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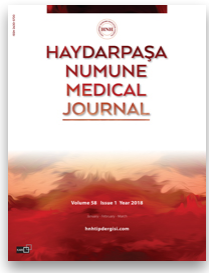

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ORIGINAL ARTICLE

The Evaluation of the Patients with Methemoglobinemia Due to Prilocaine

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Abstract

Introduction: This study aims to present the results and treatment of prilocaine-induced methemoglobinemia at three different hospital pediatric surgical clinics.

Methods: The data were obtained from hospital information systems at the University of Health Sciences Umraniye Training and Research Hospital, Prof. Dr. İlhan Varank Training and Research Hospital and Inonu University Medical Faculty Pediatric Surgery clinics between 2009 and 2019. The patients with prilocaine-induced methemoglobinemia in pediatric surgery clinics were evaluated retrospectively.

Results: A total of 11 cases were identified (10 male and 1 female). The mean age was 4.60 months (max/min: 1-12) and the mean weight was 5.570 g (max/min: 3600-11000). Local prilocaine (Citanest®), at doses 1-3 mg/kg, was injected to eight cases of circumcision, two cases of bilateral inguinal hernia and one case of undescended testicle + circumcision. In all cases, cyanosis in the skin and mucous membranes and methemoglobin in the blood gases were high (10-30%). 300 mg/kg ascorbic acid was applied to the patients for treatment, and 24 hours of methemoglobin levels were normal (1-3%).

Discussion and Conclusion: Methemoglobinemia should be suspected in cases where prilocaine is used as a local anesthetic, especially prilocaine should not be used in infants younger than six months of age, and alternative local anesthetics for prilocaine should be considered.

Keywords: Ascorbic acid; methemoglobinemia; prilocaine.

Methemoglobinemia is a rare disease in which the level of methemoglobin, which is not capable of carrying oxygen, increases in the blood. In order for hemoglobin (Hb) to carry oxygen (O_2) to tissues, iron in its structure must be in the Ferro (Fe^{+2}) form. Methemoglobinemia occurs when iron becomes trivalent Ferri (Fe^{+3}) as a result of oxidation with various oxidative stresses. Methemoglobin cannot carry O_2 and shifts the hemoglobin-oxygen dissociation curve to the left, resulting in more difficult O_2 delivery to tissues with resultant impairment of oxygenation of tis-

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Table 1. Relations among demographic data, drug dosages given and the onset of symptoms

Case	Sex	Age	Weight (gr)	Dosage of the drug (prilocaine) (mg/kg)	Onset time of symptoms (h)
Bilateral Inguinal Hernia	Female	2 mos	4400	1	3
Circumcision	Male	5 mos	3600	2	2
Bilateral Inguinal Hernia	Male	5 mos	5460	2	2
Circumcision	Male	35 days	4250	1	2
Circumcision	Male	3 mos	5200	1	2
Undescended testis + circumcision	Male	12 mos	11000	3	1
Circumcision	Male	3 mos	5300	1.5	2
Circumcision	Male	5 mos	5800	1.5	1.5
Circumcision	Male	4 mos	5500	1.5	1
Circumcision	Male	6 mos	6300	1.5	1
Circumcision	Male	4 mos	4450	2	1

sues and development of cellular hypoxia.

Acute elevations of methemoglobinemia up to 20% are well tolerated in individuals without anemia, while levels above 70% are fatal [1]. Methemoglobinemia may develop due to hereditary or acquired causes. Various chemicals and drugs, such as nitrates, chlorate, phenytoin, and local anesthetics, may cause acquired methemoglobinemia [2, 3].

Prilocaine is a local anesthetic agent used in many fields of medicine. Besides, its widespread use, it may cause methemoglobinemia, a potentially life-threatening complication [4]. In this study, we aimed to present prilocaine-induced methemoglobinemia cases and treatment outcomes in pediatric surgical clinics of three different hospitals.

Materials and Methods

In this study, data related to prilocaine-induced methemoglobinemia developed in the pediatric surgery clinics of the Health Sciences University Ümraniye Training and Research Hospital, Şehit İlhan Varank Sancaktepe Training and Research Hospital, and İnönü University Medical Faculty Hospital, and data retrieved from information systems of the cases referred to these hospital from external centers between 2009-2019 years were analyzed retrospectively after the approval of ethics committee of Health Sciences University Ümraniye Training and Research Hospital (31.05.2019/11339) was obtained. Age, sex, weight, types of surgery, amount and form of local anesthetic administered, methylene blue and ascorbic acid doses used for the treatment were investigated.

