ORIGINAL ARTICLE

Assessment of Infantile Hemangiomas Using a Handheld Wireless Diffuse Optical Spectroscopic Device

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Abstract

Background/Objectives: Infantile hemangiomas (IHs) are vascular tumors with the potential for significant morbidity. There is a lack of validated objective tools to assess IH severity and response to treatment. Diffuse optical spectroscopy (DOS), a noninvasive, nonionizing imaging modality, can measure total hemoglobin concentration and hemoglobin oxygen saturation in tissue to assess IH vascularity and response to treatment. Our objective was to evaluate the utility of a wireless, handheld DOS system to assess IH characteristics at selected points during their clinical course.

Methods: Thirteen subjects (initial age 5.8 ± 2.0 mos) with 15 IHs were enrolled. IHs were classified as proliferative, plateau phase, or involuting. Nine patients with 11 IHs were untreated; four patients with 4 IHs were treated with timolol or propranolol. Each IH was evaluated by placing the DOS system directly on the lesion as well a normal contralateral skin site. IH vascularity and oxygenation were scored using a newly defined normalized hypoxia fraction (NHF) coefficient. Measurements were recorded at various intervals from the initial visit to 1 to 2 years of age.

Results: For the nine untreated IHs, the NHF was highest at 6 months of age, during proliferation. Differences in NHFs between the proliferation and the plateau ($p = 0.02$) and involuting ($p < 0.001$) stages were statistically significant. In treated patients, the NHF normalized to 60% after 2 months. One treated IH came within 5% of the NHF for normal skin after 12 months.

Conclusions: DOS can be used to assess the vascularity and tissue oxygenation of IHs and monitor their progression and response to treatment.

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Infantile hemangiomas (IHs) are the most common pediatric vascular tumors, affecting approximately 5% of infants (1,2). Complications include ulceration, visual or airway obstruction, and potential for disfigurement (3). IH progression is documented using relatively subjective techniques relying on physical examination, visual analog scale (VAS), and review of photographs (4–9), but lesional measurements and color assessment can be inexact because the angle and lighting of photographs and measurements are largely operator dependent (5,9). The lack of an objective, quantifiable tool to assess IHs makes it difficult to decide on the correct course of lesion management and to compare the efficacies of different treatments. In addition, it has been suggested that hypoxic stress of local skin tissue brings on IHs (1,10), and a method of quantifying IH biology and severity could be useful in understanding the pathophysiological processes of IH, such as hypoxia or other mechanisms that may contribute to the risk of ulceration (2,11). Thus it is of great interest to clinicians to develop and validate evidence-based diagnostics (4,12). Doppler ultrasound has been used to measure IH size, growth, blood flow, and vessel density (13,14), but the need for an experienced ultrasonographer and operator variability limit its everyday clinical use. The commonly observed temperature difference between IHs and surrounding or contralateral skin makes infrared thermography a viable solution for monitoring IHs (15), but results have shown that infrared thermography is less sensitive to deep IHs.

To address this clinical need, we have developed a wireless handheld diffuse optical spectroscopy (WH-DOS) system. The system uses near-infrared (NIR) light to illuminate the IH and normal skin tissue and measures the light intensity that is reemitted from the tissue. Because the concentration of oxyhemoglobin ($[HbO_2]$) and deoxyhemoglobin ($[HHb]$) primarily affects NIR light absorption, these measurements can be used to derive total hemoglobin concentration ($[THb] = [HbO_2] + [HHb]$) and hemoglobin oxygen saturation in tissue (StO_2) within the microvasculature of superficial tissue. NIR light has no adverse health effects, allowing for frequent measurements in patient monitoring, including in children (16–18).

We used our WH-DOS system in a longitudinal pilot study to evaluate its utility in IH vascularity assessment. We monitored changes in $[THb]$ and StO_2 at several timepoints for up to 18 months in untreated patients or patients treated with propranolol or topical timolol. The DOS characteristics of IHs in different stages (proliferation, plateau, involuting) and IHs being treated were correlated with clinical features.

