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Case Report

Extracorporeal membrane oxygenation in fatal methemoglobinemia caused by sodium nitrite: A case report and review of the literature

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Introduction

Nitrites, as a powerful kind of oxidizing agent, can oxidize ferrous ions (Fe^{2+}) to ferric ions (Fe^{3+}), triggering the conversion of normal hemoglobin (Hb) to methemoglobin (MetHb), which loses its ability to carry oxygen, resulting in hypoxia in tissues and death in severe cases.[1] Mistaken ingestion of nitrites or excessive consumption of foods containing nitrites can cause cyanosis, headaches, confusion, coma, and respiratory failure depending on the degree of hypoxia.[2,3] Prolonged hypoxia can cause organ damage. Heart, lung, and brain damage are particularly dangerous and can lead to death. Here, we report a child who was supported by venoarterial extracorporeal membrane oxygenation (VA-ECMO) after experiencing cardiac arrest following nitrite poisoning.

Case Presentation

A 15-year-old girl was admitted to the emergency department at 04:25 due to the loss of consciousness (Figure 1). She had been diagnosed with mood disorders and treated with oral antidepressants in the past 6 months. The father denied that she had any history of hypertension, diabetes, coronary heart disease, infectious diseases, trauma or surgery, or food or drug allergies. Her vital signs included a temperature of 36.6°C, blood pressure of 117/56 mmHg, heart rate of 107 beats/min, and respiratory rate of 26 breaths/min, with oxygen saturation undetectable by pulse oximetry. She was in a deep coma with a Glasgow Coma Score of 3 points, bilateral pupils equal in size (diameter of 3.0 mm,) and an absent reflex to light. She also presented with cyanosis of the lips and extremities, closed teeth, foaming at the mouth, and a wet and cold body. An arterial blood gas analysis revealed the following: pH: 7.231; partial press of carbon dioxide ($PaCO_2$): 34.0 mmHg; partial press of oxygen (PaO_2): 410 mmHg; bicarbonate ion(HCO_3^-):14.3 mmol/L; base excess (BE): −13 mmol/L; serum sodium (Na^+): 139 mmol/L; serum potassium (K^+): 2.8 mmol/L; serum calcium (Ca^{2+}): 1.26 mmol/L; glucose: 21 mmol/L; hematocrit: 39%; Hb: 133g/L; and troponin I<0.05 ng/mL. Electrocardiography (ECG) showed no abnormalities. She was immediately given intravenous drops of insulin, potassium chloride, and sodium bicarbonate and underwent a computed tomography (CT) scan of the head, chest, and abdomen. No high- or low-density regions were found on the cerebral CT scan according to the neurological physician, and her CT scans of the chest and abdomen were similarly negative.

Unfortunately, the patient suffered a sudden cardiac arrest at 05:03 (Figure 1). Cardiopulmonary resuscitation (CPR) and invasive mechanical ventilation were immediately administered, and her spontaneous circulation returned at 05:19 (Figure 1); however, a second cardiac arrest subsequently occurred at 05:25 (Figure 1). The patient was cannulated for VA-ECMO with the consent of her family. Surprisingly, the blood from her femoral artery was a soy-sauce color and the PaO_2 value after membrane oxygenation was 459 mmHg. Nitrate poisoning was immediately suspected and an intravenous injection of 100 mg of methylene blue was promptly given. At the same time, careful collection of the medical history was completed. The patient had consumed a lot of stews refrigerated in the refrigerator for two consecutive days before the onset of her disease, which her parents did not eat as they had taken their meals in the workplace. Later, the mother checked her shopping lists and found no other records associated with nitrites. A spontaneous heart rate was restored at 07:40 (Figure 1) and her MetHb level was found to be 21.0%. At this point, the concentrations of nitrites in the blood and urine were found to be 0.03 μg/mL and 0.50 μg/mL, respectively; thus, nitrite poisoning was confirmed.

The patient was transferred to the intensive care unit (ICU) for further treatment at 08:40. As her cyanosis was not completely relieved, an additional 200 mg of methylene blue was

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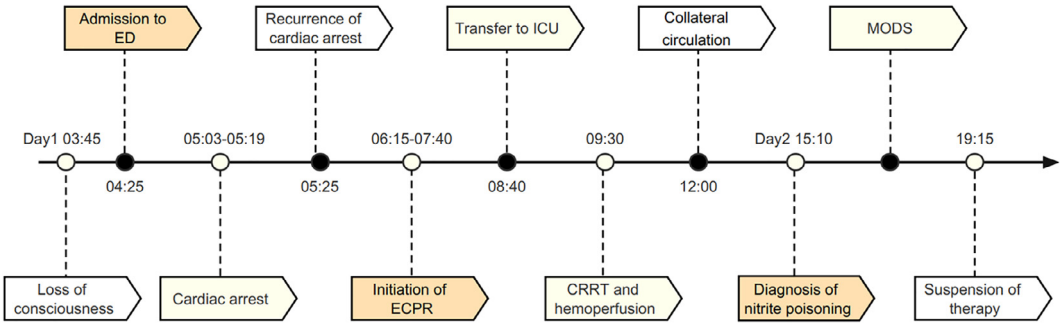

