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Case Report

The Role of Preoperative Evaluation for Congenital Methemoglobinemia

Alparslan Kuş, Derya Berk, Tülay Hoşten, Yavuz Gürkan, Mine Solak, Kamil Toker
Department Anaesthesiolgy and Reanimation, Kocaeli University Faculty of Medicine, Kocaeli, Turkey

Abstract

Preoperative care includes a clinical examination before invasive or non-invasive interventions for anaesthesia/analgesia and is the responsibility of the anaesthesiologists. Methemoglobinemia should be considered, as well as cardiac, pulmonary, and peripheral circulatory disorders in patients with central cyanosis and low oxygen saturation despite treatment with sufficient oxygen during anaesthesia. Methemoglobinemia is a serious clinical condition, associated with increased blood methemoglobin levels characterized by clinical signs, such as cyanosis and hypoxia due to lack of oxygen-carrying capacity. Here, we present our anaesthesia management in a patient with unnoticed congenital methemoglobinemia during preoperative evaluation, in whom clinical signs of methemoglobinemia developed after local anaesthesia administration before the surgery.

Key Words: Methemoglobinemia, congenital, anaesthesia, preoperative care

Introduction

Preoperative evaluation is a clinical examination prior to anaesthesia/analgesia that would be performed for invasive or non-invasive procedures and is under the responsibility of anaesthesiologist (1). A safe anaesthesia management is only possible by precise and detailed preoperative evaluation (2).

Methaemoglobinaemia should be considered in the diagnosis of patients with central cyanosis and low oxygen saturation despite adequate oxygen therapy during anaesthesia. Methaemoglobinaemia is a serious clinical condition that presents itself with increased blood methaemoglobin concentration and is characterized by clinical symptoms such as cyanosis and hypoxia due to lack of adequate oxygen supply to the tissues (3). Methaemoglobin results from oxidation of iron in the haemoglobin molecule into ferric form (Fe^{+3}) from ferrous form (Fe^{+2}) (4-6). Increased methaemoglobin, which has no ability to deliver oxygen, shifts the oxyhaemoglobin dissociation curve to the left and leads to impaired tissue oxygenation. Methaemoglobinaemia may be either congenital or more often acquired. Congenital form is divided into two as Type I and Type II. Type I erythrocyte form is divided into two as endemic homozygote or heterozygote and has non-life-threatening clinical symptoms. Type II generalized form is the fatal form that presents itself with severe mental retardation and growth retardation and is unresponsive to treatment (4, 7-9). While some chemicals, drugs and anaesthetic substances trigger acquired methaemoglobinaemia, they may worsen clinical symptoms such as hypoxia and cyanosis in asymptomatic patients with congenital methaemoglobinaemia.

In the present case report, anaesthesia management in a patient with unrecognized congenital methaemoglobinaemia during preoperative evaluation and his clinical picture associated with methaemoglobinaemia developed after local anaesthetic administration before the surgery are presented.

Case Presentation

A 25-year-old, 85 kg male patient, who underwent preoperative anaesthesia examination for septorhinoplasty, had no history of anaesthesia in the past. His physical status was considered to be ASA I. On his physical examination, presence of mild cyanosis of fingertips and around the tongue and lips was considered normal.

Address for Correspondence: Dr. Alparslan Kuş, Department Anaesthesiolgy and Reanimation, Kocaeli University Faculty of Medicine, Kocaeli, Turkey Phone: +90 532 306 32 30 E-mail: alparslankus@gmail.com

