



REVIEW

Methemoglobinemia in the Operating Room and Intensive Care Unit: Early Recognition, Pathophysiology, and Management

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ABSTRACT

The objectives of this review are to describe the acquired and hereditary causes of methemoglobinemia, to recommend the most sensitive diagnostic tests, and to enable critical care clinicians to rapidly detect and treat methemoglobinemia. To meet these objectives, Internet search engines were queried with the

keywords to select articles for review that included case reports, case series, observational, longitudinal, and surveillance studies. The most common causes of methemoglobinemia include oxidizing reactions to cocaine-derived anesthetics, such as benzocaine and lidocaine, to antibiotics, such as dapsone and other sulfonamides, and to gases, such as nitric oxide. Additionally, CO-oximetry is superior to standard pulse oximetry in detecting methemoglobinemia. Finally, effective treatments for methemoglobinemia include intravenous administration of methylene blue, ascorbic acid, and riboflavin. In this manuscript we will discuss methemoglobinemia, how it occurs, and how to treat it.

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oxide; Pain; Riboflavin

Key Summary Points

Methemoglobinemia can present as a challenge for clinicians to both diagnose and treat in the intensive care unit and the operating room.

Clinically, methemoglobinemia may manifest as dyspnea, nausea, cyanosis, and tachycardia to much more extreme symptoms such as lethargy, stupor, and deteriorating consciousness.

Methemoglobinemia can be diagnosed by a discrepancy between the SpO₂ and SaO₂ that is refractory to oxygen therapy, signs of cyanosis, decreased SpO₂ hovering at 85%, chocolate-colored blood, acidosis and tachycardia, and most effectively with use of CO-oximetry.

The most common drugs that cause methemoglobinemia include cocaine-derived anesthetics such as benzocaine and lidocaine, antibiotics such as dapsone, and gases such as nitric oxide.

A variety of inherited forms of methemoglobinemia exist including congenital methemoglobinemia, hemoglobin M disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and autosomal recessive deficiency of cytochrome b5 reductase in which oxidant drugs should be avoided and exchange transfusion may be beneficial.

Treatments of methemoglobinemia include methylene blue, ascorbic acid, riboflavin, hyperbaric oxygen therapy, and even RBC transfusion for refractory or severe cases. Methylene blue is used for cases primarily caused secondary to drug exposure.

INTRODUCTION

There are many causes of hypoxia in the perioperative period and in the intensive care unit (ICU) ranging from airway obstruction to hemoglobinopathies. Surrogate measurements such as transcutaneous oxygen saturation by pulse oximetry are often used for the rapid assessment of patient oxygenation status. Any delays in the correction of acute hypoxia can have significant consequences including cardiac arrest and brain damage. Therefore, clinicians must be able to recognize, respond to, and treat both common and uncommon causes of oxygen desaturation and hypoxia.

Methemoglobinemia is an uncommon, often overlooked, and potentially reversible cause of hypoxia in the perioperative setting. Methemoglobinemia occurs when the bound ferrous iron (Fe²⁺) of oxyhemoglobin is oxidized to the bound ferric iron (Fe³⁺) of methemoglobin. An indication of methemoglobinemia is a discrepancy between the transcutaneous oxygen saturation (SpO₂) and the calculated arterial oxygen saturation on arterial blood gas (SaO₂). Furthermore, a decreased SpO₂ often with a nadir of 85%, chocolate-colored or black/brown blood, physiologically appropriate partial pressure of oxygen (PaO₂) on arterial blood gas (ABG), metabolic acidosis, and tachycardia are all associated with methemoglobinemia.

The symptoms of methemoglobinemia relate to the level of methemoglobin in the blood [1]. Dyspnea, nausea, and tachycardia occur at methemoglobin levels generally greater than 30%, while lethargy, stupor, and deteriorating consciousness occur as methemoglobin levels reach 50% [2]. It should be noted that in patients with lifelong congenital methemoglobinemia or with a history of chronic methemoglobinemia secondary to chronic exposure to drugs or toxins, methemoglobin levels can be as high as 40% [3] and still be well tolerated with cyanosis (blueish cast to the mucous membranes of the skin) being the only presenting manifestation.

Genetic risk factors for methemoglobinemia include hemoglobin M disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and

congenital methemoglobinemia genotypes. Only early recognition of high-risk factors for methemoglobinemia will prevent perioperative hypoxia in the operating room and ICU. A discrepancy between SpO₂ and the calculated SaO₂ may be the earliest indicator of methemoglobinemia.

