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An Attempt on Methemoglobinemia: It's Treatment and Relationship between Treatment and Cerebral Oximeter Value: Case Presentation

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Abstract

Background: Our paper aimed to investigate whether there was a correlation among the pulse oximetry, cerebral oximetry (CO) and MetHb (methemoglobin) values of a patient with congenital methemoglobinemia who underwent a laparoscopic cholecystectomy operation. Case: The 35-year-old male patient with a weight of 70 kg, body massindex (BMI) of 21, American Society of Anesthesia status-2(ASA-2) category who was planned for laparoscopic cholecystectomy operation was identified to have been diagnosed with congenital methemoglobinemia as per his medical history was methemoglobin levels ranged between 12% and 20% according to the periodical measurements taken for the past 3 years. The patient received standard monitoring during anesthesia and device monitoring with a cerebral oximeter (Invos 5100C somatic/cerebral oximeter, Covidien) and a CO-oximetry (Rad −87 "Rainbow", Masimo Inc., Irvine, CA) device to continuously follow up his MetHb values was also added. During the intra-operative follow-up, the patient's methemoglobin level rose to 16%, his peripheral oxygen saturation levels decreased to 86% and his cerebral oximetry values were identified to have also decreased; therefore, methylene blue (MB) was intravenously administered to the patient. The patient continued to be followed up in the post-operative period and he did not develop any complications. Discussion: Appropriate treatment and monitoring enabled the prevention of potential complications. We believe that monitoring with NIRS and MASIMO CO-oximetry device will enable physicians to perform a safe follow-up and treatment in the intraoperative and postoperative follow-up of methemoglobinemia patients.

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Keywords

Methemoglobinemia, Anesthesiology, Cerebral Oximeter, Pulse Oximeter

1. Background

Methemoglobinemia prevalence is an unknown, rare condition [1]. Hemoglobin A (Hb) has a 95% rate of incidence among normal adult population and it contains 4 heme groups with iron atoms (Fe^{2+}) in oxidized form. When the hemoglobin molecule is oxidized, it loses one electron from the ferrum atom and MetHb is formed. This new situation causes the Fe^{2+} atom to turn into a Fe^{3+} atom, which in turn results in a loss in binding of the oxygen to this atom. Therefore, this hemoglobin molecule which cannot bind oxygen results in a leftward shift in the oxygen dissociation curve. As a result, this causes cellular hypoxia secondary to the high level of MetHb. Methemoglobinemia is also a clinical syndrome caused by congenital changes in hemoglobin synthesis or increased MetHb levels due to the side effect of certain medicines. This condition occurs with frequently (contrary to the popular belief) using some anesthetic drugs such as local anesthetics but sometimes this can't be detected by physician with pulse oxymeter .The objective of our case report is to investigate whether there is a correlation among pulse oximetry, cerebral oximetry and MetHb values in a patient with congenital methemoglobinemia (CM) who undergoes laparoscopic cholecystectomy operation.

2. Case Report

The 35-year-old male patient, 70 kg with a BMI of 21, in the ASA-2 statusand was scheduled for laparoscopic cholecystectomy operation and had history of smoking 20 packs/year, quit smoking due to cyanosis in hands and feet and shortness of breath and underwent a knee operation without complications under spinal anesthesia 3 years ago. It was learned that the patient had been using 1 table spoon (approximately 2 g) of methylene blue because of congenital Type 1 methemoglobinemia diagnosis for 18 years, his level of methemoglobin measured in the vein at his control studies 3 years ago was 23.9%, his hemoglobin electrophoresis results were HbA2: 3.2%, HbA1: 95.4%, HbF: 0.4%, he did not have any glucose-6-phosphate dehydrogenase (G6PDH) enzyme deficiency and his methemoglobin level according to his intermittent measures over the past 3 years were in the range of 12% and 20%. During his physical examination, no additional pathological findings were identified apart from the fact that his finger tips and lips were slightly cyanotic.

