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Noninvasive assessment of muscle oxygenation may aid in optimizing transfusion threshold decisions in ambulatory pediatric patients

Kenneth A. Schenkman^{1,2,4}, Douglas S. Hawkins¹, Wayne A. Ciesielski¹, Meghan Delaney^{1,3}, and Lorilee S. L. Arakaki¹

¹Department of Pediatrics, University of Washington, Seattle Children's Hospital, Seattle, Washington

²Department of Anesthesiology, University of Washington, Seattle Children's Hospital, Seattle, Washington

³Department of Laboratory Medicine, University of Washington, Seattle Children's Hospital, Seattle, Washington

⁴Department of Bioengineering, University of Washington, Seattle Children's Hospital, Seattle, Washington

Abstract

Objective—To assess the potential utility of a novel non-invasive muscle oxygen measurement to determine the presence of muscle hypoxia in patients with anemia.

Background—Recent assessment of the risk/benefit ratio of blood transfusion has led to clinical strategies optimizing transfusion decisions. These decisions are primarily based upon hematocrit (Hct), but not oxygen delivery, the primary function of red blood cells (RBCs). We hypothesized that muscle oxygenation (MOx) would correlate with Hct in patients with anemia and may be a physiologically relevant determinant of transfusion threshold.

Methods/Materials—MOx was noninvasively determined in children in the Cancer and Blood Disorders Center ambulatory clinic at Seattle Children's Hospital using a custom-designed optical probe and spectrometer. MOx was compared with contemporaneous Hct. In subjects receiving RBCs, MOx and Hct were also determined following transfusion.

Results—MOx ranged from 36.7 to 100%, and Hct ranged from 17.0 to 38.6% in 27 measurements from 16 patients. High MOx values were associated with high Hct. Mean MOx for patients with normal Hct for age (n=5) was $95.9 \pm 2.9\%$. RBC transfusion increased mean Hct from $19.1 \pm 1.5\%$ to $29.3 \pm 2.0\%$, and mean MOx from $67.9 \pm 21.1\%$ to $89.9 \pm 9.8\%$. Among six transfusion episodes (in five patients) with initial Hct < 22, only three had a pre-transfusion MOx

Address correspondence to: Kenneth A. Schenkman, MD, PhD, Associate Professor, Department of Pediatrics, University of Washington, Seattle Children's Hospital, 4800 Sand Point Way NE Box FA.2., Seattle, WA, 98105.

Conflict of Interest

Drs. Schenkman and Arakaki and Mr. Ciesielski have a significant financial interest in Opticyte, Inc., which is not directly or significantly related to the research. None of the other authors have disclosed that they have any potential conflicts of interest.

of < 70%. Patients with lowest pre-transfusion MOx had the largest increase in MOx after transfusion.

Conclusions—These preliminary data suggest that MOx may aid in making transfusion decisions when used in combination with hematocrit.

Introduction

Over the past decade there has been an increased focus on the balance of risks and benefits from red blood cell (RBC) transfusions, leading to strategies to optimize transfusion thresholds used for clinical practice. There are now several published, well-designed studies demonstrating generally equivalent clinical outcomes using restrictive versus liberal transfusion thresholds in a range of inpatient populations (Hebert et al. 1999, Holst et al. 2014), including in children (Lacroix et al. 2007). In most of these studies, decisions to transfuse were based solely on a predetermined hematocrit (Hct) threshold. The studies support the observed trend toward more restrictive transfusion thresholds in many clinical situations, including in pediatric patients.

Although using Hct provides a direct measure of RBC volume and is easily obtained in clinical settings, using Hct alone for RBC transfusion decision making may not be the most appropriate physiological endpoint because it is a one-size-fits-all approach. Klein, et al., state that, in the context of RBC transfusion, “added effort should be devoted to developing sensitive measures of tissue hypoxia and other appropriate, physiologically relevant parameters (Klein et al. 2015).” Better information about the metabolic status of patients may lead to improved therapeutic decisions for each individual patient, including decisions about when to transfuse RBCs.