Factors that increase a patient's risk for developing methemoglobinemia include having pre-existing conditions such as cardiovascular or pulmonary diseases and/or anemia. These patients should be treated regardless of symptoms when methemoglobin levels reach 10%. All patients with methemoglobin levels of 30% or more should be treated with an appropriate therapy regardless of symptoms. Those at the extremes of age are also at increased risk for developing methemoglobinemia in the perioperative setting.

The most common drugs that cause methemoglobinemia include cocaine-derived anesthetics such as benzocaine and lidocaine, antibiotics such as dapsone, and gases such as nitric oxide. Positive clinical data does exist regarding the benefits of co-administration of cimetidine in patients requiring long-term dapsone therapy. Hemoglobin M, a genetic disease which will be discussed in more detail, does not respond to ascorbic acid or methylene blue treatment. In this situation, exchange transfusion may be beneficial. Dextrose should be given in addition to methylene blue as it is used to form nicotinamide adenine dinucleotide phosphate (NADPH) through the hexose monophosphate shunt.

Treatments for methemoglobinemia will be discussed in more detail but include red blood cell exchange transfusions and hyperbaric oxygen therapy, which may be indicated in refractory cases.

The objectives of this review are (1) to describe the acquired and hereditary causes of methemoglobinemia, (2) to recommend the most sensitive diagnostic laboratory tests, and (3) to enable critical care clinicians to rapidly detect methemoglobinemia in unconscious patients and administer appropriate rescue therapies.

METHODS

To conduct this review, several Internet search engines, including Google, Google Scholar, PubMed, Ovid, and Cochrane, were queried with the keywords. The searched keywords included methemoglobinemia, benzocaine, lidocaine, dapsone, nitric oxide, methylene blue, ascorbic acid, riboflavin, and hyperbaric oxygen therapy. The scientific articles selected for review included review articles, case reports, case series, and observational and longitudinal studies. Articles excluded from review included diagnostic laboratory reports, pathophysiological reports, and clinical pathological case conference presentations. The study period was defined as 1990 to the present. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Pathophysiology of Methemoglobinemia

Methemoglobinemia is characterized by elevated blood levels of hemoglobin (Hb) containing oxidized ferric (+3) iron (Fe) rather than ferrous (+2) Fe [4]. Hb with ferric Fe cannot reversibly bind oxygen (O₂) and has increased affinity for the O₂ bound to the other functional ferrous heme groups, further preventing delivery of O₂ to tissue [5, 6]. Because methemoglobin cannot effectively deliver O₂ to peripheral tissue and organs, the oxyhemoglobin dissociation curve is shifted left and hypoxia results [7]. The pathogenesis of methemoglobinemia is either congenital or acquired and consists of four main types: severe, acute acquired, chronic mild, and chronic. Severe is life threatening and requires immediate emergency therapy. Acute acquired requires the cessation of the inducing agent and immediate emergency therapy. Chronic mild may present as asymptomatic with cyanosis (or no cyanosis), and there is no specific therapy required. Finally, chronic methemoglobinemia requires medications to reduce cyanosis such as

Types of methemoglobinemia	Treatment
Severe methemoglobinemia	Need emergency therapy (It is life-threatening)
Acute acquired methemoglobinemia	Need to stop administration of inducing agent and emergency therapy
Chronic mild methemoglobinemia	Can be fully asymptomatic with cyanosis or not and no specific therapy required.
Chronic methemoglobinemia	Medications to reduce cyanosis Methylene blue; citric acid; oxygen

Fig. 1 Types of methemoglobinemia. Reproduced from [1]

methylene blue, citric acid, or oxygen. These will be discussed in more detail below. See Fig. 1, used with permission from [1].

Risk Factors for Methemoglobinemia

Various pre-existing medical conditions can also predispose a person to developing methemoglobinemia during and outside of the perioperative setting. Under normal physiologic conditions in healthy individuals, approximately 1% of total hemoglobin exists as oxidized methemoglobin [8]. In congenital methemoglobinemia, the enzyme responsible for the reduction of ferric methemoglobin to ferrous oxyhemoglobin, cytochrome b5 reductase, is deficient which results in decreased reduction of methemoglobin back to oxyhemoglobin. This deficiency can be present in all cells, as seen in type II congenital methemoglobinemia or absent only in red blood cells (RBCs) as seen in type I congenital methemoglobinemia [9].

