Risk of Topical Anesthetic–Induced Methemoglobinemia

A 10-Year Retrospective Case-Control Study

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Importance: Methemoglobinemia is a rare but serious disorder, defined as an increase in oxidized hemoglobin resulting in a reduction of oxygen-carrying capacity. Although methemoglobinemia is a known complication of topical anesthetic use, few data exist on the incidence of and risk factors for this potentially life-threatening disorder.

Objective: To examine the incidence of and risk factors for procedure-related methemoglobinemia to identify patient populations at high risk for this complication.

Design and Setting: Retrospective study in an academic research setting.

Participants: Medical records for all patients diagnosed as having methemoglobinemia during a 10-year period were reviewed.

Exposures: All cases of methemoglobinemia that occurred after the following procedures were included in the analysis: bronchoscopy, nasogastric tube placement, esophagogastroduodenoscopy, transesophageal echocardiography, and endoscopic retrograde cholangiopancreatography.

Main Outcomes and Measures: Comorbidities, demographics, concurrent laboratory values, and specific topical anesthetic used were recorded for all cases. Each case was compared with matched inpatient and outpatient cases.

Results: In total, 33 cases of methemoglobinemia were identified during the 10-year period among 94 694 total procedures. The mean (SD) methemoglobin concentration was 32.0% (12.4%). The methemoglobinemia prevalence rates were 0.160% for bronchoscopy, 0.005% for esophagogastroduodenoscopy, 0.250% for transesophageal echocardiogram, and 0.030% for endoscopic retrograde cholangiopancreatography. Hospitalization at the time of the procedure was a major risk factor for the development of methemoglobinemia (0.14 cases per 10 000 outpatient procedures vs 13.7 cases per 10 000 inpatient procedures, $P < .001$).

Conclusions and Relevance: The overall prevalence of methemoglobinemia is low at 0.035%; however, an increased risk was seen in hospitalized patients and with benzocaine-based anesthetics. Given the potential severity of methemoglobinemia, the risks and benefits of the use of topical anesthetics should be carefully considered in inpatient populations.

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METHEMOGLOBINEMIA IS A rare but serious medical condition in which there is an increase in methemoglobin production or a decrease in its elimination. Under physiological conditions, iron in hemoglobin is in the ferrous state (Fe^{2+}), which allows for oxygen binding. Oxidation to the ferric state (Fe^{3+}) results in conversion from hemoglobin to methemoglobin, which is unable to bind oxygen, reducing the oxygen-carrying capacity of blood. This transformation is responsible for the functional anemia and clinical manifestations of methemoglobinemia.[1] It can be acquired by exposure to certain anesthetics or inherited via mutations in the cytochrome-b_5 reductase enzyme or the presence of hemoglobin defects.[2]

Oropharyngeal topical anesthetics, including benzocaine, lidocaine hydrochloride, and prilocaine hydrochloride, are used

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in many medical procedures, including bronchoscopy, nasogastric tube (NGT) placement, esophagogastroduodenoscopy (EGD), transesophageal echocardiography (TEE), and endoscopic retrograde chol-

angiopancreatography (ERCP). Topical anesthetic–induced methemoglobinemia was first reported in the 1970s.[3] While all the commonly available topical anesthetics have been reported to cause methemoglobinemia, the literature is for the most part limited to case reports, and the frequency and risk factors for topical anesthetic–induced methemoglobinemia are not well defined. The clinical presentation of methemoglobinemia may include nausea, headaches, lack of energy, gray or blue skin, increased heart rate, shortness of breath, and lightheadedness.[4] Signs of acquired methemoglobinemia that are immediately noticeable include cyanosis, dark brown discoloration of the blood, and low pulse oximetry in the presence of normal arterial blood gas readings.[2,4]

