Review Article

Unexplained Postoperative Cyanosis: Local Anesthetic–Induced Methemoglobinemia, Diagnosis and Clinical Management

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Abstract

Methemoglobinemia is a disorder characterized by the oxidation of hemoglobin iron from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state, resulting in impaired oxygen binding and reduced tissue oxygen delivery. Under normal physiological conditions, small amounts of methemoglobin are continuously formed and efficiently reduced by endogenous enzymatic systems, primarily the NADH-dependent cytochrome b5 reductase pathway. However, exposure to oxidative stress, particularly in the perioperative setting, can overwhelm these mechanisms and lead to clinically significant elevations in methemoglobin levels. Local anesthetics such as prilocaine and benzocaine represent important triggers, as their metabolites act as oxidizing agents that promote hemoglobin oxidation. The risk is further increased in susceptible individuals, including those with glucose-6-phosphate dehydrogenase deficiency, underlying cardiopulmonary disease, extremes of age, or exposure to multiple oxidizing drugs. Procedural factors, including repeated dosing of anesthetics and the use of topical agents, also contribute to the development of postoperative cyanosis. Clinically, methemoglobinemia presents with central cyanosis that is refractory to supplemental oxygen, often accompanied by symptoms that correlate with methemoglobin levels, ranging from asymptomatic cases to severe neurological and

cardiovascular compromise. A key diagnostic feature is the discrepancy between low oxygen saturation on pulse oximetry and normal arterial oxygen tension. Definitive diagnosis is established through co-oximetry. Management requires immediate discontinuation of the offending agent and supportive oxygen therapy. Methylene blue remains the first-line treatment, acting as a reducing agent to restore hemoglobin function. Early recognition and intervention are critical to prevent serious complications and ensure favorable outcomes.

Key words

Methemoglobinemia, postoperative cyanosis, local anesthetics, dyshemoglobinemia, co-oximetry, methylene blue.

Introduction

Methemoglobinemia is a condition characterized by the oxidation of hemoglobin iron, which impairs its ability to effectively bind and transport oxygen [1, 2]. This alteration in hemoglobin function results in reduced oxygen delivery to tissues and can lead to clinically significant hypoxia. The condition may be congenital, arising from genetic mutations that affect enzymatic pathways responsible for maintaining hemoglobin in its functional state, or acquired, most commonly because of exposure to oxidizing agents [1, 3].

In the perioperative and postoperative settings, methemoglobinemia represents an important and potentially underrecognized cause of unexplained cyanosis and hypoxia. A key clinical feature is the lack of response to supplemental oxygen, which distinguishes it from more common respiratory or cardiovascular causes of hypoxemia [4]. Given this atypical presentation, it is essential to differentiate methemoglobinemia from other etiologies of cyanosis in order to avoid misdiagnosis and inappropriate management [5].

A well-established association exists between methemoglobinemia and the use of certain local anesthetics. Agents such as benzocaine, prilocaine, and lidocaine have been identified as common causes of drug-induced methemoglobinemia. Among these, benzocaine has been most frequently implicated, particularly when administered in high doses or through repeated applications, increasing the risk of significant oxidative stress on hemoglobin [5, 6].

Early recognition of methemoglobinemia is critical to prevent progression to severe hypoxia and potential organ damage [7]. Confirmation of the diagnosis is typically achieved through co-oximetry, a diagnostic modality capable of accurately measuring methemoglobin levels and distinguishing it from other forms of dyshemoglobinemia [3]. Once identified, the standard treatment involves the administration of methylene blue, which acts as a reducing agent to convert methemoglobin back to functional hemoglobin. However, this therapy is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency, in whom alternative management strategies must be considered [5].

The aim of this article is to analyze methemoglobinemia as a cause of unexplained postoperative cyanosis, emphasizing its pathophysiology, association with local anesthetics, clinical presentation, diagnostic approach, and therapeutic management, in order to improve early recognition and prevent adverse outcomes in the perioperative setting.