According to the preoperative respiratory tests of the patient, the following results were identified: FEV1: 4.22 L, FVC: 5.48 L, FEV1/FVC: 82%. As per the laboratory assessment performed, Urea: 21 mg/dL, BUN: 10 mg/dL, Creatinine: 1.01 mg/dL, AST: 16 U/mL, ALT: 11U/mL, albumin: 4.7 gr/dL, sodium: 139 mEq/L, potassium: 4.55 mEq/L, chlorine: 107 mEq/L, calcium: 9.32 mg/dl, hemoglobin: 14.3 g/dL, hematocrit: 42.3%, thrombocyte: 264.000 uL, leukocyte: 7.27 uL.

The patient received standard monitoring during anesthesia and monitoring with a cerebral oximeter (Invos 5100C somatic/cerebral oximeter, Covidien) and a CO-oximetry (Rad −87 "Rainbow", Masimo Inc., Irvine, CA) device to continuously follow up his MetHb values was also added. According to the blood sample of the patient collected 10 minutes before the anesthesia induction, it was identified that the methemoglobinemia level was 13%. During the anesthesia induction, propofol 2 mg/kg, rocuronium 0.6 mg/kg, fentanyl 100 mcg were administered intravenously (IV). He was intubated in a single intervention using the endotracheal tube no. 8. For maintenance, sevoflurane at 2% volume and oxygen/air mixture (50/50%) was administered. Tramadol 2 mg/kg was administered for purposes of post-operative analgesia and metoclopramide 10 mg was administered intravenously to prevent nausea-vomiting in the post-operative period. The duration of the operation was determined was 60 min. and the anesthesia duration was 75 min. It was observed that the pulse oximeter values in the room air were between 92% and 94%. (**Table 1**) In the blood gas sample collected 5 min. after induction, the following values were measured. pH: 7.386, pO_2: 216 mmHg, pCO_2: 40.4 mmHg, SpO_2: 98.7%, lactate: 1.7 mmol/L, BE: −0.6, p50 (act): 26.96. The level of MetHb identified with simultaneous CO-oximetry was 13.3%. The values, which were identified throughout the operation and the 80-minute-long observation in the operation, are provided in the table (**Figure 1**). At minute 50 of anesthesia, the MetHb level of the patient reached the level of 16%, SpO_2 values decreased to 89%, cerebral oximeter values to 78/75% (left hemisphere/right hemisphere) and

Table 1. Mean ± Std. Deviation values of CO-oxymetry (SpMet), cerebral oxymetry (SerbOL, SerbOR) and pulse oxymetry (SpO_2) in peroperative, total and on intensive care unit. "n = 17" defines numbers of measurement periods. On peroperative period measurements were taken 5 minutes intervals and on intensive care period measurements were taken one hour periods.

Group		SpO_2 (%)	SpMet (%)	SerbOL (%)	SerbOR (%)
Peroperative (n = 17)	Mean ± Std. Deviation	94.53 ± 2.29	11.50 ± 4.74	79.06 ± 6.62	77.53 ± 7.21
İntensive care (n = 15)	Mean ± Std. Deviation	96.33 ± 3.10	2.29 ± 1.16	70.07 ± 3.67	72.33 ± 6.70
Total (n = 32)	Mean ± Std. Deviation	95.37 ± 2.81	7.18 ± 5.83	74.84 ± 7.03	75.09 ± 7.35