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After obtaining informed patient consent, sedation was provided in the recovery room using 0.03 mg kg^{-1} midazolam via IV route, and the patient was transferred to the operating room and underwent standard monitoring (ECG, NIBP, SpO_2). During monitoring, preoxygenation was initiated with 100% O_2 at a flow rate of 10 L min^{-1} for 4 min; his heart rate was 80 beats min^{-1}, blood pressure was 110/50 mmHg, and SpO_2 was 96%. Anaesthesia induction was performed using IV fentanyl (1 µg kg^{-1}) and thiopental (5 mg kg^{-1}). He had no problem during mask ventilation. After administering rocuronium bromide (0.6 mg kg^{-1}) via IV route for neuromuscular block, he was intubated using No. 8 endotracheal tube (Kendall Curity, Tracheal Tube, Tyco Healthcare Group, Thailand). Anaesthesia maintenance was provided with 2%-3% sevoflurane and 40% O_2 + 60% N_2O. Ten mL of 0.5% bupivacaine mixed with 0.25 µg adrenaline (Marcaine® 0.5%, Astra Zeneca PLC Pharmaceutical Trade Co. Ltd. Istanbul, Turkey) was injected into the nasal area, where the surgical procedure would be performed. Surgical procedure was delayed as the cyanosis became remarkable on the fingers and lips of the patient and as SpO_2 reduced to 80% following the injection of local anaesthetic. Primarily checking the technical reasons that might cause reduction in SpO_2, the location of endotracheal tube and whether both lungs were ventilated equally were confirmed by auscultation. Arterial blood gas analysis of the patient, of whom SpO_2 value (SpO_2: 82%) was not increased despite ventilation with pure oxygen, revealed that PaO_2 was 299 mmHg, PCO_2 was 30.7 mmHg, and pH was 7.43. Moreover, methaemoglobin concentration of the patient was 24.3% on CO-oximetry analysis (ABL 700 Series, Blood Gas Analyser, Radiometer, Cophenagen, Denmark), which is routinely performed in our clinic in addition to blood gas analysis. When blood sample was obtained from the patient and waited for a while, it was observed that blood colour turned into chocolate-brown. After obtaining blood sample from the patient, of whom the diagnosis of methaemoglobinaemia was verified both clinically and by laboratory findings, methylene blue (IV, 1 mg kg^{1}) (Methylene Blue Injection U.S.P, Vulcan Laboratories PVT. Ltd, India) and ascorbic acid (IV, 300 mg day^{-1}) were administered. SpO_2 value was rapidly increased and reached to the level of 94%-95% approximately half an hour after the administration of methylene blue. Repeated arterial blood gas analysis revealed that pH was 7.45, PaO_2 was 556 mmHg, and PCO_2 was 29.1 mmHg, and methaemoglobin concentration was found to be 5.5%. Septorhinoplasty surgery was allowed and methaemoglobin concentration was determined to be 1.1% at the end of surgery, which lasted for 3 hours. The patient was extubated in the operating room and transferred to the intensive care unit for monitoring. While informing the patient's family after the surgery, it was learned that his brother had been diagnosed with hereditary methemoglobinemia and was always keeping methylene blue at home but that the present patient had not been investigated for methemoglobinemia and the anaesthesiologist had not been informed. At the end of 24-h monitoring in the intensive care unit, SpO_2 of the patient was 94% and arterial blood gas analysis revealed that PaO_2 was 158.3 mmHg, PCO_2 was 44.9 mmHg, and pH was 7.34, and his methaemoglobin concentration was 2.4%. The patient was transferred to the plastic surgery clinic and recommended to refer to the genetic screening centre for the detection of enzyme defect.

Table 1. Drugs that cause methemoglobinemia and are frequently used in anaesthesia practice (10)

• Local anaesthetic agents
Lidocaine
Prilocaine
Procaine
Benzocaine
Bupivacaine
• Metoclopramide
• Sodium nitroprusside
• Nitrates/Nitrites
Nitroglycerine
Silver nitrate

Discussion

Patients with congenital methaemoglobinaemia may either be asymptomatic or have a wide range of clinical picture ranging from presence of central cyanosis to lethargy and coma. Using sulphonamides, nitrite-nitrate, phenytoin, quinine, and aniline-benzene derivatives may lead to methaemoglobinaemia in such patients. Some anaesthetic agents used in anaesthesia practice as well may cause asymptomatic patient with congenital methaemoglobinaemia to be symptomatic (Table 1) (10). We attributed development of methaemoglobinaemia in the present case, who had no history of drug use, to the use of 10 mL of 0.5% bupivacaine. In the literature, although there is no specific dose for bupivacaine to cause methaemoglobinaemia, there are methaemoglobinaemia cases developed with various concentrations of bupivacaine (11, 12).

