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Case series

Methemoglobin Levels may not Always Predict Outcome in Children with Methemoglobinemia

Shashikant Devanagre, MD, Yogiraj Chopra, MD, Archana Singh, MD, NK Dubey, MD

Abstract

Methemoglobinemia is a condition in which the iron within the hemoglobin is oxidized from the ferrous (Fe^{2+}) state to the ferric (Fe^{3+}) state, resulting in an inability to transport oxygen to the tissues. Acquired methemoglobinemia, more common than the congenital forms, has been reported following exposure to a number of medications and oxidizing substances. Presentation may vary from cyanosis to frank seizures, coma and death depending on the levels of methemoglobin (MetHb) in blood. MetHb levels more than 70% have almost always reported to have been fatal. However, the level of MetHb may not always correlate with severity of illness or predict outcomes in these cases as was seen in the two cases reported here. While a 6 year old boy with thinner ingestion and MetHb levels of 85% survived, an adolescent girl with levels of 28.5% succumbed to her injuries. Both the children presented with severe respiratory distress and cyanosis that persisted despite 100% oxygen and positive pressure mechanical ventilation. Methemoglobinemia was suspected in both cases due to the presence of 'oxygen saturation gap' and confirmed by estimating the blood MetHb levels. Despite an alarmingly high MetHb level the boy survived probably due to early presentation and aggressive goal directed resuscitation. On the other hand, the girl with levels of only 28.5% succumbed to her injuries probably due to delayed presentation and prolonged cerebral anoxia prior to presentation.

Key words: Methemoglobinemia; Methylene blue; Oxygen saturation gap.

INTRODUCTION

Methemoglobinemia is a condition in which the iron within the hemoglobin is oxidized from the ferrous (Fe^{2+}) state to the ferric (Fe^{3+}) state, resulting in an inability to transport oxygen to the tissues. Acquired methemoglobinemia, more common than the congenital forms, occurs following exposure to a number of medications and oxidizing substances. Presentation may vary from cyanosis to frank seizures, coma, and death depending on the level of methemoglobinemia (1, 2). Acute methemoglobinemia may be life-threatening when the level of the pigment exceeds half of the total circulating hemoglobin. Levels of methemoglobin exceeding 60 to 70 percent of the total pigment may be associated with vascular collapse, coma, and death. Levels more than 70% have almost always turned out to be fatal (1-4). However this correlation between methemoglobin levels and death may not always be true as was the case with the two children reported in this series. While a 6 year old boy with thinner ingestion and methemoglobin levels of 85% survived, an adolescent girl (previously reported (5)) with levels of 28.5% succumbed to her injuries. The details of these two interesting cases and the probable reasons for their unusual outcomes are discussed here.

CASE SERIES

Case 1

A 6 year old boy was brought to the emergency with vomiting and diffuse abdominal pain one hour after alleged ingestion of paint thinner. On examination he was afebrile, restless with a pulse rate of 110 per

Author's Affiliations: Department of Pediatrics, PGIMER, Dr RML Hospital, New Delhi.

Reprints Requests: Dr. N.K. Dubey, Department of Pediatrics, PGIMER, Dr RML Hospital, New Delhi.

E-mail: dr_nkdubey@yahoo.com

minute, respiratory rate of 35 per minute with signs of respiratory distress in the form of subcostal and intercostal retractions. The child had central cyanosis with a SpO_2 of 75% that didn't improve despite administration of 100% oxygen. His blood pressure was 85/60 and peripheries cool and mottled with capillary refill of >2 seconds. Chest examination revealed bilateral coarse crepitations. Rest of the systemic examination was unremarkable. Oral cavity examination had a peculiar sweet odor. Initial investigations revealed anemia with hemoglobin of 8.6 g/dl, total leucocyte count of 12400/mm^3 and a platelet count of 145000/mm^3. He had a normal blood glucose, kidney function tests, serum electrolytes and Glucose-6 Phosphate Dehydrogenase levels. Arterial blood gas done while patient was breathing 100% oxygen from a non-rebreathing oxygen mask showed a PaO_2 of 156 mmHg and arterial oxygen saturation of 75%. Repeated blood gas measurements showed similar picture of hyperoxia with low saturations (oxygen saturation gap of 62%). Methemoglobinemia was suspected and 'filter paper test' (Kronenberg test) for methemoglobinemia was done which was found to be positive (no change in color of blood drop on filter paper from chocolate brown to bright red on exposure to 100% oxygen) (8). The diagnosis of methemoglobinemia was further confirmed within 30 minutes of admission by estimation of blood methemoglobin levels which were found to be elevated, 85% (normal: 0-2%). Chest x-ray revealed bilateral alveolar opacities. Other causes of central cyanosis such as congenital heart disease, carbon monoxide poisoning and cyanide toxicity were ruled out based on initial history, physical examination and a 2-dimensional echocardiography.

