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14. ABSTRACT

Monitoring for acute blood loss is critical in surgical patients, and delays in identifying hemorrhage can result in poor outcomes. The current standard of care for monitoring patients at risk for bleeding is serial measurement of hemoglobin (Hgb) by standard laboratory complete blood count (CBC). Point-of-care testing (i.e., iSTAT) can be a rapid method of evaluating Hgb, and spectrophotometry-based devices (i.e., Radical-7) offer the advantages of being continuous and noninvasive. We sought to evaluate the accuracy of Radical-7 and iSTATin measuring Hgb and assessing for blood loss when compared with the criterion standard CBC. Adult patients at risk for hemorrhage admitted to the surgical intensive care unit of a tertiary referral, Level I trauma center were eligible for this study. Serial CBC Hgb measurements were drawn as clinically indicated. The Radical-7 device was placed on the patient for noninvasive Hgb measurements (SpHb), and at each CBC measurement, concurrent iSTAT Hgb measurements were obtained. Bland-Altman analysis was used to compare the three methods of measuring Hgb with accuracy defined as measurements within 1.0-g/dL CBC Hgb. Concordance measurements were also performed to compare trends between values. Eighty-eight patients were enrolled and underwent 572 CBC measurements. Bland-Altman analysis of SpHb versus CBC resulted in an estimated bias of 1.49 g/dL, with 95% limits of agreement ofj2.2 g/dL to 5.0 g/dL. iSTAT versus CBC resulted in an estimated bias ofj0.63 g/dL, with 95% limits of agreement ofj3.4 g/dL to 2.2 g/dL. Changes in SpHb had concordance with CBC Hgb 60% of the time, compared with 76% for iSTAT versus CBC Radical-7 SpHb was inaccurate when compared with CBC Hgb levels, and serial SpHb achieved concordance with CBC Hgb 60% of the time. As such, the clinical utility of Radical-7 as a rapid, noninvasive predictor of acute hemorrhage may be limited.

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Accuracy of noninvasive hemoglobin monitoring in patients at risk for hemorrhage

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BACKGROUND: Monitoring for acute blood loss is critical in surgical patients, and delays in identifying hemorrhage can result in poor outcomes. The current standard of care for monitoring patients at risk for bleeding is serial measurement of hemoglobin (Hgb) by standard laboratory complete blood count (CBC). Point-of-care testing (i.e., iSTAT) can be a rapid method of evaluating Hgb, and spectrophotometry-based devices (i.e., Radical-7) offer the advantages of being continuous and noninvasive. We sought to evaluate the accuracy of Radical-7 and iSTAT in measuring Hgb and assessing for blood loss when compared with the criterion standard CBC.

METHODS: Adult patients at risk for hemorrhage admitted to the surgical intensive care unit of a tertiary referral, Level I trauma center were eligible for this study. Serial CBC Hgb measurements were drawn as clinically indicated. The Radical-7 device was placed on the patient for noninvasive Hgb measurements (SpHb), and at each CBC measurement, concurrent iSTAT Hgb measurements were obtained. Bland-Altman analysis was used to compare the three methods of measuring Hgb with accuracy defined as measurements within 1.0-g/dL CBC Hgb. Concordance measurements were also performed to compare trends between values.

RESULTS: Eighty-eight patients were enrolled and underwent 572 CBC measurements. Bland-Altman analysis of SpHb versus CBC resulted in an estimated bias of 1.49 g/dL, with 95% limits of agreement of −2.2 g/dL to 5.0 g/dL. iSTAT versus CBC resulted in an estimated bias of −0.63 g/dL, with 95% limits of agreement of −3.4 g/dL to 2.2 g/dL. Changes in SpHb had concordance with CBC Hgb 60% of the time, compared with 76% for iSTAT versus CBC

CONCLUSION: Radical-7 SpHb was inaccurate when compared with CBC Hgb levels, and serial SpHb achieved concordance with CBC Hgb 60% of the time. As such, the clinical utility of Radical-7 as a rapid, noninvasive predictor of acute hemorrhage may be limited. (*J Trauma Acute Care Surg*. 2014;77: S134–S139. Copyright © 2014 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Diagnostic study, level II; care management, level III.