MATERIALS AND METHODS

Introduction and Clinical Examination

Approval was obtained from the Columbia University Medical Center Institutional Review Board and patients were recruited from the pediatric dermatology practices at Columbia University Medical Center. Infants were eligible if they were younger than 9 months at the time of the initial visit and had at least one cutaneous IH larger than 2 cm in diameter in an area accessible by our probe's 3-cm × 1-cm measurement head. Frontal facial lesions were excluded. The patient's eyes were shielded from the light using an NIR light-absorbing material. Infants were scheduled to be assessed using the WH-DOS at the initial visit and at the 2- to 4-months and 1- to 2-year follow-up visits.

Patients were assigned to the natural history cohort if no medical intervention was clinically indicated and to a treatment cohort with oral propranolol or topical timolol if medical intervention was indicated. Before DOS measurements, subjects underwent clinical examination and photographic documentation. IH stage (proliferating, plateau, involuting) and classification (superficial, deep, mixed) were determined based on parental history of IH appearance, clinical and parental photographs, patient age, and IH characteristics (e.g., color, texture) on physical examination at the time of assessment. The same treating physician performed assessments at routine clinic visits for continuity.

Study Device

All patients were scanned with our enhanced WH-DOS system (Fig. 1A,B), which is an optimized version of a previously developed device (19). The WH-DOS (Fig. 1C) illuminates tissue using four NIR wavelengths of light and detects the reemitted light intensities, which were entered into a reconstruction algorithm (19) to determine the functional parameters HbO_2, HHb, THC, and StO_2 of the underlying tissue. The measurement probe was controlled using Bluetooth with a custom-designed Android telephone application.

The WH-DOS probe head was placed on the IH and on contralateral normal skin for measurements. If the IH lay in the center of the body, a normal skin measurement was taken a minimum of 5 cm above or below the IH. Multiple measurements at different probe orientations were taken to ensure consistency of the measurement area. Individual measurements take only seconds, and the entire measurement procedure,
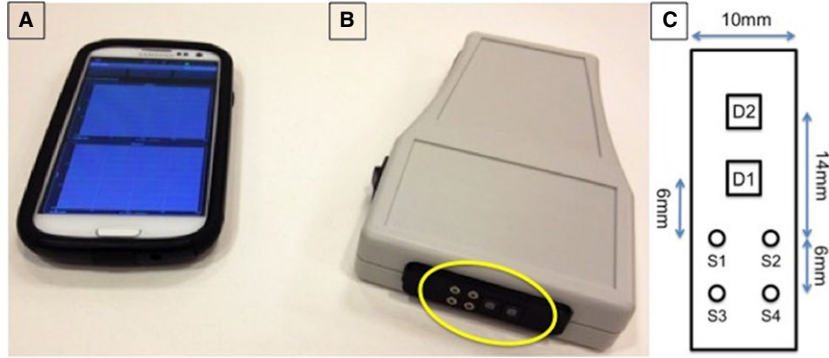
Figure 1. System for performing diffuse optical spectroscopy (DOS) measurements for infantile hemangiomas. (**A**) Smartphone with a custom-built application for system control. (**B**) Wireless handheld DOS device with measurement head (circled in yellow). (**C**) Diagram of measurement head with dimensions. S1 through S4 represent light sources at 780, 905, 850, and 808 nm, respectively. D1 and D2 represent the two detectors, with a sensing area of 5.7 mm^2, used to capture back-reflected light from skin tissue.

including placement of the probe at multiple sites, can be performed in less than a minute. Functional parameters from multiple measurements were averaged before analysis.