Healthy individuals have methemoglobin concentrations of less than 3.0% of total hemoglobin (to convert methemoglobin concentration to proportion of total hemoglobin, multiply by 0.01).[4] Above this level, the severity of symptoms and the treatment of methemoglobinemia are dependent on the concentration.[2,4] Patients with asthma, anemia, bronchitis, emphysema, heart disease, or other lung diseases may be more likely to have complications due to methemoglobinemia.[1] Smoking increases the baseline methemoglobin concentration and susceptibility to complications.[5] Individuals with methemoglobin concentrations of less than 10.0% are usually asymptomatic and can be managed with supportive care and supplemental oxygen.[2,6] Cyanosis may be observed with methemoglobin concentrations above 10.0%. Methemoglobin concentrations from 20.0% to 50.0% cause anxiety, weariness, and tachycardia, and levels above 50.0% can result in death.[1,4,7]

Methylene blue is required as an antidote when a patient's methemoglobin concentration has reached 30.0% or higher or in the presence of significant symptoms.[8] A thiazine dye, methylene blue is an electron donor that enhances the reducing capacity of the nicotinamide adenine dinucleotide phosphate methemoglobin pathway, converting the methemoglobin back into hemoglobin.[2,4] However, higher doses of methylene blue can have a paradoxical oxidizing effect that induces methemoglobinemia.[9]

Topical anesthetics are commonly used, and methemoglobinemia is a known and potentially life-threatening complication of these agents. However, little is known about the incidence of and risk factors for topical anesthetic–induced methemoglobinemia. Given the limitations of available data, we undertook a retrospective study of methemoglobinemia cases that had occurred during the last decade at a large referral center. The primary objectives of this study were to examine the incidence of and risk factors for procedure-related methemoglobinemia to identify patient populations at high risk for this complication.

METHODS

During the 10-year period from January 1, 2001, to January 1, 2011, all cases of methemoglobinemia associated with TEE, EGD, ERCP, bronchoscopy, and NGT placement were identified. Using centralized inpatient pharmacy and laboratory records, all patients who were prescribed methylene blue or had a methemoglobin concentration obtained were included for further evaluation. Clinically significant methemoglobinemia was defined as blood methemoglobin concentrations of 10.0% or above,[10] along with signs and symptoms consistent with methemoglobinemia, including fatigue, hypoxia, cyanosis, blue discoloration, shortness of breath, and mental status changes. Patients meeting criteria for methemoglobinemia who had no record of preceding TEE, EGD, ERCP, bronchoscopy, or NGT placement were excluded from the analysis.

To calculate the overall and procedure-specific incidences of methemoglobinemia, centralized medical center billing records were queried for the volume of inpatient and outpatient procedures during the entire study period. Medical center billing records have been used in prior studies[11-13] to accurately determine the numbers and timing of interventional procedures performed during a specified period. Nasogastric tube placement is not reliably captured by this method, and cases of methemoglobinemia related to NGT placement were excluded from the calculation of the overall and procedure-specific incidences. In addition, gastrointestinal endoscopic procedure volume was unavailable from January 1, 2001, until December 31, 2004; therefore, cases of methemoglobinemia that occurred after EGD and ERCP before 2005 were excluded from the calculation of the overall and procedure-specific incidences.

To evaluate potential risk factors for methemoglobinemia in patients undergoing invasive procedures, we used a case-control strategy. For each case of methemoglobinemia except those related to NGT placement, 5 outpatients and 5 inpatients matched for sex, date of procedure, and type of procedure were chosen. Recorded for all patients were demographics, smoking status, topical anesthetic used, concurrent medications, concurrent laboratory values, Charlson Comorbidity Index,[14] and intensive care vs general medical-surgical admission. For methemoglobinemia cases, we further recorded peak methemoglobin concentrations, administration of methylene blue, and outcome of methemoglobinemia, including intubation, hospitalization, admission to the intensive care unit, or death.