Complete blood count, liver, kidney function test results, glucose-6-phosphate-dehydrogenase (G6PD) level, coagulation tests, such as INR PT, and PTT, laboratory tests, such as arterial blood gases (pH, pO_2, pCO_2, HCO_3, methemoglobin levels), radiological and cardiologic findings, such as chest radiography, ECG and echocardiography with physical examination and clinical findings, such as blood pressure, pulse, respiratory cyanosis, oxygen saturation, were evaluated in preoperative, early and late postoperative periods.

Statistical Analysis

When evaluating the findings obtained in this study, IBM SPSS Statistics for analysis 22 (IBM SPSS, Turkey) program was used, and the data were analyzed using descriptive statistical methods (mean, standard deviation, median, frequency, percentage).

Results

The total number of 11 cases, including one girl and 10 male babies, constituted the study population. The mean age of the patients was 4.60 (max/min: 1-12) months, and the mean weight was 5.570 g (max/min: 3600-11000). The injectable form of prilocaine (1-3 mg/kg) (Citanest®) was applied as local anesthesia after circumcision in eight cases, bilateral inguinal hernia surgery in two cases, and undescended testis surgery + circumcision in one case.

Five of these patients were referred to our hospitals from other health centers due to cyanosis after circumcision. Demographic data, prilocaine doses and symptom onset times are also shown (Table 1).

In all cases, cyanosis, tachypnea and tachycardia were observed in the skin and mucous membranes at the earliest one hour and the latest three hours after the procedure. Higher methemoglobin levels (10-30%) were observed in blood gases, and 300 mg/kg ascorbic acid was given to

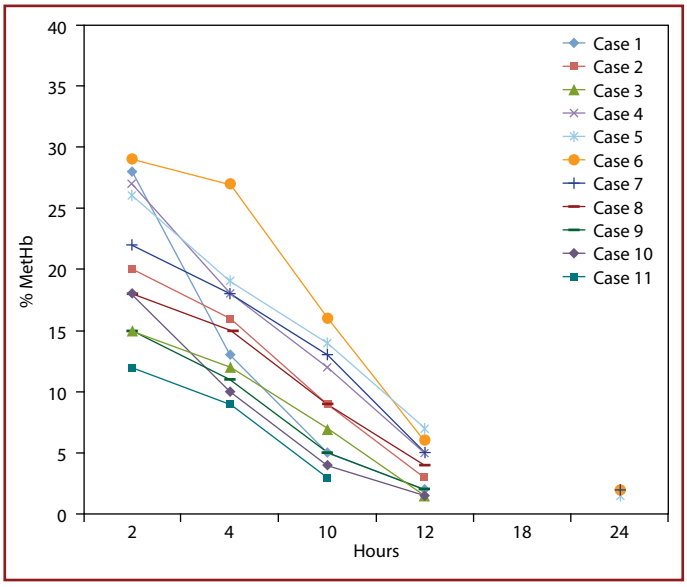

Figure 1. Methemoglobin levels of the cases within 24 hours.

the patients for treatment and they were monitored with delivered with a mask. The patients who were followed up for 24 hours were discharged without any problem when the methemoglobin levels in their blood gases returned to normal levels (1-3%) (Fig. 1).

Discussion

Under physiological conditions, methemoglobin is 1% of total Hb and does not exceed 2-3% due to the activity of cytochrome b5 reductase enzyme. Since the blood cytochrome b5 level in young children is approximately 50% of the adult values, elevated methemoglobin levels may lead to a variety of adverse outcomes ranging from mild symptoms, such as cyanosis to lactic acidosis hypoxia and death [5, 6].

Methemoglobinemia may be congenital or acquired. Congenital ones are seen in hereditary defects of hemoglobinopathies (Hemoglobin M) or cytochrome-b5 reductase enzyme. Cytochrome-b5 reductase deficiency type I is asymptomatic except manifestation of cyanosis.

