

Case Report

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The circumcision blues: a case report with literature review

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ABSTRACT

An 11-day-old Caucasian male developed acquired methemoglobinemia as a result of repeated exposure to topical lidocaine/prilocaine cream following a circumcision. Our patient responded well with treatment of a single dose of intravenous (IV) methylene blue. Methemoglobinemia is a rare but well-explained complication of local anesthetics. It is important for providers to prescribe local anesthetics safely to avoid serious complications, especially with neonates who are at higher risk of developing methemoglobinemia.

Keywords: Methemoglobinemia, Local anesthetics, Circumcision

INTRODUCTION

Methemoglobinemia is a rare condition presenting as cyanosis due to an elevated concentration of methemoglobin in the circulation. Oxygen delivery to the tissues is impaired as this form of oxidized hemoglobin cannot reversibly bind oxygen. Methemoglobinemia can be congenital or acquired. Acquired methemoglobinemia is more common and typically occurs from exposure to specific drugs or agents that cause an increase in the production of methemoglobin.¹ Local lidocaine/prilocaine cream, sometimes used in ambulatory circumcision procedures, can occasionally cause methemoglobinemia, especially in neonates.² Proper dosing and administration guidelines should be strictly followed. Providers should also be aware of complications associated with treatment or methemoglobinemia.

CASE REPORT

An 11-day-old term 3800 gram (g) Caucasian male infant presented to the emergency department with a one-day history of maternal concerns of drowsiness, decreased

alertness, and blue discoloration of the lips and fingernails. He was born via vaginal delivery with no perinatal complications. The infant passed critical congenital heart disease screening in the newborn nursery and had a normal newborn screen. The infant had no feeding issues or color changes. No history of fever or respiratory distress was reported. The infant was circumcised two days earlier on day of life 9. A 30 g tube of topical ointment consisting of 2.5% lidocaine-2.5% prilocaine was prescribed by the obstetrician with instructions to apply to the circumcision site with each diaper change. The mother reported liberal application of the ointment to the circumcision site using about half of the tube in the two days following the procedure (about 15 g, or approximately 100 mg/kg each of lidocaine and prilocaine).

On physical examination, mild tachypnea with a respiratory rate of 58 breaths/minute was noted. Room air oxygen saturation was 88%. Cyanosis was noted to the lips, nose, tongue, and extremities. Cardiovascular examination revealed a regular rate and rhythm. No murmur was noted, and normal peripheral perfusion was noted. Lungs were clear to auscultation bilaterally.

Laboratory evaluation showed normal venous blood gas, with pH of 7.4 (normal range 7.32-7.42), PCO₂ of 41.5 mmHg (41-51), PO₂ of 35 mmHg (35-45), bicarbonate of 25.8 mmol/L (24-28), BE of 1 mmol/L (-3-3). A complete blood count and complete metabolic panel results were normal. Methemoglobin level was 22.1% (0-3%) and oxyhemoglobin of 66.5% (92-100%) measured by co-oximetry. His electrocardiogram showed normal sinus rhythm with no dysrhythmia or abnormality.

Patient received 2 L of supplemental oxygen via oxygen mask with improvement in SpO₂ to 94%. The regional poison control center was contacted and recommended administration of intravenous (IV) methylene blue. The infant received methylene blue (1 mg/kg) via IV push in the emergency department. His cyanosis resolved and SpO₂ improved to 96%. The patient continued to receive supplemental oxygen at 2 L/min via simple mask and was admitted to pediatric intensive care unit (PICU) for continued observation and ongoing treatment. The infant continued to do well with no rebound cyanosis noted. Repeat co-oximetry measurement six hours after administration of IV methylene blue showed an oxyhemoglobin level of 84.6% and methemoglobin level of 2.8%. Oxygen therapy was weaned to ambient air and the infant was discharged from PICU 12 hours after admission. The mother was instructed to apply petroleum jelly instead of lidocaine/prilocaine cream to circumcision site prior to discharge.

