Reminder of important clinical lesson

A sticky situation: methaemaglobinaemia in a hand trauma patient

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Summary

We describe a case of methaemaglobinaemia (MtHb) in a previously healthy 39-year-old gentleman who presented with a traumatic glass laceration to his right wrist that required emergency surgery to control bleeding and repair his ulnar artery. The MtHb was noted on blood gas analysis by the anaesthetist after the patient had a drop in arterial oxygen saturation under general anaesthetic. We initially suspected the lidocaine local anaesthetic injected proximal to his wound for pain control in the emergency department an hour preoperatively, but then discovered that the patient was a recreational user of 'poppers' and had in fact been using these drugs just before his injury and hospitalisation. The patient's condition stabilised overnight with conservative management. Given how commonly hand surgeons and other clinical staff use local anaesthetics, we reviewed the literature on this uncommon, but potentially fatal, complication, its causes and evidence-based management.

BACKGROUND

Methaemaglobinaemia (MtHb) is a potentially fatal condition that is thought to be rare although the exact incidence is not known. Awareness of this condition is higher in anaesthetists and dentists as they encounter it more often and as it has been well published in their specialist clinical journals. MtHb is less well known to other clinicians. Its acquired form can be caused by oxidating drugs and may well be more common than is currently recognised with the volatile nitrites (poppers) and local anaesthetics. As 'poppers' are commonly available street drugs and local anaesthetics are very commonly used in clinical practice we wanted to present this relevant case. We hope the accompanying literature review will be of educational value for all clinical practitioners and help raise awareness of the evidence on the diagnosis, likely causes and best management of MtHb.

CASE PRESENTATION

A 39-year-old Caucasian man, right-hand dominant, market researcher, with a medical history of hypothyroidism was admitted with a laceration to his right wrist from punching a glass window while under the influence of alcohol. On arrival in the emergency department (ED) his vital signs were as follows:

- ▶ Oxygen saturation (SpO₂) 98%
- ▶ Heart rate 110/min
- ▶ Respiratory rate 24/min
- ▶ Blood pressure 100/60 mm Hg

On examination he was very agitated and had a 5 cm deep laceration 4 cm proximal and parallel to the wrist crease with significant bleeding from a lacerated ulnar artery, a distal sensory ulnar nerve deficit and multiple flexor tendon injuries. The blood was noted to be dark, sticky in nature and difficult to wash off one of the author's (YS) forearms after resuscitation in the ED.

The wound continued to bleed and the patient was agitated and did not tolerate elevation and direct pressure. He complained of pain despite opioid analgesia; therefore, local anaesthetic (20 ml of 1% lidocaine) was infiltrated around the wound, for analgesia and to try to improve compliance with non-operative haemorrhage control. This was unsuccessful, and the patient was promptly transferred to the operating theatre.

INVESTIGATIONS

Prior to induction of anaesthesia, the patient's SpO₂ was 90% despite over 3 min of breathing 100% oxygen. Clinically, he appeared pale and diaphoretic with cold hands and feet, and the low saturation readings were attributed to poor circulation to the extremities. Following induction of anaesthesia and intubation of his trachea it was noted that despite high-inspired oxygen concentrations, the patient's SpO₂ dropped to 85%. Bronchial intubation was excluded by auscultation. An arterial blood gas (ABG) result at this time showed a methaemoglobin fraction of 16% (normal range 0–1.5%), oxygen saturations of 81.7% and a p_aO₂ of 74.98 kPa.

DIFFERENTIAL DIAGNOSIS

- ▶ A diagnosis of MtHb was made.

TREATMENT

The MtHb was managed conservatively by continued mechanical ventilation with 100% oxygen and serial ABGs that confirmed the condition was improving without the need for treatment with methylene blue. The ulnar artery bleeding was successfully controlled and the vessel repaired. It was jointly agreed between surgeon and anaesthetist to then stop the operation and delay the definitive repair of the flexor tendons until the MtHb resolved.

OUTCOME AND FOLLOW-UP

A repeat ABG an hour later showed that the methaemoglobin fraction was 11.6% and 6 h later it had returned to normal levels.

Postrecovery discussion with the patient revealed that he regularly uses 'poppers' and admitted that he had inhaled multiple times immediately prior to his current injury and arrival to hospital. On review of his ED charts a venous blood gas sample had been taken at the time of admission. This showed a methaemoglobin level of 29.5%. The patient also reported that in the past when using 'poppers' he had regularly noticed his own and other users' lips and fingers turning blue.