The primary physiologic goal of RBC transfusion is to improve delivery of oxygen to tissues when the oxygen carrying capacity of blood is abnormally low. Invasive measurements in brain parenchyma using Clarke-type electrodes have shown improvement in cerebral oxygenation with RBC transfusion (Smith et al. 2005, Zygun et al. 2009). Similarly, noninvasive measurements using transcutaneous PO₂ devices over the skin and near-infrared spectroscopy (NIRS), primarily of brain (Seidel et al. 2013, Sandal et al. 2014), have noted improvement in tissue saturation provided by transfusion. While these findings are positive, an accurate noninvasive measurement of tissue oxygenation on which clinical decisions can be made is still lacking (Highton et al. 2010, Hirsch et al. 2010, Durandy et al. 2011). In particular, cerebral NIRS measurements are based upon an assumption that 70% of the signal is from venous blood, an assumption that has never been validated in children (Durandy et al. 2011). Further, it is well known that vascular diameter of both arteries and veins are widely dynamic, resulting in a constant changing of the ratio of arterial to venous blood in any tissue bed, including the brain (Hall 2016).

Our laboratory has developed a noninvasive measurement of muscle oxygenation (MOx) that is based on optical spectroscopy (Cohen et al. 2011, Arakaki et al. 2013). MOx is measured transcutaneously from the back of the hand. MOx is a potentially relevant indicator of overall oxygenation in the body, since peripheral muscle is not a critical organ in the body. Under oxygen-limited conditions, the body preferentially preserves blood flow to

the critical organs, i.e., the brain, heart, liver and kidneys, at the expense of the peripheral muscles. In contrast to NIRS, MOx measurement does not require assumptions about the ratio of arterial to venous blood. MOx measurements have been found to be accurate in adults with a range of body mass indices and skin tones (Arakaki et al. 2013).

In this pilot study, MOx was measured in children, including before and after RBC transfusions, in the Cancer and Blood Disorders Center at Seattle Children's Hospital. These outpatients had a range of Hct, providing an opportunity to investigate the relationship between anemia and tissue oxygenation. Of particular interest was an evaluation of MOx in patients who received RBC transfusions using a common threshold for transfusion.

Materials and Methods

MOx was determined using a custom-designed fiber optic probe that conveyed reflected light from the subject's hand to a spectrometer. Optical spectra from both the visible and near-infrared (NIR) spectral regions were analyzed using a multi-wavelength analytic approach previously described (Arakaki et al. 2013). The optical probe was placed over the first dorsal interosseous muscles and held in place with Coban.TM Five minutes of optical data were acquired from each subject. Mean MOx values were compared with Hct obtained at the time of the clinic visit. In subjects who received a blood transfusion, MOx was measured again for 5 minutes upon completion of the transfusion. A post-transfusion Hct was also obtained at that time.

Patients could have repeat MOx measurements during subsequent clinic visits as long as they remained otherwise eligible. Clinical and demographic information were recorded from the medical record. For patients who had RBC transfusions, comparison of pre- and post-transfusion Hct and MOx was by paired Student's t-test.

Subjects Studied

Children aged 3 to 18 years who were being evaluated in the outpatient Cancer and Blood Disorders Center at Seattle Children's Hospital and who had a complete blood count performed on the same day as part of routine care were candidates for study recruitment. Informed consent from parents and assent from children was obtained from all enrolled subjects. Patients were excluded from study if they had significant cardiopulmonary compromise, required inpatient hospitalization, or were unwilling to have noninvasive MOx measurements made. All subjects were ambulatory at the time of measurement and none required supplemental oxygen, were clinically distressed, or in need of inpatient hospitalization at the time of study. All subjects were discharged to home following their clinic visits. The protocol was approved by the institutional review board of the University of Washington.

Results

The diagnoses for the enrolled children are shown in Table I, and include both solid tumors and leukemia. Ages ranged from 3–17 years, and there were 5 female and 11 male subjects.

MOx values ranged from 36.7–100%. Hct ranged from 17.0–38.6%, including post-transfusion values.

