Accuracy and trending of non-invasive hemoglobin measurement during different volume and perfusion statuses

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Abstract
The evolution of non-invasive hemoglobin measuring technology would save time and improve transfusion practice. The validity of pulse co-oximetry hemoglobin (SpHb) measurement in the perioperative setting was previously evaluated; however, the accuracy of SpHb in different volume statuses as well as in different perfusion states was not well investigated. The aim of this work is to evaluate the accuracy and trending of SpHb in comparison to laboratory hemoglobin (Lab-Hb) during acute bleeding and after resuscitation. Seventy patients scheduled for major orthopedic procedures with anticipated major blood loss were included. Radical-7 device was used for continuous assessment of SpHb, volume status [via pleth variability index (PVI)] and perfusion status [via perfusion index (PI)]. Lab-Hb and SpHb were measured at three time-points, a baseline reading, after major bleeding, and after resuscitation. Samples were divided into fluid-responsive and fluid non-responsive samples, and were also divided into high-PI and low-PI samples. Accuracy of SpHb was determined using Bland–Altman analysis. Trending of SpHb was evaluated using polar plot analysis. We obtained 210 time-matched readings. Fluid non-responsive samples were 106 (50.5%) whereas fluid responsive samples were 104 (49.5%). Excellent correlation was reported between Lab-Hb and SpHb (r = 0.938). Excellent accuracy with moderate levels of agreement was also reported between both measures among all samples, fluid non-responsive samples, fluid-responsive samples, high-PI samples, and low-PI samples [Mean bias (limits of agreement): 0.01 (−1.33 and 1.34) g/dL, −0.08 (−1.27 and 1.11) g/dL, 0.09 (−1.36 and 1.54) g/dL, 0.01 (−1.34 to 1.31) g/dL, and 0.04 (−1.31 to 1.39) g/dL respectively]. Polar plot analysis showed good trending ability for SpHb as a follow up monitor. In conclusion, SpHb showed excellent correlation with Lab-Hb in fluid responders, fluid non-responders, low-PI, and high PI states. Despite a favorable mean bias of 0.01 g/dL for SpHb, the relatively wide levels of agreement (−1.3 to 1.3 g/dL) might limit its accuracy. SpHb showed good performance as a trend monitor.

Keywords Hemoglobin · Masimo · Pulse co-oximetry · Non-invasive · Fluid responsiveness
1 Introduction

Accurate assessment of blood hemoglobin is an essential step in management of both chronic and acute blood loss. Laboratory measurement is the gold standard for hemoglobin measurement [1]; however, laboratory measurement is usually time consuming and carries the risk of infection with repeated blood sampling.

Non-invasive monitors for hemoglobin measurement is a developing technology that would save time and minimize the risk of infection. Radical-7 device (Masimo corporation, Irvine, CA) is a simple and non-invasive device based on multi-wavelength co-oximetry with emerging popularity in both emergency [2] and critical care settings [3].

Acute blood loss is usually associated with impaired peripheral perfusion as well as acute hypovolemic state. Acute blood loss often requires rapid blood transfusion. The presence of an accurate, rapid, and non-invasive hemoglobin monitor during acute blood loss would improve the transfusion decision. Non-invasive hemoglobin (SpHb) monitoring using Radical-7 device has been frequently validated in the last few years with controversial results. SpHb showed clinically acceptable accuracy in the perioperative settings [4] and in trauma patients with low hemoglobin levels [5]; however, its value during low perfusion states and in hypovolemic states is not established. Pleth variability index (PVI) is a variable measured using the Radical-7 device, which is a useful measure of volume status and fluid responsiveness in ventilated paralyzed patients [6]. PI is another variable measured using Radical-7 device and is considered a measure of peripheral perfusion [7]. Perfusion index (PI) is the ratio between pulsatile and non-pulsatile components of peripheral circulation [7]. The impact of impaired perfusion on the accuracy of SpHb was not adequately investigated. The aim of this work is to evaluate the accuracy of SpHb compared to laboratory hemoglobin level (Lab-Hb) in situations of acute intraoperative hypovolemia (assessed by PVI) due to acute blood loss. The second aim is to assess the device accuracy in different perfusion states (assessed by PI). The third aim is to evaluate the accuracy of SpHb as a trend monitor during bleeding and after resuscitation.

