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Selected Topics: Toxicology

A CASE OF METHEMOGLOBINEMIA SUCCESSFULLY TREATED WITH HYPERBARIC OXYGENATION MONOTHERAPY

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□ **Abstract—Background: Methylene blue is the first-line therapy for methemoglobinemia, but it can be intermittently unavailable due to production issues. For this clinical scenario, alternative treatment options need to be explored. Hyperbaric oxygenation (HBO) is conventionally applied as an adjunctive therapy during the systemic administration of methylene blue. Currently, little is known regarding the effects of HBO monotherapy in methemoglobinemia. We report a case of methemoglobinemia that was successfully treated with HBO monotherapy. Case Report: A 41-year-old man presented to the Emergency Department with dyspnea and dizziness subsequent to smoking in a garage filled with motor vehicle exhaust gas. There were no abnormal heart or lung sounds. While administering oxygen flowing at 15 L/min via a mask with a reservoir bag, blood tests revealed high methemoglobin (MetHb) levels at 59.6%. He was treated with HBO monotherapy, and sequential tests showed that the MetHb level decreased significantly to 34.0%, 12.8%, 6.2%, and eventually, 3.5%. He was discharged with stable vital signs the next day. Why Should an Emergency Physician Be Aware of This?: HBO monotherapy is an effective alternative treatment for methemoglobinemia when methylene blue is not available.** © 2017 Elsevier Inc. All rights reserved.

□ **Keywords—hyperbaric oxygenation; methemoglobinemia; methylene blue; nitrogen compound**

INTRODUCTION

Methemoglobinemia is a disorder characterized by decreased oxygen-carrying capacity of hemoglobin owing to transformation of heme from the ferrous state to the ferric state. Methemoglobinemia can be fatal and has been commonly reported worldwide. Ash-Bernal et al. conducted a retrospective study of the regional prevalence of methemoglobinemia in the United States and identified 138 patients from two tertiary hospitals over 28 months (1). Methylene blue (MB) is the treatment of choice for methemoglobinemia. In certain cases, however, the supply of MB can be hindered by various production problems (2–4). An alternative treatment for this potentially lethal condition should be explored.

Hyperbaric oxygenation (HBO) has been conventionally applied as an adjunctive therapy during the systemic administration of MB in methemoglobinemia (5–7). Little is known about the effects of HBO monotherapy in patients with methemoglobinemia. We report a case of methemoglobinemia that was successfully treated with HBO monotherapy.

CASE REPORT

A 41-year-old man presented to the Emergency Department (ED) with dyspnea and dizziness after smoking in

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a garage filled with motor vehicle gas exhaust. The garage had no ventilation system but was not a completely closed room. He was transferred to our ED from the local hospital after being admitted for 1 day for further evaluation and proper management for methemoglobinemia. On arrival at our hospital, the patient's methemoglobin (MetHb) level was 37% per the records from the first local hospital. The patient's Glasgow Coma Scale score was 15, blood pressure was 130/90 mm Hg, heart rate was 127 beats/min, respiratory rate was 16 breaths/min, body temperature was 36.6°C, and SpO_2 was 88%. Cyanosis was observed on the body surface, and the arterial blood collected in the syringe for laboratory tests was chocolate brown in color, suggesting an elevated MetHb level. On initial physical examination, there were no abnormal heart or lung sounds. During the administration of oxygen flowing at 15 L/min via oxygen mask with a reservoir bag, laboratory tests revealed the following: pH, 7.450; PCO_2, 31.6 mm Hg; PO_2, 201.8 mm Hg; HCO_3, 22.1 mM; O_2, 93.0%; MetHb, 59.6%; and carboxyhemoglobin, 0%. Other results were within the normal range. The MetHb level increased from 37% on his visit to the previous local hospital to 59.6%, and the carboxyhemoglobin level decreased from 2.6% to 0%. No active lung lesion was noted on chest radiography, and sinus tachycardia was observed on the electrocardiogram.

We suspected that the methemoglobinemia was induced by nitrogen compounds, especially nitrite, produced by the motor vehicle engine combustion and smoking (8). The patient was administered HBO monotherapy instead of a MB injection because the latter was unavailable due to a supply problem. The protocol for the HBO therapy was as follows: HBO was administered twice at 2 atmospheres (atm) for 90 min with 3-h intervals; subsequently, this process was repeated at 2 atm for 90 min with 6-h intervals. Serial examinations of the MetHb levels showed an overt reduction over time to 34.0%, 12.8%, 6.2%, and eventually, 3.5% (Figure 1). On the third hospital day, the MetHb level was < 2%, after which the HBO therapy was discontinued and conservative care was administered. The next day, the patient was discharged with stable vital signs.

We obtained informed consent and authorization from the patient for the publication of this case report.