Incidence rates of methemoglobinemia were compared among procedure types using the Fisher exact test. Risk factors for the development of methemoglobinemia between cases and controls were evaluated using the Fisher exact test or *t* test as appropriate, followed by univariate analysis. Further multiple linear regression modeling was performed using methemoglobinemia diagnosis as the dependent variable and type of procedure, topical anesthetic used, baseline laboratory values, Charlson Comorbidity Index, and inpatient vs outpatient status as independent variables. This study was approved as a quality improvement and quality assurance initiative by the Beth Israel Deaconess Medical Center institutional review board.

RESULTS

During the 10-year study period, 94 694 procedures were performed, including 6436 TEEs, 69 369 EGDs, 13 331 ERCPs, and 5558 bronchoscopies. Of 6436 TEEs, 1780 were performed on an outpatient basis, and 4656 were performed in hospitalized patients. Of 69 369 EGDs, 61 499 were performed on an outpatient basis, and 7870 were performed in hospitalized patients. Of 13 331 ERCPs, 8053 were performed on an outpatient basis, and 5278 were performed in hospitalized patients. Of 5558 bronchoscopies, 1495 were performed on an outpatient basis, and 4063 were performed in hospitalized patients.

Table 1. Procedure-Specific Prevalence of Methemoglobinemia

Variable	No. of Procedures, 2001-2011	No. of Methemoglobinemia Cases	Prevalence of Methemoglobinemia, %	*P* Value vs Esophagogastroduodenoscopy
Esophagogastroduodenoscopy	69 369	3	0.005[a]	Not applicable
Endoscopic retrograde cholangiopancreatography	13 331	3	0.030[a]	.08
Bronchoscopy	5558	9	0.160	<.001
Transesophageal echocardiography	6436	16	0.250	<.001

[a] Prevalence rates for esophagogastroduodenoscopy (3 of 57 537) and endoscopic retrograde cholangiopancreatography (3 of 10 521) are calculated from 2005 to 2011.

Among the entire cohort of 94 694 procedures, we noted 33 cases of methemoglobinemia, for a prevalence of 0.035% (95% CI, 0.025%-0.049%). Of these 33 cases, 16 occurred after TEE, 3 occurred after EGD, 3 occurred after ERCP, 9 occurred after bronchoscopy, and 2 occurred after NGT placement. The prevalence rates were 16 of 6436 (0.250%; 95% CI, 0.150%-0.400%) for TEE, 3 of 57 537 (0.005%; 95% CI, 0.001%-0.020%) for EGD, 3 of 10 521 (0.030%; 95% CI, 0.006%-0.080%) for ERCP, and 9 of 5558 (0.160%; 95% CI, 0.080%-0.310%) for bronchoscopy. For EGD and ERCP, incidence was calculated based on cases that occurred between 2005 and 2011, because the numbers of inpatient and outpatient cases could not be accurately determined from January 1, 2001, to December 31, 2004 (**Table 1**).

Thirty-two of 33 cases occurred in association with procedures performed in the inpatient setting ($P < .001$ compared with procedures performed in the outpatient setting). Among 31 methemoglobinemia cases, the following topical anesthetic combinations had been used: 17 patients (55%) received benzocaine, 20%; 6 patients (19%) received lidocaine, 1% to 2%; 5 patients (16%) received a combination of benzocaine, 14%, butamben, 2%, and tetracaine hydrochloride, 2%; 2 patients (6%) received a combination of benzocaine, 20%, and lidocaine, 1% to 2%; and 1 patient (3%) received lidocaine of unspecified potency. In 2 patients (6%), the topical anesthetic used was not specified. Demographics of the cases are summarized in **Table 2**.

