Effect of Hydroxocobalamin on Surface Oximetry in Nonexposed Humans

Brian V. Cashin Jr., MD;[1] Aaron G. Matlock, MD;[1] Chris Kang, MD;[1] Penny S. Reynolds, PhD;[2] Brandon K. Wills, DO, MS[2,3]

1. Department of Emergency Medicine, Madigan Army Medical Center, Tacoma, Washington USA
2. Department of Emergency Medicine, VCU Medical Center, Richmond, Virginia USA
3. Virginia Poison Center, Richmond, Virginia USA

Correspondence:
Brandon Wills, DO, MS
Associate Professor, VCU Medical Center
600 East Broad St.
Richmond, VA 23219 USA
E-mail: bwills@mcvh-vcu.edu

Conflicts of interest and funding: The authors have no conflicts of interest to disclose. Funding was obtained from the Department of Clinical Investigation, Madigan Army Medical Center, Tacoma, Washington USA.

Keywords: co-oximetry; cyanide; hydroxocobalamin

Abbreviations:
AUC: area under the curve
BP: blood pressure
CO: carbon monoxide
COHb: carboxyhemoglobin
Hb: hemoglobin
HR: heart rate
MetHb: methemoglobin
O_2Hb: oxyhemoglobin saturation

Received: October 18, 2012
Accepted: November 17, 2012
Revised: December 18, 2012

Online publication: May 1, 2013

doi:10.1017/S1049023X13003518

Abstract

Introduction: The newer cyanide antidote, hydroxocobalamin, due to its pigmentation, has been found to cause interferences in some laboratory assays. Co-oximetry may also be affected by hydroxocobalamin, leading to false elevations in hemoglobin concentration, methemoglobin, carboxyhemoglobin, and false decreases in oxyhemoglobin. The Masimo Radical-7 is a medical device that performs noninvasive oximetry and estimates hemoglobin (Hb) concentration and percent carboxyhemoglobin (COHb), methemoglobin (MetHb), and oxyhemoglobin saturation (O_2Hb).

Study Objectives: The study sought to determine the effect of hydroxocobalamin on noninvasive measurement of hemoglobin indices using the Masimo Radical-7 monitor.

Methods: Seven asymptomatic volunteers who were unexposed to cyanide had baseline heart rate (HR), blood pressure (BP), and oximeter measurements recorded followed by an infusion of five grams of hydroxocobalamin over 15 minutes. The above parameters were subsequently recorded at: 5, 10, 15, 30 and 60 minutes post infusion. Data were analyzed by calculating the area under the curve (AUC) for each variable and comparing the results to expected values by paired *t* tests. Expected AUC values were calculated by extrapolating baseline values across the entire time period.

Results: The mean differences from baseline values with 95% confidence intervals and *t* tests of mean difference were: SBP: 11 mm Hg (95% CI, 0-22; $P = .051$); HR: -9 (95% CI, -15 to -3; $P = .01$); Hb: -0.1 (95% CI, -0.7 to 0.4; $P = .57$); O_2Hb: 0 g/dL (95% CI, -1 to 1; $P = .41$); COHb: -1 (95% CI, -3 to 1; $P = .25$); MetHb: -0.2 (95% CI, -0.3 to 0; $P = .03$).

Discussion: After infusion of hydroxocobalamin there was a significant elevation of systolic blood pressure and decrease in heart rate. There were no significant differences in Hb, O_2Hb, and COHb. Although percent methemoglobin concentrations were statistically lower, the authors feel this difference is of trivial clinical significance.

Conclusion: The administration of hydroxocobalamin does not significantly impact noninvasive oximetry.

Cashin B, Matlock A, Kang C, Reynolds P, Wills B. Effect of hydroxocobalamin on surface oximetry in nonexposed humans. *Prehosp Disaster Med.* 2013;28(4):367-369.

Introduction

Background

Acute cyanide poisoning occurs most commonly from smoke inhalation but can also occur from industrial accidents or suicide attempts.[1] Many smoke-inhalation victims are treated early in their clinical course with cyanide antidotes, namely hydroxocobalamin.[2,3] Due to its pigmentation, hydroxocobalamin has been found to cause interferences in many laboratory assays.[4–7] Co-oximetry also may be affected by hydroxocobalamin. Two animal studies suggest that hydroxocobalamin may cause false elevations in hemoglobin concentration, methemoglobin, carboxyhemoglobin, and a false decrease in oxyhemoglobin.[8,9]

Importance

The Masimo Radical-7 (Masimo Corporation, Irvine, California USA) is a medical device that performs noninvasive oximetry and estimates hemoglobin (Hb) concentration, carboxyhemoglobin (COHb), methemoglobin (MetHb), and oxyhemoglobin saturation (O_2Hb).

https://doi.org/10.1017/S1049023X13003518 Published online by Cambridge University Press

Hydroxocobalamin is known to cause alterations in co-oximetry measurements. The effect of hydroxocobalamin on noninvasive oximetry is unknown.

Goals of This Investigation

The effect of hydroxocobalamin on surface-probe oximetry has not been evaluated previously. Therefore, the aim of this investigation was to determine the effect of hydroxocobalamin on noninvasive measurement of hemoglobin indices using the Masimo Radical-7. The study hypothesis was that the administration of hydroxocobalamin would cause variations in Hb, O_2Hb, COHb, and MetHb.

Methods

Study Design and Setting

This prospective quantitative study compared surface oximetry readings of Hb, O_2Hb, COHb, and MetHb before and after administration of hydroxycobalamin. The study was conducted at Madigan Army Medical Center, a large military teaching hospital located in Tacoma, Washington (USA). Institutional Review Board approval was obtained.