Methodology

This manuscript was developed as a structured narrative review aimed at providing an updated and clinically integrated analysis of methemoglobinemia as a cause of unexplained postoperative cyanosis, with particular emphasis

on pathophysiological mechanisms, diagnostic strategies, perioperative risk factors, and contemporary therapeutic approaches. The review was conducted in accordance with the SANRA (Scale for the Assessment of Narrative Review Articles) framework and followed a predefined methodological protocol established prior to literature screening. Given the clinical variability of postoperative cyanosis and the broad differential diagnosis in perioperative settings, a narrative interpretative synthesis was selected over quantitative pooling in order to integrate physiological, pharmacological, diagnostic, and therapeutic considerations into a coherent and clinically applicable framework. Special attention was given to local anesthetic–induced methemoglobinemia, the role of oxidizing agents in perioperative practice, the challenges of distinguishing this condition from other causes of hypoxemia, and the implications of timely diagnosis and treatment. The objective was to provide a structured synthesis capable of supporting multidisciplinary decision-making in perioperative and postoperative care.

A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science, including peer-reviewed articles published in English or Spanish between January 2020 and march 2026. The final search was performed in march 2026. This timeframe was selected to capture contemporary advances in perioperative monitoring, diagnostic modalities, pharmacological safety, and the management of drug-induced methemoglobinemia. Foundational studies were incorporated when necessary to contextualize underlying pathophysiological mechanisms, congenital and acquired forms of the disorder, and the historical evolution of therapeutic strategies. The search strategy combined MeSH and free-text terms using Boolean operators related to methemoglobinemia, postoperative cyanosis, perioperative hypoxia, local anesthetics, benzocaine, prilocaine, lidocaine, co-oximetry, methylene blue, glucose-6-phosphate dehydrogenase deficiency, and dyshemoglobinemia. Searches were conducted in titles and abstracts as well as indexed subject headings to maximize sensitivity.

The initial search yielded 146 records. After removal of duplicates, 112 articles remained for title and abstract screening. Of these, 74 underwent full-text evaluation, and 39 studies were included in the final synthesis. Selection was performed independently by two authors, with disagreements resolved through discussion and consensus. Exclusion criteria comprised non–peer-reviewed publications, isolated case reports without broader clinical relevance, editorials without diagnostic or therapeutic outcome data, redundant datasets, and studies not directly addressing the pathophysiology, diagnosis, perioperative relevance, or management of methemoglobinemia associated with unexplained postoperative cyanosis.

Eligible studies included randomized controlled trials, observational cohorts, systematic reviews, meta-analyses, expert consensus statements, toxicology reports, and contemporary international guidelines from anesthesiology, perioperative medicine, emergency medicine, hematology, and clinical pharmacology societies. Priority was assigned to multicenter investigations, studies evaluating drug-induced methemoglobinemia in perioperative settings, and research addressing clinically relevant outcomes such as diagnostic accuracy, methemoglobin levels, response to methylene blue, need for supportive interventions, and treatment-related complications. Extracted variables included study design, patient population, perioperative context, causative agent, methemoglobin concentration, presenting symptoms, diagnostic method, therapeutic intervention, clinical response, and reported complications. Methodological quality and internal validity were assessed narratively, considering risk of bias, sample size, follow-up duration, consistency of diagnostic criteria, and reproducibility of reported outcomes. In cases of conflicting evidence, greater interpretative

weight was assigned to higher-level evidence and guideline-supported recommendations.

Reference lists of included studies were manually screened to identify additional relevant publications. Given its narrative design, this review is subject to potential selection bias and does not provide pooled quantitative estimates. Artificial intelligence–based tools were used exclusively to assist in literature organization and structural coherence, whereas critical appraisal, synthesis, and final interpretation were conducted independently by the authors to preserve methodological rigor.

