Homocysteine Levels After Nitrous Oxide Anesthesia for Living-Related Donor Renal Transplantation: A Randomized, Controlled, Double-Blind Study

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ABSTRACT

Background. Nitrous oxide anesthesia increases postoperative homocysteine concentrations. Renal transplantation candidates present with higher homocysteine levels than patients with no renal disease. We designed this study to investigate if homocysteine levels are higher in subjects receiving nitrous oxide for renal transplantation compared with subjects undergoing nitrous oxide free anesthesia.

Methods. Data from 59 patients scheduled for living-related donor renal transplantation surgery were analyzed in this randomized, controlled, blinded, parallel-group, longitudinal trial. Patients were assigned to receive general anesthesia with (flowmeter was set at 2 L/min nitrous oxide and 1 L/min oxygen) or without nitrous oxide (2 L/min air and 1 L/min oxygen). We evaluated levels of total homocysteine and known determinants, including creatinine, folate, vitamin B_{12}, albumin, and lipids. We evaluated factor V and von Willebrand factor (vWF) to determine endothelial dysfunction and creatinine kinase myocardial band (CKMB)-mass, troponin T to show myocardial ischemia preoperatively in the holding area (T1), after discontinuation of anesthetic gases (T2), and 24 hours after induction (T3).

Results. Compared with baseline, homocysteine concentrations significantly decreased both in the nitrous oxide (22.3 ± 16.3 vs 11.8 ± 9.9; $P < .00001$) and nitrous oxide-free groups (21.5 ± 15.3 vs 8.0 ± 5.7; $P < .0001$) at postoperative hour 24. The nitrous oxide group had significantly higher mean plasma homocysteine concentrations than the nitrous oxide-free group ($P = .021$). The actual homocysteine difference between groups was 3.8 μmol/L.

Conclusion. This study shows that homocysteine levels markedly decrease within 24 hours after living-related donor kidney transplantation. Patients receiving nitrous oxide have a lesser reduction, but this finding is unlikely to have a clinical relevance.

HOMOCYSTEINE is a sulphur-containing amino acid derived from the essential amino acid methionine [1]. The remethylation pathway of homocysteine regenerates methionine by methionine synthase that requires active forms of folate and vitamin B_{12} as cofactors [1,2]. Nitrous oxide irreversibly inactivates vitamin B_{12} and, as a consequence, inhibits methionine synthase [3,4]. Several prospective, randomized studies have documented that nitrous

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oxide anesthesia increases postoperative mean plasma homocysteine levels in a time and dose dependent manner in patients without hyperhomocysteinemia [5–9].

Renal impairment is characterized by elevated plasma levels of homocysteine [10–12] and renal transplant candidates present with elevated homocysteine concentrations [13]. Hyperhomocysteinemia is a strong predictor of cardiovascular disease or mortality in renal transplant recipients [14–16]. Annual mortality from cardiovascular disease is $\leq$46 times greater than the age-matched controls in the general population [15]. The high incidence of atherosclerotic events cannot be explained by only well-known risk factors for ischemic heart disease, such as diabetes, hypertension, and hyperlipidemia [17,18]. The importance of a novel risk factor such as hyperhomocysteinemia emerge from data that some renal transplant recipients have none of the more traditional risk factors but still die [19,20].

Tsukahara et al [21] have cautioned against the use of nitrous oxide anesthesia and mentioned that it may exacerbate hyperhomocysteinemia in patients with renal impairment. No studies have documented to what extent the plasma concentrations of homocysteine are elevated in patients with chronic renal disease after nitrous oxide anesthesia. Nitrous oxide–induced increases may be particularly important in renal transplant recipients because nitrous oxide–induced homocysteine levels have been associated with an increased risk for perioperative myocardial ischemia [9].

We designed this prospective, randomized, controlled study to investigate our hypothesis, namely that patients undergoing renal transplantation receiving general anesthesia with nitrous oxide develop higher homocysteine concentrations compared with patients who receive a nitrous oxide-free anesthesia.

