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How Safe is Prilocaine as a Local Anesthetic in Children Younger Than 2 Years of Age: A Case Series

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ABSTRACT

Objective: Methemoglobinemia is an urgent condition requiring early diagnosis and treatment; it may be fatal if the methemoglobin (MetHb) level is greater than 70% and tissue oxygenation is impaired. Prilocaine is a local anesthetic widely used during circumcision in children that has been associated with methemoglobinemia in therapeutic doses. Infants are vulnerable to hemoglobin oxidation because their cytochrome b5 reductase level is approximately 50% of adult values and fetal hemoglobin is more sensitive to oxidation than adult hemoglobin. Six cases of methemoglobinemia occurring after the use of prilocaine during a circumcision are described. Six patients under the age of 2 years who had undergone prilocaine anesthesia were presented with cyanosis and a methemoglobin level of 35% to 50%. Four patients were treated with methylene blue as first-line therapy. In those 4 patients, cyanosis was resolved within 30 minutes in Case 1, an hour in Case 2, 2 hours in Case 3, and 4 hours in Case 5. In Case 3, the patient developed hemolysis following the methylene blue treatment. One patient was first treated with ascorbic acid due to a temporary shortage of methylene blue. The cyanosis improved in 1 hour and had regressed completely another hour later after a dose of methylene blue. In the final case, the cyanosis improved 30 minutes after intravenous administration of only ascorbic acid. All of the patients were discharged healthy. Bupivacaine may be more appropriate than prilocaine as a local anesthetic in young children due to the risk of potentially severe methemoglobinemia side effect of prilocaine.

INTRODUCTION

Methemoglobin (MetHb) is formed by the conversion of the divalent form of iron (Fe^{2+}) in the heme group of hemoglobin (Hb) into trivalent iron (Fe^{3+}) due to oxidation. MetHb cannot transport an adequate amount of oxygen; the Hb-oxygen dissociation curve shifts to the left, interfering with the delivery of oxygen to tissues, resulting in central cyanosis.[1] A normal MetHb level is less than 1% of total Hb. A reductive system in erythrocytes usually prevents the elevation of MetHb.[2] Methemoglobinemia arises due to a disruption in the balance between oxidation and reduction. The risk of methemoglobinemia is greater in children due to the fact that cytochrome b5 (CYTB5) reductase activity, which reduces oxidized iron, is 50% lower in infants than in adults, fetal Hb (HbF) is more sensitive to the harmful effects of oxidation relative to adult Hb (HbA), and enteral colonization of nitrate-producing Gram-negative bacteria.[3] Oxidant agents, drugs, dyes, and industrialized chemical substances may transform Hb into MetHb. Acute elevations of up to 20% to 30% can be tolerated in patients without anemia; however, MetHb levels over 70% may be fatal.[4] Clinically, blue-gray cyanosis refractory to oxygen therapy is seen. Mild cases may be asymptomatic, while in serious cases, cyanosis, tachypnea, tachycardia, hypotension, confusion, and death may occur.[5]

This article is a description of 6 cases of patients under the age of 2 years who received prilocaine as a local anesthetic before circumcision and later developed methemoglobinemia.

CASE SERIES

Case 1 – A 13-month-old boy without any known disease was admitted with perioral bruising. The anamnesis revealed that he had been circumcised under local anesthesia with prilocaine. A physical examination revealed a peak heart rate (PHR) of 150/minute, blood pressure (BP) of 70/40 mmHg, and a respiratory rate (RR) of 30/minute, and that the skin and mucosa of the perioral region was markedly cyanotic.

The results of respiratory, cardiovascular, and other systemic examinations were unremarkable. The patient had an oxygen saturation level of 88% and was treated with oxygen via a mask, but his cyanosis did not resolve. A chest X-ray was evaluated as normal. His hematological parameters were: a white blood count (WBC) of 14900/mm³, an Hb level of 9.6 g/dL, a hematocrit percentage of 28.5%, and a platelet count of 459000/mm³, with blood gas analysis results of a pH value of 7.39, a pCO_2 value of 35.2 mmHg, a HCO_3 value of 21 mEq/L, and a MetHb measurement of 43%. The results of biochemical analyses and testing of the glucose 6-phosphate dehydrogenase (G6PD) level were within normal limits. A diagnosis of methemoglobinemia was made and intravenous methylene blue was administered at a dose of 1 mg/kg. Within approximately 30 minutes, the cyanosis resolved. A control blood gas analysis revealed a drop in the MetHb level to 1.4%.

