



ORIGINAL RESEARCH PAPER

Medicine

BLUE CAN SAVE BLUE

KEY WORDS:

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ABSTRACT **INTRODUCTION:** Methemoglobin represents the oxidized form (Fe³⁺) Hb of hemoglobin, which is incapable of carrying oxygen. Methemoglobinemia (MetHb) should always be considered as one of the differential diagnosis in all cyanotic patients who remain unresponsive to oxygen therapy. Severe methemoglobinemia is a life-threatening condition and may result in death. Unfortunately, pulse-oximetry (spO₂) and Arterial Blood Gas (ABG) can be misleading in these patients. ABG by co-oximeter method is an appropriate diagnostic tool to measure the MetHb level.

CASE REPORT

Three daily-wage workers were brought to the ED on 28th of May 2018, with altered sensorium and breathlessness. History from the co-workers concluded a toxic exposure to some chemical inhalant when they were unloading the goods from a truck in the go-down of a logistics company at Panvel. No other relevant history could be produced by the co workers as it was not witnessed by them when the incident took place. **Patient A:** Vitals on presentation to the ED were as follows: pulse rate -110 beats per minute ,blood pressure -130/80 mmHg, respiratory rate of 32 cycles per minute, saturation of 88% at 10 litres of oxygen via Hudson mask, afebrile, central cyanosis was present, yellowish discoloration of palms & feet. His cardio vascular system was normal, bilateral breath sounds were clear on auscultation of his chest, abdomen was soft with a GCS score of 7. An ABG was obtained which showed a reading of pH-7.36, pO₂-63, pCO₂-29, hCO₃-18.7, sO₂-91.

Patient B: Vitals on presentation were as follows: pulse rate -140 beats per minute, blood pressure-136/80 mmHg, respiratory rate of 36 cycles per minute, saturation of 73% at 10 litres of oxygen via Hudson mask , afebrile, central cyanosis was present and yellowish discoloration of palms & feet. His cardio vascular system was normal, Bilateral breath sounds were reduced on auscultation of his chest, abdomen was soft with a GCS score of 6. An ABG was obtained which showed a reading of pH- 7.23, pO₂- 27.5, pCO₂-41, hCO₃-16.5, sO₂- 46.

Patient C: Vitals on presentation were as follows: pulse rate -96 beats per minute, blood pressure-126/80 mmHg, respiratory rate of 22 cycles per minute, saturation of 86% at 4 litres of oxygen via Hudson mask , afebrile, central cyanosis was present, yellowish discoloration of palms & feet. His cardio vascular system was normal, Bilateral breath sounds were normal on auscultation of his chest, abdomen was soft with a GCS score of 6. An ABG showed a reading of pH- 7.21, pO₂- 135, pCO₂- 38, hCO₃-15.2, sO₂- 98. All the patients received the same standard of care and were managed as per standard guidelines in a limited resource setting. All the patients were connected to cardiac monitors. Continuous pulse oximetry showed a low saturation followed by which all patients were decontaminated. Patients were put on high flow oxygen & and were fluid resuscitated with 500ml of crystalloids & were found to be fluid responsive. Patients A & B still remained dyspneic & cyanosed inspite of administering high flow oxygen, following which rapid sequence intubation was done and patients A & B were intubated and mechanically ventilated. A complete blood panel including CBC, S/e, RFT , LFT, Ca²⁺, PT ,APTT, INR, CPK total, LDH, CPK MB ,Trop T & peripheral smear were taken & sent for labs. Serial ABG & VBG were sent for all the patients CXR were ordered. However, the symptoms worsened with an increasingly bluish appearance of the hands, feet, and lips, as well as deterioration of consciousness, also blood samples appeared

chocolate brown; and the colour did not change inspite of oxygen administration.



Figure 1: Patient A Figure 2 :Chocolate brown colour of blood due to methemoglobin

After initial resuscitation, a detail history was obtained from the employer and the white powder was confirmed to be **para-nitro-aniline** compound. This raise the suspicion of three possibilities :

- Methemoglobinemia
- Chemical pneumonitis post the inhalational injury .
- Cytopathic tissue hypoxia.

Now in a resource limited setting where Meth hemoglobin levels and Co-oximetry which are considered as gold standard for diagnosing methemoglobinemia are not available, we relied on the ABG -VBG gap, and the saturation gap SpO₂ (monitor) and the SaO₂ and the (ABG), for administration of methylene blue. Eventually the three patients had a saturation gap of >10 % and an A-a gradient (Alevolar- arterial) of <30 %.Following this, we administered methylene blue at a dose of 1mg/kg over 15 minutes¹.The clinical condition improved dramatically within 30 minutes, along with a gradual resolution of the cyanotic discoloration, for two of our patients- one of them had a cardiac arrest and attained an ROSC after 5 cycles of CPR. Three hours after the methylene blue injection, two of our patients were no longer cyanotic, and were extubated. Patient B remained critical in the ICU and eventually collapsed.



