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CASE REPORT Open Access

Methaemoglobinemia: a diagnosis of surprise with recent literature review and management

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Abstract

Background: Methaemoglobinemia (MetHb) is a rare entity in clinical practice which often goes undiagnosed and keeps both the anaesthesiologist and attending surgeon under tension during surgery on seeing dark or chocolate-coloured blood in the surgical field. A low oxygen saturation (SpO2) will further panic us to search for a cause but may end futile. To add further, SpO2 may not rise significantly with adequate oxygenation and may not reach 100 with a fraction of inspired oxygen (FiO2) of 1 which keeps us searching further for a cause. An arterial blood gas (ABG) finally clinches our diagnosis. It is often missed in the pre-anaesthetic evaluation due to its rarity and the patient being asymptomatic most of the time.

Case presentation: We present a case of a 61-year-old man, a reformed smoker and hypertensive on regular medication was evaluated for laparoscopic partial nephrectomy for right renal cell carcinoma. MetHb was diagnosed preoperatively in the midst of the COVID pandemic when we had all our patients' room air SpO2 recorded and thus helped us in the smooth and hassle-free management with vitamin C preoperatively for 5 days and an uneventful perioperative period.

Conclusions: MetHb is an uncommon and potentially reversible cause of hypoxia. A simple bedside SpO2 evaluation may give a hint to the diagnosis along with a high haematocrit which urges us to order for an ABG when no other cause is attributable. A preoperative diagnosis can lead to an effective and simple management with vitamin C which often reduces methaemoglobin to significantly low levels and to have a favourable outcome. According to the literature, any level of less than 20% does not have much clinical significance in asymptomatic patients and surgery need not be deferred.

Keywords: Methaemoglobinemia, Anaesthesia, Oxygen saturation, Arterial blood gas, Vitamin C, Pulse oximeter

Background

Methaemoglobinemia (MetHb) is a rare disorder where iron in the haemoglobin molecule is in the ferric state at a higher concentration. Usually, the patients remain asymptomatic and the diagnosis comes to the clinician as a surprise when the colour of the blood looks exceptionally dark. The anaesthesiologist is alarmed of such a condition only in the operating room upon cannulation or when the surgeon comments on dark blood in spite of adequate oxygenation. Oxygen saturation (SpO2) may show some discrepancy even with 100% oxygen, which may give a hint to the condition in an otherwise normal healthy individual. The surgeon often has to stop the procedure when an appreciable improvement in the colour or haemoglobin or SpO2 does not appear even with 100% oxygen. The anaesthesiologist remains on toes on the lookout for any cause of hypoxaemia. The diagnosis of MetHb on arterial blood gas (ABG) analysis

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will break the surprise and relieves our tension. Here we would like to present a case of MetHb, diagnosed in the pre-anaesthetic clinic (PAC) evaluation itself because of the prevailing corona pandemic, which helped us to manage this case without tension in a smooth way.

Case presentation

A 61-year-old man, a reformed smoker and hypertensive on regular medication was evaluated for laparoscopic partial nephrectomy for right renal cell carcinoma. Routine PAC evaluation did not reveal any systemic involvement except for a room air SpO2 which was only 84% confirmed after multiple rechecking. As a routine, now we check the room SpO2 for all patients coming to our PAC in the context of the existing COVID pandemic. Physical examination was normal with no discolouration of lips and fingernails. His complete blood count showed haemoglobin 16.7g/dl and haematocrit 50.7% which we found high and abnormal but did not suspect this condition. Chest X-ray was normal. Cardiology evaluation with echocardiogram revealed regional wall motion abnormalities, basal inferior wall hypokinesia and good left ventricular systolic function with an ejection fraction of 62%. Exercise stress test was done and was negative for inducible ischaemia. An ABG analysis was ordered which showed pH, 7.387; pCO2, 43; pO2, 92; and MetHb, 17.2%, which clinched our diagnosis. Pulmonary function test showed mild obstruction. Till then, the patient was not aware of his condition and no family history of such illness could be elicited. Vitamin C 500 mg thrice daily was advised preoperatively for 5 days, and we accepted the case as the MetHb level was below 20% with a literature support that any value below 20% does not have any clinical significance once the patient remains asymptomatic (Cefalu et al. 2020).

