CASE REPORT

Methemoglobinemia in a Patient on Maintenance Hemodialysis: A Case Report

Ruchi Gupta[1], Sumit Ray[2]

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Abstract

In recent years, India has faced an increasing number of patients requiring dialysis with the insurgence of dedicated dialysis centers. Maintenance hemodialysis presents a unique but undermined potential source of exposure to patients whereby an individual is exposed to around 300–400 L of external water as dialysate fluid. The solutes in water used, along with disinfectants like chlorine, chloramines, amines, and nitrates if not filtered appropriately and used as dialysate may cause methemoglobinemia and other complications in patients undergoing dialysis. Acquired methemoglobinemia though a rare clinical condition, in its severest form, may lead to rapid clinical deterioration and death if not identified and managed in time. The oxidized form of iron in the methemoglobin impedes its binding to the oxygen molecule leading to a drop in oxygen-carrying capacity of the blood. The first step of management is to stop the inciting agent. In a chronic kidney disease (CKD), patient excretion of inciting agent may be impeded in case of renally excreted molecules leading to prolonged exposure and persisting methemoglobinemia.

We report this rare case of severe methemoglobinemia in a patient with CKD on dialysis.

Keywords: Acquired methemoglobinemia, Amine filtration, Carbon filters, Case report, Dialysate filtration process, Filtration, Hemodialysis.

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Introduction

As of 2018, there were about 12,880 dialysis centers with 175,000 patients requiring chronic dialysis in India.

Water used as dialysate used for dialysis undergoes a multistage filtration process. The water may contain both organic and inorganic solutes which need to be adequately cleared.[1,2] The disinfectants used for treating municipal water which is mostly the source of water used for dialysis; if not cleared adequately may cause oxidative stress leading to methemoglobinemia.[3–5] We encountered one such rare occurrence of methemoglobinemia. The potential of dialysis-associated methemoglobinemia was considered after ruling out other causes.

[1,2]Department of Critical Care, Holy Family Hospital, Okhla, Delhi, India

Corresponding Author: Ruchi Gupta, Department of Critical Care, Holy Family Hospital, Okhla, Delhi, India, Phone: +91 9910695602, e-mail: ruchi_gupta.mamc@yahoo.co.in

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Case Description

A 43-year-old male patient with a history of chronic kidney disease (CKD) and hypertension on thrice-a-week dialysis, came to our emergency department with complaints of shortness of breath post dialysis done from another institute. At presentation, his saturation of peripheral oxygen (SpO_2) was 76% on room air which increased to 88% with oxygen by nasal prongs. The patient was on tablets of amlodipine, clonidine, and homeopathic treatment. The patient continued to be in respiratory distress for which noninvasive ventilation was started. Urgent hemodialysis was done.

Post dialysis also, patient's oxygenation continued to worsen with SpO_2 of 76% with peripheral cyanosis with a fraction of inspired oxygen (FiO_2) of 100% associated with worsening sensorium. Repeat arterial blood gas analysis (ABG) revealed an arterial saturation of 99% with rising lactate levels. Methemoglobin levels were 32.4% which increased to 48%. There was an associated worsening in SpO_2 to 64%, peripheral cyanosis, and worsening sensorium. Glucose-6-phosphate dehydrogenase (G6PD) levels were sent. Methylene blue (1 mg/kg) was administered. In response to it, the patient's SpO_2 improved with improvement in sensorium within 0.5 hour. G6PD levels came out to be normal. ABG after 6 hours showed a decrease in methemoglobin levels to 9.4% with an increased lactate level to 11. A repeat methylene dose was given. There was a fall in hemoglobin with signs of hemolysis in the peripheral smear along with brown discolored plasma. A unit of packed red blood cells (RBCs) was transfused.

On days 2 and 3 of the intensive care unit (ICU) stay, there was again an increase in methemoglobin levels (12.4 and 17%, respectively) for which methylene blue was repeated. The patient required four units of packed RBCs.

The drug history of the patient was reviewed. No potential attributable factor could be discerned. The only potential cause could have been dialysis-associated methemoglobinemia. A rare case of such has been reported attributed to disinfectant used to clean supply water and its inadequate clearance. The patient was getting routine dialysis outside and had developed symptoms immediately after dialysis, hence, the possibility of acquired methemoglobinemia postdialysis was kept in mind. We tested our filtered water used for dialysis for nitrates and chlorine which came within acceptable limits.

The patient's blood work revealed an increase in hepatic transaminases attributed to severe tissue hypoxia which started to decrease on day 4.

The patient was shifted from ICU on day 5 and subsequently discharged after 7 days of hospitalization.

