Case Report

Methemoglobinemia in a Newborn: A Case Report

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Abstract: *The purpose of this report was to describe a case of methemoglobinemia involving different systemic complications as a result of local anesthetic injection with lidocaine in a 2-day-old female patient. Acquired methemoglobinemia is considered a major, potentially life-threatening complication. There are several reports of this complication related to anesthetic agents, most commonly prilocaine and benzocaine. It can involve patients of different ages, but it is more common in children 6-years-old and younger, particularly those younger than 3 months. Widely used in dental practices for pain management, lidocaine is considered to be one of the safest anesthetic agents. Although rare, complications of lidocaine administration need to be addressed properly, and adequate training in diagnosis and management of these complications should be provided. Providers should weigh the risk and benefit of using these agents. (Pediatr Dent 2011;33:252-4) Received December 21, 2009 / Last Revision March 10, 2010 / Accepted March 15, 2010*

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Acquired methemoglobinemia is an uncommon complication related to the use of local anesthetics and other substances. Methemoglobinemia can also be present in congenital form. Patients with a history of congenital methemoglobinemia are at greater risk of developing the acquired form; therefore, careful review of a patient's previous medical history could be the key to preventing the condition.[1] Methemoglobinemia is often reported in the preoperative period when topical anesthetics are used.[2] It has been reported during dental, surgical, and diagnostic procedures that require the use of local anesthetics, most commonly with anesthetics such as benzocaine and prilocaine.

Case report

A 2-day-old female infant twin was diagnosed with having a natal tooth in the maxillary anterior region at the neonatal intensive care unit, Steven and Alexandra Cohen Children's Medical Center of NY, New Hyde Park, NY. The patient's medical history included Rieger syndrome, congenital glaucoma, ventricular septal defect, and atrial septal defect with no history of congenital methemoglobinemia or related enzyme disorder. She weighed 2,540 grams and had a hemoglobin level of 21 (19.3+2.2 g/dl) 1 day prior to the treatment. White blood cell counts were slightly lower than normal. Other laboratory values and vital signs were within normal limits. The natal tooth in the maxillary anterior region was attached to a vascular bulbous tissue (size=2-3 mm) at the gingival level. Prior to extraction, the patient received 0.5 ccs of 2% lidocaine 1:100,000 epinephrine via local injection to manage pain and control hemorrhage. The tooth was extracted with no complications and hemostasis achieved. The patient was observed for approximately 20 minutes and had no signs of complications.

Approximately 1 hour after the procedure, cyanosis was observed, and the patient was diagnosed with methemoglobinemia. The patient was immediately treated with 100% oxygen and 0.7 mg intravascular methylene blue (0.3 mg/kg) over 5 minutes. The patient was observed thereafter and had no recurrence of the complication. Her methemoglobin level was measured at approximately 53% during the incident and was measured again at 17% 30 minutes later and 0.5% 24 hours after treatment with methylene blue. Her hemoglobin level was measured at 19.5 1 day later. The patient was evaluated, followed-up with for other medical conditions, and discharged at a later date.

Discussion

Methemoglobinemia is a condition in which the iron within hemoglobin is oxidized from ferrous to ferric form ($Fe2+ \rightarrow Fe3+$), resulting in the inability of hemoglobin to transport oxygen and carbon dioxide. Clinical features of the condition are cyanosis and hypoxia, with dark blue appearance of the skin. It could be diagnosed with cyanosis of the oral mucosa in dark-skinned patients. Methemoglobinemia could happen at any age, but it is more common in children and patients with a history of the condition or enzyme deficiency. There are 2 forms of methemoglobinemia: (1) congenital; and (2) acquired.