In the operation room, monitors were attached. Pulse rate was 86/min with blood pressure of 130/80 mmHg and SpO2 in room air was 92%, which was better than PAC evaluation. Alprazolam 0.5mg was given the night before and pantoprazole 40 mg with alprazolam 0.5 mg at 7 am on the day of surgery, followed by intravenous (IV) glycopyrrolate 0.2 mg and midazolam 1mg, and an epidural catheter was secured at T10–T11 interspace under aseptic precautions after local anaesthetic (LA) infiltration but the test dose was avoided. The patient was preoxygenated with 100% oxygen 7 l/min and SpO2 still remained at 94% maximum. Fentanyl 70 mcg and propofol 100 mg followed by vecuronium 8 mg were given IV. A wide-bore cannula was put and the left radial artery cannulated for continuous hemodynamic monitoring and ABG analysis. ABG samples were dark brown and showed pH, 7.394; pCo2, 43.3; p02, 175; and MetHb, 11.6 (levels decreased from 17.2). Anaesthesia was maintained with 50% oxygen in air maintaining low flow and sevoflurane 1.5–2% to get a minimum alveolar concentration of 1. Buprenorphine 180 mcg was given epidurally for post-operative pain management. On incision, not to our surprise, the blood looked dark (chocolate brown) as we expected. Saturation was maintained intraoperatively at 93–94% on 50% oxygen with stable vitals. Surgery was uneventful; the patient was extubated and shifted to the intensive care unit with a SpO2 of 92% with an oxygen mask, and we made the staff aware of such a situation of reduced Sp02.

Discussion

MetHb is an uncommon and potentially reversible cause of hypoxia in the perioperative setting (Cefalu et al. 2020). It is a condition where the bound ferrous iron of oxyhaemoglobin is oxidized to the bound ferric iron of methaemoglobin (Cefalu et al. 2020). This reaction continuously occurs in vivo where ferric form gets normally reduced predominantly by cytochrome-b5 reductase (CYB5R) to keep its concentration always less than 2% in healthy humans (Lin et al. n.d.). Haemoglobin in the ferric state is incapable of binding oxygen which can lead to life-threatening hypoxemia (Hurford and Kratz 2004). Clinically significant MetHb may occur because of one of the following 3 reasons; greatly increased production of methaemoglobin; an abnormal haemoglobin which, once oxidized, is resistant to reduction and decreased activity of erythrocyte NADH-CYB5R (Chisholm and Stuart 1994).

MetHb can be of two types — congenital and acquired. Congenital MetHb is extremely rare and is of three types. Two are inherited as autosomal recessive traits: due to CYB5R and cytochrome-b5 deficiency. The third type is an autosomal dominant disorder, haemoglobin M disease, in which there is a mutation in the globin molecule. The carrier or heterozygous state of patients is characterized by an intermediate level of enzyme activity, and thus, they are more susceptible to the effects of oxidizing agents. Genetic risk factors for MetHb include haemoglobin M disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and congenital MetHb genotypes (Chisholm and Stuart 1994). The severity of symptoms may be exacerbated by complicating medical conditions and other factors, such as heart disease, lung disease, anaemia, G6PD deficiency, infancy and old age (Trapp and Will 2010). In the case report published by Lin et al. (n.d.), congenital MetHb was first suspected intraoperatively because of a mismatch of SpO2 of finger pulse oximetry and SaO2 of arterial blood and was later confirmed by multiple-wavelength co-oximetry.

MetHb commonly results from exposure to oxidizing agents which results in the oxidation of haemoglobin by

drugs or chemicals, usually exogenous oxidants such as nitrites, LA and sulfonamides (Hurford and Kratz 2004). When the production of methaemoglobin exceeds its reduction, MetHb occurs and potentially compromises tissue oxygenation (Hurford and Kratz 2004). The rate of such oxidation is accelerated by many drugs and toxic chemicals, the former including lidocaine, benzocaine, prilocaine and nitrites, which are often used in the perioperative period (Maurtua et al. 2004; Kreeftenberg et al. 2007). The most common drugs implicated in methaemoglobinemia include cocaine-derived anaesthetics like benzocaine and lidocaine, antibiotics such as dapsone (Prasad et al. 2008), and gases such as nitric oxide (Cefalu et al. 2020). Prasad et al. (2008) published a case report on acquired MetHb with dapsone in a patient who underwent an elective coronary artery bypass graft. Contamination of food during manufacture or degradation of nitrates in vegetables will also cause MetHb (Chan 1996). A high index of suspicion for MetHb should follow any presentation of hypoxic and cyanotic patients who are not improving with 100% oxygen therapy. Taking a thorough history and detailed medication with importance to the discrepancy between the SpO2 and SaO2 which is refractory to oxygen therapy is recommended.