DISCUSSION

In methemoglobinemia, the ratio of hemoglobin to MetHb decreases, and the primary clinical effect of this medical condition is a reduction in the oxygen-carrying capacity of hemoglobin to tissues. Subsequently, tissue hypoxia can be a cause of death due to multiple organ failure. Various causes of methemoglobinemia have been reported in several studies (9–11). Nitrite oxides

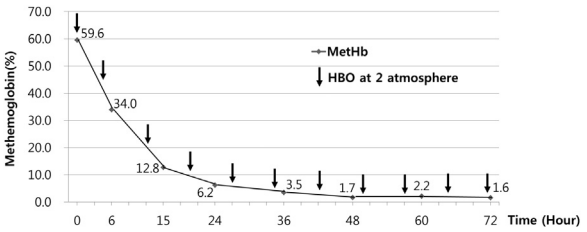

Figure 1. Changes in plasma methemoglobin concentrations according to the administration of hyperbaric oxygenation (HBO). The protocol for HBO therapy comprised administration of HBO twice at 2 atmospheres (atm) for 90 min with 3-h intervals, and then consecutive administrations of HBO at 2 atm for 90 min with 6-h intervals. Serial examination of methemoglobin (MetHb) levels showed an overt reduction over time to 34.0%, 12.8%, 6.2%, 3.5%, 1.7%, 2.2%, and eventually, 1.6%.

from vehicle gas exhaust and smoking are also causes of methemoglobinemia (8,12).

MB is the drug of choice for treating patients with methemoglobinemia (13). In the presence of nicotinamide adenine dinucleotide phosphate, MB is reduced to leukomethylene blue by erythrocyte MetHb reductase. Then, leukomethylene blue reduces MetHb to oxyhemoglobin.

Over the past 2–3 years, the supply of MB has been interrupted in South Korea. The pharmaceutical company providing MB decided to discontinue the production of this medication due to low profits. During this period, we had to identify alternative treatments for methemoglobinemia, such as high-dose vitamin C therapy and HBO.

High-dose vitamin C therapy has been reported to offer good outcomes in patients with methemoglobinemia in the absence of MB (3,4). However, we encountered a case of methemoglobinemia wherein the patient died of multi-organ failure and coagulopathy after high-dose vitamin C therapy. Upon administration of vitamin C, the MetHb level decreased significantly, along with a deterioration of liver and renal function. Furthermore, there is always an imminent threat of oxalate nephropathy secondary to high-dose vitamin C therapy regardless of the baseline renal function (14). On the other hand, HBO monotherapy showed no particular side effects.

Since the 1970s, studies have examined the effectiveness of HBO for treating methemoglobinemia (5–7). However, most of these studies applied HBO as an adjunctive therapy during the systemic administration of MB. The mechanism of HBO therapy in methemoglobinemia involves promoting the reduction of MetHb to oxyhemoglobin and allowing for immediate reoxygenation (6). More specifically, HBO reduces MetHb levels by inhibiting the oxidation of hemoglobin by nitrite (7). Goldstein and Doull induced methemoglobinemia in rats using sodium nitrite and

found that 75% of the rats died within the first 2 h, and those treated with HBO did not experience cyanotic changes or death during the 10-day observation period (7). HBO therapy can lower MetHb levels, and the rate of reduction is reported to be about 8% per hour when administered at 2.2 atm (7). In our case, we used a previously established protocol of our hospital: HBO was administered twice at 2 atm for 90 min with 3-h intervals; subsequently, the process was repeated at 2 atm for 90 min with 6-h intervals. The initial level of MetHb was 59.6%, decreasing to 12.8% after about 15 h with three sessions of HBO therapy at 2 atm. On the basis of a rate of reduction of 8%, we expected that the MetHb level would decrease to 17%. However, in our case, the level decreased to 12.8%. HBO monotherapy thus offered favorable results and clinical outcome.

A limitation to this therapy in our hospital is that the equipment for HBO therapy is a single-chamber system that has no room for any other medical support devices. Therefore, patients requiring mechanical ventilation support or those with compromised respiratory function are not eligible for HBO monotherapy. In such cases, continuous monitoring is not feasible and emergency situations may not be addressed immediately. Patients who cannot receive HBO monotherapy could instead receive normobaric oxygenation in addition to hypothermia therapy. The rationale for this approach is reducing the metabolic rate of the brain tissue, thus allowing for the supply of more oxygen to other major organs (15). In particular, this strategy has neuroprotective effects in patients with altered consciousness, and it has been successfully applied in other fields (16,17).

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

Clinical toxicology is an area of emergency medicine. Securing second-line treatments in the absence of an antidote in cases of poisoning by a specific substance is an important issue that could have fatal outcomes. HBO monotherapy is an effective alternative treatment for methemoglobinemia when MB is not available. A multi-chamber system rather than a single-chamber system of HBO therapy offers the advantage of allowing trained health care providers to be in the chamber with critically ill patients, especially patients with impaired consciousness or compromised airway.

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