Methemoglobinemia Due to High Dose of EMLA in a Pediatric Patient: Case Report

Bir Pediatrik Hastada Yüksek Doz EMLA Kullanımına Bağlı Methemoglobinemi

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Geliş Tarihi/*Received:* 03.12.2009
Kabul Tarihi/*Accepted:* 15.04.2010

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ABSTRACT Methemoglobinemia (MHb) refers to the oxidation of ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}) within the hemoglobin molecule. It is an abnormal form of hemoglobin and can exist because of hereditary or acquired reasons. One of the most important reasons of acquired or drug-induced MHb is local anesthetics, which especially include benzocaine, lidocaine and prilocaine. EMLA cream which includes lidocaine and prilocaine is used topically to provide local anesthesia for a variety of painful procedures. We report a case of local anesthetics-induced MHb resulting from EMLA cream use before the penil block and circumcision procedures. This case serves to remind MHb that can result from local anesthetic agents and the fact that prompt recognition and treatment of this disorder is so important.

Key Words: Methemoglobinemia; anesthetics, local; EMLA; circumcision, male; infant

ÖZET Methemoglobinemi (MHb), hemoglobin molekülündeki demirin ferröz formdan (Fe^{2+}) ferrik forma (Fe^{3+}) oksidasyonu sonucu oluşur. Hemoglobinin anormal bir formudur ve doğumsal veya kazanılmış sebeplerle ortaya çıkabilir. Kazanılmış veya ilaca bağlı methemoglobineminin en önemli sebeplerinden biri özellikle benzokain, lidokain ve prilokaini kapsayan lokal anestezikler-dir. Pekçok ağrılı işlemde lidokain ve prilokainin her ikisini de içeren EMLA krem topikal olarak kullanılır. Biz, bu yazıda penil blok ve sünnet işlemleri öncesinde kullanılan EMLA kreme bağlı gelişen lokal anestezi toksisitesi/methemoglobinemi olgusunu sunduk. Bu olgu; methemoglobine-minin, erken teşhisinin ve tedavisinin önemini tekrar hatırlatmak amacıyla sunulmuştur.

Anahtar Kelimeler: Methemoglobinemi; anestezikler, lokal; EMLA; sünnet, erkek; bebek

Turkiye Klinikleri J Anest Reanim 2010;8(3):246-50

Methemoglobinemia (MHb) refers to the oxidation of ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}) within the hemoglobin molecule. It is an abnormal form of hemoglobin and can be a reason of central cyanosis. This reaction impairs the ability of hemoglobin to transport oxygen and carbon dioxide, leading to tissue hypoxemia and in severe cases, death.[1]

MHb can occur by congenital and acquired reasons. Acquired MHb is by far the most commonly seen and the most common cause of MHb is ingestion or skin exposure to an oxidizing agent. Common agents are industrial chemicals, anilin, benzocaine, dapsone, nitrites, nitrates, lidocaine, prilocaine and sulfonamide antibiotics.[1,2]

Neonates experience MHb because of not having normal erythrocytes and normal reducing capacity of NADH reductase.[3,4] The reducing capacity of NADH reductase is not fully developed in neonates and does not reach adult capacity until the age of 3 months.[3] As a result of this immaturity, neonates are relatively vulnerable to the development of MHb secondary to the action of oxidizing substances, including sulphonamides and prilocaine.

EMLA is an eutectic mixture of local anesthetics that contains 2.5% lidocaine and 2.5% prilocaine. EMLA cream is applied to dry, intact skin, covered with an occlusive dressing and left for 60-90 minutes. It penetrates skin and provides topical anesthesia to a depth of 5 mm. Therefore it is so useful for painful superficial procedures, containing laser surgery, venipuncture, post-herpetic neuralgia, circumcision etc.[5]

In this case report; we discussed a 58 days' old child who had MHb following inconvenient use of local anesthetics especially EMLA for circumcision, because of reminding the importance of prompt recognition and treatment of this disorder again.

CASE REPORT

A healthy 58 days' old male infant (ASA I, 5700 g, 59 cm) was scheduled for circumcision. He had no history of any disease. Besides preoperative anamnesis and physical examination, his laboratory values were also within normal limits before the operation.

The patient was not premedicated with any of the sedation agents. When the finger probe of the pulse oximeter was placed in the theatre, an oxyhemoglobin saturation (SpO_2) of 99% was measured on room air. His heart rate (HR) and respiratory frequency were 140 beats min^{-1} and 30 breaths min^{-1}, respectively.