The patient returned to theatre for his second operation the next day to repair all the flexor tendon lacerations. He made an uneventful recovery and was discharged and did well with his rehabilitation under hand therapy. The patient expressed his greater understanding of the danger of using poppers.

DISCUSSION

Background

Methaemoglobin is a naturally occurring oxidised form of haemoglobin (Hb) and levels under 1.5% are normal in healthy adults. Hb contains the reduced ferrous iron (Fe^{2+}), whereas methaemoglobin contains the oxidised ferric ion (Fe^{3+}). This structural change leads to the inability of methaemoglobin to bind oxygen and thus impairs the delivery of oxygen to the tissues.¹ Under normal circumstances, protective enzyme systems exist to ensure methaemoglobin levels remain low. The major enzymatic system involves transferring electrons from reduced nicotinamide adenine dinucleotide to methaemoglobin, thus converting it back to Hb. This reaction is catalysed by methaemoglobin reductase, and removes 95–99% of the methaemoglobin that is produced under normal circumstances.² Pathological MtHb may be secondary to inherited or, more commonly, acquired disorders. Most cases arise from exogenous exposure to an oxidising agent.³

Inherited MtHb

There are two forms of inherited MtHb; the first is rare and due to a lack of the methaemoglobin reductase enzyme (this form is most common in those of Native American descent), the second is due to abnormal haemoglobin (HbM) that destabilises reduced Fe^{2+} making it more readily oxidised to Fe^{3+} .⁴ In addition, methaemoglobin reductase cannot interact with and therefore cannot reduce methaemoglobin. The end result is functionally impaired Hb with a decreased affinity for oxygen.

Acquired MtHb

Most cases of MtHb are due to excessive production of methaemoglobin following exposure to an exogenous substance, such as oxidant drugs, chemicals or toxins. This increased production of methaemoglobin overloads the normal physiological regulatory mechanisms.

Children and infants, perhaps due to immature reduction enzyme pathways, may be more susceptible to MtHb (Table 1).⁵

'Poppers' is a slang name for volatile nitrites taken by inhalation. Amyl, butyl and isobutyl nitrite are all used.

Table 1 Common substances known to cause a methaemoglobinaemia

Paracetamol	Hydroxylamine	Nitrosobenzene
Acetanilide	Local anaesthetics	Phenacetin
Aminophenols	Benzocaine	Phenols
Ammonium nitrate	Cocaine	Phenytoin
Amyl nitrite	Lidocaine	Primaquine
Aniline	Prilocaine	Pyridine
Celecoxib	Procaine	Pyridium
Chloroquine	Menthol	Quinones
Cobalt	Methylene blue	Resorcinol
Chlorates	Nitrates/Nitrites	Silver nitrate
Copper sulphate	Nitrofurans	Sodium nitrite
Dapsone	Nitrogen oxide	Sulfonamides
EMLA	Nitroglycerin	Trinitrotoluene
Herbicides	Nitroprusside	

The clinical effects of the volatile nitrites, which can last a minute or two, include vasodilatation, tachycardia and hypotension. Users can feel euphoric after inhalation of these drugs and they are often used to enhance a sexual experience. There is some ambiguity surrounding the law on their use, and they are commonly available to purchase on the street, in shops and even online. The volatile nitrites can cause MtHb directly through their activity as oxidising agents⁶ and they may be a more common cause than is clinically recognised.

PRESENTATION

Acute MtHb can be life threatening; therefore, obtaining a drug history of exposure to substances known to cause it is important. It is also relevant to ask about family history of both MtHb and glucose-6-phosphate dehydrogenase deficiency as some patients who are heterozygous for the condition, when physiologically stressed and exposed to oxidising agents, may develop a MtHb. Cyanosis that is not corrected by 100% oxygen is suggestive of MtHb. The clinical effects are exacerbated in the presence of anaemia. Symptoms are proportional to the methaemoglobin fraction:

- ▶ <10% no symptoms.
- ▶ 10–20% skin discolouration only (most notably on mucus membranes).
- ▶ 20–30% anxiety, headache and dyspnoea on exertion.
- ▶ 30–50% fatigue, confusion, dizziness, tachypnoea and palpitations.
- ▶ 50–70% coma, seizures, arrhythmias and acidosis.
- ▶ >70% death.