2 Methods

A prospective observational study was conducted in Cairo university hospital after institutional ethical committee approval. A written informed consent was obtained from all participants before enrolment. Patients aged between 18 and 60 years scheduled for elective major orthopedic procedures were eligible for the study. Diabetic patients and patients with peripheral vascular disease were excluded.

After routine intravenous pre-medications (metoclopramide 10 mg, ranitidine 50 mg, and midazolam 0.03 mg/kg), monitors were applied including pulse oximetry, ECG, non-invasive arterial blood pressure monitor in addition to invasive blood pressure monitor when required. Radical-7 device pulse co-oximeter (Masimo corporation, Irvine, CA) was used to monitor SpHb, perfusion index (PI), and PVI. The device probe was covered by an opaque shield and connected to the third or fourth digit of the patient’s left hand.

All patients received general anesthesia with complete muscle relaxation. Induction of anesthesia was achieved by Propofol (2 mg/kg), fentanyl (2 mcg/kg). Endotracheal intubation was performed, aided by atracurium (0.5 mg/kg). Anesthesia was maintained by isoflurane (1–1.5%) keeping arterial blood pressure within 20% of the baseline reading. Muscle relaxation was maintained through atracurium infusion (0.5 mg/kg/h administrated in a separate line). Patients were mechanically ventilated at tidal volume of 6–8 mL/kg and respiratory rate of 12–16 breath per minute, titrated to keep end-tidal CO2 between 30 and 35 mmHg.

Patients received Ringer lactate solution during the operation at a rate of 4 mL/kg/h. Packed RBCs were transfused if: (1) Estimated blood loss was obviously more than 20% of whole blood volume with mean arterial blood pressure < 60 mmHg. (2) Blood hemoglobin level was lower than 7 g/dL. (3) Continuous blood loss with mean arterial blood pressure < 60 mmHg. Bleeding patients who did not meet the criteria for blood transfusion were resuscitated by Ringer lactate solution in ratio (Ringer lactate: blood loss = 3:1).

A baseline reading was manually obtained for both Lab-Hb and SpHb 5 min after endotracheal intubation. Patients were continuously monitored for blood loss and another hemoglobin reading (both Lab-Hb and SpHb) was obtained after any attack of massive bleeding (defined as rapid loss of more than 150 mL in 1 min [8] that reached a blood loss exceeding 20% to total blood volume). A third pair of hemoglobin readings was obtained after fluid resuscitation and restoration of the euolemic state (when PVI became less than 13%). Masimo readings were obtained by a research assistant who was not involved in patient management. Patients who did not show significant intraoperative bleeding were excluded from the study. Samples obtained from patients with baseline PVI higher than 13% were considered fluid responsive samples.

Lab-Hb analysis was performed through 2 mL of venous blood drawn into an ethylene diamine tetra acetic acid (EDTA) vacutainer tube. Samples were thoroughly mixed and sent immediately to the laboratory. Automated Hemoglobin analyser (Coulter LH 750 Beckman) was used for hemoglobin measurement. Performance of the analyser was
daily monitored and calibration was verified using stable reference controls. Samples were processed and the measured values were returned according to the standard practice in our hospital.

Collected data included demographic data (age, race, and gender), blood hemoglobin (both invasive and non-invasive), number of patients who needed blood transfusion, number of transfused blood units, PI, and PVI. Masimo variables (PI, PVI, and SpHb) and Lab-Hb were recorded at three different time-points for each patient: at the baseline, during fluid responsive state, and after restoration of volume status. Collected samples were divided into: fluid non-responsive samples (with PVI less than 13%) and fluid-responsive samples (with PVI of 13% or more). Samples were also divided into: high-PI samples (with PI ≥ 1.4) and low-PI samples (with PI < 1.4).

