Anesthetic Management of a Parturient with Hyperhomocysteinemia

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High plasma levels of homocysteine are associated with an increased risk for thromboembolic events. Neuraxial anesthesia techniques may be relatively contra-indicated in anticoagulated patients, and nitrous oxide may exacerbate the condition by inhibiting the conversion of homocysteine to methionine. We describe the anesthetic implications and management of a patient with hyperhomocysteinemia undergoing an nonemergent cesarean delivery.

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Hyperhomocysteinemia and its correlation with vascular occlusive diseases and thrombosis has been extensively studied.[1] High levels of plasma homocysteine are associated with vascular injury via mechanisms of oxidative damage, vascular smooth muscle proliferation, promotion of platelet activation and aggregation, and disruption of normal procoagulant–anticoagulant balance favoring thrombosis.[2] Physiologic changes of pregnancy also induce a state of relative hypercoagulability.[3] The risk of venous thromboembolism is increased four-fold during pregnancy.[4] The conventional treatment of hyperhomocysteinemia includes folate supplementation, usually with vitamin B_6 or B_{12}.[5] Although vitamin supplementation is successful in decreasing total plasma homocysteine levels, anticoagulation therapy is required to prevent vascular occlusive pathology. The hypercoaguable state produced by homocysteinemia, and subsequent anticoagulation therapy, create a unique anesthetic circumstance that must be carefully managed. We present a case report of a pregnant patient with homocysteinemia, and describe the anesthetic implications in the peripartum period.

CASE REPORT

A 34-yr-old, G_1P_0 parturient at 39 wk of gestation, ASA physical status III, 100 kg, 180 cm, with a Mallampati class II airway, was admitted to the hospital for increased arterial blood pressure, gestational diabetes, and history of hyperhomocysteinemia.

Hyperhomocysteinemia and blindness in the right eye secondary to central retinal vein thrombosis were diagnosed 3 yr earlier. She was begun on enoxaparin, and genetically tested negative for methylene tetrahydrofolate reductase (MTHFR) mutations C677T and A1298C. During pregnancy, the patient was continued on 40 mg enoxaparin twice-daily, and daily doses of folic acid, and vitamins B_{12} and B_6. Her homocysteine level was 17 μmol/L (normal <12 μmol/L) at 4 wk and 3 μmol/L at 30 wk of the pregnancy.

Three weeks before admission the patient was switched to subcutaneous unfractionated heparin 5000 U BID. Heparin was discontinued on admission. After admission, the decision was made to induce labor because of increased arterial blood pressure and class A diabetes. No labor analgesia was administered. After a failed induction of labor, a decision was made to proceed with nonemergent cesarean delivery. Preoperative laboratory examination revealed a platelet count of 157 × 10^9/L, prothrombin time 11.3 s, activated partial thromboplastin time 27.4 s, international normalized ratio 0.7, hemoglobin 11.8 g/dL, and hematocrit 34.1%. Heparin had been discontinued for 3 days. Spinal anesthesia was induced without complications. Her estimated intraoperative blood loss was 650 mL. A live infant was delivered with Apgar scores of 9 and 9 at 1 and 5 min, respectively. The patient had an uneventful recovery and prophylactic heparin 5000 U SQ BID was started 24 h postoperatively. The patient was discharged home on postoperative day 2.

