

Utility of Lipid Sink in Treatment of Refractory Acquired Methemoglobinemia. A Case Report

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Abstract

Methemoglobinemia can be congenital or acquired. Acquired methemoglobinemia occurs as a result of ingestion of some substances such as toluene, nitrates. Patient presents with cyanosis which is not explainable by the respiratory or cardiac cause. Most frequently used drug in treatment is methylene blue. We report a case of a patient with severe acquired methemoglobinemia in 14 months old baby, due to ingestion of toluene. He was cyanosed which was refractory to oxygen therapy and without any cardiac and respiratory disease. He had persistent high levels of methemoglobin, despite giving multiple doses of methylene blue and exchange transfusion. Finally, methemoglobin levels were controlled by automated RBC exchange transfusion and intralipid infusion.

Keywords: Methemoglobinemia; Methylene blue; Toluene; Intralipid infusion; RBC transfusion

Case Report

A fourteen months old boy was taken to a hospital in Agra with Methemoglobinemia, is a life-threatening condition characterized by the presence of high levels of methemoglobin in the blood. It can be congenital or acquired. The iron molecule in hemoglobin is oxidised from ferrous to ferric form, thereby forming methemoglobin which has increased affinity for oxygen and reduced ability to release oxygen to tissues. The oxygen-hemoglobin dissociation curve is shifted to the left, which leads to tissue hypoxia. Acquired methemoglobinemia occurs due to ingestion of some medications or chemicals that alter the balance between the rate of methemoglobin formation and its rate of reduction. This case study describes the development of acquired methemoglobinemia in a 14 months old child after ingestion of paint thinner.

Management includes supportive therapy (supplemental oxygen) and close monitoring of neurologic and cardiopulmonary status. Foxworth et al. stated that after an acute exposure to an oxidizing agent, treatment should be considered when the level methemoglobin is 30% in an asymptomatic patient and 20% in a symptomatic patient [3]. Treatment should be considered at lower levels if the patient is anemic or having any cardiorespiratory problems.

First-line of treatment is intravenous methylene blue, 1 to 2 mg/kg body weight is given intravenously over 5 to 10 min and if required may be repeated after 20 min. Clinician must rule out G6PD deficiency before administering methylene blue. Exchange transfusion or

saturations around 80% with no other significant findings. He was continued on mechanical ventilation and supportive care.

On investigation, arterial blood gas revealed saturations of 99.8% and pO₂ of 441.3 mmHg with clinical cyanosis and SpO₂ of 80% on FiO₂ of 100%. When we received a more detailed history from the parents, they revealed that the child consumed paint thinner prior to this episode. Thereafter, considering the whole scenario, methemoglobinemia was kept as the possible etiology of hypoxemia in this patient and therefore, serum methemoglobin level was measured, which came out to be very high (64.4%). Before starting treatment with methylene blue, we investigated for Glucose-6-phosphate dehydrogenase (G6PD) deficiency and that was reported as normal. Methylene blue was given stat at 2 mg/kg intravenously following which saturations transiently improved to 84% and methemoglobin levels decreased to 32% after two hours. Repeated doses of methylene blue were needed (1 mg/kg) in view of uncontrolled methemoglobinemia. Whole blood exchange transfusion was done on second and third day of admission, at methemoglobin values of 28% and 33%, respectively, but only transient improvement in saturation and methemoglobin (20%) was observed. At this point of time in view of refractory methemoglobinemia literature was reviewed which showed successful use of RBC exchange transfusion and role of intravenous intralipid in cases of lipophilic toxin poisoning [1]. Therefore, on day 4 of admission, RBC exchange transfusion was done followed by administration of intravenous intralipid 20%, which again led to a transient improvement in saturation and decreased levels of methemoglobin from 30% to 21%. On day 5 of admission, whole blood exchange transfusion was done, which finally led to decreased and sustained low levels of methemoglobin (11%).

Discussion

Methemoglobin is an altered state of haemoglobin, where the iron (ferrous form, Fe^{2+}) of the heme-molecule is oxidized into the ferric state (Fe^{3+}) rendering it unavailable for transport of oxygen to the tissues. Methemoglobin thus formed is reduced enzymatically *via* two pathways. The predominant pathway is the Adenine dinucleotide (NADH)-dependent reaction which is catalyzed by cytochrome b5 reductase. There is an alternative pathway which utilizes the nicotine adenine dinucleotide phosphate (NADPH) dependent methemoglobin reductase system.

