Methylenetetrahydrofolate Reductase Deficiency: A Case Report

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Methylenetetrahydrofolate reductase (MTHFR) deficiency is an autosomal recessive disorder that results in hyperhomocysteinemia. Elevated homocysteine levels in the blood can cause arterial and venous thrombosis, atherosclerosis, recurrent pregnancy loss, and neurologic symptoms. Emerging research suggests links to other chronic illnesses as well. Anesthetic management of patients with MTHFR deficiency should focus on decreasing the risk of arterial or venous thrombosis and minimizing elevations in homocysteine levels. Thrombosis prevention includes the use of antiembolism compression stockings, intermittent pneumatic compression sleeves, subcutaneous heparin or low-molecular-weight heparin, early ambulation, and adequate hydration. Nitrous oxide is known to inhibit methionine synthase, a vitamin B12-dependent enzyme responsible for the breakdown of homocysteine, resulting in homocysteine elevation, and should be avoided in these patients. Intravenous vitamin B12 infusion before surgery may help decrease homocysteine levels; however, it is not readily available in most operating rooms. Propofol and sevoflurane do not increase homocysteine levels and are considered safe for patients with MTHFR deficiency. This case study describes a 58-year-old man with known MTHFR deficiency and his subsequent uneventful anesthetic care during a total knee replacement.

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homocysteine cannot be broken down into methionine. As a result, homocysteine levels begin to rise\(^1\) to \(^5\) (Figure 2). Elevated homocysteine levels cause inflammation of endothelial cells. Chronic inflammation of endothelial cells leads to vessel narrowing, hardening, and clotting.\(^3\),\(^6\),\(^7\) Two sequence variations (polymorphisms) of the \(\text{MTHFR}\) gene have been tested extensively by researchers: \(\text{C677T}\) and \(\text{A1298C}\).\(^2\),\(^5\) Individuals with these mutations have lower enzyme activity, higher homocysteine levels, and lower folate levels than those without this mutation. Elevated plasma levels of homocysteine can lead to thrombosis, atherosclerosis, myocardial infarction, and cerebrovascular accident. Individuals with homozygous \(\text{MTHFR}\) deficiency have a 3-fold to 6-fold increased risk of arterial or venous thrombosis compared with the rest of the population.\(^7\),\(^8\) It is estimated that greater than 25% of Hispanics, 10% to 15% of whites, and 6% of African Americans have homozygous \(\text{677C>T}\) (also called \(\text{TT}\) genotype or “thermolabile” variant).\(^9\)

Current research suggests a link between \(\text{MTHFR}\) deficiency and neural tube defects, dementia, osteoporosis, and colorectal cancer. There are many claims that chronic pain, diabetes, psychiatric illnesses, and other chronic illnesses may associated with \(\text{MTHFR}\) deficiency.\(^1\),\(^3\)-\(^5\) More research is needed to determine the link between \(\text{MTHFR}\) deficiency and chronic illness.

**Case Summary**

A 58-year-old man presented for a right total knee replacement. The patient weighed 134 kg and was 181.6 cm tall (body mass index = 40.57 kg/m\(^2\)). He had an allergy to a glucosamine supplement, resulting in hives. His medical history included hypertension treated with lisinopril, rheumatoid arthritis treated with adalimumab (Humira), laminectomy of L5-S1 performed in 2003, difficult intubation, and deep vein thrombosis (DVT) in his left leg in 2016. After the DVT, the patient was placed on a regimen of rivaroxaban (Xarelto) and underwent genetic testing since he had no known risk factors for the DVT. Genetic test results revealed factor V Leiden and \(\text{MTHFR}\) deficiency. After a discussion of the risks of surgery, the surgeon determined that rivaroxaban was to be withheld before surgery.

Laboratory studies, including a prothrombin time and international normalized ratio drawn the day of surgery, had normal results. A previous electrocardiogram (ECG) showed normal sinus rhythm with nonspecific T-wave abnormality. A review of the medical record revealed a previous difficult intubation, in which the prior anesthetist suggested use of a video laryngoscope for intubating this patient. He was assigned an ASA physical status 3. The anesthetic plan included general anesthesia with peripheral nerve block for pain management. Because of his history of \(\text{MTHFR}\) deficiency, nitrous oxide was to be avoided.