Table 1: Medications commonly implicated in acquired methemoglobinemia.¹⁶

Dapsone
Local anesthetics (benzocaine, lidocaine, prilocaine)
Nitric oxide, nitrous oxide
Nitrites (amyl nitrite)
Nitrates (nitroglycerin, sodium nitrate)
Phenazopyridine
Quinones (chloroquine, primaquine)
Sulfonamides (including sulfamethoxazole)
Sodium nitroprusside

DISCUSSION

Methemoglobin is a form of hemoglobin that has been oxidized, changing its heme iron configuration from the ferrous (Fe²⁺) to the ferric (Fe³⁺) state. Unlike normal hemoglobin, methemoglobin cannot reversibly bind oxygen and as a result oxygen delivery to the tissues is compromised.³ Methemoglobin levels are physiologically kept below 2% of total hemoglobin primarily by the reduced nicotinamide adenine dinucleotide (NADH) dependent cytochrome-b5 reductase system and reduced nicotinamide adenine dinucleotide phosphate (NADPH)-methemoglobin reductase.¹ Clinically significant methemoglobinemia occurs when there is an imbalance between the formation and reduction of methemoglobin.⁴

Methemoglobinemia may arise from genetic, dietary, or idiopathic etiologies, but most commonly results from exposure to an oxidizing agent.¹

Methemoglobin levels between 10% and 30%, may result in cyanotic skin discoloration, anxiety, headache, weakness, tachycardia, dizziness, and lethargy. When methemoglobin levels are elevated to more than 45%, neurological and cardiovascular symptoms such as malaise, fatigue, dyspnea, chest pain, heart failure, seizures, and coma can occur. Shock, respiratory, central nervous system depression, and death can occur with methemoglobin levels reaching 60% of total hemoglobin.^{5,6}

In our patient, methemoglobinemia was caused by repeated application of excessive topical 2.5% lidocaine-2.5% prilocaine cream following a circumcision. Topical anesthetic agents are one of the most common medications that cause acquired methemoglobinemia. Four types of local anesthetic agents have been reported as causing methemoglobinemia: prilocaine, benzocaine, lidocaine, and tetracaine.⁷ Prilocaine and lidocaine ointment used as a local anesthetic agent is occasionally prescribed following ambulatory circumcision procedures. Providers should be mindful of side effects when prescribing topical prilocaine/lidocaine preparations for pain control. There are limited case reports in the literature of term infants developing methemoglobinemia after lidocaine/prilocaine application on the prepuce.⁸⁻¹¹ Though rare, a high methemoglobin concentration can occur after lidocaine/prilocaine application on the prepuce. When following dosing and administration guidelines established by the manufacturer, the use of topical lidocaine/prilocaine cream in pediatric patients is usually uneventful.¹² However, excessive amounts of lidocaine/prilocaine applied to a large surface area, prolonged application time, repeated application, or administration over non-intact skin, can cause methemoglobinemia with clinical symptoms, especially in infants. When used for analgesia in the setting of circumcision, the American Academy of Pediatrics suggests 1 to 2 g of lidocaine/prilocaine may be applied to the prepuce and covered with an occlusive dressing for 60 to 90 minutes prior to procedure.¹³ The instructions provided by the manufacturer recommend individualized dosing based on age and weight and do not include recommendations for repeat dosing.¹⁴

Methemoglobinemia secondary to local anesthetic exposure is a well-documented complication, most frequently associated with benzocaine.¹⁵ Benzocaine is a commonly used topical anesthetic agent found in over the counter medications to treat teething. Benzocaine is metabolized to aniline, which is then further metabolized to phenylhydrazine and nitrobenzene, which are potent oxidants.¹⁶ Lidocaine and its metabolites are weaker oxidants than benzocaine and its metabolites, and methemoglobinemia due to lidocaine alone is a relatively rare occurrence.⁵ Prilocaine is a local anesthetic agent

found in eutectic combination with lidocaine for topical use, but is an aniline derivative that metabolizes to o-toluidine, an oxidizing agent. When used for subcutaneous infiltration, the maximum allowable subcutaneous dose of lidocaine and prilocaine is 4.5 mg/kg and 8 mg/kg, respectively.¹⁶

