

Preoperative Oral B Vitamins Prevent Nitrous Oxide-Induced Postoperative Plasma Homocysteine Increases

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Nitrous oxide increases total homocysteine (tHcy) plasma levels, which are associated with an increase in perioperative myocardial ischemia. We designed this study to determine whether oral B vitamins, which are cofactors in homocysteine metabolism, can prevent nitrous oxide anesthesia-induced tHcy increases in patients undergoing elective surgery scheduled to last longer than 3 h. Fifty-three patients presenting for elective revision knee or hip arthroplasty received in random, double-blinded fashion oral vitamin B complex (folate 2.5 mg, B₆ 25 mg, and B₁₂ 500 μg) or placebo daily for 1 wk before surgery. Anesthesia was induced with propofol and maintained with an opioid, isoflurane, and nitrous oxide/oxygen (inspired nitrous oxide

>50%). Blood samples for measurement of tHcy concentration were obtained at study enrollment, before induction, on arrival in the postanesthesia care unit, and on Day 5. Fourteen patients had their surgery rescheduled after taking their vitamins and were removed from the study. The Placebo group had a mean increase in tHcy concentration from baseline of 15% ± 31% compared with the Vitamin group, which had an initial decrease of 9.1% ± 11% ($P = 0.035$). This was maintained throughout the 5-day study period. The use of an oral B vitamin complex prevented the increase in postoperative tHcy by nitrous oxide.

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Postoperative myocardial infarction (PMI) in patients undergoing noncardiac surgery is a serious clinical problem (1). Although myocardial ischemia is known to be a marker for PMI (2) and can be decreased through the use of β -adrenoreceptor antagonists perioperatively (3,4), 30%–35% of patients either cannot take these medications or are already receiving them. We have recently shown that the peak incidence of PMI occurs on the operative night (5), suggesting that a relationship to one or more intraoperative events might be occurring and suggesting a further modifiable approach to decreasing PMIs.

Plasma total homocysteine (tHcy), when increased over the long term, is an independent risk factor for coronary artery and cerebrovascular disease (6). Acute increases *in vitro* produce direct cytotoxic effects on endothelial cells, increase platelet adhesiveness, and cause procoagulant activity (7). In volunteers, acute increases in tHcy concentrations produce endothelial

dysfunction (8,9). Furthermore, in patients with coronary artery disease who are admitted with acute coronary syndromes, tHcy concentrations larger than 14 μmol/L are associated with increased short- and long-term all-cause and cardiac mortality (10,11). The full significance of tHcy in the perioperative period remains unknown, although our recent findings in a prospective, randomized study indicated that nitrous oxide produces increased plasma tHcy levels when compared with patients anesthetized with a similar nonnitrous oxide anesthetic (12). This increase peaked immediately after surgery and would therefore coincide temporally with the incidence of PMI; it was recently shown to be associated with increased perioperative myocardial ischemia in a high-risk group of patients (13).

Nitrous oxide continues to be widely used in general anesthetics because of its potent analgesic and amnesic properties, its rapid onset and elimination, and its low cost. Although it inhibits methionine synthetase and potentially causes megaloblastic anemia after long exposures (>24 h, a rare clinical scenario), the potential effects of short exposures on homocysteine metabolism have received little attention. B vitamins are intermediate compounds in homocysteine metabolism. They reduce plasma tHcy concentrations and cause regression of carotid artery plaque (14). This

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study was designed to determine whether the administration of oral B vitamins for 1 wk before surgery could block the nitrous oxide-induced increase in plasma tHcy.

Methods

After written informed consent and IRB approval, 53 patients presenting for elective revision hip or knee surgery under general anesthesia were randomized to receive oral B vitamins or placebo. Patients were excluded if any of the following applied: anesthesia within 30 days before scheduled surgery, known vitamin B₁₂ or folate deficiency, malnutrition, severe alcoholism, megaloblastic anemia, cirrhosis, family or personal history of homocystinuria, or use of folic acid, D-penicillamine, B vitamins, methotrexate, azauradine, isoniazid, cycloserine, phenelzine, and procarbazine.

Patients were enrolled 2-3 wk before surgery in the preadmission clinic. They received a 1-wk supply of oral vitamins (folate = 2.5 mg, B₆ = 25 mg, and B₁₂ = 500 µg) or placebo to be taken daily in randomized, double-blinded fashion and instructions indicating when to begin therapy (1 wk before surgery).