MATERIALS AND METHODS

Study Design and Patient Population

Living-related donor renal transplant patients were enrolled in this randomized, controlled, blinded, parallel-group, longitudinal trial with concealed allocation (1:1) using sealed opaque envelopes randomization. After obtaining Ministry of Health Review Board approval, 112 patients scheduled for living-related renal transplantation were assessed for eligibility between November 2010 and July 2011, until 30 patients for the 2 groups were reached. All patients giving written informed consent, >18 years of age, and with a body mass index of >16 kg/m^2 were included in the study. Patients with known contraindication to the use of nitrous oxide, with known serious cardiac disease or taking drugs that are known to affect plasma homocysteine levels (penicillamine, methotrexate, azaurodine, isoniazid, cycloserin, phenelzine, procarbazine) were excluded from the study. Patients with familial hyperhomocysteinemia, who received general anesthesia within a month, who refused to participate in the study, and whose surgery started when the laboratory staff or study persons were unavailable were also excluded.

Allocation and Randomization

Eligible patients fulfilling inclusion criteria were enrolled (Fig 1). An anesthesia nurse randomized the patients to 1 of 2 groups (nitrous oxide group as 1 and nitrous oxide-free group as 2).

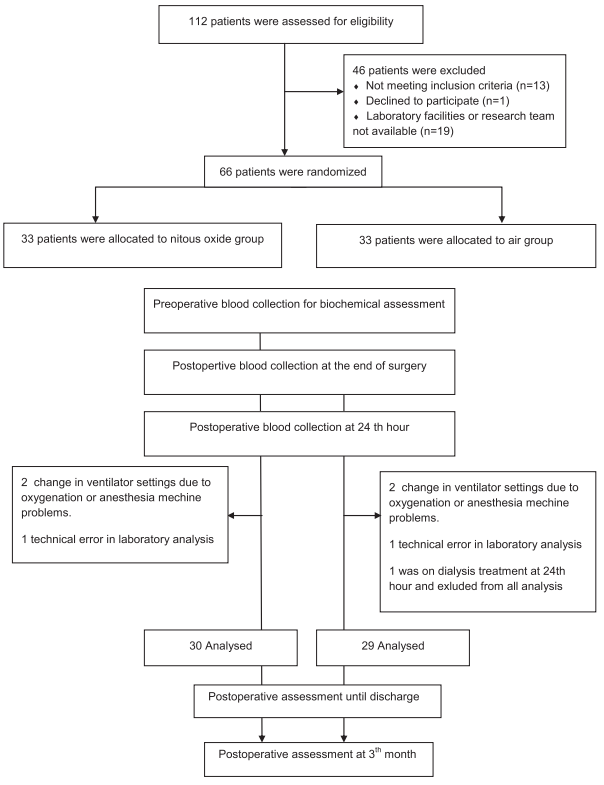

Fig 1. Study flow diagram.

Blinding

Patients, anesthetist, surgical staff, all research staff, and laboratory personnel were blinded to group assignment. The same technician set the ventilator flowmeter according to randomization and then covered the flowmeter with carbon paper.

Preoperative Evaluation and Intraoperative Interventions

Patient demographics, age, height, weight, gender, smoking habits, alcohol and coffee consumption, past dialysis history, and comorbid diseases (eg, hypertension and diabetes) were recorded. Patients taking vitamin B and folic acid were recorded. All patients received the same standardized general anesthetic regimen; in the nitrous oxide group flowmeter was set to 2 L/min nitrous oxide and 1 L/min oxygen after induction of anesthesia and until completion of surgery. In the nitrous oxide-free group (control), the flowmeter was set to 2 L/min air and 1 L/min oxygen. All patients otherwise received standard anesthetic care and monitoring. Anesthetic depth was adjusted according to clinical judgment. All other medications and fluid administration for renal transplantation surgery were according to the standard practice.

Intraoperative Recordings

Total opioid (fentanyl) and total muscle relaxant (cisatracurium) and estimated average inspired desflurane concentrations were recorded. Anesthesia and surgery times were also recorded.

Blood Samples Collection and Biochemical Analysis

Blood samples were collected from an antecubital vein 3 times: preoperatively in the holding area, after discontinuation of