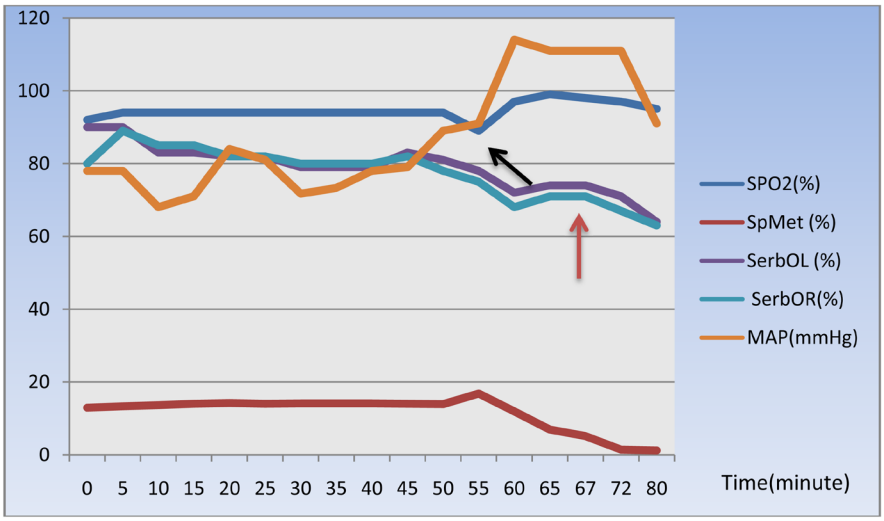

Figure 1. CO-oxymetry (SpMet), cerebral oxymetry (SerbOL, SerbOR) and pulse oxymetry (SpO_2) and mean arterial pressure (MAP) graphics thoroughout the observational period of peroperative and intensive careunit. Black arrow shows the correlation between mean arterial pressure and SpO_2 level. Orange arrow shows decrease of cerebral oxymetry values contrary of increased methemoglobine levels.

methylene blue in a 1% solution was intravenously administered to the patient at a rate of 1.5 mg/kg over a period 5 minutes. At minute 55 of the operation, a 30% decrease occurred at the peak heart rate; therefore, 0.5 mg atropine was intravenously administered to the patient. At 5 minutes after the administration of methylene blue, the MetHb level rose to 11.9% and SpO_2 value to 97% and the patient's cerebral oximeter values were identified as 72/68% (left hemisphere/right hemisphere). At 27 minutes after the administration of methylene blue, the operation was finalized, 1.5 mg neostigmine was administered intravenously and the patient was extubated; he was taken into the anesthesia intensive care for follow-up and treatment with a respiratory count of 14, MetHb of 1.4% and SpO_2 of 97%. It was noted that the cerebral oximeter values continued to decrease (**Figure 1**). According to the blood gas sample collected intravenously, the following results were identified: pH: 7.29, pO_2:88; 1 mmHg, pCO_2: 50.3 mmHg, SpO_2: % 95.8, lactate: 1.4 mmol/L, BE: −1.8, p50 (ACT): 29.43. The patient was administered 1800 mL of fluid during the operation. Intraoperatively, a urinary catheter was inserted following anesthesia induction and it was observed that urinary output continued to be above 0.5 mL/kg/hour and that urine color turned blue after the administration of methemoglobin.

In addition to standard monitoring, cerebral oximetry and continued methemoglobin measurements and blood gas samples were also collected in the intensive care unit. The patient's vital signs continued to be stable and he was not observed to have hypotension or bradycardia. It was observed that the MetHb level rose to 4.2% at the end of 24 hours and pulse oximeter values decreased to 93%. It was observed that ascorbic acid 1 g administered intravenously did not cause any changes either in the MetHb levels or SpO_2 levels or cerebral oximeter values during 4 hours. There was no requirement for repeated methylene blue administration. The administration of

methylene blue 200 mg/day was maintained for the patient; he was referred to the general surgery service with spontaneous breathing (14 respirations/min), at air temperature and with glaskow coma scale (GCS) was 15.