He was given general anesthesia by face mask. Induction was provided by 5% sevoflurane with 50% N_2O and 50% O_2. For maintenance sevoflurane was continued as 2%. After cleaning the operation site, mixture of 1.5 mL 2% prilocaine (Citanest® 400 mg) and 1.5 mL 0.5% bupivacaine (Marcain® 100 mg) was injected around the patient's penis in order to provide circular block. The circumcision procedure was completed approximately in 30 minutes without any complication. At the end of the procedure the patient was observed in recovery room for a brief period. His blood pressure, HR and respiratory frequency were stable and there was no sign of cyanosis. Therefore; he was transferred to the surgical ward. After 3 hours he became cyanotic, tachypneic and restless. His tongue and lips were almost black. Within few minutes, he was placed on 100% oxygen, transferred to post-operative care unit (PACU) and monitorised. Over the next 5 minutes; despite continued 100% oxygen with a face mask, Hb oxygen saturation decreased to 84%. His arespiratory frequency was 38 breaths min^{-1} and temperature was 36.8 ºC. Arterial blood gas (ABG) analysis demonstrated: pH: 7.36, SaO_2: 81%, pO_2: 46.8 mmHg, pCO_2: 46.7 mmHg, HCO_3: 26 mmol L^{-1}, BE: 0.6 mmol L^{-1}. Hemoglobin level was 10.1 g dL^{-1} with a methemoglobin level of 11.7%. ABG was noted as not to be dark chocolate brown in color. Even though; his ABG parameters were convenient for intubation, following his symptoms and ABG were preferred by applying 4 L min^{-1} oxygen with face mask continuously.

After the reinterrogation of the family it was understood that; mother of the patient, who is an anesthesia technician, had applied 5 g EMLA 5% cream around the penis of the patient before the operation.

His second ABG, which was after 12 hours, was showed pH: 7.41, SaO_2: 90%, pO_2: 50.8 mmHg, pCO_2: 32.7 mmHg, HCO_3: 22.4 mmol L^{-1}, BE: -2.3 mmol L^{-1}, FMHb: 6.3%. At the same time his symptoms like cyanosis, tachypnea and restlessness were disappeared. The results of his third ABG were as follows after 24 hours: pH: 7.47, SaO_2: 91.2%, pO_2: 54.8 mmHg, pCO_2: 26.7 mmHg, HCO_3: 19.4 mmol L^{-1}, BE: -4.1 mmol L^{-1}, FMHb: 3.4%. A simultaneous ABG analysis was performed, revealing a methemoglobin level of 3.4%. He was followed by ABG analysis and monitorization until his SpO_2 rose to 99%. After 2 days without any

complication and necessity for intubation or methylene blue, he was discharged by 99% of SpO_2.

The case was decided to be reported after informing the parents and receiving an approval of them.

DISCUSSION

Circumcision of a male infant is a common painful procedure in Muslims and Jewish people. It usually happens in couple of years after birth. Neonates are also capable of both perceiving and exhibiting reproducible responses to pain as adults, and that pain in neonates may have long-term effects.[6] Therefore; the routine use of analgesia during neonatal circumcision is considered essential by the American Academy of Pediatrics in 1999.[7]

The subcutaneous ring block is a simple technique causing almost no pain (if given cautiously).[8] Besides general anesthesia, it is used for decreasing the dose of inhalation and intravenous anesthetics and also for controlling postoperative pain. Stolik-Dollberg et al[9] demonstrated dorsal penil nerve block with bupivacaine for neonatal circumcision appearently confers better analgesia than lidocaine. So; we preferred using bupivacaine and prilocaine together for penil block in our clinic as usual; but during the block we were not aware of the usage of EMLA cream. Uncontrolled dose of EMLA used by the patient's mother had not been calculated before, so the overdose of local anesthetics caused MHb.

Methemoglobin molecules, which are normally only about 1% of total hemoglobin at any given time, occur by the rise of oxidation (when Fe^{2+} in hemoglobin oxidize to the Fe^{3+} state) or by the inadequate reduction.[1] Thereby transport of O_2 and CO_2 deteriorates and symptoms of hypoxia and anaerobic metabolism show up.