Methemoglobinemia can be classified as either hereditary or acquired. Hereditary methemoglobinemia, is an autosomal recessive disease caused by increase in the level of methemoglobin because of deficiency of NADH-methemoglobin reductase enzyme and it also increases the susceptibility to oxidative stress from drugs or toxins.

Acquired methemoglobinemia, is much more common than congenital methemoglobinemia and results from exposure to substances such as nitrates, toluene, chlorates and certain local anaesthetic agents, which cause the rate of methemoglobin formation to exceed its rate of reduction. This mechanism is of utmost importance in the pediatric age group and elderly people. As young babies express very low levels of functional NADH-methemoglobin reductase, whereas the elderly people have less efficient form of this enzyme. Infants are also vulnerable as hemoglobin F is more susceptible to oxidation compared to adult hemoglobin.

Acute intoxication has a wide spectrum of clinical manifestation, children are usually asymptomatic up to a level of 10-15% of methemoglobin and may present only with mild cyanosis. When levels increase beyond 20% symptoms such as headache, dyspnea, tachypnea, chest pain, and tachycardia develops. At 40-50% methemoglobin level, patient develops confusion, lethargy and metabolic acidosis leading to coma, seizures, bradycardia, hypertension and ventricular dysrhythmia. A level of around 70% is fatal. Severe symptoms occur in patients who are anemic or those having G6PD enzyme deficiency.

Methemoglobinemia is suspected based on clinical assessment and the diagnosis is supported by laboratory investigations. It should be considered when the cyanosis cannot be explained by the respiratory status of patient and is refractory to oxygen therapy [2]. Arterial blood turns chocolate brown in presence of methemoglobin, and also the blood gas analysis indicates a PaO_2 which is inappropriately high or normal. Methemoglobinemia can be detected by a simple bedside test, a few drops of blood is placed on a white filter paper, while deoxyhemoglobin brighten, methemoglobin holds its colour. Pulse oximetry is inaccurate in monitoring the oxygen saturation and therefore, multiple-wavelength co-oximetry is imperative for diagnosis and monitoring the condition of patient.

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hyperbaric oxygen is reserved only for those who do not respond to standard treatment or having methemoglobin level >50%. Exchange transfusion is more widely and rapidly available compared to hyperbaric oxygen [4]. We had done automated RBC exchange transfusion, which quickly replaces the abnormal erythrocytes and raise the hematocrit resulting in improved delivery of oxygen to hypoxic tissues, without increasing the viscosity of blood. Golden et al. published a case of refractory acquired methemoglobinemia who failed to respond with methylene blue and exchange transfusion but improved dramatically with automated red blood cell exchange transfusion [5].

In our case there was history of toluene (paint thinner) ingestion, which is highly lipophilic, so it readily crosses blood-brain barrier which also accounts for its primary effects on central nervous system. The best marker for toluene exposure is urinary benzyl-mercapturic acid, as it is not detected in non-exposed subjects. Intravenous intralipid emulsion (ILE) is an established and effective treatment for cardiovascular toxicity caused by overdose of local anaesthetic drugs (lipid soluble). Intralipid emulsion infusion creates an expanded lipid phase (lipid-sink), and the resulting equilibrium thus drives the toxic drug from tissues to the aqueous plasma phase and then finally to the lipid phase (lipid-sink phenomenon). Recent case reports suggest the efficacy of ILE for treating toxicity of non-local anaesthetic agents such as beta blockers, calcium channel blockers, herbicides and varieties of psychotropic agents. Most probably, by the lipid sink phenomenon, thereby reducing the amount of active drug in the target tissue and decreasing the toxic effects [1].

Novelty: To the best of our knowledge, this is the first case report to demonstrate the potential effectiveness of intra-lipid infusion in treatment of patients with refractory acquired methemoglobinemia after toluene ingestion. Therefore, in refractory cases of methemoglobinemia due to ingestion of lipid soluble toxin, intra-lipid infusion could be beneficial.

Limitation: Although a single case report could not be a hard evidence to validate the effectiveness of this treatment, this would encourage to report further case reports and case series to validate the effectiveness of intra-lipid in treatment of refractory methemoglobinemia due to lipid soluble toxins.

Conclusion

Severe methemoglobinemia is a medical emergency. A good history and high level of suspicion is required to make a diagnosis. It should be considered as a differential diagnosis in all patients with cyanosis that is refractory to oxygen therapy, without any prior history of cardiac or respiratory problems. Intravenous methylene blue is the treatment of choice, but in refractory cases automated exchange transfusion and intralipid infusion can be tried.

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