

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, lexicapant, glutamate/aspartate and xenon remacemide, atorvastatin, magnesium sulphate, erythropoietin, piracetam, rivastigmine, pegorgotein and 17 β -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 atorvastatin 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

tests for detecting and quantifying neurological damage and POCD, and also, there is no agreement on the optimal timing for postoperative testing for research, as well as, day-to-day clinical use. Future studies need to include a broader range of relevant clinical scenarios using a wider consensus on the methodological approaches, including timing and dosing of drug administration, patient selection and perioperative neurological and cognitive testing. The need for shared methodological approach, when clinical studies on pharmacological neuroprotection are designed, is recommended.

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Rogachev B, Tsesis S, Gruenbaum BF, Gruenbaum SE, Boyko M, Klein M, et al. The effects of peritoneal dialysis on blood glutamate levels: Implementation for Neuroprotection. *J Neurosurg Anesthesiol* 2013;25:262-6.

Glutamate, an excitatory amino acid, is released in high concentrations following brain insults and is an important causative factor for secondary neuronal damage after brain injury; elevations in extracellular fluid (ECF) glutamate levels have been seen in patients with severe head injury using cerebral microdialysis. In stroke patients too, glutamate levels are shown to correlate closely with the volume of ischaemic lesion and neurological outcome. Animal experiments have further demonstrated that infusions of glutamate-lowering drugs can improve neurological outcome after severe brain insults. Hence, human clinical trials were conducted to examine the efficacy of glutamate release inhibitors and glutamate receptors antagonists; however, these experiments were aborted due to several drug-induced adverse effects. Extracorporeal methods are suggested as other means for lowering blood and brain glutamate levels, thus serving as effective neuroprotective tools in acute and chronic brain ailments. The effectiveness of haemodialysis (HD) in lowering blood glutamate has already been demonstrated by these authors in a previous study. However, the use of HD in acute brain injury settings is limited by the requirement for heparinisation and presence of haemodynamically unstable patients. In such situations, peritoneal dialysis (PD) may be a viable option as it is a short and minimally invasive procedure that does not adversely impact patient haemodynamics. This study aims to investigate the efficacy of PD as a blood glutamate lowering method and describe the pattern of glutamate concentration changes in blood, as well as, the dialysis solution.^[1]

Eighteen patients (aged 26-87 years) with stage V chronic kidney disease on PD were studied. The study protocol was based on the routine peritoneal equilibrium test (PET), which assesses the efficacy of PD to remove water and waste from the body in patients undergoing PD. Following drainage of PD fluid from an overnight exchange, two litres of dialysis solution were infused in these patients over 10 minutes. After completing the infusion ($t = 0$), 200 mL of dialysis solution was drained every hour till completion of the test ($t = 60, 120, 180$ and 240 min). A 10 mL sample was extracted from each collected volume for analysis. Blood samples were also collected before initiation of PD and hourly thereafter in accordance with the PD sample collections. The blood samples were analysed for glutamate, creatinine, urea, glucose, glutamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT) and PD samples were analysed for glutamate, creatinine, urea, and glucose at the same time points as the blood samples. A comparison between baseline levels of glutamate and other parameters to levels over time was made.

Blood glutamate concentrations were significantly reduced by 60 minutes after the infusion of dialysis solution ($P < 0.0001$) but slowly returned towards baseline values as time progressed. The levels of glutamate in the dialysis solution were increased significantly by 60 minutes ($P < 0.0001$), maximised at 180 minutes and started to decrease thereafter. The levels of GOT, GPT, urea, creatinine, glucose, bicarbonate and pH in plasma did not change significantly throughout the experiment.

PD was capable of significantly reducing glutamate concentrations in the blood (by almost 20% when compared to baseline values) for at least an hour after dialysis solution infusion. However, the observed effect was short-lasting, which was attributed to the very small capacity of the dialysis solution and continuous shift of glutamate from peripheral ECF and intracellular compartments into the blood; it is recommended to replace the dialysis solution in the peritoneal cavity often (every 60 minutes) to avoid saturation and the deceleration of a blood glutamate-reducing effect. Thus, this study demonstrates that PD is an effective modality in reducing blood glutamate concentrations and may be potentially utilised for the treatment of acute and chronic brain disorders that are accompanied by elevated glutamate in the brain's ECF.

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