Accumulation of MHb can occur by congenital and acquired causes. Acquired MHb is by far the most commonly seen; in contrast the congenital form is rare.[2] Congenital MHb is caused by a deficiency of cytochrome b_5 reductase which is an enzyme that catalyzes NADH-dependent reduction of methemoglobin to hemoglobin or by a hemoglobin M disease that is a dominantly inherited abnormality in hemoglobin.[10]

Ninety five percent of hemoglobin reduction is accomplished by reduced NADH-methemoglobin reductase.[3] The reducing capacity of NADH reductase is not fully developed in neonates and does not reach adult capacity until the age of 3 months.[4] As a consequence of this immaturity, neonates are sensitive to the development of MHb. Surgical procedures such as circumcision and inguinal hernia are common in the neonatal period and various drugs are given for anesthesia or pain relief. However elevated MHb levels up to 5-6% are considered to be without clinical significance in neonates.[11]

The most common cause of MHb is ingestion or skin exposure to an oxidizing agent. Numerous drugs commonly administered to patients in the hospital are known to cause MHb in susceptible individuals. Among these are nitrates (nitroglycerin, nitroprusside, silver nitrate, amyl nitrite), sulfonamides, metoclopropamide, and topical anesthetics such as benzocaine, lidocaine, prilocaine or EMLA cream.[1,12-17]

A topical application of EMLA had achieved considerable popularity for its ability to diminish pain associated with circumcision.[9] However; the maximum recommended doses and application areas based on a child's age and weight should be taken into consideration. EMLA cream > 1 g should not be applied to < 10 cm^2 area of an infant, who is 0-3 months' old or < 5 kg. Brisman et al[18] studied MHb cases after usage of EMLA in term neonates and found that 1-h application of 1 g EMLA cream is safe when used on the intact skin of term neonates below 3 months of age. On the other hand in our case it was used as 5 g.

Taddio et al[19] reported that EMLA diminishes pain during circumcision; but it cannot be recommended more than other analgesic techniques with proven efficacy, such as regional nerve block with lidocaine. According to the Taddio et al's review; altough single dose of EMLA

is safe for application to the skin of neonates of GA > 26 weeks, additional researches are needed for repeated administrations of EMLA. On the other hand; Guay[20] suggested not using prilocaine (also prilocaine in EMLA) in children younger than 6-mo-old and using it in children older than 6-mo with doses lower than 2.5 mg kg^{-1}. Our patient was a term baby and he was 58 days' old. His age was appropriate for the use of EMLA according to the Taddio's study; however not to the Guay's. Moreover, although the dose was not repeated, it was so high (5 g EMLA contains 125 mg lidocaine and 125 mg prilocaine) and toxic at once.

Symptoms and signs in MHb vary depending on the underlying etiology. It is associated with the agents and the susceptibility of the patient. Simply, we did not think that our patient would have had a congenital MHb, because he was a healthy infant before the circumcision and his parents or he had not any cyanosis history. Moreover, our 5 g of high local anesthetic dose made us to think about acquired MHb. We could not see the characteristic 'chocolate colour' of the patient's blood. Our clinical findings were only such as slight cyanosis, tachypnea, tachycardia and a little bit apathy. His highest methemoglobin level was 11.7%, lowest SpO_2 was 84%, SaO_2 of the first ABG was 81%. We used pulse oximeter instead of co-oxymetry because of not having it. However; co-oxymeter is a simplified spectrophotometer that measures light absorbance at 4 different wavelengths rather than 2 (660 nm and 940 nm), and differentiate deoxyhemoglobin, oxyhemoglobin, carboxyhemoglobin, hemoglobin.[21] It determines the true percent of saturation, which is much lower than calculated O_2 saturation on ABG analysis in cases of MHb.[22] Pulse oximeter is not reliable at especially lower levels of methemoglobin, as when methemoglobin levels reach 30-35%, the light absorbance ratio reaches a plateau and the reading becomes stable in the 82-86% range independent of actual methemoglobin levels.[1]

The patient recovered only by using O_2 and iv fluid replacement, so we did not intubate or apply methylene blue to him. Since symptoms do not occur at levels less than 20-30%, treatment is not needed below that level, unless other conditions (such as anemia, respiratory distress, and cardiac disease) contribute to the clinical scenario.[23] Therefore; we avoided using methylene blue by the reason of improved clinical symptoms and side effects like dizziness, headache, mental confusion, abdominal pain, nausea, vomiting, diarrhea, the sensation of burning in the mouth, dyspnea, restlessness, hypotension, hypertension, sweating, hyperbilirubinemia, methemoglobin formation, hemolytic anemia, respiratory distress, pulmonary edema, and phototoxicity.[24,25]

In conclusion; the differential diagnosis of MHb in newborns and infants may include both hereditary and acquired forms of the disorder. Anamnesis should be taken correctly and completely by taking the most common reasons like local anesthetics into consideration. It should be remembered that MHb is not identified by most standard tests of oxygenation such as ABG or pulse oximeter. Co-oxymetry is the only one that can detect it and according to the main cause, the adequate therapy which may be lifesaving has to be arranged promptly. This case serves to remind MHb, its causes and significant lifesaving therapy again.

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