Case 2 – A 2-month-old boy who had developed cyanosis after a circumcision performed under prilocaine anesthesia was referred with the initial diagnosis of methemoglobinemia following an echocardiographic examination. A physical examination revealed a PHR of 120/minute, a BP of 65/40 mmHg, and a RR of 40/minute. His skin, and oral mucosa were cyanotic. Respiratory and cardiac sounds, as well as an examination of other organ systems were unremarkable. His oxygen saturation was 82%. The hematological parameters were as follows: a WBC of 12900/mm³, an Hb value of 12.9 g/dL, a hematocrit percentage of 38.5% and a platelet count of 306000/mm³. Blood gas analysis indicated a pH reading of 7.48, a pCO_2 value of 31.0 mmHg, an HCO_3 value of 22.6 mEq/L, and a MetHb measurement of 43.8%. His biochemical parameters and G6PD value were within normal limits. A chest X-ray did not reveal any pathology. With the diagnosis of methemoglobinemia, intravenous methylene blue was administered at a dose of 1 mg/kg, and within 30 minutes, the cyanosis of the patient resolved. A control blood gas analysis revealed that the MetHb level had been reduced to 2.8%.

Case 3 – A 30-day-old boy was referred upon the development of cyanosis following circumcision. A physical examination revealed a PHR of 130/minute, a BP of 80/45 mmHg, a RR of 45/minute, an oxygen saturation level of 80%, and cyanotic skin and mucosa. A respiratory system examination was unremarkable. Cardiac auscultation and examination of other organ systems did not reveal any pathology. His hematological values were as follows: a WBC of 10900/mm³, an Hb level of 10.9 g/dL, a hematocrit percentage of 30.7%, a platelet count of 469000/mm³, and blood gas analysis results of a pH value of 7.43, a pCO_2 value of 37.3 mmHg, an HCO_3 value of 24.7 mEq/L, and a MetHb measurement of 46.7%. No abnormal biochemical finding was detected, and a chest X-ray did not demonstrate any abnormal signs. His G6PD value was within normal limits. The patient was given methylene blue through an intravenous route at a dose of 1 mg/kg. His cyanosis resolved within 2 hours. The blood MetHb level measured at the first follow-up visit was 0.7%. When the patient was observed at an outpatient clinic 5 days later, he was jaundiced and pale, so additional blood samples were obtained and sent for biochemical analysis. A physical examination yielded the following results: a PHR reading of 140/minute, a BP measurement of 60/40 mmHg, an SaO_2 percentage of 99%, a RR of 40/minute, and pale, jaundiced skin. Both lungs were equally active in respiratory efforts, and his respiratory sounds were normal. The liver was palpated at the midclavicular line 3 cm below the costal arch. Lymphadenopathy was not detected. During cardiac auscultation, short-lived 1-2/6 systolic murmurs were heard in all foci, while the examination of other organ systems was unremarkable. All biochemical parameters were within normal limits, with the exception of direct and indirect bilirubin values (9.6 mg/dL and 9.2 mg/dL, respectively). Hematological values were: a WBC of 11000/mm³, an Hb level of 4.9 g/dL, a hematocrit percentage of 15%, a platelet count of 654000/mm³, and a mean erythrocyte volume of 98 fL. The patient was rehospitalized, and blood samples were sent for analysis to establish the differential diagnosis. His family history did not reveal any evidence of hemolytic disease. Though the G6PD value on first admission was within normal limits, testing was requested again. The results of an occult fecal blood and direct Coombs tests were unremarkable. The levels of vitamin B12 (270 pg/mL), folic acid (12.85 ng/mL), iron (177 µgr/dL), and total iron binding capacity (281 ug/dL) were within normal limits. The corrected reticulocyte count was 14%. Peripheral smears revealed fragmented erythrocytes. The results of hemoglobin electrophoresis revealed an HbF of 37.3%, an HbA1 of 47.7%, and an HbA2 of 1.1%. An erythrocyte suspension was administered. At a control visit, the Hb level was determined to be 8.9 g/dL and the hematocrit percentage was 25.6%. During follow-up of the patient, the Hb value did not decrease. The total bilirubin value

on the fourth day of the administration of the erythrocyte suspension was 3.5 mg/dL. The reticulocyte level regressed to 7%. The second measurement of G6PD level was within normal limits. Hemolysis was thought to have developed secondary to the methylene blue treatment.