Data Analysis

Because [THb] and StO_2 may differ at different skin sites around the body, each IH measurement was normalized to the measurement performed at the contralateral normal tissue site to produce [THb] and %StO_2 ratios:

$$\mathrm{rTHb} = \frac{[\mathrm{THb_{IH}}]}{[\mathrm{THb_{Normal}}]} \, , \mathrm{rStO_2} = \frac{\%\mathrm{StO_{2_{IH}}}}{\%\mathrm{StO_{2_{Normal}}}} \quad (1)$$

The rTHb provides a metric for volume measurement based on the overall vascularity observed. For example, one would expect higher rTHb values in bulkier, deep IHs than in superficial IHs. The $rStO_2$ provides a relative measure of the oxygen supply within the microvasculature between involved and uninvolved tissue.

The rTHb and $rStO_2$ features may vary greatly depending on the subtype and staging, which could make it difficult to interpret the overall state of the IH. To quantify the overall state of the IH, we derived a third index that combines the two features with equal weight, which we call the normalized hypoxia fraction (NHF):

$$\mathrm{NHF} = \frac{\mathrm{rTHb} + \frac{1}{\mathrm{rStO_2}}}{2} \quad (2)$$

This unitless index combines information about [THb] and StO_2 into one number since rTHb and $rStO_2$ may change independently over time. This index, as we found, provides the best distinction between the proliferation, plateau, and involuting stages. As the IH evolves through these stages, rTHb and $rStO_2$ will trend toward 1—suggesting that the vascular properties of the IH site are equivalent to those of the normal skin site. The three DOS-derived parameters (rTHb, $rStO_2$, NHF) were correlated to the results of the clinical examination.

Statistical Analysis

IHs at different stages were compared using one-way analysis of variance (ANOVA). The Holm–Sidak t test was used to determine individual intergroup significance. Boxplots were generated to depict the range, shape, and skewness of the data. Scatterplots showing normalization of NHF over time were produced. The repeatability of the system measurements was computed by measuring the coefficient of variance of [THb] and StO_2 for each patient.

RESULTS

Demographic Characteristics

Thirteen infants with 15 hemangiomas were enrolled. All were female. A summary of enrolled patients is found in Table 1.

Untreated Infants with IH

We performed 23 measurements on 13 untreated IHs, including two pretreatment measurements from 2 of the 4 treated infants for our analysis of untreated patients. Three IHs were scanned three times, five were scanned twice, and four were scanned once.

TABLE 1. *Demographic Features and Clinical Classifications of All Subjects*

	Age (mos)	Classification, *n*			Location, *n*		
		Superficial	Deep	Mixed	Trunk	Extremities	Head
All IH (*n* = 15)	5.8 ± 2.0	8	2	5	10	3	2
Untreated IH (*n* = 11)	6 ± 1.9	5	2	4	8	1	2
Treated IH (*n* = 4)	3.8 ± 1.9	3	0	1	2	2	0

IH, infantile hemangioma.

Three measurements from two subjects were excluded because of user error of the WH-DOS, which was discovered after the scans had been performed. At the time of measurement, the IHs were classified as being in the proliferation (*n* = 6; mean age 5.1 ± 2.2 years), plateau (*n* = 12; mean age 9.1 ± 2.3 years), or involuting stage (*n* = 5; mean age 14.0 ± 7.9 years) and correlated with patient age.

The NHF index peaked at 6 months of age (2.9) (Fig. 2) and decreased and trended toward normal skin over time. The NHF index for IHs with a deep component (deep or mixed IH) reached a minimum value of 1.46 and the NHF index of superficial IHs reached a minimum value of 1.03, showing that no deep or mixed IH was fully involuted before the age of 23 months.

Overall, mean NHF indices decreased significantly as IHs progressed from proliferative to involuting (Fig. 3; ANOVA, p = 0.002). Using the Holm–Sidak *t* test, the NHF index during the proliferative stage was significantly higher than during the plateau (p = 0.02) and involuting (p = 0.001) stages. There was no significant difference in the NHF index between plateau- and involuting-stage IHs (p = 0.12). A summary of the statistical results can be found in Table 2, which shows that NHF distinguishes the plateau from the involuting stage better than the measures of vascularity or oxygenation do by themselves.

