Evaluation of Noninvasive Hemoglobin Monitoring for Hematological Disorders

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The Astrim is a noninvasive hemoglobin monitoring device that uses near-infrared radiation. We studied the usefulness of this device for patients with hematological disorders. We measured hemoglobin levels 309 times in 140 subjects, using an automated hematology analyzer (K-4500) and the Astrim. The coefficient of correlation between Hb levels with the K-4500 (K-Hb) and the Astrim (A-Hb) was $r=0.591$ ($P<0.001$). The coefficient of correlation between A-Hb and K-Hb from 174 specimens with anemia and 135 without anemia was $r=0.531$ ($P<0.001$) and $r=0.345$ ($P<0.001$), respectively. In the 309 specimens, the Astrim showed a diagnostic sensitivity and specificity for anemia of 78.3% and 69.0%, respectively. While the r -values, sensitivity, and specificity were passable, they appeared to be insufficient for an accurate evaluation. We believe this was caused by the measurement

conditions (i.e., the finger selected for measurement, the finger position in relation to the CCD camera, and the finger temperature). On the other hand, the precision test results were good. Therefore, if careful attention is paid to measurement conditions, the noninvasive Astrim is clinically useful for continuous hemoglobin monitoring of hematological disorders and patients with hemorrhagic diseases, such as perioperative hemorrhage and gastrointestinal bleeding. However, it is difficult to determine Hb concentrations in one measurement using the Astrim because the r -values, sensitivity, and specificity are insufficient for accurate evaluations of inpatients, particularly patients with advanced diseases. Therefore, we believe it is necessary to improve the system so that A-Hb can be accurately determined in one measurement. *J. Clin. Lab. Anal.* 19:1–5, 2005. © 2005 Wiley-Liss, Inc.

Key words: hemoglobin; noninvasive technology; hematological disorders; hemoglobin monitoring device

INTRODUCTION

In biological examinations in vitro, all optical phenomena, such as spectra, fluorescence, luminescence, scattering, and reflections, can be measured. With the use of light, one can obtain safe and easy (compared to X-rays and magnetic fields) noninvasive measurements of the human body. However, for biological examinations in vivo, light currently has very limited applications. Several noninvasive measuring methods using infrared radiation have been described (1–7). The Astrim, which was developed by Sysmex (Kobe, Japan), readily detects light that has passed through a finger, and measures hemoglobin levels without the necessity of collecting blood samples (8). We studied the usefulness of this device for patients with hematological disorders.

MATERIALS AND METHODS

Subjects

A total of 140 patients undergoing treatment for hematological disorders at Osaka City University Hospital and Wakakoukai Hospital, and five healthy volunteers employed at Wakakoukai Hospital were registered for this study between November 2001 and March 2003. The patients' characteristics are shown in

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Table 1. The patients' diagnoses included aplastic anemia (AA, n=19), autoimmune hemolytic anemia (AIHA, n=3), acute lymphocytic leukemia (ALL, n=6), acute myelocytic leukemia (AML, n=19), adult T cell leukemia/lymphoma (n=2), chronic myelocytic leukemia (CML, n=5), iron deficiency anemia (IDA, n=1), immune thrombocytopenic purpura (ITP, n=12), myelodysplastic syndrome (MDS, n=7), multiple myeloma (MM, n=13), myoproliferative disease (MPD, n=8), non-Hodgkin's lymphoma (NHL, n=42), pernicious anemia (PA, n=2), and pure red cell aplasia (PRCA, n=1). We measured hemoglobin concentration 309 times in these 140 subjects using a hematology analyzer and the Astrim (Fig. 1).

Astrim

The Astrim noninvasive hemoglobin analyzer is configured as follows: an infrared or near-infrared light source is positioned over the dorsal side of a finger, and a CCD camera is positioned underneath the finger (Fig. 2). This configuration visualizes venous flow near the skin surface. When the fingertip is irradiated with light of different wavelengths, the optical density of the

Fig. 1. The Astrim noninvasive blood vessel monitoring apparatus.

Fig. 2. Measurement principle of Astrim. Light sources shine infrared and near-infrared rays through a finger. The light penetration is photographed with a CCD camera under the finger. The resulting blood vessel image depends on the amount of hemoglobin in the blood. Therefore, one can calculate the hemoglobin level by analyzing the picture.

TABLE 1. Patient characteristics

No. of patients ^a	140 (309)
Age	
Median	58
Range	16–83
Sex	
Male	59
Female	81
Diagnosis ^a	
AA	19 (28)
AIHA	3 (12)
ALL	6 (7)
AML	19 (46)
ATL/L	2 (2)
CML	5 (5)
IDA	1 (1)
ITP	12 (22)
MDS	7 (11)
MM	13 (22)
MPD	8 (28)
NHL	42 (119)
PA	2 (5)
PRCA	1 (1)

AA, aplastic anemia; AIHA, autoimmune hemolytic anemia; ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; ATL/L, adult T cell leukemia/lymphoma; CML, chronic myelocytic leukemia; IDA, iron deficiency anemia; ITP, immune thrombocytopenic purpura; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPD, myeloproliferative disease; NHL, nonHodgkin's lymphoma; PA, pernicious anemia; PRCA, pure red cell aplasia.