Case 4 – The physical examination findings of a 42-day-old patient who was presented with cyanosis developing a short time after circumcision performed local anesthesia with prilocaine were as follows: a PHR of 130/minute, a BP of 65/40 mmHg, a RR of 45/minute, and cyanotic skin and mucosa. Both lungs were active in respiration. Upon auscultation of the chest, the respiratory sounds were within normal limits. Cardiac auscultation findings and an examination of other organ systems were unremarkable. The oxygen saturation level on admission was 78%. The hematological test results were: a WBC of 11600/mm³, an Hb value of 10.2 g/dL, a hematocrit percentage of 30.1%, and a platelet count of 356,000/mm³. The blood gas analysis revealed a pH value of 7.39, a pCO_2 value of 35.4 mmHg, an HCO_3 value of 21.2 mEq/L, and a MetHb percentage of 44.5%. The biochemical parameters and G6PD values were within normal limits. Since methylene blue was not available at the time, the patient was given 300 mg intravenous ascorbic acid. The cyanosis resolved within 30 minutes. The MetHb level was measured at 2.1% at a control visit.

Case 5 – A 12-day-old boy without any known disease developed cyanosis 4 hours after circumcision, and was presented 10 hours later. The recorded PHR was 146/minute, the RR was 44/minute, and the BP was 70/40. His hands and lips appeared cyanotic; however, examination findings of other organ systems were within normal limits. The oxygen saturation level was measured at 81%. The results of blood gas analysis were: a pH value of 7.42, a pCO_2 value of 39.8 mmHg, an HCO_3 value of 32.2 mEq/L, and a MetHb of 39.2%. The remaining blood parameters were within normal limits. Methylene blue treatment was initiated at a daily dose of 1 mg/kg/g, and the blood MetHb level dropped to 3.6%, 4 hours later. The cyanosis was resolved.

Case 6 – The patient was referred without any known disease on the postnatal 10th day with bruising, which started within 15 to 20 minutes after circumcision performed under local anesthesia with prilocaine. His PHR was 128/minute, the RR was 42/minute, and the BP was 75/50 mmHg. He had peripheral cyanosis, but the examination of his other organ systems was unremarkable. The blood gas values were as follows: a pH of 7.42, a pCO_2 of 40.9 mmHg, an HCO_3 of 23.6 mEq/L, and a MetHb value of 46.4%. The other relevant parameters were within normal limits. Since methylene blue was not initially available, he was given 2 daily doses of 200 mg/kg ascorbic acid. One hour later, the MetHb level was 19.4%. The patient was then given a single oral dose of methylene blue solution. The blood MetHb value decreased in 30 minutes to 1.5%, and another hour later it was recorded as 0.7%. The cyanosis of the patient resolved.

DISCUSSION

Prilocaine is a local anesthetic agent frequently used during circumcision, and as a result of its metabolite o-toluidine, there is a risk of methemoglobinemia. Even at therapeutic doses of 1 to 2 mg/kg, prilocaine may induce a small degree of methemoglobinemia, though it generally will not lead to cyanosis. The risk of methemoglobinemia increases with larger doses (especially >2.5 mg/kg).[6,7] The half-life of MetHb is 55 minutes, and the effects tend to occur 2 to 3 hours after administration of the drug.[8] Oxygen saturation drops, and cyanosis may be observed.[9,10] The blood turns into a dark color, similar to chocolate. Even at levels that do not interfere with tissue oxygenation, a hypoxic signal may appear. Cyanosis becomes apparent when the methemoglobinemia level exceeds 1.5 g/dL or constitutes 8% to 12% of hemoglobin. If the level of MetHb is between 30% and 50%, fatigue, tachypnea, tachycardia, and confusion are often seen, and if it is greater than 50%, then arrhythmia, acidosis, coma, and convulsions may occur. Levels greater than 70% may be fatal.[11,12] In the 6 patients of this study, the MetHb level ranged between 35% and 50% and all of the patients had cyanosis. Tachycardia was only detected in the 13-month-old patient.

Methemoglobinemia, which damages tissue oxygenation by shifting the oxygen-hemoglobin curve to the left and leads to hypoxia, is a life-threatening emergency that requires early diagnosis and treatment. Diagnosis may be established using co-oximetry, which measures MetHb absorption in the blood.[9] In addition, fragmented erythrocytes, spherocytes, and with special staining methods, Heinz bodies, which are all related to hemolysis developing secondary to oxidative stress, may be seen on a peripheral smear.[8]

If the MetHb level is less than 20%, treatment to eliminate the culprit agent typically suffices. At greater levels, methylene blue treatment at a dose of 1 to 2 mg/kg may be administered through an intravenous route for at least 5 minutes, and if required, the dose may be repeated 1 hour later. Methylene blue reduces the level of MetHb using reduced nicotinamide adenine dinucleotide phosphate (NADPH) as a cofactor, and a different reductase system than that of the CYTB5R enzyme. Since normal hexose monophosphate intubation is required for NADPH, methylene blue should not be used in cases of G6PD deficiency. It is ineffective, and may cause severe oxidant hemolysis. In such an instance, instead of methylene blue, oral/intravenous ascorbic acid at daily doses of 200 to 500 mg may be used.[9,12,13] If the MetHb level is above 70%, then blood exchange or hyperbaric oxygen therapy should

also be applied.[13] In all 6 of the present cases the MetHb level ranged between 35% and 50%. In 4 cases, methylene blue was administered intravenously at a dose of 1 mg/kg.