3. Discussion

MetHb is formed in two ways in human beings [2] [3]. The form that is most frequently seen is nicotinamide adenine dinucleotide-dependent methemoglobin reductase (NADH-MetHb reductase), also known as cytochrome-b5 reductase. The second form is physiologically less important. This second path, which is mediated by NADPH-MetHb reductase, requires a co-factor or an electron transmitter such as methylene blue or flavine [3]. NADH-MetHb reductase enzyme deficiency causes the development of methemoglobinemia and results in hereditary methemoglobinemia. In this case, oxidizing pathways are continuously suppressed and caution should be exercised for exposure to certain medicines or agents. This condition especially emerges during the clinical use of local anesthetics and nitrites [4]. The clinical sign of MetHb is the decrease of oxygen transporting capacity, thereby the reflection of tissue hypoxia. The clinical signs depend on the level of MetHb [5]. When the MetHb is under 3%, no signs and symptoms are observed. The disease is generally symptom-free at rates between 3% and 15%. Cyanosis starts above the level of 15% and is not responsive despite oxygen administration. When the level is 15% - 30%, the color of the patients' blood turns chocolate-coffee color. Dyspnea is generally seen at the levels of 30% - 50%. At this level, SpO_2 is approximately 85%. Again, dizziness, headache, weakness and syncope may be seen. The severe forms are accompanied by metabolic acidosis, cardiac arrhythmia, central nervous system depression, seizures and coma. Death occurs at the levels of 70% [6]-[8]. Certain clinical evidence to diagnose patients under anesthesia with methemoglobinemia includes lack of recovery from hypoxia in spite of increased oxygen fraction that is inhaled, abnormal blood color, physiologically adequate levels of partial oxygen pressure in blood gas sampling in spite of low pulse oximeter values (saturation deficit), hypoxia following intake of agents with oxidative properties and/or onset of cyanosis [3].

SpO_2 is a simple and non-invasive, specific diagnostic application in assessing arterial oxygenation with its wide scope of clinical use. The absorption rates of oxy and deoxyhemoglobin in these two different wavelengths are shown as percentage of saturation. SpO_2 may become an incorrect oxygenation indicator in the presence of carbonmonoxide poisoning or dyshaemoglobins as in methemoglobinemia [9]. The measurement of dishemoglobins such as MetHb and carboxyhemoglobin has gained importance due to the vital hazards that they cause. For that reason, CO-oximeter devices such as Masimo Rainbow-SET Rad-57 and Rad-87 have been developed. (Masimo Inc., Irvine, CA) Rad 57 and Rad 87 devices use eight wavelengths [10]. MetHb light absorption spectrum is 631 nanometers and it is absorbed evenly at 660 and 940 nanometers. As a result, oxygen saturation is observed to be 85% in parallel with increased methemoglobin levels. However, the wavelength of MetHb is outside this range, therefore, it is not possible to identify the carboxy and hemoglobin levels using conventional pulse oximeters. In contrast with conventional pulse oximeters, CO-oximeters have been developed. These devices are able to measure values at 600 nanometers (carboxyhemoglobin), 631 nanometers (MetHb), 660 nanometers (deoxyhemoglobin) and 940 nanometers (oxyhemoglobin). Therefore, CO-oximeters may be used in the diagnosis of multiple hemoglobinopathies. As for the oxygen saturation (SaO_2) in the arterial blood gas, it is defined as the ratio of hemoglobin bound by oxygen in the arterial blood gas to the one that is not bound and it is a relative clinical indicator for the oxygen distribution among tissues.

And it may be formulated as $SaO_2 = (O_2Hb)/(RHb + O_2Hb)$. Another important point is fractional hemoglobin saturation.

This is defined as $\% O_2Hb = (O_2Hb)/(RHb + O_2Hb + COHb + MetHb) = (O_2Hb)/(Total\ Hb)$ [10].

The arterial blood gas analyses are based on electro-chemical parameters. The voltage changes are measured using high impedance electrodes to obtain pH and pCO_2 values. At the same time, changes in electrical current ensure PO_2 measurement. PO_2 shows dissolved oxygen. It does not show hemoglobin-bound oxygen molecules and the PO_2 levels may be normal with methemoglobinemia. Serum sodium bicarbonate and hemoglobin oxygen saturation may be calculated based on Handerson Hasselbach equation using PH and pCO_2 values. However, this is applicable in the presence of normal hemoglobin. Oxygen that cannot be transported due to the presence of dishemoglobinemia may cause a false positive result of high oxygen saturation values. Methemoglobin, sulfhemoglobin and carboxyhemoglobin may raise the calculated oxygen saturation wrongly [11] [12]. On the other hand, the cerebral oximeter device that we used in our study provides an approach to ensure continued, non-invasive monitoring of brain oxygenation. This monitoring may be used in the identification of the onset of