Initial management of methemoglobinemia includes withdrawal of the triggering substance and supportive care. Common pharmacologic agents causing methemoglobinemia are listed in Table 1. Supplemental oxygen should be administered immediately and titrated to optimize oxygen delivery via non-oxidized hemoglobin. Methylene blue, the treatment of choice for methemoglobinemia, is converted in vivo by NADPH methemoglobin reductase to leukomethylene blue, a potent reducing agent that converts methemoglobin back to its non-oxidized form. Methylene blue may be administered to a symptomatic patient with a methemoglobin level less than 20% or an asymptomatic patient with a methemoglobin level greater than 30%.¹⁷ Initial dosing of methylene blue for the treatment of methemoglobinemia is 1-2 mg/kg given intravenously over about five minutes, with peak effects expected within 30 minutes. The dose may be repeated when the cause of methemoglobinemia is a medication such as dapsone, which may have prolonged elimination and contribute to ongoing production of methemoglobinemia.^{24,25} Caution should be exercised with use in patients receiving concomitant serotonergic agents, as methylene blue may precipitate serotonin syndrome in those patients due to inhibition of monoamine oxidase.^{25,26}

Most individuals have rapid clinical improvement following methylene blue administration with reduction of methemoglobin levels to <10% within 10 to 60 minutes. However, treatment with methylene blue can be complicated by the presence of underlying enzyme deficiencies, such as glucose-6-phosphate dehydrogenase (G6PD) deficiency. Patients with G6PD deficiency have an impaired ability to produce NADPH. This affects the reduction of methylene blue to leukomethylene blue, which is needed to reduce the iron component of hemoglobin from its ferric to ferrous state. Furthermore, G6PD-deficient patients may be more susceptible to methylene blue-induced hemolysis. Ascorbic acid has been used to treat methemoglobinemia with varying success, including pediatric patients and patients with G6PD deficiency, or in settings with limited access to methylene blue. Optimal dosing for this indication has not been determined.^{3,18-21} A detailed past medical history and family history is important prior to initiating treatment with methylene blue.

Clinicians should be aware that certain patient populations are at higher risk for developing methemoglobinemia. Neonates are more susceptible to developing methemoglobinemia because fetal hemoglobin is more easily oxidized than adult-type hemoglobin. Young infants have lower levels of cytochrome-b5 reductase in their red

blood cells during the first four months of life, and underdeveloped hepatic and renal function, resulting in a lower capacity to reduce methemoglobin.^{1,5} These risk factors combined with reconstitution of formula with well water high in nitrates in some areas are another common source of methemoglobinemia in infants and younger children. American Eskimo and Indian populations are known to have hereditary methemoglobinemia.²² This recessive trait is likely due to absence of an enzyme or other factors necessary for complete reduction of hemoglobin.²³

CONCLUSION

Topical anesthetic agents are one of the most commonly-implicated medications that can cause acquired methemoglobinemia. Providers should follow proper dosing and administration guidelines. Clinicians should be aware that certain patient populations such as neonates and infants are at higher risk for developing methemoglobinemia. Patients with G6PD-deficiency may be more susceptible to methylene blue-induced hemolysis. Methylene blue may precipitate a serotonin syndrome due to inhibition of monoamine oxidase in those patients taking serotonergic agents. Prompt recognition and treatment of methemoglobinemia is essential to restore oxygen delivery and avoid serious complications from tissue hypoxia.

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REFERENCES

1. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. Ann Emerg Med. 1999;34(5):646-56.
2. Taddio A, Ohlsson A, Einarson TR, Stevens B, Koren G. A systematic review of lidocaine-prilocaine cream (EMLA) in the treatment of acute pain in neonates. Pediatrics. 1998;101(2):E1.
3. Prchal J. Methemoglobinemia. 2020. Available at: https://www.uptodate.com/contents/methemoglobinemia?search=methemoglobinemia&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Last accessed on 25 May 2020.
4. Maran J, Guan Y, Ou CN, Prchal JT. Heterogeneity of the molecular biology of methemoglobinemia: a study of eight consecutive patients. Haematologica. 2005;90:687.
5. Barash M, Reich K, Rademaker D. Lidocaine-Induced Methemoglobinemia: A Clinical Reminder. Journal of the American Osteopathic Association. 2015.
6. Ng JS, Edwards EM, Egelund TA. Methemoglobinemia induced by rasburicase in a pediatric patient: a case report and literature review. J Oncol Pharm Pract. 2012;18(4):425-31.