The cyanosis of Cases 1, 2, and 4 regressed within 30 minutes. Case 3 was resolved in 2 hours, Case 5 in 4 hours, and Case 6 methylene blue was not initially available, so it was given subsequent to a dose of ascorbic acid. The cyanosis regressed 30 minutes later.

Methylene blue is an oxidant substance, while its metabolite, leukomethylene, is a reductive agent. Therefore, at high doses, they may induce hemolysis due to the oxidant effect.[14] In Case 3, since there was resolution of the cyanosis after the administration of methylene blue, and a normal G6PD level was found in repeated tests, G6PD insufficiency was not considered. No other etiological factor that would explain the development of hemolysis and anemia was found, and so the development of hemolysis was thought to be related to the methylene blue solution, even though it was administered at a normal dose.

Methemoglobinemia has toxic and hereditary forms; the toxic form of methemoglobinemia is seen more frequently. The NADH CYTB5 enzyme, responsible for the reduction of MetHb, is encoded by the CYTB5R gene on chromosome 22. Four types of hereditary NADH CYTB5 enzyme deficiency have been defined. In Type 1, NADH CYTB5 activity is only deficient in erythrocytes, and generally there is no symptom other than cyanosis. In Type 2, enzyme deficiency is widely seen in all tissues, and in infants, it is characterized by encephalopathy, mental retardation, spasticity, microcephalus, and growth retardation. Type 3 defines a phenotype with cyanosis but without neurological abnormalities with CB5R deficiency in leukocytes, platelets, and erythrocytes. In Type 4, only erythrocytes are devoid of the CYTB5 enzyme.[5] Cyanosis is present from birth. The degree of cyanosis is correlated with the level of MetHb, and it does not respond to oxygen therapy. A divided daily dose of 200 to 500 mg ascorbic acid is used in the treatment of hereditary methemoglobinemia. The development of methemoglobinemia following prilocaine use followed by normalization of the MetHb level after treatment did not suggest the presence of hereditary methemoglobinemia in the present patients.

A relatively lower level of the NADH CYTB5R enzyme, the vulnerability of HbF to the harmful effects of oxidation, and enteral colonization of nitrate-producing Gram-negative bacteria predispose infants to methemoglominemia. If acidosis is present, or if oxidant drugs are to be used, then the risk of methemoglobinemia increases further. Therefore, for safety reasons bupivacaine is recommended as a local anesthetic during the first 3 months of life.[13,15,16]

In conclusion, during infancy, the administration of prilocaine as a local anesthetic may lead to serious complications, including cyanosis refractory to oxygen therapy, tachypnea, tachycardia, hypotension, confusion, and even death. Due to the risk of methemoglobinemia, bupivacaine may be more appropriate as a local anesthetic agent than prilocaine.

Informed Consent

Written informed consent was obtained from the patient's parents for the publication of the case reports.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: M.G., N.H., P.B., G.T.; Design: M.G., N.H., P.B., G.T.; Data collection &/or processing: M.G., P.B., G.T.; Material: M.G., N.H.; Analysis and/or interpretation: M.G.; Literature search: M.G.; Writing: M.G.; Critical review: M.G.

Conflict of Interest

None declared.