Physiological Basis and Pathophysiology

Hemoglobin is a tetrameric protein composed of two alpha and two beta subunits, each containing a heme group capable of binding oxygen. The iron within the heme group is normally in the ferrous (Fe^{2+}) state, which is essential for effective oxygen binding and transport throughout the body [8]. However, when the iron is oxidized from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state, hemoglobin is converted into methemoglobin, a form that is unable to bind oxygen, thereby impairing oxygen delivery to tissues [7].

Under physiological conditions, the oxidation of hemoglobin occurs at low levels as part of normal cellular processes, but this phenomenon can be significantly amplified under conditions of oxidative stress, leading to increased concentrations of methemoglobin. In more extreme oxidative environments, the formation of ferryl heme (Fe^{4+}) may occur, a highly reactive species capable of inducing additional cellular damage due to its strong oxidizing properties. These alterations in iron oxidation states play a central role in the pathophysiology of methemoglobinemia [8].

Methemoglobin formation results directly from the oxidation of hemoglobin iron from Fe^{2+} to Fe^{3+}, rendering the molecule incapable of oxygen binding [7]. This process may be triggered by a variety of exogenous agents, including drugs and chemical substances, ultimately leading to decreased oxygen delivery and the clinical manifestation of cyanosis [9]. Additionally, certain hemoglobin variants with high oxygen affinity, such as hemoglobin Rothschild, may further impair tissue oxygen delivery despite apparently normal oxygen saturation levels, as these variants retain oxygen more tightly and limit its release to peripheral tissues [10].

To counterbalance these processes, the body relies on endogenous reduction systems that maintain hemoglobin in its functional state. The primary mechanism is the NADH-dependent cytochrome b5 reductase pathway, which utilizes NADH as a cofactor to reduce methemoglobin back to functional hemoglobin. In addition, an auxiliary NADPH-dependent pathway contributes to this reduction process, although its role is less significant compared to the NADH-dependent system [11].

In the perioperative context, local anesthetics represent a key trigger for methemoglobinemia through the generation of oxidative metabolites. Prilocaine, for example, is metabolized into o-toluidine, a potent oxidizing agent that promotes the formation of methemoglobin. Similarly, benzocaine, particularly when used topically or in repeated doses, has been strongly associated with the development of methemoglobinemia, especially in susceptible individuals [7]. The risk is further amplified by factors that enhance oxidative stress, including genetic predispositions, the concomitant use of other oxidizing drugs, and underlying medical conditions, all of which contribute to increased susceptibility and severity of the condition [9].

Epidemiology and Risk Factors

The incidence of postoperative cyanosis varies depending on the type of procedure and underlying patient characteristics, with higher rates observed in specific perioperative contexts. Patients undergoing procedures involving regional anesthesia and endoscopic interventions

appear to have an increased risk. Pulmonary complications, including cyanosis, are more frequently reported in individuals with pre-existing pulmonary hypertension undergoing endoscopic procedures, with a documented rise in postoperative pulmonary complications within this population [13].

Several patient-related factors contribute to an increased susceptibility to postoperative cyanosis and methemoglobinemia. Among these, glucose-6-phosphate dehydrogenase deficiency is of clinical relevance, as affected individuals are predisposed to oxidative stress and may develop methemoglobinemia, a condition that can manifest as cyanosis. This is especially important given that methylene blue, the standard treatment for methemoglobinemia, is contraindicated in this population, complicating management strategies [5]. Additionally, patients with underlying cardiopulmonary diseases, including pulmonary hypertension, are at increased risk of postoperative cyanosis due to their limited physiological reserve and higher incidence of respiratory complications such as respiratory failure and pneumonia [13, 14]. Extremes of age also represent a significant risk factor, as both neonates and elderly patients exhibit increased vulnerability. In elderly individuals, particularly those undergoing cardiopulmonary bypass, the incidence of postoperative pulmonary complications is notably high and may present with cyanosis [15].