global and local cerebral hypoxia during hypothermic circulatory arrest or carotid endarterectomy. This device also enables the measurement of oxy and deoxyhemoglobin concentration in the tissue in a non-invasive way via light transmission and absorption principles as in pulse oximeter and mixed venous oximeters. 90% of the oxygen is transmitted from the vascular site to mitochondria and it functions here as the final electron receiver in the electron transport chain. These electrons are transferred to the oxygen by means of the enzyme AA3 (CYTAA3). This enzyme is also known as cytochrome oxidase. Anoxia rapidly results in a complete decrease in these enzyme levels. All the optical spectrometers contain the same essential components. They are composed of a light source (LED or laser diodes), light detector (photo diodes or photon multiplying tubes) and a part that converts the changes in this light density into clinically useful information (such as CYTAA3 concentration oxidized to HbO_2, Hb or oxide) [13]-[15]. It is recommended that all oxidizing agents are avoided in hereditary methemoglobinemia patients. Methylene blue is a thiazine dye agent that is dose-dependent and has an antiseptic and oxidizing content [16] [17]. Intravenously administered methylene blue is oxidized into leucomethylene blue by receiving electrons from NADPH in the presence of NADPH-MetHb reductase enzyme. Leucomethylene reduces methemoglobin to hemoglobin. Methylene blue is administered in such a way that it is delivered in five minutes intravenously at a dose of 1 - 2 mg/kg. The symptoms are quickly improved. The MetHb levels return to their basal values 36 hours later. Repeated doses are administered if the symptoms persist. The side effects of methylene blue include blue-purple staining of the urine and skin, confusion, chest pain, dizziness and vomiting. Furthermore, hyperbaric oxygen and exchange transfusion are also recommended for cases where methylene blue treatment is not effective. Its administration is contraindicated in patients with glucose-6-phosphate deficiency [18]. N-acetyl cystein may also be used for such patients [19]. The administration of vitamin C (100 - 500 mg PO or IV) at a high dose is done between treatments; however, its long-term administration may potentially cause oxalate stones.

Returning to our case after these detailed explanations, a significant correlation was identified among SpO_2, cerebral oximeter and MetHb levels as a result of the statistical evaluation of the correlation of decrease seen in SpO_2 values down to 86% and decrease observed in the cerebral oximeter values along with the onset of increase in continuously measured MetHb levels following the induction of general anesthesia ($p < 0.05$) (**Tables 1-3**) (Graph 1).

For our case, intravenous administration of methylene blue started since MetHb measurements taken by CO-oximeter rose to the levels of 16.8% and SpO_2 values decreased to 86% and the MetHb levels were identified to be 11.9%; SpO_2 levels 97%; cerebral oximeter values (right/left) 72/68% at 26 minutes later and MetHb values were identified as 1.4%, SpO_2 values 97%, cerebral oximeter values (left/right) 71/67% at 16 minutes later. Cerebral oximeter values decreased to the levels of 69/65% and MetHb values to the levels of 6.9% and they displayed a rising trend after that point. Throughout the 24-hour-long follow-up, a slow decrease in cerebral oximeter values in parallel with the slow increase in MetHb levels attracted attention. It was determined that ascorbic acid 1 g administered at Hour 20 did not result in a significant decrease in MetHb values for 4 hours while SpO_2 values showed a 1% increase 2 hours later and cerebral oximeter values did not show any changes (Graph

Table 2. Nonparametric Correlations group = peroperative. "n = 17" defines numbers of measurement periods. On peroperative period measurements were taken 5 minutes intervals and on intensive care period measurements were taken one hour periods.

