

Influence of Mutations in the *MTHFR* Gene on Homocysteine Levels after Nitrous Oxide Anesthesia

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Introduction: Exposure to nitrous oxide (N₂O) leads to a sustained increase in homocysteine levels and an inhibition of all Vit. B₁₂-dependent enzymes. Mutations in the *MTHFR* gene result in higher homocysteine levels due to inhibited enzyme activity. Based on several case reports that linked disastrous neurological outcomes after N₂O anesthesia with high levels of homocysteine, we hypothesized that patients carrying two common alleles in the *MTHFR* gene are at a high risk of developing abnormal homocysteine levels after N₂O anesthesia.

Methods: We included 140 ASA I-II patients who gave written, informed consent and were scheduled for elective orthopedic surgery (based on a 12% prevalence of the most common homozygous *MTHFR* allele in the general population). All patients received a standardized anesthetic regimen including 66% N₂O. We collected the following blood samples before anesthesia, after 2 hrs and at the end of surgery: homocysteine, folate, Vit. B₁₂, holo-TC. Patients were subsequently tested for two mutations in the *MTHFR* gene: 677 C>T and 1298A>C (wildtype/ heterozygous/ homozygous). The study was approved by our IRB.

Results: We identified 6 different combinations of the two alleles in the *MTHFR* gene in our patient population. In all 6 groups, anesthesia with N₂O led to an increase in homocysteine levels (figure). Patients who were homozygous for the 677 C>T (n=17) and 1298A>C (n=8) *MTHFR* mutation had the highest homocysteine levels after N₂O exposure, reaching potentially detrimental levels (>15 μmol/L). Being heterozygous for both alleles carried a slightly elevated risk of higher homocysteine levels after N₂O compared to patients who were wt/wt or het/wt. We did not observe patients with a double homozygous mutation or the combination hom/het. Baseline patient characteristics and creatinine and albumin levels among the groups did not differ.

Conclusions: Our results show that patients carrying a homozygous mutation (677C>T and 1298 A>C) in the *MTHFR* gene are at a higher risk of developing abnormal homocysteine levels after N₂O anesthesia.

