

The Incidence of Methemoglobinemia Due to Prilocaine Use in Circumcision

Prilokain ile Yapılan Sünnetlerde Methemoglobinemi İnsidansı

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What's known on the subject? and What does the study add?

Prilocaine is more frequently encountered as a cause of acquired methemoglobinemia in newborns and children compared to adults. Determining the causative factor for methemoglobinemia and undertaking early and effective application of methylene blue or ascorbic acid can be life-saving.

Abstract

Objective: Local anesthesia with prilocaine is widely used in circumcision procedures. However, the incidence of methemoglobinemia due to prilocaine use during these procedures remains unknown. Therefore, this retrospective study was planned to determine the possibility of development of prilocaine-associated methemoglobinemia during circumcision.

Materials and Methods: Medical records of 2.431 patients who were circumcised between 2008 and 2015 in University of Health Sciences, İzmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, Türkiye, were evaluated. Prior to all circumcision procedures, 1.5 mg/kg of local anesthetic was subcutaneously administered to the penis root at 4-5 points from a 20 mL vial containing 400 mg (20 mg/mL) of prilocaine (2%).

Results: Of the 2.431 patients included in the study, two (0.008%) developed methemoglobinemia requiring treatment. According to the medical records, five patients (0.021%) developed mild bruising on the hands, feet and sides of the lips.

Conclusion: Prilocaine is more frequently encountered as a cause of acquired methemoglobinemia in newborns and children compared to adults. Determining the causative factor for methemoglobinemia and undertaking early and effective application of methylene blue or ascorbic acid can be life-saving.

Keywords: Prilocaine, Circumcision, Methemoglobinemia, Local anesthesia, Complications

Öz

Amaç: Sirkümsizyon işleminde prilokain ile lokal anestezi uygulaması yaygın olarak kullanılmaktadır. Sirkümsizyon esnasında prilokain kullanımına bağlı methemoglobinemi insidansı bilinmemektedir. Bu retrospektif çalışma sirkümsizyon sırasında kullanılan prilokaine bağlı methemoglobinemi gelişme olasılığını ortaya koymak amacıyla planlanmıştır.

Gereç ve Yöntem: Sağlık Bilimleri Üniversitesi, İzmir Dr. Suat Seren Göğüs Hastalıkları ve Cerrahisi Eğitim ve Araştırma Hastanesi, Üroloji Kliniği'ne 2008-2015 arasında gelen 2431 hastanın dosyaları incelendi. Tüm sirkümsizyon işlemlerinden önce, 20 mL'lik her flakonda 400 mg (20 mg/mL) prilokain (%2) içeren lokal anestetik 1,5 mg/kg olarak penis köküne 4-5 noktadan deri altına uygulandı.

Bulgular: Sağlık Bilimleri Üniversitesi, İzmir Dr. Suat Seren Göğüs Hastalıkları ve Cerrahisi Eğitim ve Araştırma Hastanesi, Üroloji Kliniği'ne 2008-2015 arasında gelen 2431 hastanın dosyaları incelendi. Çalışmaya dahil edilen 2431 hastadan iki hastada (%0,008) tedavi gerektiren methemoglobinemi gelişti. Beş hastada (%0,021) ise el, ayak ve dudak kenarlarında hafif düzeyde morarma olduğu anamnezde tespit edildi.

Sonuç: Yenidoğan ve çocuklarda edinsel methemoglobinemi olgularının erişkine oranla görece sık methemoglobinemi sebeplerinden biri olarak karşımıza çıkmıştır. Methemoglobinemiye neden olan faktörün saptanması, erken ve etkin şekilde askorbik asit veya metilen mavisi uygulanması yaşam kurtarıcı olmaktadır.

Anahtar Kelimeler: Prilokain, Sirkümsizyon, Methemoglobinemi, Lokal anestezi, Komplikasyon

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Introduction

Circumcision is one of the most widespread procedures in the world undertaken for religious reasons among Muslims and Jews and for hygienic or pathological phimosis-related medical conditions in males. Although circumcision can be performed with patients under general anesthesia, some surgeons prefer local anesthesia. In both cases, local anesthesia is applied around the penis to reduce pain during or after circumcision. With its short-acting profile in infiltration anesthesia, prilocaine is one of the most commonly used amide-type local anesthetics. Allergic reactions, such as edema, urticaria, dermatitis, and pallor are among the predominant side effects from low-dose prilocaine infiltration (1). One of the less frequently seen side effects is methemoglobinemia. Hemoglobin (Hb) is a molecule found in the erythrocytes that transport O_2 to tissues. For this process, the iron in the structure of Hb must be in the Fe^{+2} form. Methemoglobinemia occurs when this iron becomes Fe^{+3} , resulting in various oxidative stresses. Methemoglobin (MetHb) cannot carry O_2 and shifts the Hb- O_2 dissociation curve to the left, making it more difficult for O_2 to be delivered to the tissues. However, its concentration is reduced to less than 1% by the cytochrome-b5 reductase enzyme system; namely, the intracellular MetHb reductive system. Infants are more susceptible to oxidation since their cytochrome-b5 reductase enzyme levels are 50% lower than in adults (2). When the blood MetHb level is about 10-15%, cyanosis develops, and if it exceeds 35%, systemic symptoms including fatigue due to tissue hypoxia, tachycardia, respiratory distress, nausea, and vomiting occur. In cases where the blood MetHb level is 55% or above, lethargy, stupor and syncope develop, and if it is over 70% and treatment action is not taken, then it usually results in death (3).