Pharmacological factors also play a central role in the development of postoperative cyanosis. The administration of high or repeated doses of local anesthetics has been associated with the development of methemoglobinemia, which leads to impaired oxygen delivery and clinically evident cyanosis. Furthermore, the concomitant use of oxidizing agents, such as benzocaine, can precipitate or exacerbate this condition, particularly in patients with repeated exposure during the perioperative period [5].

Perioperative factors further contribute to the risk profile. The use of topical anesthetics, especially benzocaine, has been strongly associated with the development of methemoglobinemia and subsequent cyanosis, with the risk increasing in cases of repeated application [5]. In addition, polypharmacy is a relevant consideration, as the concurrent use of multiple medications may increase the likelihood of drug interactions and cumulative oxidative effects, particularly in complex surgical settings where various anesthetic and analgesic agents are administered [16].

Clinical Presentation

Methemoglobinemia is characteristically associated with refractory central cyanosis that does not improve with supplemental oxygen therapy. This phenomenon occurs because methemoglobin is unable to bind and transport oxygen, resulting in impaired tissue oxygen delivery despite normal arterial oxygen tension. As a result, patients may present with persistent hypoxia that appears disproportionate to measured oxygen levels. In this context, pulse oximetry often demonstrates low oxygen saturation values that remain unchanged even after oxygen administration, a pattern that has also been observed in conditions such as hemoglobin M disease [17, 18].

The clinical presentation of methemoglobinemia varies according to the percentage of methemoglobin present in the circulation. At levels below 10%, patients are typically asymptomatic, as oxygen delivery is not significantly compromised, a pattern also observed in certain hemoglobin variants such as hemoglobin Köln [19]. When levels increase to between 10% and 20%, visible cyanosis becomes apparent, often in the absence of other symptoms [18]. At concentrations ranging from 20% to 50%, patients commonly develop symptoms such as dyspnea, headache, and fatigue, reflecting more significant impairment in oxygen delivery. For example, phenazopyridine-induced methemoglobinemia has been reported in a

patient presenting with dyspnea and a methemoglobin level of 32.2% [7]. As levels approach or exceed 50%, more severe manifestations may occur, including neurological impairment and cardiac arrhythmias, which require urgent medical intervention. At levels around 70%, the condition becomes life-threatening and necessitates immediate treatment, typically with methylene blue [5].

In addition to clinical symptoms, several characteristic findings can support the diagnosis. One of the most distinctive features is the presence of "chocolate-colored" blood, which results from the oxidized state of iron within methemoglobin and has been documented in clinical cases of the condition [20]. Another important diagnostic clue is the discrepancy between oxygen saturation measured by pulse oximetry and arterial oxygen levels. While pulse oximetry may indicate low saturation, arterial blood gas analysis often reveals a normal partial pressure of oxygen. This discordance reflects the inability of methemoglobin to effectively carry oxygen, leading to a state of functional anemia despite adequate oxygen availability [18].

Diagnosis

Clinical suspicion of methemoglobinemia should arise in the presence of unexplained postoperative cyanosis, particularly when there is no adequate response to supplemental oxygen therapy. In such cases, the persistence of cyanosis despite appropriate oxygen administration suggests the presence of underlying conditions beyond simple hypoxemia, including dyshemoglobinemias such as methemoglobinemia or sulfhemoglobinemia, in which abnormal hemoglobin species impair effective oxygen transport [3]. Similarly, a lack of improvement in oxygen saturation despite high-flow oxygen therapy indicates a non-respiratory etiology, which may include right-to-left cardiac shunts or disorders affecting hemoglobin function [21, 22].

The evaluation of suspected methemoglobinemia requires careful interpretation of monitoring tools and laboratory findings. Pulse oximetry, although widely used in perioperative settings, has important limitations in this context. The presence of dyshemoglobins such as methemoglobin or carboxyhemoglobin can result in falsely low or inaccurate readings, as pulse oximeters rely on specific wavelengths that may not distinguish between different hemoglobin species [3, 23]. Consequently, reliance solely on pulse oximetry may lead to misinterpretation of the patient's oxygenation status.