KEYWORDS: Hemorrhage; noninvasive monitoring; hemoglobin.

Acute anemia and bleeding are major causes of morbidity and mortality in both surgical and nonsurgical patients. Even with the technologies available in the modern intensive care unit (ICU), ongoing hemorrhage in a critically ill surgical patient can be difficult to detect. Delays in identifying hemorrhage and providing intervention can result in poor patient outcomes. These diagnostic challenges and the sequelae of delayed therapy are even greater in austere conditions. Transport of the critically ill over great distances has become common, and despite dramatic progress in technology, the ability to obtain laboratory tests remains limited to point-of-care testing. In addition to monitoring vital signs, base deficit, and lactate as well as serial measurements of coagulopathy and hemoglobin (Hgb) concentration are frequently used to evaluate for ongoing hemorrhage. At present, the photometric cyanmethemoglobin method is the most widely used technique for measuring Hgb in the laboratory and is currently the criterion standard, as defined by the International Committee for Standardization in Hematology.[1,2] In addition to its reliability, laboratory analysis with complete blood count (CBC) can provide additional diagnostic information, such as platelet count, which can be useful when attempting to achieve hemostasis in the bleeding patient. However, this multistep process has several potential disadvantages. The time required for blood sampling, transport to the laboratory, analysis of the sample, verification of results, data entry, and retrieval of the actual laboratory value can delay receipt of these critical data from minutes to hours. Repeated sample collection can also result in progressive anemia, which may contribute to the need for transfusion. Lastly, performing such testing requires a fixed facility and trained personnel and is unavailable during transport of the critically ill.

In contrast, immediate Hgb measurements are available with portable point-of-care devices, which use an extremely small quantity of blood (10 μL) for analysis. These devices can produce a measurement of Hgb concentration in less than 1 minute, making this potentially advantageous when timing of results is critical and assets are limited. Although use of point-of-care testing has become common in the emergency department, neonatal unit, operating room, and critical care transport,[3–5] it remains invasive. In addition, the accuracy of these devices has been reported to vary with Hgb concentration,

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potentially rendering this modality less accurate in detecting blood loss when compared with the criterion standard of laboratory analysis.

Recently, a noninvasive, spectrophotometry-based monitoring technology (Radical-7 Pulse CO-Oximeter; Masimo Corp., Irvine, CA) that provides continuous Hgb measurement (SpHb) has been developed. This technology measures the differential optical density of wavelengths of light passed through the finger in a method similar to conventional pulse oximetry. Transmitted light is captured by photodiode receptor and analyzed to create an analog signal that, in turn, is converted to a digital signal. While the accuracy and potential utility of noninvasive Hgb measurements using various devices have been previously described,[6–9] only a few studies have examined its application to patients with the potential for bleeding, and these have reported mixed results.[10–14] If these noninvasive methods of Hgb measurement can be validated in patients at risk for ongoing hemorrhage, the use of this technology may result in earlier detection of ongoing hemorrhage, expedite appropriate resuscitation, and improve patient outcomes.

The specific aim of this prospective cohort study was to compare the accuracy of noninvasive Hgb measurement (Radical-7) and point-of-care testing (iSTAT Abbott Point of Care, Princeton, NJ) with invasive Hgb monitoring (standard laboratory evaluation) in patients at risk for blood loss.

PATIENTS AND METHODS

Adult patients (>18 years of age) with the potential for hemorrhage and who were admitted to the surgical ICU of a tertiary referral, Level I American College of Surgeons–verified trauma center were eligible for the study. The risk of hemorrhage was determined by the admitting surgical service—any patient who had serial CBC measurements ordered at least every 8 hours was screened for the study. The frequency of Hgb measurements was based on clinical indications as determined by the admitting service. Exclusion criteria included incarcerated individuals and patients unable to use a pulse oximetry device (i.e., extremity amputation, burns). Consent for the participation was obtained directly from participating patients, or in cases where the patient was not able to provide consent, the consent from a legally authorized representative or next of kin was used. The study was approved by the institutional review board of the University of Cincinnati and registered in ClinicalTrials.gov with ID NCT01709786 (CONSORT diagram attached, http://links.lww.com/TA/A464).