DIAGNOSIS

MtHb should be suspected in a patient with central cyanosis and SpO_2 of approximately 85%, despite high inspired oxygen concentration. Arterial blood will be a characteristic 'chocolate brown' colour that does not turn red on exposure to air. ABG analysis will show a high p_aO_2 and elevated methaemoglobin levels, which will confirm the diagnosis. In MtHb due to drug exposure, patients will have an elevated level of methaemoglobin associated with a normal activity of methaemoglobin reductase. In hereditary MtHb, the enzyme's activity is less than 20% of normal.

THE EFFECT OF MTHB ON PULSE OXIMETRY

Pulse oximeters emit light of two different wavelengths: 660 and 940 nm, and this light is partially absorbed by Hb. Under normal circumstances the extent of absorption of each wavelength of light is then used to calculate the proportion of oxygenated Hb. Since MtHb absorbs the oximeter's light waves in the same proportions as would normal Hb at 85% saturation, the presence of MtHb causes the oximeter to display 85% irrespective of the patient's true oxygen saturation.

TREATMENT

The aim of treatment is to restore the oxygen-carrying and unloading capability of the Hb molecule. Foxworth *et al*⁷ suggest that patients with methaemoglobin levels of less than 30% require close monitoring only. As the half-life of methaemoglobin is 55 min, most cases resolve with in 24–48 h following clearance of the offending agent.

In patients who present following an acute exposure to an oxidising agent, treatment should be considered when the methaemoglobin fraction is greater than 30% in an asymptomatic patient or 20% in a symptomatic patient. First-line treatment would be with methylene blue. Wendel⁸ first described this treatment in 1937. Typically 1–2 mg/kg is given intravenously over 5–10 min and repeated 20 min later if cyanosis persists.⁴ Methylene blue acts as a cofactor for methaemoglobin reductase, therefore, greatly increasing the reduction rate of methaemoglobin. Paradoxically, higher doses of methylene blue (>7 mg/kg) will oxidise haemoglobin to methaemoglobin instead of acting as a reducing agent. This may cause haemolysis and persistent cyanosis.⁹ Side effects of methylene blue include nausea, vomiting, diarrhoea, dyspnoea, restlessness, perspiration and a burning sensation in the mouth and abdomen.

Guay¹⁰ reviewed 242 cases of local anaesthetic-related MtHb, which were published between 1949 and 2007. Only 12 cases included the administration of lidocaine as the sole local anaesthetic. Seven of these 12 patients had been given an additional oxidative drug (eg, nitrates, trimethoprim and dapsone). Guay concluded that the capability of lidocaine to induce a MtHb following appropriate clinical use is less well demonstrated than with other local anaesthetics such as prilocaine and benzocaine, with reports of the latter causing MtHb in a dose-dependant manner.^{10–11} In view of its widespread clinical use with almost no reports of this condition, we would agree that pure lidocaine-induced MtHb must be extremely rare and only seems likely when it is given in combination with other local anaesthetics or oxidising agents¹² or in the young who might be more susceptible to this complication.^{10–13} We note the recent hypothesis by Skold and Klein¹⁴ of a 'Multiple Hit' where simultaneous exposure to two or more causative agents makes the likelihood of MtHb greater. However, we feel that this is not likely in our case given the methaemoglobin fraction was greater on admission (before the lidocaine was administered) than afterwards in theatre, leaving the poppers as the most likely cause.

Learning points

- ▶ Methaemoglobinaemia (MtHb) is a rare, but potentially life-threatening complication of exposure to many oxidising agents including common local anaesthetics and recreational drugs such as 'poppers'.
- ▶ Lidocaine has very rarely been implicated as the isolated cause, whereas other local anaesthetics like prilocaine and oxidising agents like the volatile nitrates (poppers) can cause MtHb more commonly and particularly when co-administered.
- ▶ Tissue oxygenation may be compromised by MtHb, and this effect may be exacerbated in the context of blood loss or anaemia.
- ▶ This diagnosis requires a high level of suspicion, but in this case resolved uneventfully with conservative management.
- ▶ Methylene blue is not always required to reduce methaemoglobin levels to normal.

Competing interests None.

Patient consent Obtained.

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