General anesthesia was induced with propofol, an opioid (fentanyl or sufentanil), and a nondepolarizing muscle relaxant and was maintained with an opioid, isoflurane, and nitrous oxide/oxygen (inspired nitrous oxide concentration more than 50%). After emergence and extubation, patients were monitored in standard fashion in the postanesthesia care unit (PACU) and transferred to the ward. Postoperative care followed routine standards under the care of the surgical team.

All patients were monitored with standard clinical monitors (e.g., electrocardiogram, pulse oximetry, capnography, end-tidal anesthetic and CO₂ monitoring, temperature probe, peripheral nerve stimulator) throughout the anesthetic period. Anesthetic depth, blood pressure control, neuromuscular blockade, and ventilation were at the discretion of the responsible anesthesiologist. The study database recorded preoperative medications, cardiac risk factors, anesthetics and amounts, and hemodynamic variables before surgery, after induction, and after PACU arrival.

On study enrollment, immediately before surgery, on arrival in the PACU, and 5 days after surgery, blood samples were obtained for tHcy analysis. Blood samples were analyzed for tHcy concentration by personnel blinded to treatment groups by using high-performance liquid chromatography as described previously (12). By using this technique, the coefficient of variation was 6.8% at 5.0 µmol/L.

The primary outcome measure was the change in plasma tHcy concentration, for which the estimated value in the Control group was 9.6 ± 5.2 µmol/L (12);

a detectable difference was 4.8 µmol/L (a 50% reduction in the nitrous oxide effect). By using GPOWER software for Macintosh (Apple Computer, Inc., Cupertino, CA) (15), an α of 0.05, and a power of 0.80, the required total sample size was calculated to be 32 patients. Statistical analysis of demographic and intraoperative data consisted of unpaired Student's *t*-tests for parametric data and χ^2 analyses for nonparametric data, whereas analysis of variance for repeated measures was used to compare changes in plasma tHcy concentrations. A value of $P < 0.05$ was considered significant.

Results

Of the 53 patients enrolled in the study, 14 patients had their surgery rescheduled after taking their vitamins and were removed from the study, leaving 39 patients (20 Placebo, 19 B Vitamin). There were no significant differences between the B Vitamin and Placebo groups in terms of demographic (age, height, weight, and sex) or intraoperative data (duration of anesthesia; opioid usage in fentanyl equivalents, where 1 µg sufentanil = 7 µg fentanyl; nitrous delivered in MAC-h, calculated as N₂O delivered in % × time in hours) (16), as shown in Table 1.

The B Vitamin group seemed to have a greater mean baseline tHcy level; however, this difference was not significant ($P = 0.21$). After the 1-wk course of oral B vitamins, there was a significant decrease of $9.1\% \pm 11\%$ in tHcy over time that was significantly different from the Placebo group, which had a mean increase in tHcy of $15\% \pm 31\%$ ($P = 0.035$) over time, as shown in Figure 1.

Discussion

This prospective, randomized, single-blinded study confirmed earlier findings that the use of nitrous oxide leads to significant increases in postoperative plasma tHcy concentrations (12,13). Patients receiving the placebo had an increase of approximately 15% in plasma tHcy levels, whereas those receiving a 1-wk course of oral B vitamins had an overall reduction in the tHcy levels of 9%. This result occurred despite the fact that the mean baseline tHcy concentrations were not the same in the two groups. This finding is consistent with the known tHcy-decreasing effects of B vitamins in patients with hyperhomocystinemia or carotid artery disease (14,17). The increase in tHcy levels in the Placebo patients is somewhat less than that of our earlier results. This is possibly caused by the combination of a decreased nitrous oxide exposure, because the mean duration of anesthetic time was only 175 minutes, as opposed to 300 minutes in our first study (12), or by a decreased initial mean tHcy level (9.7 vs 12.7 µmol/L