Hemoglobin M disease is an autosomal dominant genetic disorder resulting from mutation in either the alpha, beta, or gamma chains of the hemoglobin molecule. These mutations result in hemoglobin that resists reduction from the oxidized ferric state back to the ferrous state. This causes a permanent increase in levels of methemoglobin ranging between 15% and 30%.

Heterozygotes of the autosomal recessive deficiency in cytochrome b5 reductase are at an increased risk of developing clinically significant methemoglobinemia in the perioperative setting when compared to homozygotes. This may result from the lack of compensation

present in the heterozygotes, which is otherwise present in the homozygotes from the chronicity of phenotype [10]. Even in light of the varying degrees of compensation seen in patients with congenital methemoglobinemia, conditions causing imbalances in the supply/demand ratio of O₂ can lead to decompensation and development of severe symptoms of hypoxia [11].

Pre-existing conditions including cardiovascular disease and/or anemia place all patients at an increase susceptibility to develop acute symptoms of hypoxia in the setting of exposure to various oxidizing agents in the environment and perioperative setting [12]. Thus, it is recommended for patients intolerant to reduction in oxygen carrying capacity, including those with coronary artery disease, peripheral vascular disease, cerebrovascular disease, sepsis, respiratory disease, acidosis and/or anemia, that they be treated regardless of symptoms when methemoglobin levels reach 10%. Furthermore, it is recommended that all patients with methemoglobin levels of 30% or more be treated with an appropriate therapy regardless of symptoms [11].

Infants and premature infants have only half the erythrocyte cytochrome b5 reductase activity seen in adults. As such, they are more susceptible to the development of methemoglobinemia [13]. The elderly are also at an increased risk of developing methemoglobinemia [8]. Patients with G6PD deficiency are at an increased risk of developing methemoglobinemia because the deficit in the G6PD enzyme causes red blood cells to prematurely break down. G6PD is the most prevalent enzyme deficiency, occurring almost exclusively in male individuals, with an estimated 400 million people affected worldwide [14]. Overall, however, the majority of cases of methemoglobinemia are due to exposure to medications and others toxic agents [4, 11]. Common agents implicated in causing methemoglobinemia are listed in Table 1 [15].

Diagnosis of Methemoglobinemia

Methemoglobinemia can be assessed in the intraoperative setting through several methods.

Table 1 Agents that may cause methemoglobinemia. Modified from [15]

Classes	Drugs
Acetamides	Phenacetin
Analgesics	Phenazopyridine
Antibiotics	Dapsone, trimethoprim, sulfonamides
Antigout agents	Rasburicase
Antimalarials	Chloroquine, primaquine
Antineoplastic agents	Cyclophosphamide, flutamide
Industrial/household products	Aniline dyes, naphthalene, aminophenols, chlorates, bromates, herbicides, and pesticides
Local anesthetics	Articaine, benzocaine, lidocaine, prilocaine
Nitrate derivatives	Nitrates salt, nitroglycerin
Nitrite derivatives	Nitroprusside, amyl nitrite, nitric oxide
Prokinetic agents	Metoclopramide

See Fig. 2, reused with permission [1]. One of the first and most readily available clues that methemoglobinemia is present is cyanosis, or a blueish hue to the mucous membranes of the hands and feet and is easily detected by the naked eye. Furthermore, sulfhemoglobinemia, a rare but potentially comorbid condition to methemoglobinemia, may also occur and present as cyanosis. Sulfhemoglobinemia is caused by excess sulfhemoglobin in the blood, which is the product of the irreversible binding of sulfur by the hemoglobin in red blood cells which makes them unable to transport oxygen. It can result from ingestion of dapsone, phenacetin, and sulfonamides; therefore, the health care provider must consider this as a differential diagnosis [10]. The most clinically effective method of methemoglobin detection is through use of a CO-oximeter, which directly measures the light wavelength absorption of