Treated Infants with IHs

In the treated subjects (*n* = 4), three IHs were classified as superficial and one as mixed. All subjects responded to propranolol treatment according to clinical criteria or size, volume, and color. Of the four infants, two did not have complete measurement data and were omitted from the analysis. Of the remaining two subjects, one had 39.2% improvement in the NHF index over a 3-month span of treatment with topical timolol.

The final patient (Fig. 4) presented at 1 month of age with a large, segmental, superficial, proliferative IH of the left lower extremity and was started on oral propranolol. Pre- (1 mo) and posttreatment (3 and 13 mos) measurements were obtained from the IH and the contralateral, unaffected leg.

The baseline DOS measurements demonstrated hypoxia in the IH (NHF 2.38), which normalized to normal skin oxygenation (NHF 0.96) after 2 months of propranolol treatment. This correlated with clinical observations of a decrease in red discoloration and papules (Fig. 4 and Table 1). After propranolol
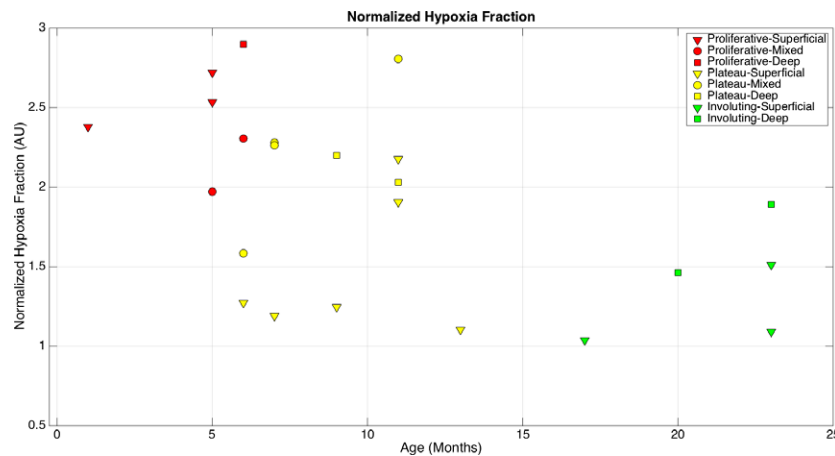

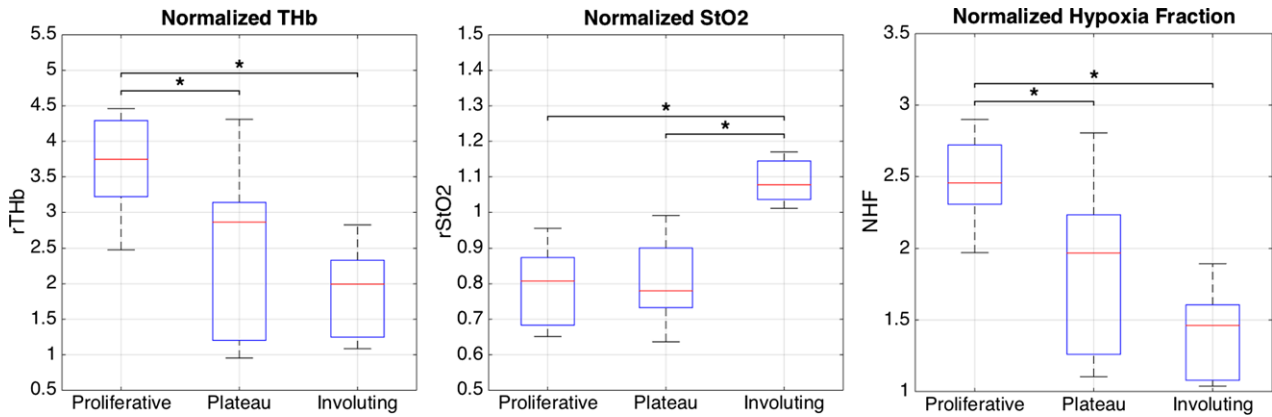**Figure 2.** Scatterplot of normalized hypoxia fraction measurements of untreated subjects.