The child was mechanically ventilated with settings of tidal volume of 6 ml/kg, positive end expiratory pressures of 6 cmH_2O, FiO_2 of 100% and rates of 25 on pressure regulated volume control mode. He also required 2 fluid boluses of 20 ml/kg each after which his perfusion improved and remained stable during the rest of stay. Once the diagnosis of methemoglobinemia was confirmed intravenous (IV) methylene blue (1%) at a dose of 1mg/kg was administered slowly over 5 mins through a peripheral cannula. This was repeated every 30 minutes till the levels became '0'. A total of 4 doses were administered which lead to improvement in saturations from 75% to 92% and took 4 hours duration. Even after the methemoglobin levels had normalized child continued to saturate at 88-90% on 100% oxygen. He was therefore treated on the lines of acute lung injury possibly due to thinner aspiration while vomiting. His peak oxygenation index was 21% on a setting of PEEP of 10 cmH_2O with tidal volume of 6 ml/kg and FiO_2 of 100%. Settings were gradually reduced after his clinical as well as radiological condition improved and the child was eventually extubated after 98 hours of ventilation. He was discharged after a total duration of hospitalization of 5 days. On follow up at 3 months after discharge child is asymptomatic and doing well.

Case 2

A 16-year-old girl working as a laborer in a paint and dye–casting factory for 6 months presented to the emergency room in an unconscious state with complaints of fever and headache for three days followed by loss of consciousness and bluish discoloration of the body. She had been prescribed chloroquine for her illness 3 days prior to presentation and her altered sensorium and cyanosis developed a day after starting chloroquine. On examination, the child was febrile and comatose with a glassgow coma scale (GCS) score of 8. Her heart rate was 144/min with feeble peripheral pulses, capillary refill time was 4 seconds with cool extremities, and BP was 92/46 mmHg (<5th centile). Her respiratory rate was 28/min with no evidence of increased work of breathing and chest was clear on auscultation. Her SpO_2 was 79% on room air which remained unchanged despite administration of 100% oxygen. There was marked central and peripheral cyanosis with no icterus or clubbing. Oral cavity examination had no peculiar odour suggestive of poisoning. Per abdominal examination revealed a palpable spleen with a dimension of

2.5 cm below costal margin and hepatomegaly with a span of 10 cm. Initial investigations revealed anemia with hemoglobin of 7.2 g/dl, total leucocyte count was 28000/cmm with 83% polymorphs, 17% lymphocytes, and the platelet count was 300000/cmm. The Peripheral blood film showed a hemolytic picture with marked anisopoikilocytosis, large number of fragmented cells, polychromatic cells, and nucleated RBCs 25-28/100 WBC. Reticulocyte count was 8%. Her G-6PD screening was normal. Repeated peripheral smear examinations did not reveal any malarial parasite. However, rapid malarial antigen test (Optimal-IT Malaria Test Kit- manufactured by TCS Biosciences Ltd) was positive for Plasmodium Vivax. Her X-ray chest was normal. Her blood glucose levels were normal and there was no evidence of disseminated intravascular coagulation (DIC). Non-contrast CT scan of the head was normal. Arterial blood gas done while patient was breathing 100% oxygen from a non-rebreathing oxygen mask showed a PaO_2 of 137 mmHg, PCO_2 of 34 mmHg, a normal pH of 7.38 mmHg and an oxygen saturation of 79%. The 'oxygen saturation gap' was 58%. Methemoglobinemia was suspected and confirmed by estimation of blood methemoglobin levels which were found to be elevated, 28.75%. Congenital heart disease with eisenmenger syndrome was ruled out on initial history and physical examination. Other causes of oxygen saturation gap such as carbon monoxide poisoning and cyanide toxicity were also ruled out as there was no setting for these intoxications and the methemoglobin levels were elevated. Anemia severe enough to cause such low saturations is usually associated with other complications such as congestive heart failure (CHF). The index case had no clinical or radiological evidence of CHF. Therefore this possibility was also ruled out.

In view of her poor GCS and persistent low saturations at presentation to the intensive care unit, she was intubated and ventilated. Packed cells were transfused to improve her hemoglobin levels. Once the diagnosis of methemoglobinemia was confirmed intravenous (IV) methylene blue (1%) at a dose of 1mg/kg was administered slowly over 5mins through a peripheral cannula. A total of 3 doses, 1 hour apart were administered, which lead to immediate improvement in saturations from 79% to 87-90% and fall in methemoglobin levels to 2%. In addition to methylene blue, 250 mg of ascorbic acid was also administered through nasogastric tube. Though her saturations improved following treatment with methylene blue, her sensorium continued to deteriorate and preterminally she developed features of cerebral anoxia in the form of neurogenic ventilation and abnormal brainstem reflexes with dilated and fixed pupils.