3 Statistical analysis

In a recent study, our group had reported a correlation coefficient (r) of 0.879 between Lab-Hb and SpHb in patients with low hemoglobin levels [5]. We made a conservative assumption that could detect a correlation coefficient (r) of 0.25 for all samples and a correlation coefficient (r) of 0.4 for each subgroup of samples. Using MedCalc Software version 14 (MedCalc Software bvba, Ostend, Belgium), a minimum number of 202 was calculated for all samples and 75 for each subgroup of samples was needed for a study power of 95% and alpha error of 0.05.

Statistical package for social science (SPSS) software, version 15 for Microsoft Windows (SPSS inc., Chicago, IL, USA) and Medcalc software were used for data analysis. Data were presented as mean ± standard deviation (SD), Median (quartiles), and frequency (%). Continuous data were tested for normality using Shapiro–Wilk test. Normally distributed data were presented as mean and standard deviation. Skewed data were presented as median and quartiles. Analysis of variance (ANOVA) for repeated measures with Bonferroni correction was conducted to compare hemoglobin readings with both methods. Correlation between SpHb and Lab-Hb was performed using Spearman’s correlation coefficient. Bland–Altman analysis was preformed to estimate the mean bias and the degree of agreement between both measures. A P value less than 0.05 was considered statistically significant. Polar coordinates for trending analysis was performed using Excel 2007 (Microsoft TM Office Excel TM 2007; Microsoft TM Corp., Redmond, WA, USA) and SigmaPlot TM 12.0 (Systat TM Soft-ware, San Jose, CA, USA). Polar plot analyses were performed as suggested by Critchley et al. [9]. Trending ability was considered sufficient in clinical practice if polar plot analysis showed an angular bias within ±5°.

4 Results

One hundred and 72 patients were eligible for the study. Of these, 100 and two patients did not complete the study because they did not experience significant intraoperative bleeding (Fig. 1). Seventy patients were available for final analysis with median (quartiles) age of 49 (39,55) years. All our patients were Caucasians. Thirty (43%) patients were male, baseline mean ± SD blood hemoglobin was 11.9 ± 1.1 g/dL, and baseline median (quartiles) PI was 2.1 (1.2,3.2). Fifty patients (71%) received blood transfusion. Demographic data and patient characteristics are presented in Table 1.

Two-hundred and ten time-matched samples were obtained from our patients. 106 of them were fluid non-responsive samples [36 samples from the baseline measure and all samples of the third measure (70 samples)], and 104 were fluid-responsive samples [34 samples from the baseline measure and all samples of the second measure (70 samples)]. Low-PI samples were 80 (38%), whereas high-PI samples were 130 (62%).

Excellent correlation was observed between Lab-Hb and SpHb ($r = 0.938$, 95% confidence interval 0.919–0.953) (Fig. 2). Bland–Altman analysis showed low bias with moderate limits of agreement among all samples, fluid non-responsive samples, fluid-responsive samples, high-PI samples, and low-PI samples [Mean bias (limits of agreement): 0.01 (−1.33 and 1.34) g/dL, −0.08 (−1.27 and 1.11) g/dL, −0.11 (−1.43 and 1.21) g/dL, −0.16 (−1.54 and 1.22) g/dL].

![Fig. 1 Consort chart for patient recruitment](image-url)
0.09 (−1.36 and 1.54) g/dL, 0.01 (−1.34 to 1.31) g/dL, and 0.04 (−1.31 to 1.39) g/dL respectively] Figs. 3, 4). Margin of error (95% confidence interval) was 1.9 (0.3, 2.9)%, 0.99 (−0.37, 2.35)% , 0.63 (0.5, 1.8)%, and 0.2 (−1.4, 1.8)% in euvolemic samples, hypovolemic samples, high-PI samples, and low-PI samples respectively. Using polar plot analysis, the angular bias of the modified Critchley’s polar plots was depicted in Fig. 5. A total of 140 hemoglobin change were included for analysis. The angular bias (precision) was −4° (8.9°) denoting clinical acceptable trending.