All 33 patients had clinical signs of methemoglobinemia, including low pulse oximetry readings and normal arterial blood gas readings. The overall mean (SD) initial methemoglobin concentration was 32.0% (12.4%). The mean methemoglobin concentrations were similar across the procedures, with 32.9% for TEE, 27.7% for EGD, 33.0% for ERCP, 30.1% for bronchoscopy, and 35.0% for NGT placement ($P = .97$ between groups). Most patients who developed methemoglobinemia were inpatients, while only one outpatient (3%) developed methemoglobinemia. This patient was undergoing TEE. Overall, 22 of 33 patients who had methemoglobinemia were treated with methylene blue intravenously, and the remaining 11 patients were treated conservatively with supplemental oxygen. Five of 33 patients were admitted to the intensive care unit. One death was attributed to methemoglobinemia, for a case fatality rate of 3%.

To evaluate potential risk factors for methemoglobinemia, each case was compared with 5 procedure-matched and date-matched outpatients and 5 procedure-matched and date-matched inpatients. Factors evaluated for potential methemoglobinemia risk modification included age, sex, race/ethnicity, smoking status, topical anesthetic used, inpatient vs outpatient status, hemoglobin level and hematocrit, serum urea nitrogen level and serum creatinine level, and a history of pulmonary or cardiovascular disease. On univariate analysis, the following were associated with higher risk of methemoglobinemia: TEE ($P < .001$), bronchoscopy ($P < .001$), younger age ($P = .045$), lower hemoglobin level ($P = .009$), lower serum urea nitrogen level ($P = .045$), hospitalization at the time of procedure ($P < .001$), and history of pulmonary disease ($P < .001$) and cardiovascular disease ($P = .01$). Sex, race/ethnicity, smoking status, and Charlson Comorbidity Index were not associated with risk of methemoglobinemia. The use of individual topical anesthetics was not significantly related to risk of methemoglobinemia; however, benzocaine-containing topical anesthetics were 3.7-fold more likely to be associated with methemoglobinemia than products not containing ben-

Table 2. Demographics of Methemoglobinemia Cases vs Controls

Variable	Cases (n = 33)	Controls (n = 299)	*P* Value
Age, mean (SD), y	50.7 (18.4)	60.8 (15.3)	.005
Race/ethnicity, No. (%)			
White	26 (78.8)	248 (82.9)	.82
African American	2 (6.1)	15 (5.0)	>.99
Hispanic	1 (3.0)	13 (4.3)	>.99
Other	0	4 (1.3)	>.99
Unspecified	4 (12.1)	19 (6.4)	.27
Female sex, No. (%)	15 (45.5)	138 (46.2)	>.99
Smoking status, No. (%)			
Current	7 (21.2)	46 (15.4)	.45
Past	6 (18.2)	90 (30.1)	.22
Never	14 (42.4)	104 (34.8)	.44
Unspecified	6 (18.2)	59 (19.7)	>.99
History of renal insufficiency, No. (%)	7 (21.2)	32 (10.7)	.09
History of cardiovascular disease, No. (%)	19 (57.6)	105 (35.1)	.01
History of pulmonary disease, No. (%)	15 (45.5)	52 (17.4)	<.001
Benzocaine-containing anesthetic use, No. (%)[a]	24 (77.4)	109 (53.2)	.01

[a] Among 31 cases and 205 controls with the use of a specified topical anesthetic.

Table 3. Risk Factors for Topical Anesthetic–Induced Methemoglobinemia

Variable	No.	Mean (SD)	*P* Value
Hematocrit, %			
Case	33	32.96 (8.60)	.06
Control	265	35.54 (7.13)	
Hemoglobin level, g/dL			
Case	33	10.74 (3.02)	.009
Control	260	12.35 (3.33)	
Charlson Comorbidity Index			
Case	33	2.27 (2.10)	.73
Control	297	2.14 (2.08)	
Serum urea nitrogen level, mg/dL			
Case	32	15.25 (7.45)	.045
Control	247	21.56 (17.46)	
Serum creatinine level, mg/dL			
Case	32	0.84 (0.51)	.18
Control	250	1.07 (0.94)	
Age, y			
Case	33	50.73 (18.39)	.005
Control	298	60.77 (15.27)	

SI conversion factors: To convert hematocrit to proportion of 1.0, multiply by 0.01; hemoglobin level to grams per liter, multiply by 10.0; serum creatinine level to micromoles per liter, multiply by 88.4; and serum urea nitrogen level to millimoles per liter, multiply by 0.357.

zocaine ($P = .01$) (Table 2 and **Table 3**). On multiple linear regression analysis, the use of benzocaine-containing anesthetics ($P = .02$) and inpatient status ($P < .001$) remained significantly associated with risk of methemoglobinemia (**Table 4**). For the overall multiple linear regression model, the R^2 value was 0.552 ($P < .001$).