Figure 3. Boxplots show the distribution of normalized hypoxia fraction measurements according to stage classification: proliferation ($n = 6$), plateau ($n = 12$), and involuting ($n = 5$). *Statistically significant based on the Holm–Sidak t test.

TABLE 2. *P-values of Features Comparing the Three Stages of Infantile Hemangioma (Proliferative, Plateau, Involuting)*

Feature	Proliferative versus plateau	Plateau versus involuting	Proliferative versus involuting
rTHb	0.0236*	0.3355	0.0027*
rStO$_2$	0.9343	0.0001*	0.0010*
NHF	0.0204*	0.1206	0.0005*

*Statistically significant changes.

discontinuation at 13 months, NHF continued to be normal (0.97). These parameters suggest that total hemoglobin content decreased (Table 3) and oxygen saturation in the IH increased toward normal skin values during propranolol treatment.

DISCUSSION

We have developed a WH-DOS device that provides an objective, reproducible, nonionizing, noninvasive, portable tool to measure hemoglobin content and oxygen saturation in IHs of all stages without the need for sedation. By using these measures of normalized THb, StO$_2$, and hypoxia fraction, DOS can tell us more about IHs in different stages and how the vascular information from the device can provide a better understanding of the pathophysiology.

Using the WH-DOS, we have defined an NHF index as a measure of tissue hypoxia and vascularity that correlates well with clinical appearances and stages of IHs. NHF peaks at 6 months of age, correlating with the end of the most active proliferative period. By 13 months of age, a plateau phase, the NHF is steadily decreasing. This is an indication that IHs become more like normal skin as they mature and become less hypoxic. This might explain why IHs are more likely to ulcerate during rapid growth periods (20). Furthermore, propranolol-treated IHs had normalized NHF earlier than untreated IHs, suggesting that propranolol may target IHs in part by correction of the hypoxic state. This demonstrates that, with successful treatment of IHs, DOS may be able to track accelerating involution or movement toward normalization.

There are limits to this study. Although this system can be used for facial IHs, we decided to take a conservative approach for ease of recruiting subjects, given that greater ocular protection would be required

Figure 4. Photographs of a subject with a large segmental superficial infantile hemangioma. Left: subject at 1 month of age, just before treatment; middle: subject after 2 months of treatment; right: subject after 12 months of treatment.

TABLE 3. *Normalized Total Hemoglobin Concentration Ratio (rTHb), Tissue Oxygen Saturation Ratio (rStO$_2$), and Normalized Hypoxia Fraction (NHF) Results from the Treated Subject*

DOS measurements			
	1 mo	3 mos	13 mos
rTHb	3.22	0.85	0.98
rStO$_2$	0.65	0.94	1.04
NHF	2.38	0.96	0.97

Measurements were made at 1 month of age, just before treatment, and at 3 and 13 months of age after propranolol was administered.

to use the device on lesions closer to the eye. The use of protective goggles caused infants to become more active, and as a result, repeatability measurements were difficult to acquire. We did not use a formal VAS to assess the patient's IH progression. Ultrasound was performed only as clinically indicated, and we do not have data for all patients. In cases in which ultrasound was performed, the clinical classification (superficial versus having a deeper component) correlated with our clinical impression. Ulcerated IHs were excluded because the WH-DOS interface requires contact with the skin. Future versions of the WH-DOS could have a noncontact interface for measuring ulcerated lesions and to improve repeatability.

DOS has the potential to aid in monitoring IHs in their growth and involuting stages, which may aid in management decisions and quantify treatment efficacy. The high variability in the size and classification of IHs requires more subjects for a more complete analysis. The treatment cohort was small and anecdotal and our findings need to be confirmed in a larger study. Future studies are required to compare DOS with other objective measures of IH growth, such as VAS and ultrasound, and to assess its applicability in complicated IHs.

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