For definitive diagnosis, arterial blood gas analysis with co-oximetry is considered the gold standard. This technique allows for accurate differentiation between oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin, providing a comprehensive assessment of oxygen-carrying capacity and confirming the presence of dyshemoglobinemia [3, 24].

The differential diagnosis of postoperative cyanosis is broad and must be systematically approached. Respiratory causes of hypoxemia, including atelectasis, pneumonia, and acute respiratory distress syndrome, should be considered, particularly when there is supporting clinical or imaging evidence of impaired pulmonary function [25]. Pulmonary embolism, although less common, remains an important consideration in cases of sudden hypoxemia and should be evaluated using appropriate imaging modalities such as computed tomography pulmonary angiography [21]. In addition, congenital methemoglobinemia should be considered in patients with persistent or unexplained elevations in methemoglobin levels, which can be confirmed through co-oximetry. Sulfhemoglobinemia, while rare, is another potential cause of cyanosis and is typically associated with exposure to specific drugs or chemical agents [3].

Prevention

Preventive strategies for methemoglobinemia and related postoperative complications rely on the rational use of local anesthetics, careful identification of high-risk patients, and the implementation of appropriate perioperative protocols. Avoiding excessive or repeated dosing of local anesthetics is essential, as overdosing can lead to systemic toxicity, which represents a significant risk factor for complications such as postoperative cyanosis. Adherence to recommended dosing guidelines is therefore critical in minimizing this risk. For example, intravenous lidocaine should be administered cautiously, with doses not exceeding 1.5 mg/kg, calculated based on the patient's ideal body weight, and should not be used concurrently with other local anesthetic interventions [26].

In addition to dose control, appropriate selection of the anesthetic agent is a key component of prevention. Certain agents, such as lidocaine, have been frequently associated with systemic toxicity, particularly in vulnerable populations such as pediatric patients, in whom neurological and cardiac complications have been reported. Consequently, the choice of anesthetic should be individualized, taking into account patient-specific factors including age, body weight, and underlying comorbidities [27].

The identification of high-risk patients represents another critical aspect of preventive care. Preoperative screening allows for the recognition of individuals who may be more susceptible to local anesthetic systemic toxicity. Conditions such as obesity hypoventilation syndrome are particularly relevant, as they may exacerbate postoperative respiratory compromise and increase the likelihood of adverse outcomes [28]. Furthermore, obtaining a detailed medication history is essential to identify potential drug interactions and contraindications, especially in patients with pre-existing conditions that may predispose them to increased sensitivity to local anesthetics [29].

Perioperative protocols also play a fundamental role in reducing the incidence of complications. Continuous monitoring of respiratory parameters, including the use of continuous pulse oximetry, enables early detection of hypoxia and respiratory depression, thereby facilitating timely intervention [30]. In parallel, staff education and awareness are essential components of patient safety. Training healthcare providers to recognize the early signs and symptoms of local anesthetic systemic toxicity, as well as reinforcing adherence to established dosing guidelines, can significantly reduce the risk of postoperative complications. Educational initiatives and structured training programs enhance the ability of clinical teams to respond promptly and effectively to emerging adverse events [29].

Therapeutic Management

The management of methemoglobinemia in the postoperative setting begins with prompt initial measures aimed at limiting further oxidative injury and improving tissue oxygenation. Immediate discontinuation of the offending agent is essential, particularly when drugs or chemicals known to induce methemoglobinemia, such as dapsone or phenazopyridine, have been administered. In parallel, supplemental oxygen should be provided to help alleviate symptoms of hypoxia, although it does not directly reduce methemoglobin levels or reverse the underlying pathophysiological process [7, 9].