COMMENT

Methemoglobinemia is a rare but potentially life-threatening condition that may be precipitated by the topical anesthetic sprays used in procedures involving the oropharynx. The condition can be treated effectively if promptly recognized; however, complications are frequently reported, including respiratory failure, hypoxic encephalopathy, myocardial infarction, and death.[15] Although methemoglobinemia has been recognized for many years, few controlled investigations have examined the incidence of and risk factors for the development of this potentially severe complication, and most of what has been published focuses on benzocaine-induced methemoglobinemia in patients undergoing TEE.[1,16-18]

Since 1977, when the first case of benzocaine spray–induced methemoglobinemia was reported,[3] approximately 200 cases have been documented in the literature, more than half of which were associated with topical anesthetic use for TEE.[1,16-24] Two of the larger studies reviewed 28 478 TEEs[1] and 4336 TEEs[22] and reported topical anesthetic–induced methemoglobinemia rates of 0.07% (95% CI, 0.04%-0.10%) and 0.12% (95% CI, 0.04%-0.27%), respectively, for this procedure. Clinical factors associated with the development of methemoglobinemia in these studies included sepsis, anemia, and hospitalization. Overall, most published data have been limited to case reports and small case series, making assessment of prevalence and risk factors difficult. For example, the largest reported series on oropharyngeal topical anesthetic–induced methemoglobinemia comprised 132 methemoglobinemia cases believed related to benzocaine use that had been submitted nationally to the Food and Drug Administration during a 5-year period.[8] The study reported a case fatality rate of 1.5% and serious adverse events in 81.0%; however, no information about procedure type or patient clinical characteristics was available.

With this as a background, our study aimed to determine all cases of periprocedural topical anesthetic–induced methemoglobinemia seen at our institution in the last decade, during which approximately 95 000 procedures were performed. Unlike prior studies, methemoglobinemia cases resulting from multiple different procedures (TEE, EGD, ERCP, bronchoscopy, and NGT placement) and various topical anesthetics were included, allowing assessment of differential risk, as well as a greater mix of patient comorbidity and procedure-specific prevalence. Comparison with matched control populations also allowed for the evaluation of clinical and demographic factors predisposing to methemoglobinemia. We chose to define clinically significant methemoglobinemia as a blood level of 10.0% or above, along with signs and symptoms consistent with methemoglobinemia, because it has been shown that methemoglobin concentrations below this level are rarely associated with illness, even in compromised patients.[10]

Our results suggest that methemoglobinemia is an infrequent complication of topical anesthetic use, affecting approximately 3.5 of every 10 000 cases, within the range of the aforementioned TEE studies.[1,22] Notably, the risk varies significantly with type of procedure, topical anesthetic used, and inpatient vs outpatient status. Procedure setting seems to be the most important risk factor for methemoglobinemia, with an incidence of 0.14 cases per 10 000 outpatient procedures vs 13.7 cases per 10 000 inpatient procedures ($P < .001$). While the per-procedure risk is low, the cumulative number of benzocaine spray–induced methemoglobinemia cases may be significant given the large number of these procedures performed annually. For instance, it is estimated that 3.5 million EGDs,[25] 600 000 ERCPs,[26] 500 000 bronchoscopies,[27] and 700 000 TEEs[28,29] are performed annually in the United States. Using the rates derived from this study, as many as 3000 cases of methemoglobinemia overall (1740 related to TEE, 180 related to EGD, 170 related to ERCP, and 820 related to bronchoscopy) may occur annually in the United States.