Table 1. Demographic Data and Intraoperative Variables

Variable	Group	
	Placebo	B Vitamin
Age (yr)	67 ± 11	68 ± 16
Height (cm)	166 ± 12	164 ± 9
Weight (kg)	87 ± 14	83 ± 16
Sex (M/F)	11/9	9/10
Medications		
ASA	4 (20)	6 (32)
β-blockers	3 (15)	7 (37)
CCB	3 (15)	3 (16)
ACE inhibitors	6 (30)	6 (32)
Statins	1 (5)	3 (16)
Anesthetic time (min)	179 ± 65	175 ± 62
Procedure		
Revision TKJR	14	12
Revision THJR	6	7
Opioids (μg)		
fentanyl equivalents	373 ± 193	448 ± 217
Nitrous oxide (MAC-h)	1.73 ± 0.60	1.68 ± 0.65
Baseline tHcy (Φmol/L)	9.7 ± 3.4	12.1 ± 7.1

Values are means ± SD or n (%). There were no significant differences. MAC = minimum alveolar concentration; TKJR = total knee joint replacement; THJR = total hip joint replacement; tHcy = total homocysteine; ASA = acetylsalicylic acid; CCB = calcium channel blockers; ACE inhibitors = angiotensin-converting enzyme inhibitors; statins = hydroxymethylglutaryl coenzyme A reductase inhibitors.

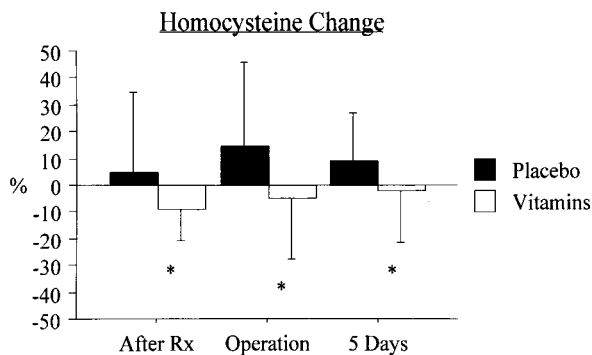


Figure 1. Homocysteine values at the designated measurement times, where Rx = vitamin or placebo. Values are means ± SD, *P = 0.035.

in the latest study) (13). We chose orthopedic patients because they often receive standard anesthetic management and are routinely seen two or three weeks before surgery, allowing vitamin supplementation. Despite this, however, 14 patients had their surgery rescheduled and were potentially unable to benefit from vitamin therapy.

We chose vitamin treatment of daily folic acid 2.5 mg, pyridoxine (vitamin B₆) 25 mg, and 500 μg vitamin B₁₂ for one week. We chose this dosage because the use of this combination over six weeks decreases increased levels of plasma tHcy (17) and, over one to two years, slows the progression of carotid atherosclerosis (14). Most patients are assessed in a preoperative clinic one to two weeks before surgery,

and we therefore chose a one-week course of therapy as a practical means of allowing these patients to receive therapy without postponing their surgery. Despite our best efforts, however, 14 patients had their surgery rescheduled after taking their vitamins, indicating the potential difficulties of this treatment approach. We did not determine whether a shorter time course or single dose was also effective. The use of methionine loading to decrease tHcy levels, although effective in lymphocyte cell cultures, has not been effective in blocking the nitrous oxide-induced tHcy increase in humans undergoing general anesthesia and is not recommended (18).

This study did not measure differences in clinical outcome. We have, however, shown that nitrous oxide-induced tHcy increases are associated with increased postoperative myocardial ischemia (13). This is consistent with the evidence that long-term increases in plasma tHcy lead to increased risks of cardiovascular and cerebrovascular disease (6), whereas short-term increases to the same levels of tHcy cause endothelial dysfunction measured as an inhibition of flow-mediated vasodilation (8,9) and produce procoagulant effects (7). These effects are probably mediated in part by the consumption of nitric oxide, the production of hydrogen peroxide (19), or both. The recent findings that myocardial infarctions in noncardiac surgery occur with a peak incidence on the first postoperative day (5) would temporally coincide with increases that we have shown in nitrous oxide-induced plasma tHcy concentrations. Because nitrous oxide is used in a large proportion of general anesthetics, confirmation of any such linkage with adverse cardiac outcomes, such as myocardial infarction and death, would be significant.

In summary, we have shown in a prospective, randomized, single-blinded study that preoperative B vitamins inhibit nitrous oxide-induced increases in plasma tHcy concentrations that occur after surgery. The difficulty in scheduling may limit potential benefits of vitamin use unless a shorter course of therapy also proves effective.

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