Diagnostic test
Arterial blood gas (ABG)
Co-oximetry (more accurate) or Pulse oximetry
Potassium cyanide test (metHb and sulfhemoglobin differentiation)
Bedside tests for methemoglobinemia (using filter paper for blood color evaluation or using 100% oxygen to aerate a tube of blood)
CT of the head
Chest radiography (pulmonary and cardiac disease exclusion)
Complete blood count (CBC), reticulocyte counts, lactate dehydrogenase (LDH), indirect bilirubin, haptoglobin
Liver function tests, electrolyte concentrations, blood urea nitrogen (BUN), creatine
Urine pregnancy tests
Heinz body preparation
Serum level of nitrites or inducing drugs
Enzyme assays

Fig. 2 Diagnosis of methemoglobinemia. Reproduced from [1]

methemoglobin in the blood. In standard pulse oximetry, light absorption is measured at wavelengths of 660 nm and 940 nm, allowing calculation of the oxyhemoglobin to deoxyhemoglobin ratio. The pulse oximeter then translates this ratio into an estimated percentage of blood oxygen saturation, with an oxyhemoglobin to deoxyhemoglobin ratio of 1 corresponding to an oxygen saturation of approximately 85% [16]. This is of clinical importance since methemoglobin absorbs light equally at wavelengths of 660 nm and 940 nm [16]. Thus, as methemoglobin levels in the blood increase, oxygen saturation would be expected to hover around 85% due to the equal absorbance occurring at the 660 nm and 940 nm wavelengths.

The advantage of CO-oximetry in evaluating methemoglobinemia is that it measures light absorbance at two additional wavelengths, 600 nm and 631 nm, compared to standard pulse oximetry [16]. Multiple wavelength CO-oximetry, thus, provides physicians with a non-invasive method for intraoperatively assessing methemoglobin, which also absorbs light at a 631 nm wavelength. The specificity of CO-oximetry for detecting methemoglobin can be further improved by addition of the Evelyn-Malloy assay, also known as the acid diazo coupling method, which is the most widely used industrial reaction in the production of dyes, helps to eliminate methylene blue and sulfhemoglobin as possible false positives [12].

The assay provides cyanide binding of methemoglobin and subsequent alteration of the 631 nm absorption peak.

Hypoxia and cyanosis in the setting of discrepancy between the SpO2 and the SaO2 that is refractory to oxygen therapy should elevate methemoglobinemia on the differential list. In addition to this “saturation gap,” signs and symptoms classically associated with methemoglobinemia include cyanosis refractory to oxygen therapy, decreased SpO2 often with a nadir of 85%, chocolate-colored [12] or black/brown blood [6, 8, 9], physiologically appropriate PaO2 on ABG, acidosis and tachycardia [12]. These are described in Table 2 [1].

Management of Methemoglobinemia

Current treatments for methemoglobinemia vary depending on the contributing factors whether genetic and/or drug exposure. For hereditary methemoglobinemia oxidant drugs should be avoided, but ascorbic acid may be of benefit if used daily [17].

For methemoglobinemia caused primarily by drug exposure, methylene blue infusion is used typically when methemoglobin levels are 30% for asymptomatic and 20% for symptomatic patients. If the patient has underlying anemia, cardiac, or pulmonary comorbidities, lower thresholds of methemoglobin levels should be considered for administration of methylene blue. Interestingly, patients with hemoglobin M disease do not respond to ascorbic acid or methylene blue treatment, because individuals with this disease do not have symptoms. However, exchange transfusion may be used.

Because methylene blue depends on the availability of reduced NADPH, dextrose should be given in addition to methylene blue as it is used to form NADPH through the hexose monophosphate shunt [18]. Nicotinamide adenine dinucleotide (NADH) is also reduced from NAD+ by catabolism of dextrose in glycolysis and therefore addition of dextrose helps replenish NADH. Alternative methods such as riboflavin are effective via flavin reductase in human erythrocytes and the reduction of methemoglobin. Ascorbic acid is a water-soluble

Table 2 Signs and symptoms associated with MetHb blood concentrations. Reprinted from [12]. Copyright (2014), with permission from Elsevier