While the large sample size, varied patient population, and systematic ascertainment of methemoglobinemia cases suggest that the results of our study are robust, a few limitations should be noted. First, we were able to assess only clinically recognized cases of methemoglobinemia, and milder cases may have been missed. Although the inclusion of subclinical cases would increase the incidence, the clinical relevance of mild topical anesthetic–induced methemoglobinemia is unclear because these cases would be expected to resolve without specific treatment. Second, while the combination of searches of our laboratory database for methemoglobin concentrations combined with phar-

Table 4. Multiple Regression Model of Risk Factors for Topical Anesthetic–Induced Methemoglobinemia

Variable	Nonstandardized β (SE) [95% CI]	Standardized β	*t* Statistic	*P* Value
Constant	0.721 (0.281) [0.166 to 1.275]	Not applicable	2.563	.01
Benzocaine-containing anesthetic	0.114 (0.050) [0.015 to 0.213]	0.157	2.277	.02
Hematocrit	−0.001 (0.004) [−0.008 to 0.007]	−0.012	−0.168	.87
Hemoglobin level	0.006 (0.008) [−0.009 to 0.021]	0.060	0.788	.43
Serum urea nitrogen level	0.001 (0.002) [−0.003 to 0.006]	0.059	0.637	.53
Serum creatinine level	0.009 (0.034) [−0.058 to 0.075]	0.023	0.254	.80
Inpatient status	0.190 (0.053) [0.085 to 0.295]	0.260	3.557	<.001
Age	0.003 (0.002) [−0.001 to 0.006]	0.116	1.584	.12
Race/ethnicity	0.004 (0.062) [−0.118 to 0.125]	0.004	0.057	.95
Smoking status	−0.032 (0.047) [−0.125 to 0.060]	−0.048	−0.694	.49
History of cardiovascular disease	0.022 (0.051) [−0.079 to 0.123]	0.031	0.428	.67
History of pulmonary disease	0.071 (0.058) [−0.043 to 0.186]	0.087	1.234	.22
Charlson Comorbidity Index	0.003 (0.012) [−0.020 to 0.026]	0.019	0.266	.79

macy records of methylene blue orders is expected to reliably capture cases of clinical methemoglobinemia, the study was retrospective, so cases may have been missed. Third, we were unable to estimate the dose of topical anesthetic administered, which may affect the risk of methemoglobinemia. However, the results of prior studies[8,15,30] suggest that this complication is largely idiopathic and not directly related to anesthetic dose. Fourth, this study was performed at a single center, and results may vary in other settings.

In conclusion, we evaluated the incidence of and risk factors for topical anesthetic–induced methemoglobinemia occurring after approximately 95 000 procedures. Our results suggest that this complication is uncommon but that patients at particularly high risk can be predicted based on readily available clinical information. Decreased use of benzocaine-containing topical anesthetics in hospitalized patients may reduce the risk of this complication. Improved understanding of this potentially fatal complication may help to risk stratify patients and avoid exposure in patients who are at particularly high risk of methemoglobinemia, as well as to improve recognition of methemoglobinemia, allowing for more effective management.

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EDITOR'S NOTE

Serious Adverse Effects Can Occur With Minor Procedures

Minor procedures can have serious adverse effects. The article by Chowdhary et al quantitates a serious but rare adverse effect, namely, methemoglobinemia associated with the use of topical oropharyngeal anesthetics for invasive procedures. The studies for which the topical anesthetics are used are common procedures that are typically thought to be safe, such as transesophageal echocardiography and upper gastrointestinal tract endoscopy. The association of methemoglobinemia with topical anesthetics cannot be eliminated, although it was less common when the anesthetics did not contain benzocaine. However, before any procedure is performed, even one we think of as very safe, we can ensure that the benefits outweigh the risks.

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