As soon as a subject was eligible for the study, the Radical-7 noninvasive oximeter was attached to a finger from either hand via a nondisposable sensor. The sensor was placed on the first or second digit on the hand opposite the clinical pulse oximeter sensor whenever possible. If the need arose to place the Radical-7 probe on the same hand as the clinical oximeter sensor, the Radical-7 was shielded with a light impermeable cover so as to prevent "cross talk" between the two sensors. Data from the oximeter were continuously recorded to the device and downloaded for later analysis. No data were collected from a subject's medical record until consent had been obtained. CBC analysis was performed on a Beckman Coulter LH780 Hematology analyzer (Beckman Coulter, Brea, CA). Each time the CBC was drawn, Hgb was also measured using point-of-care testing (iSTAT) (Abbot Point of Care). Additional data collected included patient demographics, use of vasopressors, arterial oxygen saturation (Spo_2), and blood product transfusions. As SpHb may be affected by jaundice,[14] bilirubin was recorded when available.

The accuracy of SpHb measurement can also be affected by the perfusion at the site of the probe. The perfusion index (PI) provides a relative numeric indication of the pulse strength at the monitoring site. PI values greater than 1.00 are desired,[14] but PI greater than 0.5 also provides acceptable data (Lake J, personal communication, September 2012). Subset analysis of SpHb was performed on points with PI of 0.5 or greater and PI of 1.00 or greater.

Results are expressed as mean (SD). The Bland-Altman technique with correction for multiple measurements was used to compare the Hgb measurements obtained from the iSTAT and Radical-7 devices with the Hgb measurement from the CBC.[15] CBC Hgb was considered the criterion standard, with accuracy defined as ±1.0 g/dL.

To examine if serial Hgb measurements obtained by iSTAT and Radical-7 changed in the same direction (increased vs. decreased) as the CBC Hgb, concordance measurements for paired temporal differences were performed with calculations of McNemar statistic used to test for agreement.

RESULTS

Eighty-eight patients completed the study between August 2012 and July 2013, with 572 CBC Hgb measurements performed (range, 2–15 measurements per patient). Of the 88 patients, 53 were male (60%), with 84% Caucasian, 15% African American, and 1% Asian. There were 42 trauma patients (48%) with injuries to the spleen (16), liver (10), pelvis (5), kidney (4), vascular (4), lung (2), and heart (1). Twenty-one patients had undergone liver transplantation, and 11 patients were admitted for gastrointestinal bleeding. Other diagnoses included ischemic bowel (4); hepatic resection (3); pancreas (3), genitourinary (2), and retroperitoneal hematoma (1); and necrotizing fasciitis (1). Forty-five percent of the group received at least 1 U of red blood cells, 35% received at least 1 U of fresh frozen plasma, 27% received at least 1 U of platelets, and 14% received at least 1 U of cryoprecipitate.

Of the 572 measurements, 86 (15%) were performed, while the subject was on vasopressors (norepinephrine and/or vasopressin). Spo_2 was 97.6% ± 2.7%, and mean arterial pressure was 78 ± 13.5 mm Hg. Radical-7 and iSTAT Hgb measurements could not be obtained in 88 (15.4%) and 50 (8.7%) of the CBC measurements, respectively. Of the missing Radical-7 measurements, 53 (12%) of 459 were not able to be obtained in Caucasian patients, while 33 (31%) of 108 were missing in African American patients. Missing iSTAT measurements were primarily because the sample was not drawn or testing was not completed at the time of CBC draw.

Bland-Altman analysis of Radical-7 versus CBC resulted in an estimated bias of 1.49 g/dL, with 95% limits of agreement of −2.0 to 5.0 (SpHb measurement averages 1.49 g/dL higher than CBC Hgb and could be as much as 2.0 g/dL lower or 5.0 g/dL higher than the CBC) (Fig. 1). iSTAT compared