REFERENCES

1. Tabel Y, Sandıkkaya A, Güngör S, Özgen Ü. Methemoglobinemia after injection of prilocaine for pre-medication of circumcision [Article in Turkish]. Dicle Tıp Dergisi 2009;36:53–5.
2. Jaffe ER. Methemoglobinemia in the differential diagnosis of cyanosis. Hosp Pract (Off Ed) 1985;15:92–110. [CrossRef]
3. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. Ann Emerg Med 1999;34:646–56. [CrossRef]
4. Coleman MD, Coleman NA. Drug-induced methaemoglobinaemia. Treatment issues. Drug Saf 1996;14:394–405. [CrossRef]
5. Quirolo K, Vinchinsky E. Hemoglobin Disorders. In: Behrman RE, Kliegman RM, Jenson HB, Stanton BF, editors. Nelson textbook of pediatrics. 18th ed. Philadelphia: Saunders; 2008. p. 1623–34.
6. Kızılyıldız BS, Sönmez B, Karaman K, Çaksen H. Toxic methemoglobinemia due to prilocaine use. J Emerg Med 2010;38:663–4.
7. Taddio A, Stevens B, Craig K, Rastogi P, Ben-David S, Shennan A, et al. Efficacy and safety of lidocaine-prilocaine cream for pain during circumcision. N Engl J Med 1997;336:1197–201. [CrossRef]
8. Gülgün M, Kul M, Sarıcı SÜ, Alpay F. Prilokaine bağlı methemoglobinemi: iki olgu sunumu ve literatüre bakış. Erciyes Tıp Dergisi 2007;29:322–5.
9. Lunenfeld E, Kane GC. Methemoglobinemia: sudden dyspnea and oxyhemoglobin desaturation after esophagoduodenoscopy. Respir Care 2004;49:940–2.
10. Balicer RD, Kitai E. Methemoglobinemia caused by topical teething preparation: a case report. Scientific World Journal 2004;4:517–20.
11. Armstrong C, Burak KW, Beck PL. Benzocaine-induced methemoglobinemia: a condition of which all endoscopists should be aware. Can J Gastroenterol 2004;18:625–9. [CrossRef]
12. Bayard M, Farrow J, Tudiver F. Acute methemoglobinemia after endoscopy. J Am Board Fam Pract 2004;17:227–9. [CrossRef]
13. Aydoğan M, Gedikbaşı Toprak D, Türker G, Zengin E, Arısoy ES, Gökalp AS. Intravenous ascorbic acid treatment in prilocaine-induced methemoglobinemia: report of two cases [Article in Turkish].

Çocuk Sağlığı ve Hastalıkları Dergisi 2005;48:65–8.
14. Rehman HU. Methemoglobinemia. West J Med 2001;175:193–6.
15. Sinisterra S, Miravet E, Alfonso I, Soliz A, Papazian O. Methemoglobinemia in an infant receiving nitric oxide after the use of eutectic mixture of local anesthetic. J Pediatr 2002;141:285–6. [CrossRef]
16. Hahn IH, Hoffman RS, Nelson LS. EMLA-induced methemoglobinemia and systemic topical anesthetic toxicity. J Emerg Med 2004;26:85–8. [CrossRef]

Lokal Anestezik Olarak Prilokain İki Yaş Altı Çocuklarda Ne Kadar Güvenli?: Olgu Serisi

Amaç: Methemoglobinemi, doku oksijenizasyonunun bozulduğu ve MethHb düzeyinin %70'i aşması durumunda ölümcül seyredebilen, erken tanı ve tedavi gerektiren acil bir durumdur. Prilokain çocuklarda sünnet sırasında sıklıkla kullanılan ve terapötik dozlarda bile methemoglobinemi riski olan bir lokal anesteziktir. Süt çocuklarında okside demirin indirgenmesini sağlayan sitokrom b5 redüktaz aktivitesinin erişkine göre %50 oranında daha düşük olması ve baskın hemoglobin olan Hb F'in Hb A'ya göre oksidasyona daha duyarlı olması, methemoglobinemi riskini artırmaktadır.

Gereç ve Yöntem: Bu yazıda sünnet öncesi lokal prilokain anestezisi uygulanan ve sonrasında methemoglobinemi gelişen altı olgu sunulmuştur.

Bulgular: Prilokain anestezisi uygulanan iki yaşından küçük altı hastada methemoglobin düzeyi %35–50 arasında olup siyanoz vardı. Dört olguda ilk etapta metilen mavisi bulunduğu için hastalara 1 mg/kg dozunda metilen mavisi damar içi verildi, bir olguya metilen mavisi sonradan bulunarak verildi. İlk olgunun 25 dakika, ikinci olgunun bir saat, üçüncü olgunun iki saat, beşinci olgunun ise dört saat içinde siyanozu geriledi. Diğer olguya damar içi askorbik asit verildikten 30 dakika sonra siyanozun düzeldiği gözlendi. Bir hastada metilen mavisine bağlı hemoliz görüldü. Tüm hastalar şifa ile taburcu edildi.

Sonuç: Süt çocukluğu döneminde ciddi yan etkiler ve methemoglobinemi riski nedeniyle lokal anestezik prilokain yerine, bupivakain kullanımı daha uygun gözükmektedir.

Anahtar Sözcükler: Methemoglobinemi; prilokain; sünnet.