Discussion

A CKD patient on routine dialysis may be exposed to around 300–400 L of dialysate water in 1 week; and hence, to various organic and inorganic solutes. During dialysis aluminum, chloramine, copper, fluoride, lead, nickel, nitrate, sulfate, and zinc have been found to be toxic.[1,2,6]

The source of water used for this purpose is usually the municipal water. Water used for dialysis has to undergo a multi-stage filtration process to be deemed fit for use. The municipal water used is treated with various disinfectants to decrease the bacterial load. However, the chemicals added if not adequately cleared by the filtration system may lead to increased oxidative stress and may lead to methemoglobinemia.[3–5]

Methemoglobin is an oxidized state of hemoglobin consisting of ferric (Fe^{3+}) moiety instead of ferrous (Fe^{2+}) which does not bind to oxygen. Cytochrome B5 reductase (Cytb5) and nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) reductase reduce ferric to ferrous form to limit methemoglobin levels. The latter pathway is activated using methylene blue to treat and reverse methemoglobinemia. Increased oxidative stress in the body overwhelming the physiological Cytb5 reductase pathway may lead to clinically significant methemoglobinemia. Potential oxidants in tap water include sodium hypochlorite, chloramines, copper, and nitrates.[1,2,6]

Water used for dialysis before use is subjected to reverse osmosis before being used for the same. However, the process of reverse osmosis does not remove smaller molecules especially if present in higher concentrations. Carbon adsorption filters are required to clear the smaller molecules namely chloramines and chlorine added to municipal water as disinfectants.[2,6,7] Both are toxic to patients and can additionally damage the reverse osmosis membrane. Owing to the great role of carbon filters for water purification for dialysis along with reverse osmosis, the American Society of Nephrology recommends using dual granular activated carbon filters. The filters are provided with sampling ports for testing the chlorine levels which need to be monitored regularly among other safety standards to deem the water fit for use.[2]

The efficiency of the filtration unit is also greatly dependent on the quality of water used like its bacterial load, small molecule load, disinfectants used, etc. Water fed into the filtration system for dialysis has to meet certain standards to be adequately filtered. The concentration of various organic and inorganic compounds has an effect on the clearing of solutes, hence it becomes imperative for any organization to monitor it.[2,5]

Because of the longevity of chloramines, most of the water treatment plants in developed countries are moving towards its use for disinfection rather than chlorine. Many cases of dialysis-associated methemoglobinemia have been reported there on the introduction of chloramine to municipal water. Medarov et al. found chloramines used for water disinfection to be the cause of methemoglobinemia during dialysis.[8]

In the developed countries when chloramine became the primary disinfectant, there was a surge in methemoglobinemia cases during the transition from chlorine to chloramine.[3–5] Now in most countries chloramine levels are routinely monitored multiple times a day during the filtration process used for dialysate fluid. As the efficiency of the filtration process is also dependent on the water fed into the system, it is recommended to routinely check the water source for changes in composition at regular intervals.[7]

As chloramine is not a method of water disinfection in India, it is not routinely monitored in the dialysis filtration process. In India, chlorine is used as a water disinfectant. Chlorine itself is not toxic however it damages the carbon filter thereby decreasing its efficiency in clearing chloramines and other organic materials.[2,7]

Nitrate levels are increased in water due to excessive use of fertilizers, sewage contamination, and animal waste contamination of water. As per WHO maximum allowable nitrate content in drinking water is 50 mg/L. For use in dialysis nitrogen content of water has to be reduced to ≤2.0 mg/L. This is achieved by various processes of filtration, like ion exchange, reverse osmosis, etc.[2]

As per the Bureau of Indian Standards (Amendment No. 1 June 2015) acceptable limit in drinking water for chloramine is 4 mg/L, chloride (as Cl) is 250 mg/L, nitrate (as NO_3) is 45 mg/L, copper (as Cu) is 0.05 mg/L.[9] As per the American Society of Nephrology and Association for the Advancement of Medical Instrumentation; the water used for dialysis, should have a concentration of chloramine ≤ 0.10 mg/L, free chlorine ≤ 0.50 mg/L, nitrates (as N) ≤ 2.0 mg/L, and copper ≤ 0.10 mg/L.[7]

Medarov et al. in their evaluation of methemoglobinemia during dialysis found that increased chloramine levels were not picked up by their routine analysis of dialysis fluid and were noted only when a different test was used. The variability of the tests makes it necessary to rethink dialysis as a cause of toxicity even with normal test results.[8]

In our patient, we ruled out any other cause of methemoglobinemia. The nitrate and chlorine levels in our dialysis unit were checked which came to be in prescribed limit. Chloramine levels were not monitored, and as we still don't use chloramine to disinfect municipal water, its significance is not known. We also did a random sampling of patients undergoing dialysis in our institute. No new case of increased methemoglobin levels could be found. Our patient continued to have persistent methemoglobinemia for 3 days probably attributable to continued oxidative stress due to decreased clearance.

The cause of methemoglobinemia in this patient still eludes us, with a possibility of acquired methemoglobinemia from dialysis done outside as a likely cause.

Conclusion

With the growing number of dialysis and the sheer volume of fluids that these patients are exposed to, water needs to be considered a source of any organic and inorganic toxicities. Organizational setups need to provide adequate filtration processes with frequent monitoring systems in place. The source of water and any change in it should also be monitored periodically. Any change should alert the dialysis unit.

Orcid

Ruchi Gupta https://orcid.org/0000-0003-2419-165X
Sumit Ray https://orcid.org/0000-0001-5192-4711

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