Patients with cytochrome b5 reductase deficiency type II may have severe neurological sequelae along with cyanosis. Acquired patients may generally occur due to the use of chemicals with acidosis or oxidant potential. Most commonly nitrate-containing vegetables, quinines, aminobenzene, phenytoin, chloroquine, sulfonamides and local anesthetic drugs have acidosis or oxidant potential. Prilocaine is a commonly used local anesthetic. The injectable form of prilocaine (Citanest®) and prilocaine-lidocaine (EMLA®) cream are used. Prilocaine at therapeutic doses (1-3 mg/kg) generally causes low levels of methemoglobin formation that will not produce cyanosis and the higher the dose of prilocaine, the higher the risk of methemoglobinemia [7]. We should note that, however, in the literature, as in our patients, the development of methemoglobinemia after the use of therapeutic dose has been reported [8]. Most of these patients are neonates and infants. In the first trimester of life, the risk of methemoglobinemia due to toxic substances is higher since methemoglobin reductase activity is low, and fetal hemoglobin is more easily oxidized. In our study, we think that eight of ten patients may be predisposed to the development of methemoglobinemia since eight of them aged fewer than six months.

When the level of methemoglobin exceeds 10%, cyanosis occurs first. The first symptom was cyanosis, except one of our patients. Therefore, methemoglobinemia should be kept in mind in the differential diagnosis of patients presenting with cyanosis. The cause of methemoglobinemia in all our cases was prilocaine used as a local anesthetic agent.

In widespread use of injectable or local cream forms, ortho-toluidine, a metabolite of prilocaine, is responsible for the formation of methemoglobinemia [9]. Prilocaine has a half-life of approximately 55 minutes, and methemoglobinemia occurs 20-60 minutes after drug administration [1]. In our cases, the earliest symptom appeared after one hour and after three hours at the latest. Therefore, we think that local anesthesia should be observed at least one hour after the procedure.

In the treatment of methemoglobinemia, methylene blue is used priorly. In addition, ascorbic acid, riboflavin, blood transfusion and hyperbaric oxygen are among the other treatments that can be applied [10, 11]. If the level of methemoglobin is less than 20%, improvement is usually seen with cessation of the causative drug.

If methemoglobin level is higher than 20-30% in symptomatic cases, 1% methylene blue at a dose of 1-2 mg/kg may be administered intravenously. The same dose may be repeated if cyanosis does not regress within one hour. However, methylene blue increases methemoglobinemia in Glucose 6 Phosphate Dehydrogenase (G6PD) deficiency and is contraindicated as it may cause dyspnea, chest pain, tremor, cyanosis and hemolytic anemia, and ascorbic acid may be used in such G6PD deficient cases. G6PD enzyme levels were found to be normal in all of our cases

The basic elimination of methemoglobin levels in erythrocytes is mediated by electron carrier molecules (cytochrome-b5 and NADH). Another alternative way is through the production of nicotinamide adenine dinucleotide phosphate (NADPH) via the hexose monophosphate pat-

hway with G6PD. Ascorbic acid reduces methemoglobin non-enzymatically in vitro due to its antioxidant effect. The reduction of methemoglobin with ascorbic acid in physiological conditions is much less important relative to the NADH-dependent methemoglobin reductase system.

The place of ascorbic acid in the treatment of methemoglobinemia is related to long-term and more frequent oral use in hereditary methemoglobinemia [1]. In all of our cases, the use of methylene blue was initially planned, but as methylene blue was not available, ascorbic acid (300 mg/kg) was administered intravenously. However, although ascorbic acid directly decreases methemoglobin, it is slow-acting and its use in high doses may cause other problems in patients with renal failure.

If the methemoglobin level is above 70%, then, hyperbaric oxygen and blood exchange may be required [12]. The highest methemoglobin level detected in our cases was 29%. Therefore, blood exchange and hyperbaric oxygen therapy were not required in any one of the cases.

Conclusion

In conclusion, methemoglobinemia is a potentially fatal emergency. Since the clinical findings of prilocaine appear about one hour after its administration, patients who have been given prilocaine should be observed for at least one hour after the procedure. Prilocaine should not be used, especially in infants younger than six months and local anesthetics alternative to prilocaine should be preferred [13]. Methylene blue and ascorbic acid should be available for the possible development of methemoglobinemia.

Ethics Committee Approval: Analyzed retrospectively after the approval of ethics committee of Health Sciences University Ümraniye Training and Research Hospital (31.05.2019/11339) was obtained.

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