Selection of Participants, Data Collection and Processing

Eligible patients were healthy, male, nonsmoking volunteers age 18 years or older who were unexposed to cyanide. Exclusion criteria included: known anemia, blood dyscrasias, recent exposure to carbon monoxide or cyanide, medications known to induce methemoglobinemia, peripheral arterial disease, hypertension, and hypersensitivity to hydroxocobalamin or cyanocobalamin. Additionally, subjects with a pre-test systolic blood pressure <100 mm Hg were excluded due to potential for poor monitoring performance. Written informed consent was obtained for all subjects.

Methods of Measurement

Study operators were trained on use of the Masimo Radical-7 noninvasive monitor and were proficient in its use prior to initiation of the study. Total hemoglobin (Hb), carboxyhemoglobin (COHb), methemoglobin (MetHb), and oxyhemoglobin (O_2Hb) readings were obtained using the monitor. The probe was placed on the left fourth finger (ring finger) of each subject's hand and remained in place throughout the study. A baseline Hb, COHb, MetHb, and O_2Hb reading was obtained and recorded. Each of the volunteers received 5 g of hydroxocobalamin diluted in 200 cc of normal saline intravenously over 15 minutes in the contralateral upper extremity. Hydroxocobalamin dosing for this study followed the prescribing information from the Cyanokit (Meridian Medical Technologies, Inc., Columbia, Maryland, USA) package insert.[4] Demographic data was recorded as well as baseline blood pressure and heart rate. Readings for all hemodynamic and hemoglobin parameters were recorded at 5, 10, 15, 30 and 60 minutes. If values were less than five percent of baseline, the study was terminated at 60 minutes. If values were not less than five percent of baseline at 60 minutes, monitoring was to be extended to semi-hourly monitoring, up to six hours post infusion.

Primary Data Analysis

The primary end point was the difference between pre- and post-infusion readings of CO and MetHb obtained by the noninvasive monitor. Additional readings included Hb, O_2Hb, blood pressure, and heart rate. Data were analyzed by calculating the area under the curve (AUC) for each variable and comparing the results to expected values by paired *t* tests using Excel (Microsoft Corporation, Redmond, Washington, USA). Expected AUC values were calculated by extrapolating baseline values across the entire time period.

Data from the authors' previous institutional quality assurance testing of the Masimo Radical-7 device for hemoglobin measurements revealed a standard deviation of 1.3 for the difference between probe measurements and laboratory confirmation. Therefore, a conservative estimate of five was chosen for the standard deviation of this protocol. An effect size of four was selected, which was felt to be a clinically significant change for carboxyhemoglobin measurements. Sample size was determined to be 12 with a power of 0.8 and two-sided alpha of 0.05 to detect a difference between pre-infusion and post-infusion measurements.

Results

Initially eight subjects were enrolled. The study protocol was discontinued after one subject experienced sinus bradycardia at 28 bpm with mild light-headedness, which resolved with discontinuation of the infusion. After complete data were available on seven subjects, an interim analysis was performed by the request of the Institutional Review Board to determine if additional subjects would be needed. The mean difference from baseline values with 95% confidence interval and *t* test of mean difference were: SBP: 11 mm Hg (95% CI, 0-22; $P = .051$); HR: -9 (95% CI, -15 to -3; $P = .01$); Hb: -0.1 (95% CI, -0.7 to 0.4; $P = .57$); O_2Hb: 0 g/dL (95% CI, -1 to 1; $P = .41$); COHb: -1 (95% CI, -3 to 1; $P = .25$); MetHb: -0.2 (95% CI, -0.3 to 0; $P = .03$). After reviewing these data, the authors felt that additional subjects would not be justified given a trivial influence on the primary endpoint of COHb and MetHb concentrations.

Discussion

Statistically significant differences were identified for pre- and post-infusion heart rate, blood pressure, and methemoglobin concentration; however the difference in methemoglobin concentration (-0.2%) is unlikely to be clinically significant. No statistically significant differences were observed in hemoglobin, carboxyhemoglobin, or oxyhemoglobin concentrations.

Results of this study suggest that surface oximetry may be a viable alternative to traditional co-oximetry for measurement of hemoglobin indices after administration of hydroxocobalamin. Smoke-inhalation victims may be exposed to both cyanide and carbon monoxide. Hydroxocobalamin is often empirically administered in the prehospital environment, prior to any diagnostic testing. In these settings, surface oximetry may provide an accurate assessment of hemoglobin indices in patients receiving hydroxocobalamin.

Limitations

This study involved single baseline measurements rather than several measurements over time. This prevented determining device variability independent of hydroxocobalamin. The study was terminated before reaching the a priori sample size due to safety concerns in light of the trial being nontherapeutic. Despite not having robust statistical power, the authors felt the small sample size resulted in minimal impact on co-oximetry readings. The study subjects were all nonexposed volunteers, and it is not clear if the performance of surface oximetry in

https://doi.org/10.1017/S1049023X13003518 Published online by Cambridge University Press

actual cyanide-exposed victims receiving hydroxocobalamin would be different.

Conclusion

Using the Masimo Radical-7 device, administration of hydroxocobalamin does not significantly impact noninvasive oximetry. Accuracy of measurements in smoke-exposed individuals will require additional study.

Acknowledgements

The opinions and assertions contained herein are the views of the authors and are not to be construed as official or as reflecting the views of the United States Department of Defense. The authors express their gratitude to Dr. Amoroso, Dr. Patten, and the Department of Clinical Investigation (Madigan Army Medical Center, Tacoma, Washington USA) for their support and funding.

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