Methemoglobin concentration (g/dL)	% of total hemoglobin	Symptoms
< 1.5	< 10	None
1.5–3.0	10–20	Mild symptoms. Cyanotic (blue/slate gray) skin discoloration, chocolate brown blood, no hypoxic symptoms
3.0–4.5	20–30	Anxiety, light-headedness, headache, tachycardia, breathlessness, syncopal attacks
4.5–7.5	30–50	Fatigue, confusion, dizziness, tachypnea, increased tachycardia, weakness
7.5–10.5	50–70	Coma, seizures, arrhythmias, lactic acidosis, CNS depression, dysrhythmias
> 10.5	> 70	Profound hypoxia, death

reducing agent and a donor antioxidant. Cimetidine inhibits conversion of dapsone to its oxidizing metabolite, dapsone hydroxylamine, by the cytochrome P450 system, thereby preventing further development of dapsone-induced methemoglobinemia [2]. Ketoconazole has shown a similar mechanism of action in treatment of dapsone-related methemoglobinemia [19]. There is conflicting data regarding the efficacy of N-acetyl cysteine

and its ability as a reducing agent in methemoglobinemia. In vitro studies have demonstrated positive results, while a randomized control crossover study concluded that intravenous administration of *N*-acetyl cysteine failed to enhance methemoglobin reduction [1, 3, 12].

Treatment for symptomatic methemoglobinemia involves promoting the reduction of methemoglobin back to oxyhemoglobin through the use of methylene blue, ascorbic acid, riboflavin, and hyperbaric oxygen therapy. As a last resort in emergency situations where the previous therapies are insufficient, unavailable, or contraindicated, red blood cell transfusion therapy can be attempted in cases of critically elevated methemoglobin levels exceeding 70% [11].

The detailed treatment for methemoglobinemia is intravenous administration of 1% methylene blue, in a dose of 1–2 mg/kg over a 5-min interval, with repeat doses every 30 min to an hour if necessary. The total amount of methylene blue given should not exceed 7 mg/kg and any dose 15 mg/kg or greater will result in direct lysis of red blood cell. Rebound methemoglobinemia may occur up to 18 h after methylene blue administration, due to prolonged absorption of lipophilic agents (benzocaine) from adipose tissue. Serial measurements of methemoglobin levels should be performed following treatment with methylene blue [14]. Of note, methylene blue increases the reducing capacity of the NADPH-MHb reductase system by acting as a cofactor in the electron transfer from NADPH to the oxidized methemoglobin [8]. Therefore, an adjuvant therapy to consider is ascorbic acid, which works by non-enzymatically reducing methemoglobin, although to a much lesser extent than methylene blue [11, 20]. The substitution of ascorbic acid for methylene blue is necessary in circumstances where methylene blue is not available or is contraindicated. With regard to hemoglobin M disorder, methemoglobinemia does not respond to either ascorbic acid or methylene blue [4]. Methylene blue is also contraindicated in patients with G6PD deficiency. In these patients, the use of methylene blue can worsen methemoglobinemia and promote red blood cell lysis. This is because the

reduction of methemoglobin by methylene blue is dependent on NADPH generated by G6PD [20]. Methylene blue can also act by reversibly inhibiting monoamine oxidase A (MOA), leading to a rise in serotonin levels. Therefore, methylene blue is also contraindicated in individuals on selective serotonin reuptake inhibitor therapy. Of note, there have been reported cases of methylene blue-induced acute encephalopathy and serotonin syndrome [21]. Therefore, the health care provider should be sure to take a detailed patient history, including any and all medications and/or supplements before making the decision to administer methylene blue.

There is no consistent recommendation regarding dosage of ascorbic acid for treatment of methemoglobinemia provided in the literature. The dosages and duration of treatment vary widely across these cases ranging from 1 g ascorbic acid as a one-time dose [reportedly lowering the patient's methemoglobin level from 26.2% to 2.1% within 6 h of dosing] [22] to high-dose 10 g ascorbic acid every 6 h [22]. Dosing recommendations from four case reports of successful resolution of methemoglobinemia using only vitamin C have been outlined in a 2016 review by Sahu et al. [23]. See Fig. 3, used with permission from [24].

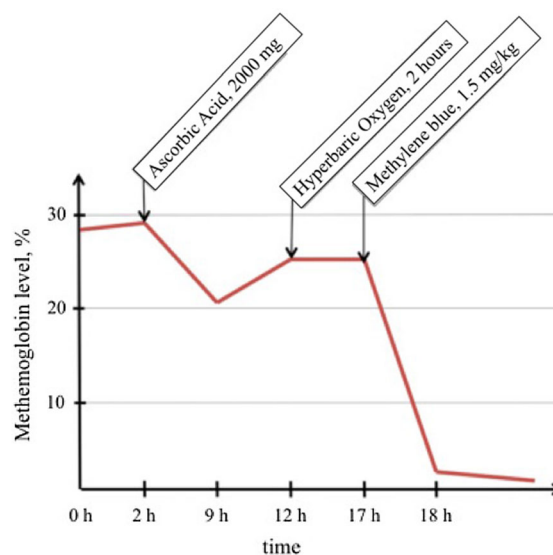


Fig. 3 Chronologic observation of patient's methemoglobin levels and its relation to treatments. Reproduced from [24]

