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Case Report

Methemoglobinemia After Prilocaine Application During Neonatal Circumcision and Treatment with Ascorbic Acid

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ABSTRACT

Methemoglobinemia occurs when the hemoglobin molecule is oxidized from the normal ferrous state to the ferric state. Rarely, it may be a congenital condition (methemoglobin-reductase deficiency), but more frequently it is a result of oxidant exposure. Among the large number of agents that can cause acquired methemoglobinemia is prilocaine, commonly used for local anesthesia during circumcision. Methylene blue is known to be the best treatment option; however it is not always available, and there is no universally accepted alternative. Vitamin C has been reported as an alternative treatment in recent years, but there is no definitive information about efficacy, dose, and renal side effects at high doses. Presently described is the case of an infant who developed cyanosis after a local application of prilocaine during circumcision who was successfully treated with the intravenous administration of vitamin C.

INTRODUCTION

Methemoglobinemia occurs when the normal ferrous state of the hemoglobin molecule is oxidized to a ferric state. Rarely, it may be a congenital condition (methemoglobin-reductase deficiency), but more frequently, it occurs as a result of oxidant exposure. Numerous agents have been reported to cause acquired methemoglobinemia, including the application of prilocaine, which is commonly used for local anesthesia in circumcision procedures. It has been established that methylene blue is the optimal treatment; however, alternative treatments include the administration of vitamin C, though there is no clear information about efficacy, dose, or renal side effects at high doses. This report describes a neonatal patient who developed cyanosis after a local prilocaine application during circumcision who was successfully treated with intravenous vitamin C in the absence of methylene blue.

CASE REPORT

A newborn male patient weighing 3430 g, who was born at term via spontaneous vaginal delivery to a healthy mother and without postpartum problems, was hospitalized in the neonatal unit after pallor and cyanosis were detected at a polyclinic control visit on the 22nd day after birth. The patient had been circumcised that day, including the use of local anesthesia, and there were no problems immediately after the circumcision; however, cyanosis developed approximately 2 hours after the procedure.

There was no family history available for the patient. He weighed 3940 g, and exhibited signs of cyanosis with a blood pressure reading of 70/45 mmHg, pulse rate of 144 beats/minute, and a respiratory rate of 60 breaths/minute. Further physical examination findings were normal, and other system examinations were normal. The results of

the complete blood count were: leukocyte count of 8990/mm^3, hemoglobin count of 12.5 g/dL, hematocrit value of 35%, and a platelet count of 406000/mm^3. Routine biochemistry was normal. Additional results were: blood gas Ph of 7.46, pO_2 of 52.4 mmHg, HCO_3 of 29.5 mmol/L, and lactate level of 3.3 mmol/L. Pulse oximeter readings included a saturation rate of 70% and a methemoglobin (metHb) level of 28.5. Dextrose solution 10% and 10 L/minute oxygen via hood was administered with a diagnosis of methemoglobinemia. As no methylene blue was available, intravenous 100 mg vitamin C was provided in 20 cc of 10% dextrose for 2 hours. The cyanosis decreased significantly and the metHb level in the blood gas decreased to 12.1% in the first hour and 2.4% in 9 hours. The metHb level was 1.6% on the second day, and the patient was discharged after 48 hours.

DISCUSSION

MetHb is an oxidized and non-oxygen-binding form of hemoglobin. Severe methemoglobinemia is rare, but it is an important potential cause of cyanosis in the very young. The hemoglobin molecule contains 4 ferrous ($Fe2^+$) ions, binds with oxygen and transports it to tissues. When iron is oxidized to a ferric state (metHb or hemoglobin M) it cannot carry oxygen and the oxygen dissociation curve slips to the left, causing tissue hypoxia and lactic acidosis.[1] Erythrocytes contain approximately 1% (0-3%) metHb. It is provided through 2 mechanisms: nicotinamide adenine dinucleotide (NADH) diaphorase I (cytochrome b5 reductase) and glucose-6-phosphate dehydrogenase (G6PD), and via the hexose monophosphate pathway and the nicotinamide adenine dinucleotide phosphate hydrate (NADPH) diaphorase II system (NADPH-reductase metHb). This second pathway for reduction of metHb is mediated by NADPH-(flavin) methemoglobin reductase. It uses NADPH generated by G6PD in the hexose monophosphate (pentose phosphate) shunt as a source of electrons. However, there is normally no electron carrier present in red blood cells to interact with NADPH. As a result, electron acceptors or redox dyes, such as methylene blue, (Fig. 1) can activate this pathway.[2]