Figure 1. The flowchart of the patient's course.
CRRT: Continuous renal-replacement therapy; ECPR: Extracorporeal cardiopulmonary resuscitation; ED: Emergency department; ICU: Intensive care unit; MODS: Multi-organ dysfunction syndrome.

administered alongside high doses of vitamin C. With ECMO support, continuous renal replacement therapy, and hemoperfusion were conducted via the ECMO circuit, and the color of her arterial blood gradually turned bright red. Moreover, the oxygen saturation on pulse oximetry increased from 61% to 96% at 09:30 (Figure 1) and her cyanosis of the lips and extremities improved. The MetHb value also decreased to 3%.

Ultimately, the child was deemed neurologically impaired due to a total CPR time of approximately 2 h. Liver failure was documented, with an alanine aminotransferase level of 1747 U/L and an aspartate aminotransferase level of 1385 U/L. Echocardiography revealed that the left ventricular ejection fraction was only 40%, with a high level of troponin I (>30 ng/mL). Her creatinine value was 97 μmol/L and her urea nitrogen level was 8.25 μmol/L. Failure of multiple organs, including the brain, heart, lungs, and liver, together with coagulation dysfunction, was noticed, with further progressive deterioration. The parents decided to give up on treatment at 19:15 and were discharged then (Figure 1).

Discussion

An overabundance of sodium nitrite in the blood causing methemoglobinemia and an associated systemic alteration of the blood can be fatal if not recognized and treated promptly.[1] Nitrites have a paralyzing effect on the central nervous system, especially on the vasomotor center, causing extreme vasodilation of blood vessels, resulting in blood pressure reduction and even circulatory failure. There have been multiple case reports of the accidental over-ingestion of sodium nitrate or sodium nitrite, including several fatalities.[1,2,4]

Exposure to nitrite-containing toxic salts is a recognized cause of acquired methemoglobinemia. Several possible etiologies of methemoglobinemia have been identified, including drugs and industrial chemicals, dietary ingestion of compounds such as nitrites and nitrates, genetic enzymatic deficiencies, and idiopathic cases often related to systemic acidosis.[5]

It is known that anemic (or transport) hypoxia refers to tissue hypoxia caused by changes in the quantity or quality of Hb, resulting in the reduction of arterial oxygen content levels or the release of oxygen bound in oxygenated Hb, while PaO_2 levels remain normal in the environment. One of the conditions that can cause Hb elimination is methemoglobinemia, where nitrites, perchlorate, sulfonamide, and other such compounds reach toxic levels, causing a large percentage of Hb in the blood (20%–50%) to be converted into MetHb. The formation of MetHb occurs because Fe^{2+} in Hb is oxidized to Fe^{3+} under the action of oxidants such as nitrites.[6]

Despite the strong and compelling evidence supporting recent sodium nitrite ingestion as a trigger for fatal MetHb in most reported cases, measured postmortem MetHb saturations range widely in the literature from 6% to 89%.[1] In this regard, thorough documentation of the patient presentation, including noting the characteristic purple–grey lividity of the skin in affected patients, is an important tool to help determine whether a toxic salt such as sodium nitrate or sodium nitrate may have been ingested. Perhaps the most common screening methodology is detecting MetHb saturation in the blood. It is noted that we focused on testing for the end result of MetHb to establish the cause of death in our case.

In the absence of corroborating information, nitrite poisoning should be highly suspected in a cyanotic and hypoxic patient who presents without respiratory disease. In case of this suspicion, one should contact the poison testing agency immediately. Diagnostic tests include arterial blood gas analysis, electrolyte levels, MetHb level, glucose, and ECG, and the test results should be obtained as soon as possible.

Methylene blue is a specific antidote to sodium nitrite and resultant methemoglobinemia. The appropriate dose of methylene blue in this context is 1–2 mg/kg. Intravenous injection of methylene blue can be repeated, with a maximum dose of 7 mg/kg, if the cyanosis of the skin and mucosa does not subside in 30–60 min. Vitamin C can promote the transformation of MetHb into Hb because of its strong reducing effect. If treatment with methylene blue does not work, the possibility of Hb sulfide should be considered. The use of a sedative compound may also be employed in those planning to die by suicide via toxic salt–induced methemoglobinemia. In this case, our testing noted that the child had no ethanol or psychiatric medications (with possible sedative effects) in the blood.