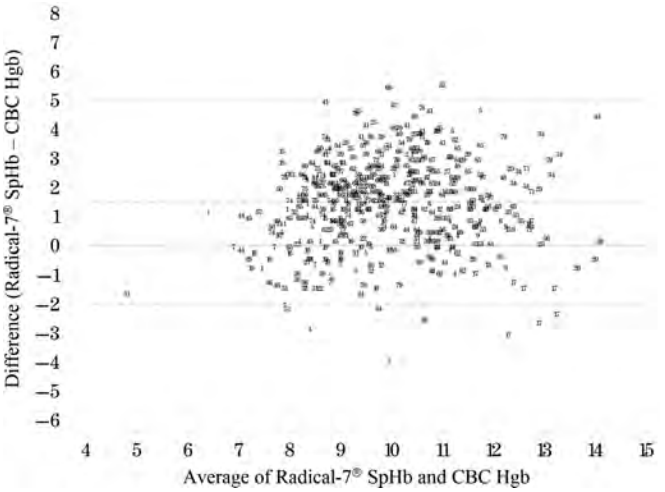

Figure 1. Bland-Altman plot of Radical-7 versus CBC Hgb measurements. Numbers indicate patient identification number. *Dashed lines* represent limits of agreement.

with CBC resulted in an estimated bias of −0.63 g/dL with 95% limits of agreement of −3.4 g/dL to 2.2 g/dL (Fig. 2). Radical-7 compared with iSTAT resulted in a bias of 2.1 g/dL, with 95% limits of agreement of −1.7 g/dL to 5.9 g/dL (Fig. 3).

Subset analysis comparing SpHb with CBC Hgb was performed examining only points with PI of 0.5 or greater and PI of 1.00 or greater to eliminate the effect of poor perfusion. This did not improve the overall accuracy of SpHb when compared with CBC Hgb (Table 1). Subset analysis of SpHb was also performed based on ethnicity (Caucasian and African American groups) and patients with jaundice (those with highest bilirubin > 3 mg/dL vs. highest bilirubin ≤ 3 mg/dL) and anemia (CBC Hgb ≤ 8 g/dL vs. CBC Hgb > 8 g/dL). There were no significant changes in the accuracy of Radical-7 within these subsets. Results are shown in Table 1.

Radical-7 Hgb showed concordant changes when compared with CBC in 240 (60%) of 400 measurements, with

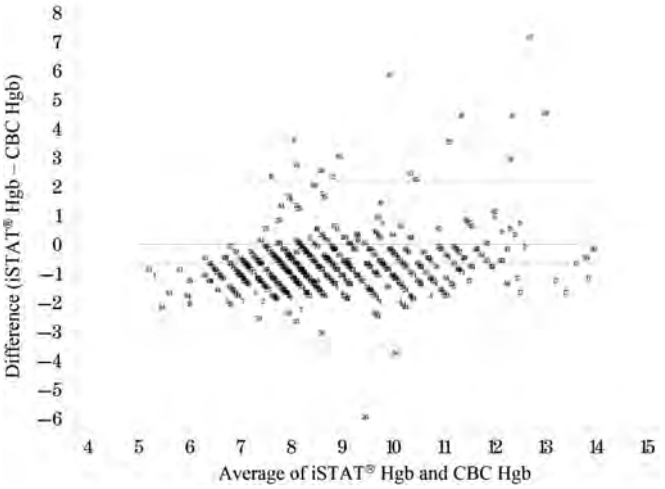

Figure 2. Bland-Altman plot of iSTAT versus CBC hemoglobin measurements. Numbers indicate patient identification number. *Dashed lines* represent limits of agreement.

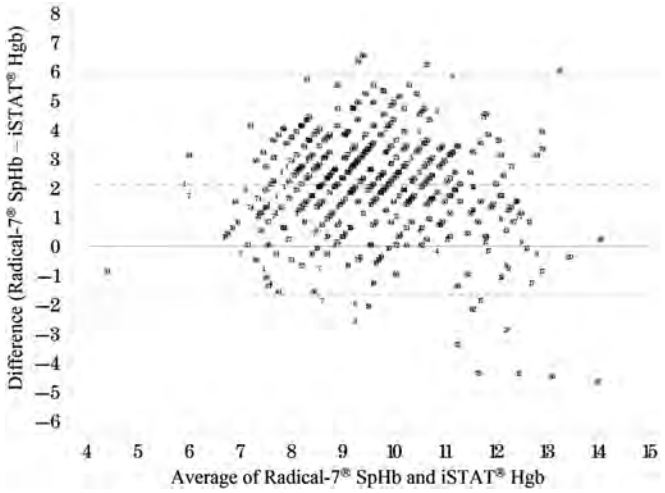

Figure 3. Bland-Altman plot of Radical-7 versus iSTAT Hgb measurements. Numbers indicate patient identification number. *Dashed lines* represent limits of agreement.