7. Guay J. Methemoglobinemia related to local anesthetics: a summary of 242 episodes. *Anesth Analg.* 2009;108(3):837-45.
8. Kumar AR, Dunn N, Naqvi M. Methemoglobinemia associated with a prilocaine-lidocaine cream. *Clin Pediatr.* 1997;36:239-40.
9. Couper RTL. Methaemoglobinaemia secondary to topical lignocaine/prilocaine in a circumcised neonate. *J Paediatr Child Health.* 2000;36(4):406-7.
10. Uygur O, Esen S, Tanrıverdi S. Noninvasive diagnosis and continuous monitoring of local anesthetic-induced methemoglobinemia in a neonate. *Indian J Hematol Blood Transfus.* 2014;30(Suppl 1):180-2.
11. Kuiper-Prins E, Kerkhof GF, Reijnen CG, van Dijken PJ. A 12-Day-Old Boy with Methemoglobinemia After Circumcision with Local Anesthesia (Lidocaine/Prilocaine). *Drug Saf Case Rep.* 2016;3(1):12.
12. Tran AN, Koo JY. Risk of systemic toxicity with topical lidocaine/prilocaine: a review. *J Drug Dermatol.* 2014;13(9):1118-22.
13. Task Force on Circumcision. Circumcision policy statement. American Academy of Pediatrics. *Pediatrics.* 1999;103(3):686-93.
14. EMLA® [package insert]. Wayne, PA: Astra Pharmaceuticals, LP. 2007.
15. Sztajnkrycer MD. Local Anesthetics. In: Nelson LS, Howland M, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS. eds. *Goldfrank's Toxicologic Emergencies*, 11e New York, NY: McGraw-Hill. Available at: <http://accesspharmacy.mhmedical.com/content.aspx?bookid=2569§ionid=210274249>. Accessed on 25 May 2020.
16. Price DP. Methemoglobin Inducers. In: Nelson LS, Howland M, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS. eds. *Goldfrank's Toxicologic Emergencies*, 11e New York, NY: McGraw-Hill. Available at: <http://accesspharmacy.mhmedical.com/content.aspx?bookid=2569§ionid=210264643>. Accessed on 25 May 2020.
17. Skold A, Cosco DL, Klein R. Methemoglobinemia: pathogenesis, diagnosis, and management. *South Med J.* 2011;104(11):757-61.
18. Rino PB, Scolnik D, Fustiñana A, Mitelpunkt A, Glatstein M. Ascorbic acid for the treatment of methemoglobinemia: the experience of a large tertiary care pediatric hospital. *Am J Ther.* 2014;21(4):240-3.
19. Mohammed EA, Abdelkader SI, Mohmoud AE. Effective role of ascorbic acid as an alternative treatment of methemoglobinemia: A case report. *Int J Case Rep Images* 2018;9:100941Z01EM2018.
20. Park SY, Lee KW, Kang TS. High-dose vitamin C management in dapsone-induced methemoglobinemia. *Am J Emerg Med.* 2014;32(6):684.e1-e6843.
21. Toker I, Yesilaras M, Tur FC, Toktas R. Methemoglobinemia caused by dapsone overdose: Which treatment is best?. *Turk J Emerg Med.* 2016;15(4):182-4.
22. Scott EM, Hoskins DD. Hereditary Methemoglobinemia in Alaskan Eskimos and Indian. *Blood.* 198;13:795-802.
23. Balsamo P, Hardy WR, Scott EM. Hereditary methemoglobinemia due to diaphorase deficiency in Navajo Indians. *Pediatrics.* 1964;928-31.

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