*Correlation is significant at the 0.05 level (2-tailed).			SpO_2 (%)	SpMet (%)	SerbOL (%)	SerbOR (%)
Spearman's rho	SpO_2 (%) n = 17	Correlation Coefficient-r	1.000	−0.704**	−0.657**	−0.553*
		p	0.	**0.002**	**0.004**	**0.021**
	SpMet (%) n = 17	Correlation Coefficient-r	−0.704**	1.000	0.366	0.505*
		p	**0.002**	**.**	0.149	**0.039**
	SerbOL (%) n = 17	Correlation Coefficient-r	−0.657**	0.366	1.000	0.907**
		p	**0.004**	0.149	.	**0.000**
	SerbOR (%) n = 17	Correlation Coefficient-r	−0.553*	0.505*	0.907**	1.000
		p	**0.021**	**0.039**	**0.000**	.

**Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed).

Table 3. Nonparametric Correlations group = intensive care unit n = 17' defines numbers of measurement periods. On peroperative period measurements were taken 5 minutes intervals and on intensive care period measurements were taken one hour periods.

			SpO_2 (%)	SpMet (%)	SerbOL (%)	SerbOR (%)
Spearman's rho	SpO_2 (%) N = 15	Correlation Coefficient-r	1.000	−0.776**	0.917**	0.838**
		p	.	**0.001**	**0.000**	**0.000**
	SpMet (%) N = 15	Correlation Coefficient-r	−0.776**	1.000	−0.708**	−0.763**
		p	**0.001**	**.**	**0.003**	**0.001**
	SerbOL (%) N = 15	Correlation Coefficient-r	0.917**	−0.708**	1.000	0.853**
		p	0.000	0.003	.	**0.000**
	SerbOR (%) N = 15	Correlation Coefficient-r	0.838**	−0.763**	0.853**	1.000
		p	0.000	0.001	0.000	.

**Correlation is significant at the 0.01 level (2-tailed).

1). In the literature, high levels of methemoglobin revealed on the basis of decreased peripheral oxygen saturation levels especially following the use of benzocain-containing local anesthetic spray during bronchoscopy, cyanosis onset and arterial blood gas analyses were stated [20]. Furthermore, cases that developed secondary to nitrites in food items were also reported. These cases showed a dramatic recovery following methylene blue administration [21]. However, no publications on the use of cerebral oximeter and continuous methemoglobin follow-up in patients with methemoglobinemia were encountered.

There are some publications indicating that cerebral oximeter was influenced by extracranial structures, it fell of demonstrating cerebral oxygenation in hyperbilirubinemia cases and showed values at a rate of 30% - 40% lower than the basal values following methylene blue administration [22]-[24]. In our case, it was also observed that the cerebral oximeter values continued to be much lower than the basal values following methylene blue administration. Methylene blue demonstrates a strong absorption band at 660 nanometers while the INVOS device uses two near-infrared waves at 730 and 805 nm [25]. It seems possible that interference, albeit at a small rate, may develop since the wavelengths are close to each other. We believe that the fact that cerebral oximeter values remained within fixed limits throughout the period of 24 hours was also consistent with the process of cleansing of methylene blue from the tissue. Emphasizing that cerebral oximeter is a trend monitoring; we argue that it has undeniable benefits in the tissue oxygenation follow-up also in cases with dishemoglobinemia.

We also observed that the increases of the mean arterial pressure just after the methylene blue administration as shown in **Figure 1**. This finding was correlated with some experimental and clinical experiences with the use of methyleneblue as a selective inhibitor of the NO-cGMP pathway in anaphylaxis, and distrubutive shock [26].

In our case report, monitoring methods enabling the tracking of MetHb levels, NIRS and continuous methemoglobin levels were employed before, during and after the operation in a patient with methemoglobinemia, which ensured the administration of methylene blue treatment at the optimal time and amount (**Table 2** & **Table 3**). Our patient was in a high risk group and we completed his anesthetic monitoring safely and under minimum risk. We prevented potential complications via appropriate treatment and monitoring.

We believe that monitoring with NIRS and MASIMO CO-oximetry devices would equip physicians with the ability to perform safe monitoring and treatment in the intraoperative and postoperative follow-up of methemoglobinemia patients.

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