There were 27 independent measurements of MOx made from 16 patients. Comparison between measured MOx and contemporaneously recorded Hct is shown in Figure 1 in all subjects at all time points measured. There was a clear association between high MOx values and high Hct, as expected. Five children who had a normal Hct for age had a mean MOx of $95.9 \pm 2.9\%$. Low MOx values ($< 70\%$) were measured in four of the 27 evaluations. Three of these were associated with low Hct. Of the six evaluations with Hct < 22 , only three had MOx $< 70\%$. A threshold of 70% was chosen based upon our experience measuring MOx in various clinical settings, but definitive normal values for MOx in children have not yet been fully defined.

In five children, MOx and Hct were measured at both pre- and post-transfusion time points. These values are shown in Table II. In one patient, pre- and post-transfusion measurements were obtained from two separate transfusions seven days apart. RBC transfusion increased Hct and MOx in all cases. Mean Hct increased from $19.1 \pm 1.5\%$ to $29.3 \pm 2.0\%$, for an average increase in Hct of 10.5%. The mean pre-transfusion MOx was $67.9 \pm 21.1\%$ and increased to a mean post-transfusion MOx of $89.9 \pm 9.8\%$ ($p < 0.05$ for both comparisons by paired sample t-test). The changes in MOx with blood transfusion are shown in Figure 2, Panel A. Although MOx increased in all cases, some subjects had a much greater increase in MOx compared with others. The mean increase in MOx for those with an initial MOx $> 70\%$ was only 10.5% compared with an increase in MOx of 33.4% for those with an initial MOx $< 70\%$. As expected, heart rate generally decreased with transfusion (Figure 2, Panel B.)

Discussion

In the United States, approximately 15 million units of RBCs are transfused each year (Whitaker et al. 2011). Blood transfusions are associated with inherent risks, high costs, and limited inventory (Goodnough et al. 2013). While RBC transfusions can be life-saving, transfusion recipients, as a group, have been found to have longer hospital stays, higher mortality rates, and to incur higher medical costs than patients who were not transfused, even when accounting for confounding factors (Vincent et al. 2002, Shander et al. 2011, Leal-Noval et al. 2013). These findings highlight the need for a clearer determinant of when RBC transfusions should be used.

Most commonly, transfusion decisions are based on Hct or hemoglobin threshold without knowledge of the presence or degree of tissue hypoxia. The recent large studies and meta-analyses demonstrating relatively clinically equivalent outcomes for large populations of critically ill patients receiving restrictive vs. liberal transfusion thresholds (Hebert et al. 1999, Lacroix et al. 2007, Carless et al. 2010, Holst et al. 2014) were based on a single hemoglobin threshold. There is evidence that certain sub-populations (e.g., patients with coronary ischemia and those on extra-corporeal life support (Lelubre et al. 2016)) would benefit from different thresholds than the standard ones.

Compensatory mechanisms aimed at improving oxygen delivery and decreasing metabolism are activated in patients with anemia that develops gradually over time. These mechanisms generally allow the patients to tolerate lower hemoglobin levels than patients with acute blood loss anemia. Indeed, a recent report describes a fully conscious child who presented with a hemoglobin of 1.6 g/dl, due to malaria and underlying sickle cell disease (Dhabangi et al. 2014). Thus, transfusion thresholds for patients with acute blood loss anemia probably should be higher than those with chronic anemia, but how should clinicians determine these thresholds? Clearly there may be different optimal thresholds for transfusion between inpatient and outpatient settings, and for different causes of anemia. An approach based on patient-specific physiologic data, especially data related to the presence or degree of tissue hypoxia is needed.

The preliminary data presented here demonstrate two relevant findings that, if substantiated in future larger studies, could have a marked impact on transfusion decisions. First, MOx had a clear correlation with Hct (Figure 1). As Hct decreased, MOx became significantly low in some cases. From a physiologic perspective, this observation is consistent with oxygen delivery becoming limited with worsening anemia, causing a drop in muscle cellular oxygenation.

The second finding is that patients with the same (and low) Hct had very different MOx, and thus may not have had equivalent needs for RBC transfusion. The wide range in MOx seen in patients with Hct between 17–22% (Figure 1) suggests that not all of these patients needed transfusions at the time of these measurements. This idea is also supported by the greater increase in MOx for some patients compared to others (Figure 2, panel A), all of whom had Hct < 22% at the time of their transfusions.