Methemoglobinemia can be congenital or acquired. There are four types of congenital methemoglobinemia, all of which result from inherited autosomal recessive disorders in various enzyme systems. To date, many chemicals and drugs have been reported to cause acquired methemoglobinemia, including nitrotoles, phenacetin, chloroquine, dapson, phenytoin, sulfonamides, and local anesthetics. Methemoglobinemia due to the treatment dose of prilocaine as a local anesthetic is very rare (4).

The exact incidence of methemoglobinemia is not known. Our clinic is one of the centers in which circumcision has been widely practiced for many years. This retrospective study was planned to determine the incidence of methemoglobinemia due to prilocaine in our patients.

Materials and Methods

Ethics approval by the institutional review board of our hospitals had been obtained for data collection and analysis (number: 21/02/2018/1771). Before POP surgery, all patients were requested to sign an informed consent approved by the Institutional Review Board of University of Health Sciences, İzmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital. Medical records of 2.431 patients circumcised between 2008 and 2015 in University of Health Sciences, İzmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, Türkiye were evaluated retrospectively. The mean age of the patients was 7.2 years (ranging from 14 days to 13 years). None of the patients had any additional disease. Furthermore, no pathology had been detected during prenatal follow-ups or delivery. Prior to all circumcision procedures, 1.5 mg/kg of local anesthetic was subcutaneously administered to the penis root at 4-5 points from a 20 mL vial containing 400 mg (20 mg/mL) of prilocaine (2%). All surgeries were performed under local anesthesia.

Results

Of the 2.431 patients included in the study, two (0.008%) developed methemoglobinemia requiring treatment. According to the medical records, five patients (0.021%) developed mild bruising on the hands, feet and sides of the lips. However, no medical interventions were undertaken for these five patients since there was no problem in their general condition.

Case 1 was a 105-day-old infant who was hospitalized for the treatment of methemoglobinemia that developed after circumcision. He had been delivered via spontaneous vaginal route and had a birth weight of 3.100 g. Early circumcision was planned due to phimosis, but he had no other health problems in the previous 105 days. Two hours after circumcision, the parents brought the infant to the emergency department with the complaint that the whole body of the infant was bruised. On arrival, the child's blood pressure was 85/55 mmHg, respiratory rate was 33/min, and heart rate was 130/min. SO_2 was measured as 70% using a pulse oximeter. Arterial blood gas pH was 7.43, HCO_3 was 20 mEq/L, PCO_2 was 36 mmHg, and PO_2 was 94 mmHg. The MetHb level was 41.5%. According to the complete blood count analysis, the Hb level was 11.2 g/dL, hematocrit was 34.6%, and thrombocyte was 245000/mm³. Based on these findings, methemoglobinemia was considered, and 100 mg/day of ascorbic acid and methylene blue was administered to the patient via 1 cc/kg/dose intravenous infusion from a 1% solution. Thirty minutes after the administration of methylene blue, pH was measured as 7.36, HCO_3 as 22 mEq/L, PCO_2 as 34.3 mmHg, PO_2 as 98 mmHg, and MetHb as 5.4%. At this stage, the patient's cyanosis completely resolved, and he had a normal

glucose-6-phosphate dehydrogenase (G6PD) level. The patient was monitored for 24 hours and discharged without cyanosis and with all vital signs stabilized.

Case 2 was a 35-day-old infant delivered through vaginal route weighing 2.950 g. Circumcision had been planned in the early period due to the development of pathological phimosis with no other health problems occurring in the first 35 days. Approximately one hour after circumcision, he was admitted to the emergency department due to his entire body being bruised. Upon admission, his blood pressure was 90/55 mmHg, respiratory rate was 34/min, and heart rate was 126/min. SO_2 was found to be 72% using a pulse oximeter. Arterial blood gas pH was 7.37, HCO_3 was 20 mEq/L, PCO_2 was 36 mmHg, and PO_2 was 95 mmHg. The MetHb level was measured as 42%. Complete blood count assessment showed that the Hb level was 11.0 g/dL, hematocrit was 33.2%, and thrombocyte was 215000/mm³. These findings indicated methemoglobinemia; thus, 100 mg/day of ascorbic acid and methylene blue was administered to the patient via intravenous infusion as 1 cc/kg/dose of a 1% solution. Thirty minutes after methylene blue was administered, pH was found to be 7.36, HCO_3 21 mEq/L, PCO_2 35.4 mmHg, PO_2 97 mmHg, and MetHb level 5.6%. At this time, the patient's cyanosis had completely resolved. The patient also had a normal G6PD level. After being observed for a further 24 hours, the patient was discharged without cyanosis and with all vital signs stable.