Monitoring arterial oxygenation by pulse oximetry is the standard method of assessing tissue oxygen delivery in anaesthetic practice (Hurford and Kratz 2004). A discrepancy between SpO2 and the calculated SaO2 may be the earliest indicator of MetHb (Cefalu et al. 2020). The pulse oximetry readings may be inaccurate or not informative if patients have higher levels of MetHb, carboxyhaemoglobin or other abnormal haemoglobin species (Lin et al. n.d.). Co-oximetry using multiple wavelengths can measure the levels of haemoglobin, oxyhaemoglobin, carboxyhaemoglobin, and MetHb and can demonstrate values in fractional saturation (Lin et al. n.d.). Furthermore, a decreased SpO2 often with a nadir of 85%, chocolate-coloured or black/brown blood, physiologically appropriate PaO2 on ABG, metabolic acidosis, and tachycardia are all associated with MetHb (Cefalu et al. 2020). Also, the oxyhaemoglobin dissociation curve is shifted to the left and hypoxia results (Prasad et al. 2008).

The classic appearance of "chocolate brown blood" of blood is present with MetHb as low as 15%; at 20%, the patient may experience anxiety, light-headedness, and headaches; and with 30–50%, there may be tachypnea, confusion, and loss of consciousness. The patient is at risk for seizures, dysrhythmias, metabolic acidosis, and coma at 50% and levels above 70% are fatal (Chan 1996). It should be noted that in patients with lifelong congenital MetHb or with a history of chronic MetHb secondary to chronic exposure to drugs or toxins, the levels can be as high as 40% and still be well tolerated with cyanosis (bluish cast to the mucous membranes of the skin) being the only presenting manifestation (Wilkerson 2010).

Treatment is based on the degree of MetHb levels, the severity of symptoms, the etiological process (acute or chronic) and the presence of complicating medical conditions. Symptomatic treatment includes promoting the reduction of MetHb back to oxyhaemoglobin using methylene blue, ascorbic acid, riboflavin, and hyperbaric oxygen therapy. As a last resort in emergency situations, red blood cell transfusion therapy can be attempted in cases of critically elevated methaemoglobin levels exceeding 70% (Somervaille 2001). When the methaemoglobin level is less than 20% and oxygenation is adequate, conservative treatment could suffice. However, the administration of 100% oxygen, correction of metabolic acidosis and use of methylene blue if the patient is symptomatic is recommended. In a patient with acute toxic MetHb, the first step in treatment consists of correcting metabolic abnormalities, discontinuing potential offending pharmaceuticals, and maintaining dextrose-containing fluids, which can adequately supply substrates for the production of NADH and NADPH.

Methylene blue activates NADPH diaphorase, an enzyme capable of reducing methylene blue to leukomethylene blue, and the latter, via a non-enzymatic pathway, reduces MetHb to haemoglobin. The IV administration of 1–2 mg/kg over a period of 5 min significantly reduces its level within 1 h. It can be repeated if necessary in 30–60 min provided the total does not exceed a maximum dosage of 7 mg/kg. It should be noted that excessive administration may produce haemolysis because methylene blue can also act as an oxidant (do Nascimento et al. 2008). Ascorbic acid is cheap and easily available and a good alternative (Sahu et al. 2016).

Conclusions

Early detection of MetHb in the PAC itself by a simple pulse oximetry can avoid the tension of seeing dark blood in the operating room and a futile search for the cause of low levels of SpO2 or hypoxemia in ABG. In asymptomatic cases with low levels of MetHb, ascorbic acid is a useful agent with a faster response, and anaesthetic management can be tailored by avoiding the agents which may aggravate the oxidation of iron and have a favourable outcome.

Abbreviations

ABG: Arterial blood gas; CYB5R: Cytochrome-b5 reductase; FiO2: Fraction of inspired oxygen; G6PD: Glucose-6-phosphate dehydrogenase; IV: Intravenous; LA: Local anaesthetic; MetHb: Methaemoglobinemia; PAC: Pre-anaesthetic clinic; SpO2: Oxygen saturation.

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Authors' contributions
SS took a detailed history and physical examination of the patient. VAN worked up on the patient and gave medical and anaesthetic management, along with a manuscript edition. DVG contributed to the writing up of the manuscript by performing the literature review. SRJ was the operating surgeon whose helping hand was there throughout the process. All authors read and approved the final manuscript.

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