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Nagele P, Brown F, Francis A, Scott MG, Gage BF, Miller JP, VINO Study Team. Influence of Nitrous Oxide Anesthesia, B-Vitamins, and MTHFR Gene Polymorphisms on Perioperative Cardiac Events: The Vitamins in Nitrous Oxide (VINO) Randomized Trial. Anesthesiology 2013;119:19-28.

Nitrous oxide is the oldest and most widely used general anaesthetic. Some studies have reported an increased risk for perioperative myocardial ischaemia and infarction with its use during general anaesthesia in patients with cardiac risk factors. Nitrous oxide causes an acute increase in plasma homocysteine by irreversible inactivation of vitamin B12, which has been proposed as the cause for the increased perioperative myocardial infarction risk. The present authors have earlier reported that patients homozygous for the C677T or A1298C variant in the methylenetetrahydrofolate reductase (*MTHFR*) gene, which is the most important genetic determinant of plasma homocysteine, developed higher plasma homocysteine concentrations after nitrous oxide anaesthesia. The purpose of this double-blind, randomised, placebo-controlled trial was to determine whether patients who were homozygous for the *MTHFR* C677T or A1298C variant had an increased risk for perioperative cardiac events after nitrous oxide anaesthesia, and whether this risk could be mitigated by B-vitamins, which reliably lowers plasma homocysteine.[1]

Adult patients diagnosed with or at risk for coronary artery disease, who were scheduled for elective non-cardiac surgery under general anaesthesia lasting more than 2 hours, were included. The total sample size was 500 patients. All patients received nitrous oxide throughout surgery at a concentration of 60% and were randomised to receive either, 1 mg vitamin B12 and 5 mg folic acid in 100 ml of normal saline before and after surgery (nitrous oxide/B vitamin group; n = 250), or a placebo infusion of 100 ml normal saline (nitrous oxide/placebo group; n = 250). A nitrous oxide-free non-randomised reference group (n = 125) was added to determine if nitrous oxide had an effect on perioperative cardiac events independent of homocysteine increase. For outcome assessments, patients had five serial blood collections and electrocardiograms at the following time points: Preoperative (baseline), end of surgery, and postoperative days 1, 2 and 3. Plasma total homocysteine, serum troponin I and high-sensitivity troponin T were measured at all the time points; serum folate and vitamin B12 were measured at baseline and on postoperative day 1. *MTHFR* genotypes (rs1801131, rs1801133) were determined by the Sequenom MassARRAY. The study endpoints were the incidence of myocardial injury, defined by cardiac troponin I increase (peak concentration >0.07 μg/l) within the first 72 hours after surgery, the incidence of myocardial infarction within the first 72 hours after surgery, and a composite of 30-day mortality and nonfatal myocardial infarction. Patients were grouped according to their *MTHFR* genotype in homozygotes and wild type or heterozygotes.

Patients in the nitrous oxide/B-vitamin group had significantly higher postoperative vitamin B12 and folate concentrations compared to baseline and both the other groups. Plasma total homocysteine concentrations rose in all patients who received nitrous oxide, regardless of *MTHFR* genotype. The increase was significantly blunted in patients receiving B-vitamins. The *MTHFR* C677T and A1298C allele status did not influence the extent of plasma total homocysteine increase. Neither the *MTHFR* genotype, nor the B-vitamin treatment, had an effect on cardiac study outcomes. Patients who were homozygous for either *MTHFR* C677T, or A1298C gene variant (n = 98; 19.6%) had no increased rate of postoperative cardiac troponin I increase compared with wild type and heterozygous patients (11.2 vs. 14.0%; relative risk 0.96; 95% CI, 0.85-1.07; P = 0.48). B-vitamins blunted the rise in homocysteine, but had no effect on

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cardiac troponin I increase compared with patients receiving placebo (13.2 vs. 13.6%; relative risk 1.02; 95% CI 0.78–1.32; *P* = 0.91). No adverse events were related to the administration of intravenous B-vitamins.