Five other patients aged 14 days, 43 days, 63 days, 82 days and 1.5 years were found to have mild bruising only in hands and feet, and, thus, were diagnosed with methemoglobinemia. All these patients were discharged without any medical intervention after close observation in which no complication was identified.

Discussion

Methemoglobinemia can be seen in two forms, congenital or acquired. The diagnosis of congenital methemoglobinemia is based on the level of the intracellular cytochrome b5 reductase enzyme. A large number of agents are known to cause the development of acquired methemoglobinemia with most implicated examples being sulfonamides, local anesthetic drugs, and nitrate-containing vegetables (5). Circumcision is a commonly performed religious practice in Turkiye, and prior to this procedure, prilocaine is generally used to manage pain.

Four types of local anesthetics have been reported to cause methemoglobinemia; prilocaine, benzocaine, lidocaine, and tetracaine. It is well known that ortho-toluidine, a metabolite of prilocaine, leads to Hb oxidation (6,7). In clinical practice, the injectable form of prilocaine (Citanest®) and prilocaine-lidocaine (EMLA®) cream are the two most commonly used commercial preparations. At therapeutic doses (1-2 mg/kg/dose), prilocaine causes MetHb formation at levels that are usually too low to

induce cyanosis, however, the risk of methemoglobinemia increases with the increased dose (8,9).

The main reasons why children are more susceptible to methemoglobinemia include inadequate soluble form of the nicotinamide adenine dinucleotide (NADH)-cytochrome b5 reductase enzyme, which deoxidizes MetHb and facilitates oxygen transport, fetal Hb being more sensitive to oxidation, and intestinal colonization with nitrate-producing bacteria. The risk of developing methemoglobinemia is higher particularly in newborns and infants since their MetHb reductase enzyme activity is low (10,11). However, in the literature, the development of methemoglobinemia has also been reported after topical use of local anesthetics at therapeutic doses, as in our patients (12,13).

Methemoglobinemia associated with local anesthetics can lead to life-threatening conditions (e.g., coma, seizures, respiratory depression, and shock) and permanent damage (e.g., hypoxic encephalopathy and myocardial infarction), and even death (14). Congenital heart diseases, pulmonary diseases, anemia and serious infections should be considered in the differential diagnosis of cases presenting with cyanosis suspected of having methemoglobinemia. In the absence of heart and lung diseases, cyanosis that does not respond to high-flow O_2 should be considered as an indication of methemoglobinemia. MetHb is normally formed in small quantities and is rapidly destroyed by the NADH-MetHb reductase (cytochrome b5 reductase) enzyme in the erythrocytes, however, congenital methemoglobinemia patients have a deficiency of this enzyme. "NADPH-MetHb reductase" is another MetHb reductase enzyme system that uses NADPH as a cofactor. This system is physiologically inactive but it becomes active in the presence of redox components. The mechanism of action of methylene blue in the treatment of methemoglobinemia is through the NADPH-MetHb reductase system. NADPH required for an effective treatment is derived from the hexose monophosphate pathway, therefore, the G6PD level should be normal (15,16). Thus, in individuals with G6PD deficiency, methylene blue does not have a role in the treatment of methemoglobinemia.

Since the G6PD level seen in our patients was normal, the methylene blue treatment was beneficial. In the treatment, the main objective is to terminate the application of the agent, which is primarily responsible for the condition. If the level of MetHb is less than 20%, recovery can be achieved by stopping the causative drug, but newborns and infants may still require treatment. If the MetHb level is greater than 70%, hyperbaric O_2 therapy and exchange transfusion can be undertaken (17,18). Since case 1 was an infant with a MetHb value of 41.5% and his cyanosis did not improve after the application of methylene blue, we administered 100 mg/day ascorbic acid. Since cyanosis continued to be observed, without waiting for an ascorbic acid

response, 1% methylene blue was applied by slow infusion under monitoring. Approximately half an hour after the administration of methylene blue, cyanosis was reduced and the MetHb level decreased to 5.4%. It should also be noted that ascorbic acid can be safely used in the treatment of methemoglobinemia when methylene blue is not available.

Conclusion

As a local anesthetic, prilocaine is more frequently encountered as a cause of acquired methemoglobinemia in newborns and children compared to adults. Determining the causative factor for methemoglobinemia and undertaking early and effective application of methylene blue or ascorbic acid can be life-saving.

Ethics

Ethics Committee Approval: The approval was obtained from University of Health Sciences, İzmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital (number: 21/02/2018/1771).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.A., G.Y., Concept: D.A., Design: D.A., M.O.Ş., Data Collection or Processing: D.A., G.Y., M.O.Ş., Analysis or Interpretation: D.A., M.O.Ş., Literature Search: D.A., M.O.Ş., Writing: D.A., G.Y., M.O.Ş.

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