Before induction, the patient was given 2 mg of midazolam intravenously (IV) as sedation for a right femoral and sciatic peripheral nerve block. A total of 20 mL of 0.5% bupivacaine was used for the block. A 5-lead ECG, pulse oximeter, train-of-four monitor, and blood pressure cuff were applied to the patient according to standard protocol. Induction was achieved with 100 µg of fentanyl, 40 mg of lidocaine, 200 mg of propofol, and 160 mg of succinylcholine IV. A 7.5-mm endotracheal tube was placed easily using a video laryngoscope and was secured at 23 cm at the teeth; placement was confirmed with bilateral lung auscultation. Cefazolin, 3 g, was given IV within 30 minutes before incision. After induction, 1,000 mg of acetaminophen IV was administered.
dition, a total of 1 mg of hydromorphone IV was given for pain management. Anesthesia was maintained with sevoflurane and rocuronium. A few boluses of phenylephrine were required to keep the mean arterial pressure within 20% of baseline, for a total of 400 µg IV.

At the end of the case, neuromuscular blockade was reversed with 3 mg of neostigmine and 0.4 mg of glycopyrrolate IV. Intravenous famotidine (20 mg) and dexamethasone (8 mg) were given after induction, and 4 mg of ondansetron IV before reversal for prevention of postoperative nausea and vomiting. Vital signs were stable throughout the procedure. No ECG changes were noted.

The patient was successfully extubated and transported to the postanesthesia care unit. The patient’s hospital stay was uneventful, and he was discharged home 4 days later without complications.

Discussion

In the general population, the incidence of hyperhomocysteinemia is unknown. Most patients with hyperhomocysteinemia are heterozygous for multiple MTHFR substitutions. It is suggested that certain medications be avoided during anesthesia in patients with known MTHFR deficiency. One such drug is nitrous oxide. Nitrous oxide is commonly used during general anesthesia in the United States. Nitrous oxide is known to cause hyperhomocysteinemia because it inactivates cobalamin (vitamin B₁₂) through irreversible oxidation. Cobalamin-dependent methionine synthase is inhibited, impairing homocysteine breakdown, thus causing increased homocysteine levels. Vitamin B₁₂ infusion before exposure to nitrous oxide has theoretical benefits. A study conducted in 2014 by Kisarani et al. found that vitamin B₁₂ when infused before exposure to nitrous oxide significantly decreased homocysteine levels but when infused after exposure to nitrous oxide did not significantly reduce homocysteine levels. It is important to note this study was conducted with only IV and not orally or subcutaneously administered vitamin B₁₂. Halogenated and intravenous anesthetics are generally considered safe for MTHFR deficiency. Orhon et al. found both propofol and sevoflurane did not elevate homocysteine levels in children with MTHFR deficiency.

In our case, the focus was on the patient’s medical history and avoiding his risks involving the administration and management of anesthesia. Nitrous oxide was avoided because of an increased risk of hyperhomocysteinemia. We also carefully administered fluids and vasoressors to prevent extreme hemodynamic changes such as hypertensive or hypotensive events. The patient’s anesthetic care also involved attentiveness to the ECG and any potential change indicating ischemia or heart strain as well as monitoring ventilation and end-tidal carbon dioxide for signs of pulmonary embolism.

Generally, anesthetic management for patients with MTHFR deficiency should include the following:
- Avoid nitrous oxide.
- Prevent DVT.
- Monitor for signs and symptoms of pulmonary embolism, myocardial infarction, and cerebrovascular accident.
- Restart anticoagulant therapy when safe.

Conclusion

Methylenetetrahydrofolate reductase deficiency is an autosomal recessive disorder that results in elevated homocysteine levels. High levels of homocysteine in the blood can cause arterial and venous thrombosis,
Atherosclerosis, and neurologic symptoms. Anesthetic management of patients with MTHFR deficiency should focus on decreasing the risk of arterial or venous thrombosis and minimizing elevations in homocysteine levels. Thrombosis prevention includes the use of antiembolism compression stockings, intermittent pneumatic compression sleeves, subcutaneously administered heparin or low-molecular-weight heparin, early ambulation, and adequate hydration. Nitrous oxide is known to inhibit methionine synthase, a vitamin B12-dependent enzyme responsible for the breakdown of homocysteine, resulting in homocysteine elevation, and should be avoided. Intravenous vitamin B₁₂ preoperatively may help decrease homocysteine levels before exposure to nitrous oxide if it must be given. Propofol and sevoflurane do not increase homocysteine levels and are considered safe for patients with MTHFR deficiency.

As genetic testing becomes more commonplace, it is critical that healthcare providers become familiar with genetic disorders in order to properly care for their patients. As anesthesia providers, we must be knowledgeable and well informed of the multiple genetic disorders and their effects on anesthesia management. Although healthcare is ever-changing with the advancements in technology, the primary focus of high-quality, safe patient care remains unchanged.

REFERENCES

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DISCLOSURES
The authors have declared no financial relationship with any commercial entity to the context of this article. The authors did not discuss off-label use within the article.