In the present case, increase in methaemoglobin concentration, low SpO_2 that was unresponsive to oxygen therapy, and remarkable cyanosis occurred following bupivacaine injection into the surgical area, which was used as a local anaesthetic. When such a patient is encountered, blood gas analysis, in addition to standard monitoring (ECG, blood pressure and SpO_2), should be performed by a device that is able to directly measure O_2 and saturated haemoglobin, as well as methaemoglobin if possible; because, SpO_2 does not reflect actual partial oxygen pressure value in patients with methaemoglobinaemia. If methaemoglobinaemia is in question, approximately 85% O_2 saturation is obtained in pulse oximetry because of red and infrared rays are absorbed equally with an absorption ratio of 1/1. Nevertheless, actual haemoglobin

saturation is higher. At high concentrations of methaemoglobin, SpO_2 is misinterpreted as low when arterial O_2 saturation is over 85% and as high when arterial O_2 saturation is below 85% (13). Simultaneous decreases in saturation and in partial pressure are not parallel. Misinterpretation rate increases particularly in case of low saturation. For instance, PaO_2 is lower than 65 mmHg when saturation is 90% (14). Arterial blood gas analysis provides great facility for the anaesthesiologist in diagnosing methaemoglobinaemia if arterial blood gas analyser has the property of indicating methaemoglobin concentration. Besides, presence of cyanosis and the cyanosis's not improving with oxygen therapy despite normal PaO_2 concentration in arterial blood gas in methaemoglobinaemia cases is an important finding. In some cases, O_2 saturation may decrease and may show inconsistency with PaO_2 concentration (15). Another diagnostic tool in methaemoglobinaemia is the CO-oximeter. CO-oximeter is a simplified spectrophotometer and differentiates oxyhaemoglobin from deoxyhaemoglobin, methaemoglobin and carboxyhaemoglobin by measuring light absorption at four different wavelengths (16, 17). In addition to laboratory detection of methaemoglobin concentration, there are also methods that could be performed rapidly at the bedside and facilitate the diagnosis of methaemoglobinaemia (11). It is known that the blood sample taken from patient turns into chocolate-brown with waiting or dripping the blood onto the white filter paper causes no colour change when contacted with atmospheric oxygen in case of high blood methaemoglobin concentrations (18). If the blood from a suspected patient turns into bright red-purple colour when dropped on the white filter paper suggests unoxygenated blood and excludes methaemoglobinaemia (18).

Many people with congenital methaemoglobinaemia may be asymptomatic with relatively high methaemoglobin concentrations without realizing their disease. Methaemoglobin concentration in normal healthy people accounts for about 1%-2% of total haemoglobin concentration. When methaemoglobin concentration increases to 10%, peripheral cyanosis develops, when it exceeds 35%, fatigue, tachycardia, tachypnoea, nausea, vomiting, headache, and dizziness occur, when it exceeds 55%, arrhythmia, acidosis, lethargy, and syncope occur, and when it exceeds 70%, this may be fatal (19-21). The blood methaemoglobin concentration in the present patient, in whom the mild cyanosis of fingertips and around the tongue and lips observed during preoperative evaluation was considered normal, increased to 24.3% following local anaesthetic injection; however, the symptoms like fatigue, headache, dizziness, nausea, vomiting or syncope could not be determined as the patient was under general anaesthesia. Only the clinical signs such as tachycardia, cyanosis, and hypoxia were observed.

In the management of methaemoglobinaemia, discontinuation of the agent that is considered to cause methaemoglobinaemia, supportive treatment, and treatment with methylene blue in patients with blood methemoglobin concentration higher than 20% are recommended. One-two mg kg^{-1} of 1% methylene blue should be administered via IV route for at least 5 min. The maximum total dose should not exceed 7 mg kg^{-1} in repeated administrations (22). After a single dose of 85 mg (1 mg kg^{-1}) methylene blue administered via IV route, methemoglobin concentration of the present case dramatically regressed to 5.5% from 24.3%, his cyanosis alleviated, and no additional dose was required. Ascorbic acid as well, which *in vitro* degrades methemoglobin enzymatically route, can be used at a dose of 100-300 mg day^{-1}, as was used in the present study (22). Exchange transfusion and hyperbaric oxygen are also among therapeutic options in the presence of severe cyanosis (22).