^aThe number of times measured hemoglobin.

vascular portions of the images obtained at the respective wavelengths reflects the amount of light absorbed by hemoglobin. On the other hand, the amount of blood that contributes to absorption in the vascular portion of the image can be determined by direct vascular diameter measurement because the blood vessel has a nearly circular cross section. From the amount of light absorption and blood measured, the blood hemoglobin content can be determined.

Hemoglobin Measurement

Before the Astrim measurement was performed, the subjects rested in a sitting position at room temperature. Each subject's middle finger was placed on the detection probe of the Astrim, and hemoglobin levels (A-Hb) were

determined automatically. On the day we performed this examination, we also took 2 mL of peripheral blood from each of the subjects and measured Hb levels (K-Hb) with a K-4500 (Sysmex). According to the World Health Organization, anemia is defined as <13.0 g/dL of hemoglobin in men, and <12.0 g/dL in women (9).

Clinical Sensitivity, Specificity, and Efficiency

A true table analysis determined the results as true positive (TP, anemia), true negative (normal), false positive (FP), or false negative (FN). The FP ratio, FN ratio, sensitivity, specificity, and efficiency were defined as follows:

$$\text{FP ratio} = (\text{FP}/(\text{FP} + \text{TN})) \times 100\%$$

$$\text{FN ratio} = (\text{FN}/(\text{FN} + \text{TP})) \times 100\%$$

$$\text{Sensitivity} = (\text{TP}/(\text{TP} + \text{FN})) \times 100\%$$

$$\text{Specificity} = (\text{TN}/(\text{TN} + \text{FP})) \times 100\%$$

$$\text{Efficiency} = ((\text{TP} + \text{TN})/(\text{TP} + \text{TN} + \text{FP} + \text{FN})) \times 100\%$$

Statistical Analysis

Statistical analyses were performed with StatView V software (SAS Institute, Cary, NC). The A-Hb and K-Hb results were examined and compared by regression analysis. The Pearson method was employed for correlation coefficient testing, and a paired t-test was used for comparison analysis. $P < 0.05$ was considered significant. Values are expressed as mean $\pm$ standard deviation.

RESULTS

Precision Test

We used the Astrim to measure hemoglobin 10 consecutive times in five patients with anemia, and five healthy volunteers. The coefficients of variation (CVs) were 3.42–11.1% (patients) and 3.77–7.38% (healthy volunteers) (Table 2).

TABLE 2. Precision results*

Hemoglobin(g/dL)	Healthy volunteer					Patients				
	1	2	3	4	5	1	2	3	4	5
Mean	14.7	13.2	14.3	14.6	13.8	11.3	10.9	9.2	10.4	10.4
SD	0.72	0.98	0.59	0.55	0.79	0.73	0.37	0.72	0.51	1.2
%CV	4.88	7.38	4.12	3.77	5.74	6.48	3.42	7.83	4.91	11.1
Minimum	13.9	11.3	13.7	13.4	12.7	10.3	10.3	8.3	9.9	8.6
Maximum	15.7	14.1	15	15.3	14.8	11.5	11.5	10.4	11.7	12.1

*Hemoglobin (g/dL) measured with Astrim at 10 times.
SD, Standard deviation; CV, coefficient of variation.

Correlation Between A-Hb and K-Hb

The regression equation between A-Hb and K-Hb in 309 specimens (A-Hb: 12.1 ± 2.2 g/dL; K-Hb: 11.6 ± 2.1 g/dL) was $y = 0.57X + 4.74$ with a correlation coefficient of $r = 0.591$ ($P < 0.001$) (Fig. 3). The regression equations between A-Hb and K-Hb in 174 specimens with anemia (A-Hb: 11.4 ± 2.2 g/dL; K-Hb: 10.5 ± 1.5 g/dL) and 135 without anemia (A-Hb: 13.3 ± 1.5 g/dL; K-Hb: 13.9 ± 1.2 g/dL) were $y = 0.33X + 6.48$ with a correlation coefficient of $r = 0.531$ ($P < 0.001$), and $y = 0.27X + 9.90$ with $r = 0.345$ ($P < 0.001$), respectively.

The coefficients of correlation between K-Hb and A-Hb in 13 patients were measured with the Astrim more than seven times on different days (max $r = 0.606$, min $r = 0.048$). In nine patients (69.2%) the coefficient of correlation was $r = < 0.345$.

Truth Table Evaluation

The A-Hb truth table evaluation is presented in Table 3. In 309 samples, we observed 83 TP results (78.3%), 140 TN results (69.0%), 63 FP results (31.0%), and 23 FN results (21.7%).

TABLE 3. Truth table and sensitivity and specificity of total samples for hemoglobin level

Truth Table		
N = 309		
Astrim Hemoglobin		
K4500 Hemoglobin	True positive 83(78.3%)	False negative 23(21.7%)
	False positive 63(31.0%)	True negative 140(69.0%)
Sensitivity and Specificity	Sensitivity	78.3%
	Specificity	69.0%
	Efficiency	72.2%

Fig. 3. Correlation between Hb levels as determined by the Astrim and the K-4500.