McNemar statistic of 0.9 ($p = 0.34$). iSTAT Hgb showed concordant changes when compared with CBC in 330 (76%) of 434 measurements, with McNemar statistic of 8.65 ($p = 0.003$), indicating statistically significant agreement. Concordance data are shown in Tables 2 and 3.

DISCUSSION

Detecting hemorrhage in the critically ill can be difficult based solely on clinical evaluation, and the use of serial Hgb measurements is an accepted method of monitoring patients at known risk for hemorrhage. Current standard of care for measuring serum Hgb requires invasive blood draws, which, when repeated, can contribute to ongoing anemia. Laboratory testing can take significant time, resulting in delays in the recognition and management of acute blood loss. Finally, the equipment required for this type of testing requires a fixed facility and laboratory personnel and is not practical in austere environments. Point-of-care testing, most commonly the iSTAT, is widely used in the hospital setting and austere environments where rapid results are necessary. However, the use of point-of-care measurements still requires testing either at predetermined intervals or due to clinical suspicion of hemorrhage and, as such, continues to have the potential for diagnostic delay.

An accurate and reliable noninvasive Hgb measuring device could assist in the early detection of hemorrhage without the limitations of current technology. This study was designed to evaluate the accuracy of Radical-7 and iSTAT in measuring Hgb when compared with the criterion standard CBC testing in patients at risk for hemorrhage. In addition, we sought to examine if trends in Radical-7 and iSTAT measurements correlated with changes in CBC Hgb. Unlike most previous studies that evaluated patients at steady state, this study examined the use of noninvasive Hgb monitoring in critically ill patients at significant risk for hemorrhage in which such devices would have direct applicability and benefit over existing standards of care.

TABLE 1. Bland-Altman Analysis of Hgb Measurements From Radical-7 Versus CBC, iSTAT Versus CBC, and Radical-7 Versus iSTAT

Comparison	Group	Bias	Limits of Agreement	Interval Width	SE
Radical-7 vs. CBC	All measurements	1.49	−2.02 to 5.00	7.01	1.28
	PI ≥ 0.5	1.58	−1.73 to 4.90	9.90	1.15
	PI ≥ 1.0	1.75	−1.59 to 5.10	6.69	1.26
	Caucasian	1.55	−2.01 to 5.10	7.02	1.33
	African American	1.21	−2.09 to 4.52	6.61	1.03
	Highest bilirubin > 3	1.38	−2.49 to 5.25	7.74	1.41
	Highest bilirubin ≤ 3	1.55	−1.79 to 4.89	6.68	1.24
	CBC Hgb ≤ 8	2.14	−0.75 to 5.02	5.77	1.28
	CBC Hgb > 8	1.29	−2.02 to 4.60	6.62	1.31
iSTAT vs. CBC	All measurements	−0.63	−3.44 to 2.18	5.63	0.63
	Caucasian	−0.58	−3.39 to 2.22	5.61	0.65
	African American	−0.80	−3.62 to 2.01	5.63	0.51
	Highest bilirubin > 3	−0.78	−3.44 to 1.88	5.32	0.60
	Highest bilirubin ≤ 3	−0.55	−3.43 to 2.34	5.77	0.64
	CBC Hgb ≤ 8	−0.44	−2.80 to 1.92	4.72	0.86
	CBC Hgb > 8	−0.69	−3.16 to 1.78	4.94	0.66
Radical-7 vs. iSTAT	All measurements	2.09	−1.68 to 5.86	7.54	1.32
	PI ≥ 0.5	2.17	−1.50 to 5.84	7.64	1.28
	PI ≥ 1.00	2.33	−1.66 to 6.32	7.98	1.58
	Caucasian	2.11	−1.79 to 6.01	7.80	1.39
	African American	1.97	−1.14 to 5.08	6.22	0.93
	Highest bilirubin > 3	2.18	−1.84 to 6.20	8.04	1.48
	Highest bilirubin ≤ 3	2.04	−1.61 to 5.70	7.31	1.25
	CBC Hgb ≤ 8	2.57	−0.80 to 5.95	6.75	1.46
	CBC Hgb > 8	1.94	−1.71 to 5.59	7.30	1.36