Conclusion

Precise anamnesis and physical examination during preoperative evaluation of patients are much more important than routine laboratory tests and cardiovascular and pulmonary tests (23). In our young case who was in ASA I class and considered healthy during preoperative anaesthesia evaluation, presence of cyanosis that was accepted normal and subsequent life-threatening situation due to methemoglobinemia once more emphasized the importance of anamnesis and physical examination.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

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References

1. Garcia-Miguel FJ, Serrano-Aguilar PG, Lopez-Bastida J. Preoperative assessment. Lancet 2003; 362: 1749-57. [CrossRef]
2. Macpherson DS, Lofgren RP. Outpatient internal medicine preoperative evaluation: a randomized clinical trial. Med Care 1994; 32: 498-507. [CrossRef]
3. Mansouri A, Lurie AA. Concise review: Methemoglobinemia. Am J Hematol 1993; 42: 7-12. [CrossRef]
4. Beutler E; Methemoglobinemia and other causes of cyanosis: Williams Hematology, 6 th ed. In Beutler E, Litchman MA, Coller BS, Kipps TJ, Seligsohn U. (eds): New York: McGraw-Hill, Inc, 2001: 611-7.
5. Rehman HU. Methemoglobinemia. Evidence based case review. West J Med 2001; 175: 193-6. [CrossRef]
6. Tobias JD, Ramachandran V. Intraoperative diagnosis of unsuspected methemoglobinemia due to low pulse oximetry values. J Int Care Med 2009; 24: 273-7. [CrossRef]

7. Percy MJ, Lappin TR. Recessive congenital methaemoglobinaemia: cytochrome b(5) reductase deficiency. Br J Haematol 2008; 141: 298-308.
8. Percy MJ, Gillespie MJ, Savage G, Hughes AE, McMullin MF, Lappin TR. Familial idiopathic methemoglobinemia revisited: original cases reveal 2 novel mutations in NADH-cytochrome b5 reductase. Blood 2002; 15: 3447-9. [CrossRef]
9. Ewenczyk C, Leroux A, Roubergue A, Laugel V, Afenjar A, Saudubray JM, et al. Recessive hereditary methaemoglobinaemia, type II: delineation of the clinical spectrum. Brain 2008; 131: 760-1. [CrossRef]
10. Tobias JD, Ramachandran V. Intraoperative diagnosis of unsuspected methemoglobinemia due to low pulse oximetry values. J Intensive Care Med 2009; 24: 273-7. [CrossRef]
11. Özgencil GE, Hasdoğan M, Can ÖS, Sezer G, Erdoğdu P, Ökten F. The Discussion of Methemoglobinemia Caused by Local Anesthetics in Four Cases. Turk J Anaesth Reanim 2006; 34: 327-32.
12. Schroeder TH, Dieterich HJ, Muhibauer B. Methemoglobinemia after axillary block with bupivacaine and additional injection of lidocaine in the operative field. Acta Anaesthesiol Scand 1999; 43: 480-2. [CrossRef]
13. Tremper KK, Barker SJ. Pulse oximetry anesthesiology 1989; 70: 98-108.
14. Miller RD. Respiratory monitoring anesthesia, Churchill Livingstone 1994: 1253-91.
15. Kizilyildiz BS, Sönmez B, Karaman K, Caksen H. Toxic methemoglobinemia due to prilocaine use. J Emerg Med 2010; 38: 663-4. [CrossRef]
16. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology and clinical management. Ann Emerg Med 1999; 34: 646-56. [CrossRef]
17. Bardoczky GI, Wathieu M, D'Hollander A. Prilocaine-induced methemoglobinemia evidenced by pulse oximetry. Acta Anaesthesiol Scand 1990; 34: 162-4. [CrossRef]
18. Marguiles DR, Manookian CM. Methemoglobinemia as a cause of Respiratory Failure. J Trauma 2002; 52: 796-7. [CrossRef]
19. Karahan MA, Aydoğan H, Nacar H, Yücel T, Yalçın Ş. Methaemoglobinaemia after Prilocaine: A case report. Journal of Harran Medical Faculty 2011; 8: 123-4.
20. Maurtua MA, Emmerling L, Ebrahim Z. Anesthetic management of a patient with congenital methemoglobinemia. J Clin Anesth 2004; 16: 455-7. [CrossRef]
21. Gupta A, Jain N, Agrawal A, Khanna A, Gutch M. A fatal case of severe methaemoglobinemia due to nitrobenzene poisoning. Emerg Med J 2012; 29: 70-1. [CrossRef]
22. Caner İ, Ziraatçi Ö, Taştekin A. Methemoglobinemia due to prilocaine which treated with oral methylene blue. Turkish J. Pediatr. Dis 2011; 5: 172-6.
23. Michota FA, Frost SD. The preoperative evaluation: Use the history and physical rather than routine testing. Cleve Clin J Med 2004; 71: 63-70. [CrossRef]