DISCUSSION

Homocysteinemia is defined as an elevation of homocysteine levels in the blood. Plasma levels of homocysteine are controlled by two distinct metabolic pathways. Homocysteine may be salvaged to methionine by remethylation, or degraded to cysteine by trans-sulfuration (Fig. 1).[6] Homocysteine may acquire a methyl group from either N-5-methyltetrahydrofolate (MTHF) or from betaine to reform methionine (Fig. 1). Remethylation to methionine is catalyzed by the ubiquitous enzyme, methionine synthase (MS). This enzyme uses vitamin B12 (methycobalamin) as a cofactor, and MTHF as methyl donor. MTHF is formed from folic acid by the enzyme,
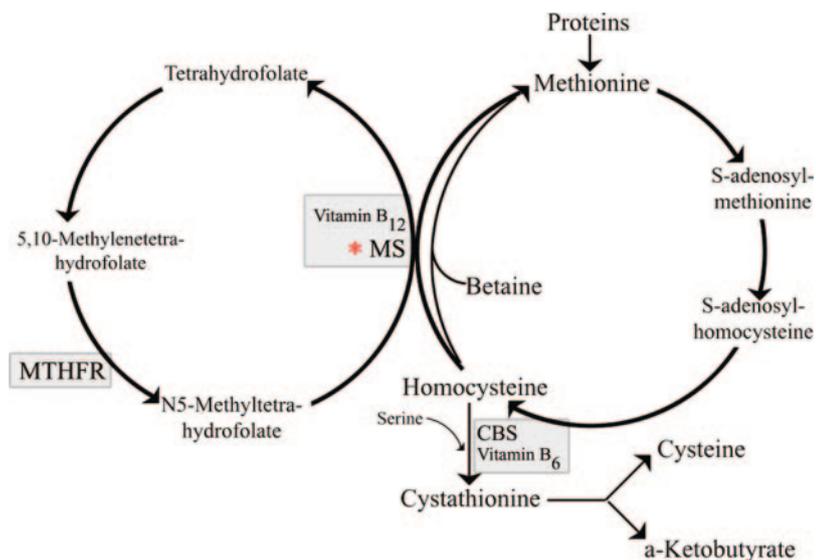
Figure 1. The metabolic pathway of homocysteine. Homocysteine may be remethylated to form methionine by a folate-dependent reaction that is catalyzed by methionine synthase (MS), a vitamin B_{12}-dependent enzyme, or via betaine. Alternately, homocysteine may be metabolized to cystathionine in a reaction catalyzed by a vitamin B_6-dependent enzyme, cystathionine β-synthase (CBS). * indicates the inhibitory site of action of nitrous oxide. MTHFR = methylenetetrahydrofolate reductase.

5,10-methylene tetrahydrofolate reductase (MTHFR). Homocysteine is diverted to the trans-sulfuration pathway when methionine concentrations exceed the capacity of the methionine cycle or when the synthesis of cysteine is required.[7] Cystathionine β-synthase (CBS) and vitamin B_6 are required for trans-sulfuration.[6] CBS catalyzes the union of homocysteine and serine to form cystathionine. Cystathionine is hydrolyzed to form cysteine and α-ketobutyrate.

The accumulation of homocysteine and its metabolites is caused by a disruption of any of the required enzymes or cofactors involved in the pathways of methionine metabolism. These abnormalities could arise from genetic predisposition and/or nutritional and environmental factors. The most common cause of homocysteinemia, encompassing 95% of the patients, is a deficiency of the cofactor pyridoxine (vitamin B_6), folate, cobalamin (vitamin B_{12}), or the enzyme CBS.[7] The resulting hyperhomocysteinemia is mild to moderate. Genetic abnormalities in MTHFR impair the synthesis of MTHF. MTHFR defects result in severe increases in plasma homocysteine, up to 100 μmol/L, and are associated with symptoms such as motor and gait abnormalities, seizures, and psychiatric manifestations. However, compared with vitamin B_6 or B_{12} deficiencies, MTHFR abnormalities are a far less common cause of hyperhomocysteinemia.[1] There are more than 20 mutations in the MTHFR gene; most are not associated with an increase in homocysteine levels. The two most common polymorphisms are C677T and A1298C. Because of this, genetic testing for MTHFR mutations generally encompasses these two polymorphisms. Our patient tested negative for both the C677T and A1298C MTHFR mutations. Unfortunately, she was not tested for the other MTHFR mutations or for mutations in other enzymes required for methionine metabolism, such as CBS. Most likely, our patient's homocysteinemia was caused by a vitamin or MS deficiency. Other reasons for hyperhomocysteinemia

are renal or liver diseases, diabetes, psoriasis, cancer, and smoking.

Homocysteine plasma levels above 10 μmol/L are associated with a doubling of vascular risk.[8] The increase in risk is a result of homocysteine acting as an atherogenic, thrombophilic amino acid that increases procoagulant activity.[9] Plasma levels over 12 μmol/L should be treated aggressively with folic acid supplementation.[10] Initiation of therapy with B_{12}, folic acid, and B_6 tends to normalize homocysteine levels in 4–8 wk. In fact, maternal homocysteine levels decline almost by half in pregnant compared with nonpregnant women due to hemodilution,[11] changes in endocrinology resulting in increased MS activity,[12] and vitamin supplementation.[13] Four weeks into her pregnancy, our patient had a homocysteine level of 17 μmol/L, and at 30 wk gestation her homocysteine level was 3 μmol/L.