DISCUSSION

Blood oxygen saturation can be quantified from oxidized and reduced hemoglobin concentrations because blood oxygen is for the most part irreversibly bound with hemoglobin in red blood cells. Since oxidized and reduced hemoglobin differ widely in terms of absorbance in the infrared to near-infrared zones, they are particularly suited for analyses of noninvasive measurements. The pulse oxymeter enables noninvasive measurement of arterial oxygen saturation on the basis of the light-transmission difference between two wavelengths in synchronization with the pulsating components of the artery. Although the pulse oxymeter derives blood-component information by means of pulse waves, it does not provide spatial information. Therefore, that instrument is incapable of measuring absolute concentrations of oxidized and reduced hemoglobin, although it is possible to determine their ratio. Asano (10) thought that blood-component information could be obtained by means of image measurements (spatial information), and he developed a noninvasive hemoglobin analyzer for that purpose. In this study, we evaluated the efficacy of the Astrim for measuring Hb in patients with hematological disorders.

The relationship between A-Hb and K-Hb in patients with and without anemia was statistically significant ($P < 0.001$). However, the r -values were 0.591 for the total 309 specimens, 0.531 for 174 specimens with anemia, and 0.345 for 135 specimens without anemia. The diagnostic sensitivity and specificity for anemia, as determined in 309 specimens with the Astrim, were 78.3% and 69.0%, respectively. While the r -values, sensitivity, and specificity were passable, they appeared to be insufficient for an accurate evaluation.

We considered that the insufficient r -values, sensitivity, and specificity could have been caused by the low correlation coefficient of each subject. Therefore, we investigated the correlation coefficient between K-Hb and A-Hb in 13 patients measured with the Astrim more than seven times on different days. There were insufficient r -values (< 0.345) in nine patients. We also measured A-Hb and K-Hb in 21 specimens from healthy volunteers because the coefficient of correlation between A-Hb and K-Hb was low in the specimens from patients without anemia. The coefficient of correlation between A-Hb and K-Hb in the healthy volunteers was good (A-Hb: 13.7 ± 1.63 g/dL; K-Hb: 13.6 ± 1.14 g/dL, $r = 0.735$). The poor correlation in patients with hematological disorders was not caused by different measurement conditions with the Astrim, because the measurements were obtained under the same conditions (i.e., the subjects were in a sitting position at room temperature). We considered that the cause could have been inaccurate finger position and varying finger temperatures (5). Therefore, in 10 healthy volunteers we measured hemoglobin while tilting the middle finger away from the CCD camera in the Astrim. As a result, measurement errors occurred frequently and A-Hb levels in the tilting position ($n = 20$, 13.1 ± 1.18 g/dL) were lower than in the normal position ($n = 25$, 15.5 ± 0.52 g/dL; $P < 0.05$). Moreover, measurements were obtained in 10 healthy volunteers when the middle-finger temperature was altered (low temperature: finger soaked in ice water (0°) for 1 min; high temperature: finger soaked in hot water (40°) for 1 min). A-Hb levels at both the low ($n = 25$, 14.8 ± 1.29 g/dL) and high (14.1 ± 2.14 g/dL) temperatures were lower than under normal conditions ($n = 25$, 15.6 ± 0.52 g/dL; $P < 0.05$). Yonemura (12) reported that low finger temperature decreases blood flow, and A-Hb is inaccurate compared with Hb measured with a hematology analyzer. He also reported that A-Hb is 1–2 g/dL lower when the finger position is incorrect, as compared with Hb measured with a hematology analyzer. We confirmed that two causes of the poor correlation between A-Hb and K-Hb in patients with hematological disorders were finger temperature and inaccurate finger position in relation to the CCD camera when the Astrim was used.

When measuring Hb levels with the Astrim, care must be taken regarding the following: 1) The finger must be positioned straight and flat in relation to the CCD camera. Although we principally measured A-Hb using the middle finger, discordance between A-Hb and Hb measured with an automated hematology analyzer may occur because of the vascular stream position of the middle finger. Thus it is important to choose a suitable finger for each patient. 2) While the precision test results were good, the CV among five patients was compara-

tively broad (4.3–11.3%). Accordingly, it is important to use the average of hemoglobin levels measured several times as the A-Hb for patients with hematological disorders.

Under the above-mentioned measurement conditions, the noninvasive Astrim is clinically useful for hematological disorders and hemorrhagic diseases, such as perioperative hemorrhage and gastrointestinal bleeding. However, it is difficult to determine Hb concentration by Astrim in one measurement because the low r-values, sensitivity, and specificity are insufficient for an accurate evaluation of in-patients, particularly those with advanced diseases who cannot maintain a stable finger position and temperature. Therefore, we believe it is possible to accurately evaluate A-Hb concentrations only in patients and other subjects in generally good health who can maintain strict finger positions and demonstrate good performance status. The Astrim system must be improved so that A-Hb can be accurately determined in one measurement. Such improvements would include changing from a fixed infrared light source and light-receiving CCD camera system to a mobile system, and developing compensation programs for the finger position and the low/high finger temperature.

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