperative data consisted of unpaired t-tests for parametric data and χ^2 analysis for nonparametric data, whereas analysis of variance for repeated measures was used to compare plasma homocysteine concentrations. A P value < 0.05 was considered significant.

Results

There were no significant differences between the nitrous oxide and nonnitrous oxide groups in terms of demographic (age, weight, gender) or intraoperative (time, procedure, and opioid administered) data, as shown in Table 1. The nonnitrous oxide group did receive a significantly larger mean estimated isoflurane concentration than the nitrous oxide group (1.02 ± 0.11 vs 0.86 ± 0.19; P = 0.036).

Although there was a trend to differing baseline homocysteine levels, there was a significant increase (22.6 ± 11.4 vs 13.0 ± 4.7 μmol/L; P = 0.0038 for postoperative versus preinduction values) in mean plasma homocysteine concentration in the nitrous oxide group by the time of arrival in PACU that was maintained for at least 24 h (see Figure 1). In the nonnitrous oxide group, mean plasma homocysteine concentrations did not change (9.5 ± 1.9 vs 9.8 ± 1.6; P = 0.86 for postoperative versus preinduction values). The nitrous oxide and nonnitrous oxide groups were also different (P = 0.0031) with respect to the mean change in plasma homocysteine concentrations (Figure 2)—there was no change in the nonnitrous oxide group. All patients in the nitrous oxide group had increased plasma homocysteine concentrations, whereas 6 of 10 patients in the nonnitrous oxide group had decreased plasma homocysteine concentrations.

Table 1. Demographic and Intraoperative Variables

	Nitrous oxide	Non-nitrous oxide	P value
Age (yr)	54 ± 13	46 ± 12	0.18
Weight (kg)	79 ± 21	82 ± 20	0.74
Gender (m/f)	3:7	5:5	0.36
OR time (min)	303 ± 64	327 ± 98	0.51
Procedure			
Aneurysm	3	3	
Tumour	3	4	0.29
Other	4	3	
Homocysteine (μmol/L)	13.0 ± 4.74	9.76 ± 1.61	0.055
Fentanyl (μg)	650 ± 220	620 ± 230	0.77
Inspired isoflurane (%)	0.86 ± 0.19	1.02 ± 0.11	0.036

OR = operating room.

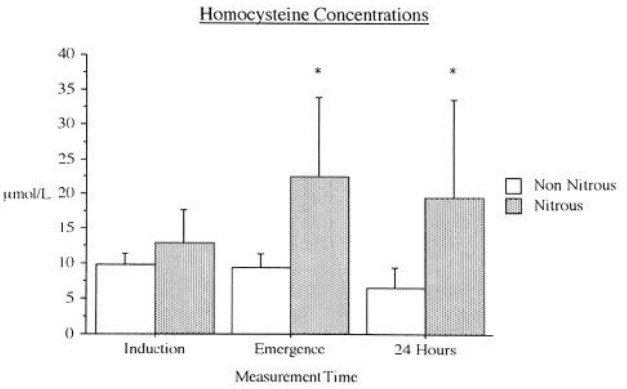

Figure 1. Comparison of mean plasma homocysteine concentrations as a function of time. Values are mean ± SD. *P = 0.0038 for induction versus emergence and 24 h.

Discussion

This randomized, controlled study confirmed earlier findings that the use of nitrous oxide leads to significant increases in perioperative plasma homocysteine concentrations. Our patients experienced an increase of approximately 10 μmol/L in plasma homocysteine levels, which is consistent with the findings of others (7,8). Those studies, however, suffered from methodologic flaws, including lack of a nonnitrous oxide control group (7), or lack of randomization, and poor choice of control group (multiple procedures and different patient numbers per group) (8). Our use of only

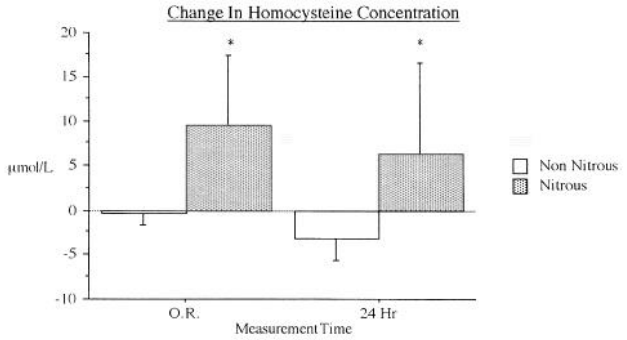

Figure 2. Comparison of mean change in plasma homocysteine concentration as a function of time. Values are mean ± SD. *P = 0.0031 for the nitrous oxide versus nonnitrous oxide groups.

patients undergoing craniotomy, randomization, and a control group receiving identical anesthetic management (with the exception of the use of nitrous oxide) was designed to overcome these deficiencies. Despite the fact that the mean baseline homocysteine concentrations were not the same in the two groups, we found that the change in homocysteine concentrations was significantly different and that all patients receiving nitrous oxide had increased plasma homocysteine concentrations, whereas 6 of 10 patients in the nonnitrous oxide group actually had decreased homocysteine concentrations. In our study, the only difference in intraoperative management was the small increase in inspired isoflurane concentration, which was necessary to supply the additional anesthesia that nitrous oxide would have contributed.

In this study, we did not measure differences in clinical outcome. This is potentially important, because long-term increases in plasma homocysteine lead to increased risks of cardiovascular and cerebrovascular disease (1,2), whereas short-term increases produce procoagulant effects (3) and inhibit flow-mediated vasodilation (12). These effects are probably mediated by the consumption of nitric oxide and/or the production of hydrogen peroxide (13). The findings that myocardial infarctions in noncardiac surgery occur with a peak incidence of the first postoperative day (9) temporally coincide with increases that we have shown in nitrous oxide-induced plasma homocysteine concentrations. Because nitrous oxide is used in a large proportion of general anesthetics, the potential ramifications of any such linkage with an outcome difference would be significant.

In the event that nitrous oxide-induced increases in plasma homocysteine are linked with negative outcomes, potential options include the avoidance of nitrous oxide or vitamin pretreatment in at-risk individuals. Vitamin treatment would consist of the use of folic acid, pyridoxine (vitamin B_6), and vitamin B_{12}. Their use over 6 wk reduces increased levels of plasma homocysteine (14) and, more importantly, slows the progression of carotid atherosclerosis (15). The appropriate dose and timing of vitamin therapy to prevent perioperative nitrous oxide increases is, however, unknown. The use of methionine loading to decrease homocysteine levels, although effective in lymphocyte cell cultures, has not been effective in blocking the nitrous oxide-induced homocysteine increase in humans undergoing general anesthesia (7).

In summary, we have shown in a randomized, controlled study that nitrous oxide leads to significant increases in plasma homocysteine concentrations postoperatively. The clinical significance of these findings was not determined.

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