The NADPH diaphorase II system is pharmacologically active and constitutes the basis of methylene blue treatment.[3,4] Exposure to oxidizing agents causes 100 to 1000 times more metHb formation than normal. Infants less than 3 months of age are particularly prone to acquired methemoglobinemia. Hemoglobin F, which is more prevalent in infants, is more susceptible to oxidation than hemoglobin A, and the NADH diaforase I system is immature in infants. Furthermore, the cytochrome b5 metHb reductase activity and concentration are low before 6 months of age.[4,5] Other factors include the higher gastric pH in infants and the higher proliferation of nitrate to nitrite-converting bacteria in the gut. The presence of nitrite facilitates the conversion of hemoglobin to metHb.[6]

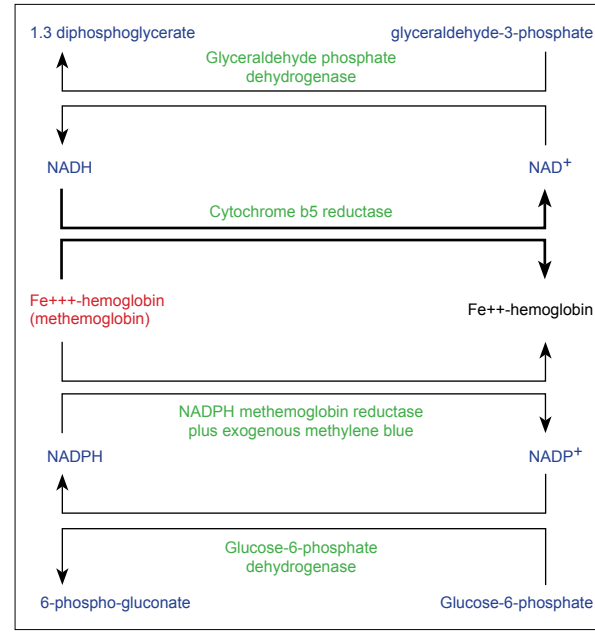

Figure 1. The major pathway for methemoglobin reduction is via cytochrome b5 reductase (bold arrows). An alternative pathway, which requires an exogenous electron acceptor, such as methylene blue, is via nicotinamide adenine dinucleotide phosphate methemoglobin reductase. Fe: Ferrous; NAD: Nicotinamide adenine dinucleotide; NADH: Nicotinamide adenine dinucleotide + hydrogen; NADP: Nicotinamide adenine dinucleotide phosphate; NADPH: Nicotinamide adenine dinucleotide phosphate hydrate.

One of the drugs that can cause methemoglobinemia is prilocaine, a sodium channel blocker used as a local anesthetic. Ortho-toluidine, which is a metabolite of prilocaine, can induce methemoglobinemia. The half-life of prilocaine is about 55 minutes, and methemoglobinemia can occur 20 to 60 minutes after drug administration.[7] Prilocaine-associated methemoglobinemia is age- and dose-dependent; doses of 2–2.5 mg/kg or more are considered a predisposing risk factor. It has been reported in the literature that prilocaine may also cause methemoglobinemia in therapeutic doses, as well as the use of prilocaine-containing creams (EMLA 5%).[3,7] The dose administered in our case was above these doses.

An increased metHb level induces clinical symptoms by causing functional anemia and tissue hypoxia. In healthy subjects without anemia, only minor symptoms will appear with a metHb level of less than 15%; however, cyanosis may appear at a level greater than 15%, and at 20% to 45%, mental changes, headache, lethargy, tachycardia, malaise, dizziness, or syncope may be seen. Dysrhythmia, convulsion, coma, and fatalities have been reported at levels exceeding 50%.[3] In our case, the metHb level was 28.5% and

perioral and peripheral cyanosis, tachypnea, and uneasiness were apparent in the patient.

Patient history is important in the diagnosis process. Drug applications that may cause methemoglobinemia should be considered and investigated in cases of oxygen-resistant cyanosis and an absence of cardiopulmonary disease. It is also a clue if the difference between the arterial blood gas oxygen saturation value and that measured with pulse oximetry is more than 5%. Pulse oximeters cannot distinguish between different abnormal hemoglobin types. The blood count should be checked, as anemia aggravates the symptoms, and the lactate level and acid base balance will reveal tissue ischemia. In our case, the lactate level was 3.3 mmol/L, which was slightly high. In patients with methemoglobinemia, blood is chocolate brown or very dark red in color, and this color does not change even when the blood has contact with oxygen. It is also important that fresh samples are used when measuring metHb levels because the count will increase with waiting time.