Definitive treatment is typically achieved with methylene blue, which remains the first-line therapy in clinically significant cases. Methylene blue acts as an electron donor, facilitating the reduction of methemoglobin back to functional hemoglobin through activation of the NADPH-dependent methemoglobin reductase pathway [31]. The recommended dose is 1 to 2 mg/kg administered intravenously, a regimen that has demonstrated effectiveness across both adult and pediatric populations. Following administration, patients generally exhibit rapid clinical improvement, including enhanced oxygenation

and stabilization of hemodynamic parameters. Studies have also reported improvements in mean arterial pressure and a reduction in vasopressor requirements after treatment with methylene blue [32, 33].

In cases where methylene blue is contraindicated, particularly in patients with glucose-6-phosphate dehydrogenase deficiency, alternative therapeutic options must be considered. Ascorbic acid may be used as a reducing agent, although its onset of action is slower compared to methylene blue. In more severe or refractory cases, exchange transfusion may be indicated to rapidly decrease circulating methemoglobin levels and restore effective oxygen-carrying capacity. Additionally, hyperbaric oxygen therapy may be employed in selected cases to enhance oxygen delivery to tissues, although its use remains less common and is generally reserved for situations where conventional therapies are insufficient or contraindicated [7].

Prognosis and Complications

The prognosis of postoperative cyanosis largely depends on the timeliness of recognition and the effectiveness of early management. Prompt identification of the underlying cause and initiation of appropriate treatment are associated with generally favorable outcomes. Early therapeutic interventions, such as the administration of methylene blue in conditions like vasoplegic syndrome, have been shown to improve hemodynamic parameters and reduce the need for vasopressor support, although these interventions do not appear to significantly influence long-term survival [33].

Despite favorable short-term outcomes with appropriate treatment, long-term prognosis may vary depending on the underlying etiology of cyanosis. In specific clinical contexts, such as patients undergoing the Fontan operation, persistent or recurrent cyanosis has been associated with increased late mortality. This highlights the need for ongoing monitoring and long-term follow-up to identify and manage complications that may arise over time [34].

If left untreated, postoperative cyanosis can lead to significant complications, particularly due to sustained impairment in oxygen delivery. Neurological injury is among the most serious consequences, as inadequate cerebral oxygenation during procedures such as cardiopulmonary bypass has been associated with postoperative complications including delirium and cognitive dysfunction. Maintaining adequate cerebral perfusion and oxygenation is therefore critical in minimizing the risk of neurological damage [35, 36]. In addition, unexplained circulatory failure may occur, potentially related to autonomic nervous system dysfunction, leading to cardiovascular instability. In such cases, identifying and addressing underlying causes, including coronary artery disease, is essential to prevent recurrence and deterioration [37].

Further complications may arise in both neurological and cardiovascular domains. Neurological complications such as nonconvulsive status epilepticus and other deficits represent significant concerns, particularly following cardiac surgery. Early electroencephalographic monitoring and timely intervention are important strategies to reduce secondary brain injury and improve outcomes [38]. From a cardiovascular perspective, persistent cyanosis and associated hemodynamic disturbances may contribute to ongoing instability, necessitating careful monitoring and management to prevent adverse clinical outcomes [39].

Conclusions

Methemoglobinemia represents a pathophysiological state in which oxidative conversion of hemoglobin iron from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) form impairs oxygen transport, leading to tissue hypoxia and clinically evident cyanosis. In the perioperative setting, this process is frequently triggered by local

anesthetics and potentiated by patient-related, pharmacological, and procedural risk factors, highlighting the multifactorial nature of its development.

The condition is characterized by refractory cyanosis with diagnostic discrepancies between pulse oximetry and arterial oxygenation, requiring co-oximetry for confirmation. Early recognition and prompt treatment, particularly with methylene blue, are essential to prevent severe neurological and cardiovascular complications, as well as to ensure favorable clinical outcomes.

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