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In the congenital form, which is an autosomal recessive disorder, methemoglobinemia is divided into 2 categories:

1. the altered form of hemoglobin (hemoglobin M) which involves an amino acid substitution near the heme pocket that affects the heme-globin bond, resulting in an oxidized form of hemoglobin which resists reduction; and
2. 2 different enzyme deficiencies which involve the NADH cytchrome b5 reductase deficiency and glucose-6-phosphate dehydrogenase (G6PD) deficiency in the hexose monophosphate shunt as an alternative pathway.[3]

G6PD enzyme deficiency per se is not the cause of methemoglobin, but rather it may cause a poor response to treatment with methylene blue as the primary source of NADPH in the process of reducing methemoglobin.[4] Patients with the congenital form of methemoglobinemia are generally asymptomatic, other than cyanosis. Life expectancy is normal, unless the methemoglobin levels are above 25% to 40%. In the acquired form, methemoglobinemia occurs as the result of exposure to local anesthetic agents or other substances.

Oxidant agents oxidize the iron in hemoglobin, causing methemoglobinemia.[2] Benzocaine, prilocaine, nitric oxide, sulfanamides, aniline dyes, antimalarials, and dapson are considered high risk.[1] Lidocaine, mepivacaine, articaine, bupivacaine, etidocaine, aspirin, acetaminophen, and nitrous oxide are considered substances with moderate risk of inducing methemoglobinemia. In particular, patients with heart disease, anemia, age younger than 3 months, and G6PD and NADH reductase deficiencies, as well as the elderly, are considered to be at increased risk of developing methemoglobinemia.[3] Methemoglobin levels in blood are in the normal range of 1%. It could increase to very high levels, however, when there is exposure to the previously mentioned substances.

Methemoglobin blood levels of 10% to 20% are usually tolerated with no clinical signs. Levels of 30% to 40% and above are associated with headaches, dyspnea, dizziness, acidosis, arrhythmias, seizures, and comas. Levels of 70% and above are often fatal.[3] Lidocaine is considered one of the safest anesthetics used in dental practice. Combination products containing prilocaine and lidocaine have a low risk when used for dental analgesia.[3] In a study, elevation of methemoglobin levels after administration of intravenous lidocaine were shown to be statistically but not clinically significant.[7] There have been 12 methemoglobinemia episodes related to lidocaine without association of prilocaine or benzocaine.[6] In children older than 6 months, plain prilocaine (at doses greater than 2.5 mg/kg) can induce clinically symptomatic methemoglobinemia.[6] A single spray of benzocaine may do the same.

In the reviewed studies, after using topical benzocaine and ELMA (lidocaine-prilocaine) cream, methemoglobinemia was a common complication—particularly in children and infants. Rebound methemoglobinemia (benzocaine on mucous membranes) can happen up to 18 hours after methylene blue administration.[6] Treatment includes administration of 100% oxygen as the first step. Methemoglobin levels of greater than 30% may require intravenous methylene blue administration up to 1 to 2 mg/kg as a 1% solution over 5 minutes; it may be repeated in 1 hour if necessary.

Methylene blue is an oxidant at levels greater than 7 mg/kg and, therefore, may worsen the condition. Hence, care must be taken when administering this drug. Methylene blue is contraindicated in G6PD deficiency patients because it can lead to severe hemolysis. Administration of oral ascorbic acid (200-500 mg) as an antioxidant also may help with reducing methemoglobin. Progressive studies have shown that N-acetylcysteine will reduce methemoglobin, but it is not yet approved for treatment of this condition. In severe cases, exchange transfusion may be necessary.

Even though lidocaine-induced methemoglobinemia is a relatively rare malady, clinicians should be aware of this condition to ensure prompt diagnosis and effective treatment. Consultation with other specialists, such as hematologists, cardiologists, and pulmonologists, may be required to assist in the search for the cause and investigation of a previous history of methemoglobinemia. Although neuroanatomic structures necessary for transmission of pain impulses are present in the fetus, immaturity in the pathways for transmission of the impulse and lack of inhibitory processes for such suggest that the infant may even be hyperalgesic. Because of "plasticity" or changeability of the nervous system of the infant and young child, insults during this time period may negatively alter the final architecture of their adult pain system. After all, pain management for young infants remains suboptimal. There is need for more research to determine the risk and benefit management of using anesthetics in infants.

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