Prevention of further exposure to the oxidizing agent is the first step in treatment. Infants can tolerate a metHb level of 10% to 20% asymptomatically if there is no anemia.[6] Treatment with 1–2 mg/kg methylene blue for 5 minutes is usually recommended in patients with a metHb blood level of >20% if symptomatic, and >30% in asymptomatic patients.[3,4] However, methylene blue is always available in our country for emergency treatment. In addition, methylene blue does not have an effect on the clinic in G6PD-deficient patients and it can trigger hemolysis as a source of oxidant stress. It has also been reported to induce hemolysis in patients without G6PD deficiency.[8] It may be impractical to measure a patient's G6PD level, particularly in an emergency situation. The use of ascorbic acid is recommended in patients with a known G6PD deficiency. Other potential side effects of methylene blue are chest pain, dyspnea, hypertension, diaphoresis, and a paradoxical increase in the metHb level. Urine may be blue in color because it is excreted via the kidneys, and the dose of methylene blue should be adjusted with consideration for renal function.[3]

Although there is an accepted need for an alternative to methylene blue, there is currently no universally accepted alternative for treatment of methemoglobinemia. In recent years, the administration of high-dose vitamin C has been reported to be a fast, safe, and effective option;[1–4] however, concerns about a slow response and renal complications as a result of high doses of vitamin C have deterred use.[8,9]

The mechanism of high-dose vitamin C treatment for methemoglobinemia is the reduction of metHb through its antioxidant effect using a non-enzymatic pathway. Intravenous high dose administration of vitamin C is the best way to rapidly increase the plasma concentration of vitamin C. Peak plasma concentration has been achieved in less than 1 hour with 10 g or more administered intravenously. Vitamin C administration can increase urinary oxalate excretion and has been reported lead to oxalate nephropathy in patients with renal disease or insufficiency. There is little information available on short-term high-dose vitamin C administration in patients with no history of kidney failure.[10] A dose of 100-300 mg/day,[6] or 200-500 mg/kg/day has been recommended.[7] In our case, 100 mg was administered intravenously. Vitamin C may also be used orally for long periods to treat congenital methemoglobinemia; however, up to now the dose recommendations remain uncertain.

CONCLUSION

Prilocaine, a local anesthetic, may cause methemoglobinemia. That disorder can cause cyanosis and other serious symptoms even at treatment doses in infants 3 months of age and younger. Methemoglobinemia should be considered in the differential diagnosis of oxygen-resistant cyanosis in infants. Vitamin C may be used as a safe alternative to methylene blue treatment for patients without renal insufficiency if methylene blue is unavailable or ineffective/the patient is unresponsive.

Informed Consent

Written informed consent was obtained from the parents of the patient for the publication of the case report and the accompanying images.

Peer-review

Internally peer-re viewed.

Authorship Contributions

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

Conflict of Interest

None declared.

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Sünnette Prilocain İle Lokal Anesteziye Bağlı Askorbik Asit İle Tedavi Edilen Methemoglobinemi: Bir Yenidoğan Olgusu

Methemoglobinemi hemoglobin molekülünün normal ferroz durumdan ferik duruma okside olması ile oluşur. Nadiren doğumsal (methemoglobin redüktaz eksikliği) veya daha sıklıkla oksidanlarla karşılaşma sonucu edinsel olarak görülebilmektedir. Edinsel methemoglobinemi yapan çok sayıda ajan bildirilmekte olup, nedenlerinden biri de sünnet pratiğinde lokal anestezi için sık kullanılan prilocain uygulamasıdır. Tedavide kullanılan metilen mavisine ihtiyaç olduğu bilinmekle birlikte genel olarak kabül edilmiş alternatif tedavi yoktur. Bu tedaviler içinde son yıllarda bildirilen C vitaminin; etkinliği, dozu ve yüksek dozda renal yan etkileri konusunda net bilgi bulunmamaktadır. Sünnet sırasında lokal prilocain uygulaması sonrası siyanoz gelişen yenidoğan olgusu metilen mavisi bulunamadığı için intravenöz vitamin C ile başarı tedavi edilmesi nedeniyle sunulmuştur.

Anahtar Sözcükler: Askorbik asit; methemoglobinemi; prilocain; sünnet; yenidoğan.