Figure 3: Patient A, post methylene blue treatment. Figure 4: Patient C, methylene blue . being excreted in urine

DISCUSSION:

Methemoglobinemia is a rare cause of cyanosis which should be promptly recognized and treated urgently. Some cases of acquired methemoglobinemia may result from exposure to certain chemicals.

The symptoms of methemoglobinemia can range in severity from mild dizziness to coma and eventually death.

Healthy patients who have normal hemoglobin concentrations do not usually develop clinically significant effects until the methemoglobin level rises above 20% of the total haemoglobin^{2,3}. Normal levels of methemoglobin in our body is less than 2%. As the levels of methemoglobin keep increasing in the body, it leads to several harmful effects >15% can cause cyanosis, >20% can lead to headache, anxiety, dizziness, >30% - dyspnea, fatigue, confusion, >50% can lead to seizures, acidosis, arrhythmias and eventually death⁴⁻⁷ which happened in one of our patients (patient B). In normal circumstances, the enzyme nicotinamide adenine dinucleotide-methemoglobin reductase reduces methemoglobin to hemoglobin, preventing the accumulation of methemoglobin. If this usual mechanism is overwhelmed by exogenous oxidative stress, acquired methemoglobinemia ensues. A second enzymatic pathway uses nicotinamide deosine dinucleotidephosphate and nicotinamide adenosine dinucleotide phosphate-methemoglobin reductase, which is important for the antidotal effect of methylene blue when administered exogenously⁵. Methemoglobinemia should be considered as one of the first differential diagnosis in patients who present with cyanosis, and is particularly suspected in those whose cyanosis does not improve with supplemental oxygen⁶. The ability to detect this discoloration is improved when compared directly with normal blood, can be done during blood sample collection using vacutainer, or blotting paper⁴⁻⁷.

Pulse oximetry results should be interpreted cautiously in patients with Methemoglobinemia. In patients with methemoglobinemia, the pulse oximeter will report a falsely elevated value for arterial oxygen saturation percentage. At methemoglobin concentrations >30%, the pulse oximeter typically trends toward a constant 80% to 85% value⁸. Gold standard for identification of dyshemoglobinemias requires co-oximetry, which is an in vitro spectrophotometric method that is capable of differentiating among oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin species⁹. Pulse co-oximeters are considered as the gold standard for diagnosing methemoglobinemia as they use additional wavelengths of light as compared with the traditional pulse oximeters and are able to measure four hemoglobin species¹⁰. Antidotal therapy with methylene blue is reserved for only symptomatic patients or for those asymptomatic patients with methemoglobin levels >25%, because there is a very high risk of methylene blue itself causing a methemoglobinemia. Methylene blue serves to indirectly accelerate the enzymatic reduction of methemoglobin by NADPH-methemoglobin reductase¹¹. After managing the primary airway, breathing, circulation and decontaminating the patient, methylene blue is administered - initial dose is 1 to 2 milligrams/kg (0.1 mL/kg of the 1% solution or approximately 7 mL in an adult) IV over 15 minutes¹¹⁻¹². >7 milligrams/kg, is the maximum dose which can be administered. Beyond that methylene may actually induce methemoglobin formation. A glucose-6-phosphate dehydrogenase deficiency must always be ruled out before administration of methylene blue¹³.

RESULTS:

All 3 critically-ill patients were hypoxic and cyanosed; and required urgent respiratory support. MetHb was part of the differential diagnosis including cytopathic tissue hypoxia and severe chemical pneumonitis.

Due to the lack of availability of co-oximetry; saturation-gap, ABG-VBG comparison, A-a gradient, blot paper test and other methods were used to confirm MetHb. Diagnostic-Therapeutic issues were explored and besides supportive care, all 3 patients received treatment with Methylene Blue after risk/benefit estimation. 2 out of the 3 patients survived and 1 died despite treatment. Lab values (reported later) confirmed MetHb diagnosis.

CONCLUSION:

MetHb should always be part of workup for an unexplained cyanosed patient especially with a history of unknown toxin exposure. Early diagnosis, rapid supportive care and appropriate antidote treatment with Methylene Blue are crucial in treating this emergency. Alternative methods can be useful tools when co-oximetry is unavailable. Alternative safer but less effective therapies and ruling out a G6PD deficiency should always be considered. Careful strategic consideration must be done prior to treatment with antidote in unconfirmed cases. Prevention is better than cure: Appropriate protective gear is important but sensitization amongst the workers about their safety at work should be compulsory.

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