NIRS has been used extensively in clinical studies to measure cerebral and tissue oxygenation (Scheeren et al. 2012, Samraj et al. 2015). The need for noninvasive, continuous monitoring has spurred the development of several NIRS devices, but so far no NIRS device has attained widespread clinical acceptance. In general, NIRS devices do not provide cerebral or tissue oxygenation measurements that are accurate enough on which to base clinical decisions (Steppan et al. 2014).

Our device differs substantially from NIRS devices in that we measure continuous bands of wavelengths of light in the visible and NIR regions. NIRS devices measure only a few single wavelengths in the NIR. With the much greater information content available in our spectral measurement compared to NIRS, our device yields absolute, accurate MOx values. Our algorithm has been trained on healthy subjects with a wide range of age, body mass index, and skin tone. The variations allow accurate MOx measurements to be made from patients with different body and hand characteristics (Arakaki et al. 2013).

We have investigated the depth of sampling in our measurements using tissue phantoms (Asplund et al. 2014). This has given us confidence that our system samples tissue deep enough to pass through skin and the underlying fat layer to interrogate muscle in the hand. Since we are sampling deeper than just the superficial skin layer, effects from local skin vasoconstriction and surface temperature changes are likely minimized, though these

variables may contribute to the measured MOx. Edema in the hand will increase the distance between the surface probe and the underlying muscle, and may also affect the MOx measurement. Although not measured quantitatively, none of the subjects enrolled in this study had notable hand edema at the time of these measurements.

Changes in hemodynamic status of these subjects may have also contributed to improvements in their MOx measurements. Although these subjects were relatively healthy outpatients at the time of measurement, improved cardiac output as a result of blood transfusion may have contributed to improvements in MOx, distinct from the increase in oxygen carrying capacity afforded by increased hematocrit.

MOx values have the potential to contribute substantially to clinical decision making. While the results presented here are preliminary and based upon small numbers, the findings demonstrate that Hct alone may be insufficient to determine when anemia is associated with tissue hypoxia. If our findings are confirmed in a larger study, MOx could be incorporated into a more nuanced algorithm to determine when RBC transfusion is indicated, supporting a more restrictive use of RBC transfusion. We believe that noninvasive measurement of MOx may provide useful and real-time clinical information about an individual patient's muscle cellular oxygen status that could in the future be used to guide transfusion decisions.

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Fig. 1.

Muscle oxygenation (MOx) compared with **contemporaneous** hematocrit (Hct) for each of 27 sets of measurements from 16 subjects. Low Hct is generally associated with low MOx, but not in all cases. The three points in the left lower shaded quadrant may represent patients for whom transfusion is most beneficial.

Fig. 2.

In Panel A, an increase in MOx is seen for each patient receiving a transfusion of red blood cells (RBCs). Some patients show a greater improvement in MOx than others, suggesting a possible greater benefit of RBC transfusion for these patients. Five subjects received blood transfusions, one of whom had two transfusions during two distinct clinic visits. Heart rate decreased in 5 of the 6 instances of transfusion, as shown in Panel B.

Table I

Diagnoses of enrolled subjects

Diagnosis	n
Sarcoma	
Osteosarcoma	3
Rhabdomyosarcoma	2
Ewing sarcoma	1
Undifferentiated sarcoma of bone	1
Desmoplastic small round cell tumor	1
Other solid tumors	
Wilms tumor	2
Neuroblastoma	1
Hepatoblastoma	1
Langerhans cell histiocytosis	1
Acute lymphoblastic leukemia	3

Table II

Hematocrit and MOx values before and after transfusion

Pre-transfusion MOx (%)	Post-transfusion MOx (%)	Pre-transfusion Hematocrit (%)	Post-transfusion Hematocrit (%)
75.5	97.9	21.1	29.9
36.7	97.2	17.0	31.8
86.1	91.4	19.6	27.8
56.5	75.3	18.9	30.4
59.3	80.1	20.1	–
93.4	97.3	17.6	26.8