There are several key points and difficulties that arose during the course of treatment in this case. First, as cardiac arrest occurred twice in a short time, we were unable to maintain the patient's autonomic heart rate with continuous CPR, which suggested that there was an extracorporeal CPR indication. The VA-ECMO system is connected to both a vein and an artery and is used when there are problems with both the heart and lungs. In most cases, VA-ECMO is used to address severe acute circulatory failure.[7] In our case, the patient required cardiac support, so we chose VA-ECMO. Second, after VA-ECMO initiation,

we observed that blood samples from the artery end (returning blood to the heart) and vein end (drawing blood to the periphery) were both a soy-sauce color; in general, after VA-ECMO has started, the proximal blood should be the color of normal venous blood (dark red) and the distal blood (arterial blood) following processing by the ECMO oxygenator should be a bright red. To uncover the reason for this discrepancy, we first excluded the problem of catheterization because femoral vein catheterization was performed under the guidance of ultrasound and the femoral artery incision was made under direct visualization by the cardio-vascular surgeon. Next, we examined the retro-membranous blood gas of the ECMO system, which indicated that the oxygen pressure was as high as 400 mmHg, from which we could infer that the ECMO system was working well and achieving normal oxygenation. We then considered whether there was something wrong with the oxygenation process.

In the physiological state, a small amount of MetHb is continuously formed in the blood, but it can be reduced to Fe^{2+} by reducing agents such as nicotinamide adenine dinucleotide, as it is a reducing coenzyme (NADH), vitamin C, and reduced glutathione so that the content of MetHb in normal blood is limited to 1–2% of the total amount of Hb.

With repeated inquiries about her medical history, the patient's parents revealed that the patient had consumed meals stored overnight in recent days. Eating rotten, newly pickled, improperly processed vegetables, and cooked vegetables stored for too long can easily lead to nitrite poisoning and methemoglobinemia, which will impair oxygen-carrying and oxygen-release functions, and cyanosis is the main symptom of this phenomenon.

Considering the symptoms of vomiting, diarrhea, and cyanosis, the diagnosis of nitrite toxicity could not be excluded. With this belief, five methylene blue antagonists were given and about 20 min later, to our surprise, the patient's ECG monitoring showed normal ventricular fibrillation waves. Subsequently, a single defibrillation was performed, and the patient recovered her autonomic heart rate. The patient was then transferred to the ICU, where ECMO was continued and another administration of methylene blue and high-dose vitamin C was performed. One hour after being admitted to the ICU, the patient's finger pulse oxygen saturation had gradually increased to about 97%, her cyanosis of the lips and limbs had gradually improved, and the blood color of the ECMO femoral artery catheterization had gradually changed from dark red to bright red.

All these signs suggested the possibility of nitrite toxicity. To confirm this diagnosis, blood and urine samples were taken from the patient for poison detection, and the toxicology test indicated excessive nitrite levels, confirming our diagnosis. At this time, her blood gas MetHb value was 1.3% (0–1.5%). Notably, this value is not high, which may be the result of the therapeutic measures of antagonistic drugs, blood purification, and ECMO.

To confirm the diagnosis further, we found the blood samples previously collected when the patient arrived at our emergency department. Using these samples, the MetHb and nitrite concentrations in blood samples at two different time points—one after the patient was admitted to the emergency department (the first blood sample, without antidote) and the other after 100 mg of methylene blue was administered—were detected. The results of blood gas analysis showed that the MetHb levels at these points were 21.0% and 3.0%, respectively. This high value of MetHb before antidote usage and the lower value of MetHb after antidote usage further confirmed the diagnosis.

When cardiac arrest occurs outside the hospital, with a long time of no perfusion of tissues and organs, the prognosis of patients with long CPR times is poor.[8] Although VA-ECMO was successfully given, the damage to the heart, brain, kidneys, and other important organs in this case was difficult to reverse. We searched the literature and found that there was only one case report of acquired methemoglobinemia rescued by venovenous ECMO.[9] To our knowledge, our case is the first report of a patient with nitrite toxicity who received VA-ECMO therapy.

Conclusions

In summary, this is the case of a patient with fatal methemoglobinemia caused by sodium nitrite toxicity who received VA-ECMO in China. Our experience suggests that ECMO can play a role in the life-saving salvage of severely ill patients. This case also provides a reminder that clinicians should consider the diagnosis of methemoglobinemia in unexplained coma patients and emphasizes the importance of diagnostic procedures.

Author Contributions

Xiaoshu Zuo: Writing- Original draft preparation, Formal Analysis. Xiaoyu Fang: Writing- Original draft preparation, Visualization. Guang Li: Project administration, WritingReviewing and Editing. Liying Zhan: Conceptualization, Supervision, Funding acquisition.

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Ethics Statement

Written informed consent was obtained from the guardian of patient for publication of this case report and any accompanying images.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data in this case report are available from the corresponding author upon reasonable request.

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