Subset analysis was performed on data points with PI of 0.5 or greater, PI of 1.00 or greater, ethnicity (white vs. African American), patients with jaundice (those with highest bilirubin > 3 vs. highest bilirubin ≤ 3), and anemia (CBC Hgb ≤ 8 vs. CBC Hgb > 8). PI provides a relative numeric indication of the pulse strength at the monitoring site.

The Radical-7 device has been studied in the operating room and in the ICU; these studies have had mixed results regarding the accuracy of noninvasive Hgb measurements and provide impetus for this study.[5,7,10] Causey et al.[11] examined noninvasive monitoring in surgical and ICU patients, finding mean noninvasive Hgb to be within 0.5 g/dL in both groups, and Frasca et al.[8] found even closer correlation (0.0 ± 1.0 g/dL) between Radical-7 measurements and CBC standards. In contrast, however, other studies have found variability that may compromise the clinical utility of noninvasive Hgb monitoring.[9,12,13,16] Lamhaut et al.[16] compared the Radical-7 and point-of-care testing with laboratory measurements and found that although bias for both groups did not differ significantly from standard measurements, the accuracy (defined as ±1.0 g/dL) of the Radical-7 was much worse than the point-of-care device. Gayat et al.[9] noted that SpHb measurements were significantly lower than CBC Hgb, with a mean difference of 1.59 g/dL (95% confidence interval, −1.82 to −1.37; $p < 0.0001$). Furthermore, SpHb could not be obtained in 8% of patients, particularly older patients with lower diastolic blood pressure, lower CBC Hgb, and lower Spo_2. In a study of patients undergoing pelvic or abdominal surgery, Applegate et al.[13] noted that Radical-7 bias increased with blood loss of more than 1,000 mL, Hgb of less than 9 g/dL, and any intraoperative transfusion, common scenarios in patients at risk for hemorrhage.

In this study, the Radical-7 lacked accuracy, significantly limiting its utility in measuring Hgb or monitoring temporal trends. The bias for Radical-7 measurements was outside the defined range of 1.0 g/dL of the CBC Hgb measurement. More importantly, the Radical-7 had large limits of agreement, indicating a high degree of variability of this device.

As the Radical-7 monitor operates using spectophotometric-based technology, analyzing light transmittance through tissue, it would seem plausible that any environment and/or patient factors affecting light transmittance would have the potential to alter the reading. In fact, the accuracy the Radical-7 device is reported to be affected by low arterial perfusion, low oxygen saturation, high bilirubin, and severe anemia; however, specific definitions of these conditions have not been delineated. In an effort to evaluate these factors, multiple subset analyses were performed. In this trial, SpHb was unable to be obtained 15% of the time, and these results are similar to those found in the study by Gayat et al.[9] There were no significant differences in mean

TABLE 2. Concordance Measurements for Radical-7 SpHb Versus CBC Hgb

	Change in Radical-7 SpHb	
Change in CBC Hgb	Decrease	Increase or No Change
Decrease	122 (30.5%)	86 (21.5%)
Increase or no change	74 (18.5%)	118 (29.5%)

McNemar statistic, 0.90 ($p = 0.34$).