CONCLUSIONS

Methemoglobinemia can present as a challenge for clinicians in both diagnosis and treatment. Clinically, methemoglobinemia may manifest as dyspnea, nausea, cyanosis, and tachycardia to much more extreme symptoms such as lethargy, stupor, and deteriorating consciousness. Methemoglobinemia can be diagnosed by a discrepancy between the SpO₂ and SaO₂ that is refractory to oxygen therapy, signs of cyanosis, decreased SpO₂ hovering at 85%, chocolate-colored blood, acidosis, and tachycardia, and most effectively with use of CO-oximetry. The most common drugs that cause methemoglobinemia such as benzocaine and lidocaine, antibiotics including dapsone, and gases including nitric oxide are summarized in Table 3. A variety of inherited forms of methemoglobinemia exist including congenital methemoglobinemia, hemoglobin M disease, G6PD deficiency, and autosomal recessive deficiency of cytochrome b5 reductase in which oxidant drugs should be avoided and exchange transfusion may be beneficial. Treatment of methemoglobinemia includes methylene blue, ascorbic acid, riboflavin, hyperbaric oxygen therapy, and even RBC transfusion for refractory or severe cases. Methylene blue is used for cases primarily caused secondary to drug exposure. Methylene blue is given in these cases for greater than 30% in asymptomatic patients and greater than 20% in symptomatic patients; however, lower thresholds should be considered for infants, premature infants, the elderly, and patients with underlying anemia, cardiac, or pulmonary comorbidities.

LIMITATIONS

Only clinically relevant information was gathered, analyzed, and presented in this paper. We were unable to recommend experimental therapies such as intralipid infusion, ketoconazole, cimetidine, or even hyperbaric oxygen because of lack of further research. The Evelyn-Malloy assay can be used to increase specificity, but there is a lack of evidence on quantifying the increase itself or mention of its effects on sensitivity. There is a lack of data on the use of daily ascorbic acid as a preventative measure within populations mentioned prior to being at an increased risk. There are multiple studies on animal models on adjunct therapy with methylene blue but no mention of synergistic effects. On the basis of the low side effect profile of both ascorbic acid and riboflavin and enough data published on their possible effects, we recommend their use prior to methylene blue when enzyme testing is underway in emergent settings or methylene blue is unavailable. No consistent recommendations exist regarding effective dosages of ascorbic acid or riboflavin for treatment of methemoglobinemia and vary from study to study. Further studies with larger sample sizes of treatment strategies for different conditions with methemoglobinemia are recommended.

FINAL RECOMMENDATIONS

With the over the counter availability of topical anesthetics and frequent use in the emergency room for airways management, intubation in

Table 3 Incidence of most drugs that cause methemoglobinemia. Modified from [15]

Class of drugs	Common	Uncommon	Rarely
Analgesics	Phenazopyridine, phenacetin		Acetaminophen, fentanyl
Anticonvulsants			Phenobarbital
Anti-infectious agents	Dapsone, primaquine	Sulfonamides	Nitrofurantoin, chloroquine
Local/topic anaesthetics	Benzocaine, prilocaine	Tetracaine, cetacaine, amethocaine	Lidocaine
Vasodilators	Nitrite derivatives	Nitrate derivatives	
Miscellaneous		Methylene blue, metoclopramide	

the operating room, and endoscopic procedures there have been a significant number of cases of methemoglobinemia reported in the past decade. A high suspicion for methemoglobin should follow any presentation of hypoxic and cyanotic patients who are not improving with 100% FiO₂ oxygen therapy. Taking a thorough history and investigating recent medication exposure while giving great importance to a discrepancy between the SpO₂ and the SaO₂ recorded on an ABG that is refractory to oxygen therapy is recommended. The most clinically effective measurement method is through use of a CO-oximeter, which directly measures the light wavelength absorption of methemoglobin in the blood. Methylene blue infusion is recommended when methemoglobin levels are 30% for asymptomatic and 20% for symptomatic patients [11].

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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