Our patient also had a history of retinal vein thrombosis. Fifteen to 25% of thromboembolic events in pregnancy are recurrent events. However, the risk of recurrent thromboembolism is significantly reduced in women who receive thromboprophylaxis.[14] The preferred agents for anticoagulation in pregnancy are heparin compounds.[15] Neither heparin nor low-molecular-weight heparin (LMWH) crosses the placenta, and both are considered safe for pregnancy.[16,17] Women are often converted from LMWH to unfractionated heparin at 36–37 wk of gestation because the therapeutic half-life of unfractionated heparin is less than LMWH.

Neuraxial blockade is relatively contraindicated in patients receiving anticoagulant therapy. The American Society of Regional Anesthesia and Pain Medicine convened its second Consensus Conference on Neuroaxial Anesthesia and Anticoagulation in 2002 and concluded that subcutaneous (mini-dose) thrombophylaxis with unfractioned heparin does not contraindicate the use of neuraxial anesthetic techniques.[18]

Although general anesthesia was not administered to our patient, we feel that it is important to discuss the anesthetic issues related to the use of nitrous oxide (N_2O) in a hyperhomocysteinemic patient. N_2O irreversibly inhibits MS, thus slowing the conversion of homocysteine to methionine, acutely increasing the level of homocysteine, and further reducing the level of methionine (Fig. 1).[19] In other words, N_2O administration exacerbates homocysteinemia and, as a result, impairs endothelial function and promotes procoagulant activity, such as platelet adhesiveness, factor V activation, protein C inhibition, and antithrombin and plasminogen activator binding.[20,21,22] In a randomized, prospective study, N_2O anesthesia caused a 12–24 μmol/L increase in postoperative plasma homocysteine levels in patients without hyperhomocysteinemia.[22] Zanardo et al.[23] measured plasma homocysteine levels in 50 consecutive women undergoing either vaginal delivery or elective caesarean delivery under N_2O general anesthesia. Plasma homocysteine levels were significantly higher in both the maternal and umbilical venous plasma of women who delivered by cesarean compared with those who delivered vaginally. This suggests a transplacental inhibitory effect of N_2O on methionine metabolism[23] or a small maternal–fetal homocysteine gradient in late pregnancy. Malinow et al.[24] hypothesized that maternal homocysteine crosses the placenta to the fetus and may be involved in a number of metabolic reactions required for fetal development.[24]

The effect of N_2O anesthesia and postoperative plasma homocysteine levels on myocardial ischemia were evaluated in a randomized controlled trial by Badner et al.[22] Patients undergoing carotid endarterectomy were monitored for ischemic events with a three-channel Holter monitor. The investigators found an association between elevated homocysteine levels and a significantly increased incidence and duration of postoperative ischemia in the patients treated with N_2O.[22]

Theoretically, the use of N_2O in a patient with hyperhomocysteinemia or severe cobalamin deficiency could also result in a functional disorder of the nervous system because of an extreme methionine deficiency in the brain. The activated form of methionine, S-adenosylmethionine, is the principal substrate for methylation in many biochemical reactions, including assembly of the myelin sheath, methyl substitutions in neurotransmitters, and DNA synthesis in rapidly proliferating tissues.[25] Several cases of N_2O-induced exacerbation of vitamin B_{12} deficiency syndrome that resulted in neurological deterioration in adults have been reported.[26–31] In one report, a 40-yr-old man with a history of hyperhomocysteinemia had a combined total N_2O exposure of 11 h during evaluation and management of right lower-limb arterial insufficiency.[28] Four weeks after exposure to N_2O, this patient exhibited severe sensorimotor deficits that were improved with vitamin B supplementation.[28] Selzer

et al.[19] reported the neurologic deterioration and death of a child who was diagnosed with heterozygous MTHFR polymorphisms, C677T and A1298C, as well as the heterozygote substitution G1775A, after being anesthetized twice with N_2O. An autopsy showed asymmetric cerebral atrophy and severe demyelination, with astrogliosis and oligodendroglial-cell depletion in the midbrain, medulla, and cerebellum. Two additional case reports describe infants with severe cobalamin deficiencies who experienced neurological impairment after a single exposure to N_2O[32,33] After repletion of cobalamin, the neurological conditions stabilized in both cases.[32,33]

In conclusion, this case report discusses several important anesthetic issues relevant to the management of pregnant patients with hyperhomocysteinemia, including peripartum anticoagulation and the theoretical risk of using N_2O.

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