The authors concluded that prophylactic use of vitamin B12 and folic acid successfully blunted the nitrous oxide-induced increase in plasma homocysteine but had no effect on perioperative cardiac outcomes. Patients who are homozygous for the *MTHFR* C677T and A1298C gene variants had no increased risk for perioperative cardiac events after nitrous oxide anaesthesia and the acute increase in plasma homocysteine caused by nitrous oxide was not associated with perioperative cardiac troponin increases. The authors have questioned the prevailing notion that acute nitrous oxide induced hyperhomocysteinaemia has a causal effect on perioperative myocardial ischaemia and infarction and believe that homocysteine may be a marker, rather than a cause of atherosclerotic disease and increased cardiovascular risk. The ENIGMA trial, the only large clinical trial investigating nitrous oxide and cardiovascular outcomes, has reported an inconclusive, statistically non-significant increase in the incidence of myocardial infarction in patients receiving nitrous oxide. The on-going ENIGMA-II trial, a large-scale multicentre clinical trial, will provide robust and definitive evidence to the question of the association between nitrous oxide and perioperative myocardial infarction. Though many practitioners have abandoned the use of nitrous oxide for patients with cardiac risk factors, the authors believe that, as yet, there is no proven increased cardiac risk from acute nitrous oxide-induced hyperhomocysteinaemia.

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Bilotta F, Gelb AW, Stazi E, Titi L, Paoloni FP, Rosa G. Pharmacological perioperative brain neuroprotection: A qualitative review of randomized clinical trials. Br J Anaesth 2013;110 (suppl 1):i113-20.

Perioperative brain damage resulting in new postoperative neurological deficits like transient ischaemic attack (TIA), stroke and postoperative cognitive decline (POCD) are among the most serious adverse complications of surgery and anaesthesia. An increased risk of perioperative stroke is observed in cardiovascular and neurovascular procedures and in patients with predisposing risk factors such as previous stroke, carotid stenosis, patent foramen ovale, atrial fibrillation, infective endocarditis, diabetes, renal failure and old age. Perioperative brain damage remains a concern because it increases mortality, lengthens hospitalisation, impairs postoperative quality of life and increases perioperative costs. Various drugs with different mechanisms of action have been tested over the years for pharmacological perioperative neuroprotection, though with conflicting results. This qualitative review of randomised controlled clinical trials (RCTs) addresses this issue and reports the effects of tested therapies on new postoperative neurological deficit, POCD and mortality rate.[1]

To identify trials for inclusion in this review, a detailed, systematic research using Cochrane Central Register of Controlled Trials and MEDLINE was performed. RCTs that met the following criteria: (i) Used any pharmacological therapy for perioperative brain neuroprotection, (ii) evaluated pre- and postoperative neurological status, (iii) measured pre- and postoperative cognitive status and (iv) included adult patients undergoing elective surgery, were analysed. The details of study population, interventions and outcomes were extracted using a standardised data extraction form. The outcome measures in this review were new postoperative neurological deficit defined as stroke, POCD and mortality.

Of the 5,904 retrieved studies, 25 RCTs (which included, 3,274 patients in the age range 22-86 years) met the inclusion criteria. The tested therapies were lidocaine, thiopental, S (+)-ketamine, propofol, nimodipine, GM1 ganglioside, lexipafant, glutamate/aspartate and xenon remacemide, atorvastatin, magnesium sulphate, erythropoietin, piracetam, rivastigmine, pegorgotein and 17b-estradiol. New postoperative neurological deficit was reported in 10 RCTs that tested nine drugs. The incidence was observed to be lower in studies that tested atrovastatin and magnesium sulphate, was associated with conflicting results for thiopental and did not differ between treated patients and control group for the other tested drugs. The POCD was evaluated in 24 RCTs that tested 16 drugs. The use of lidocaine, ketamine and magnesium sulphate was associated with controversial results on POCD, and there was no difference between treated patients and control group for the other tested drugs. The use of remacemide and piracetam, although not effective in reducing POCD, yielded a better postoperative 'neurocognitive performance'. Mortality was evaluated in 16 RCTs that tested 12 drugs and none of these drugs was associated with a reduction in mortality rate.

In some experimental paradigms, pharmacological brain neuroprotection might reduce the incidence of new postoperative neurological deficits and POCD, while no benefits on perioperative mortality are described. However, the methodological inconsistencies and weakness and the small number of studies do not allow any firm conclusions. There is no consensus yet on the best neuropsychometric