TABLE 3. Concordance Measurements for iSTAT Versus CBC Hgb

	Change in iSTAT Hgb	
Change in CBC Hgb	**Decrease**	**Increase or No Change**
Decrease	157 (36.2%)	67 (15.4%)
Increase or no change	37 (8.5%)	173 (39.9%)

McNemar statistic, 8.65 ($p = 0.003$).

arterial pressure and oxygen saturation when SpHb was unable to be obtained when compared with time points where SpHb was able to be measured. Furthermore, in these patients, the use of vasopressors had no appreciable effect on the ability to obtain SpHb reading. Eliminating patients with clinical jaundice (bilirubin > 3) from data analysis did not improve the accuracy of SpHb. It should be noted, however, that this subset analysis used all measurements from patients with highest bilirubin greater than 3, as concomitant bilirubin measurements were not performed for all Hgb measurements. SpHb measurements may not be as accurate in patients with severe anemia. Radical-7 SpHb measurements with concomitant CBC Hgb greater than 8 were indeed more accurate; however, the bias in this subset analysis (1.3 g/dL) still fell outside our definition of accuracy. The definition of anemia in the ICU has evolved during the last decade, with guidelines suggesting that in many patients, transfusions may be delayed until Hgb values fall to less than 7 g/dL without increased mortality.[17,18] As such, many critically ill patients may be maintained with Hgb between 7 g/dL and 8 g/dL. In this study, CBC Hgb was less than 8.0 g/dL in 23% of the measurements. The utility of a device, which cannot monitor Hgb accurately in this range, may be limited. Lastly, there was an apparent increase in the missed reading in those patients with increase skin pigmentation (12% vs. 31% respectively), although the numbers are insufficient to draw conclusions.

The trend in serial Hgb measurements, rather than absolute Hgb concentration, is often used to evaluate ongoing hemorrhage or clinical response to transfusion. We examined the concordance of changes in serial Radical-7 and iSTAT Hgb measurements to the CBC Hgb measurements. In this study, SpHb was only concordant with changes in CBC Hgb 60% of the time, making it difficult to predict ongoing blood loss using the trends of noninvasive Hgb measurements. Hgb measurements using the iSTAT device were more accurate than those obtained with Radical-7. iSTAT Hgb bias fell within ±1.0 g/dL of the CBC Hgb, meeting the definition of accuracy in this study. iSTAT limits of agreement still demonstrated a large interval (−3.4 to 2.2); however, this was significantly less than limits for SpHb (−2.0 to 5.0). Furthermore, concordance data suggested that serial measurements of iSTAT Hgb agreed with CBC trends more frequently than SpHb as well.

There are several limitations to this study. In establishing standards, definitions are paramount. Although there is no standard definition of device accuracy, our definition (±1.0 g/dL) has been used in other similar studies.[13,19] In addition, a frequently used clinical rule of thumb is that a decrease in Hgb by 1.0 g/dL roughly corresponds to the loss of 1 U of blood. However, the true clinical significance of a measurement error of this magnitude may need to be taken in context of the actual Hgb; a 1.0-g/dL variability at an Hgb of 14 g/dL carries a different clinical connotation than a 1.0-g/dL variability at an Hgb of 8.0 g/dL. Although some may argue that transfusion decisions in patients with low baseline Hgb may be based on clinical, rather than laboratory, data, it is frequently in the anemic patient where accurate measured data may be most useful. Finally, almost half of the patients in this study received blood transfusions. It is possible that posttransfusion blood sampling was performed before complete intravascular equilibration and that regional tissue perfusion and noninvasive tissue Hgb measurements may be affected by fluid redistribution in a manner different from intravascular Hgb.

In conclusion, Radical-7 SpHb differs by more than ±1.0 g/dL from criterion standard automated laboratory Hgb measurements, with a wide confidence interval in patients at risk for hemorrhage. Furthermore, concordance with CBC Hgb changes only occurred in 60% of the cases, and SpHb measurements could not be obtained 15% of the time. These findings limit the utility of the Radical-7 noninvasive Hgb monitor in detecting ongoing hemorrhage. In contrast, the iSTAT point-of-care device was more accurate, had better concordance with laboratory values, and may be more useful as a method of assessing for acute blood loss in critically ill patients.

AUTHORSHIP

B.J.T. contributed in the study design, data interpretation, and manuscript preparation. D.J.H. performed the data analysis. M.J.B. performed the data collection. T.C.B. contributed in the data collection, data interpretation, and manuscript preparation. S.H.Y. contributed in the literature search, study design, and data collection. R.D.B. performed the data interpretation. T.S.G. contributed in the study design, data interpretation, and manuscript preparation.

DISCLOSURE

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