DISCUSSION

The cause of methemoglobinemia in the boy was clearly thinner ingestion which is often reported to cause this dreadful condition. The toxicity of paint thinner is due to the compound nitroethane which has oxidizing properties. There are number of cases reported worldwide of thinner poisoning leading to methemoglobinemia including one case from India (6,7). However in none of them the levels of methemoglobin reported were as high as in this one. Although the high methemoglobin levels demoralized our team in the beginning because of the high risk of mortality reported with such levels, with careful and continuous monitoring and goal directed approach we could achieve normal MetHb levels within a short time span in this child. No child with methemoglobin levels as high as 85% has ever been reported to have survived till date. Even in animal experiments the level of MetHb found to be fatal ranged from 58-62% (8). Undoubtedly, the reasons for good outcome in this case could have been the early presentation (within 1 hour) and aggressive goal directed intervention.

In the adolescent girl chronic exposure (6 months) to aniline dyes coupled with ingestion of chloroquine tablets could have probably contributed to methemoglobinemia in her. Aniline dyes have oxidizing properties. When the oxidizing capacity of dyes exceeds the reducing capacity of the body, MetHb level

rises. Exposure to aniline dyes has been associated with life threatening methemoglobinemia in children (9, 10). However, in view of the temporal association of her deterioration (in the form of cyanosis and worsening of sensorium) soon after administration of chloroquine tablets, a possible contribution of chloroquine cannot be ruled out. Most of the antimalarials cause methemoglobinemia by oxidizing the ferrous iron (fe2+) to ferric (fe3+) state. Methemoglobinemia due to usual doses of chloroquine has previously been reported only in adults (11, 12). In a case series published by Cohen et al (11), 6 adult soldiers developed methemoglobinemia related symptoms following administration of chloroquine chemoprophylaxis. Investigations revealed low NADH-dependent MetHb reductase enzyme levels in all of them. The authors presumed that the enzyme deficiency was responsible for the condition. We did not estimate the levels of this enzyme because of logistic reasons. The possibility of such deficiency state cannot therefore be ruled out in this child. The other study a randomized, nonblinded, controlled clinical trial by Carmona Fonsesca et al(12) on 112 adult subjects with P. vivax infection showed that methemoglobin levels were elevated in majority of the subjects receiving varying doses of Primaquine. In this study a combination of chloroquine and primaquine was used hence one cannot be sure about which of the two agents was responsible for the elevated methemoglobin levels in these patients.

Various systems in the body normally operate to keep methemoglobin (MetHb) at physiologic level, which is less than 1% of the total hemoglobin concentration (3). MetHb is reduced to hemoglobin mainly by cytochrome b5, nicotinamide adenine dinucleotide, ascorbic acid, glucose-6-phosphate dehydrogenase (G6PD), and glutathione reduction enzyme systems (3, 13). When the reducing capacity of the body's defense mechanisms is overwhelmed by the intake of various oxidizing chemicals, methemoglobinemia results (3).

The clinical picture in methemoglobinemia may range from being asymptomatic with cyanosis only to severe anoxic symptoms like seizure, lethargy, stupor. The severity of symptoms usually depends upon the blood methemoglobin levels (14). Levels greater than 70% may result in vascular collapse and death (15, 16). However fatal cases with lower levels have also been reported in the literature in adults (levels of 10.8%) (17).

In the case of the adolescent girl, despite having low levels of methemoglobin she succumbed possibly because of the prolonged cerebral anoxia which she had suffered due to her delayed presentation to the hospital. The other potential cause for her death could be the underlying disease- cerebral malaria. Though the malarial parasite could not be identified on multiple occasions, the diagnosis could not be ruled out completely given that she had been treated with antimalarials prior to referral. However, given the temporal correlation of symptoms (especially encephalopathy) to the administration of chloroquine, one cannot attribute the patient's condition only to malaria. In doing so, potential cases of methemoglobinemia amenable to treatment may be missed.

The management of methemoglobinemia comprises of supportive care and administration of methylene blue. Methylene blue is the drug of choice for the specific management (18, 19). It is recommended at a dose of 1-2 mg/kg followed by bolus of 25-30 ml of normal saline. The dose can be repeated after an interval of an hour till a maximum dose of 7 mg/kg over 24 hours. Second dose may be given if cyanosis has not cleared within 1 hour. Any dose beyond 7 mg/kg/day will be harmful as the oxidizing action of methylene blue will become more than the reducing action of leucomethylene blue. Even after resolution of symptoms one should be cautious to look for recurrences (10). Methylene blue belongs to a group of drugs considered to be potential hemolytic agents when given to persons with G6PD deficiency. Hence before administering methylene blue to the patient, G6PD deficiency should be ruled out (20). Alternative therapies include ascorbic acid, exchange transfusion and hyperbaric oxygen (14, 16).

CONCLUSION

To conclude initial methemoglobin levels may not always predict the severity or outcome in children with acquired methemoglobinemia. Definitive therapy in the form of methylene blue may be life saving in these children if instituted early before the occurrence of cerebral anoxia.

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