5 Discussion

We reported low bias (0.01 g/dL), moderate limits of agreement (−1.33 and 1.34 g/dL) and good trending for SpHb compared to Lab-Hb within our cohort of surgical patients. Slightly better accuracy was observed in fluid non-responsive samples compared to fluid responsive samples and in high-PI samples compared to low-PI samples. Determining the device accuracy during acute blood loss would be of great importance as this is the usual situation for transfusion decision.

European guidelines for management of perioperative bleeding had suggested using non-invasive hemoglobin devices only as trend monitors [10]. The available data regarding the accuracy of non-invasive hemoglobin monitoring suggests acceptable bias and moderate precision between SpHb and Lab-Hb in perioperative patients (mean bias of 0.39 ± 1.32 g/dL) [4]; our results showed lower bias (0.01 g/dL) with the same limits of agreement (−1.3 to 1.3 g/dL). A higher bias had been reported in intensive care patients [4]. In trauma patients, the accuracy of SpHb was not clinically acceptable [11, 12]; however, this was recently debated in a study conducted by our group on 70 major trauma patients with low hemoglobin levels [5]. We had reported a mean bias of 0.12 g/dL and limits of agreement between −0.56 to 0.79 g/dL suggesting excellent accuracy in both absolute and

Table 1 Demographic data and baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 (39,55)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>30/40</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>1650 (1400,1850)</td>
</tr>
<tr>
<td>Transfusion (units)</td>
<td>50 (71%)</td>
</tr>
<tr>
<td>Crystalloids</td>
<td>2300 (1850, 2550)</td>
</tr>
<tr>
<td>Number of units</td>
<td></td>
</tr>
<tr>
<td>No transfusion</td>
<td>20 (29%)</td>
</tr>
<tr>
<td>One unit</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Two units</td>
<td>33 (47%)</td>
</tr>
<tr>
<td>Three units</td>
<td>13 (19%)</td>
</tr>
<tr>
<td>Four units</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Baseline Lab-Hb (mg/dL)</td>
<td>11.9 ± 1.1</td>
</tr>
<tr>
<td>Baseline Sp-Hb (mg/dL)</td>
<td>11.8 ± 1.5</td>
</tr>
<tr>
<td>Baseline PI</td>
<td>2.1 (1.2, 3.2)</td>
</tr>
<tr>
<td>Baseline PVI (%)</td>
<td>12 (11.15)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation, median (quartiles), and frequency (%)

Lab-Hb laboratory hemoglobin, Sp-Hb Masimo hemoglobin, PI perfusion index, PVI plethysmography variability index

Fig. 2 Scatter plot for Lab-Hb and Sp-Hb

Fig. 3 Bland–Altman analysis. Solid line represents the mean bias, while dashed lines represent the 95% confidence interval. a All pairs (n = 210), b fluid non-responsive pairs (n = 106), c fluid responsive pairs (n = 104)
trend values [5]. According to the available data, we suggest that the accuracy of SpHb is acceptable in the perioperative settings. A randomized controlled trial was conducted in our hospital and reported that using SpHb has shortened the time to transfusion and decreased the number of transfused blood units during neurosurgical operations [13].

Most of the available studies had been conducted in euvolemic state. Only two studies investigated the accuracy of SpHb in controlled hypovolemic states; however, none of them was conducted in real bleeding patients: Marques et al. [14] had conducted a volunteer study where they investigated the accuracy of SpHb in 12 volunteers subjected to controlled hemorrhage (10 mL/kg for 15 min). Marques and colleagues had reported good precision during hemorrhage and replacement; however, they suggested that the SpHb accuracy is not sufficient for blood transfusion decision. Dewhirst et al. [15] investigated the accuracy of Masimo Radical-7 device during preoperative phlebotomy trying to simulate a state to hypovolemia. They reported low bias (0.1 g/dL) between Lab-Hb and SpHb, which is not affected with acute blood loss; However, the degree of precision does not allow it to guide the transfusion decision solely.

Eighty (38%) of our samples were obtained during impaired perfusion (with PI lower than 1.4). The accuracy of SpHb in shocked patients is an area of interest as this special population is the neediest for blood transfusion. Few data are available about the accuracy of SpHb with different states of peripheral perfusion. In line with our findings, a Japanese study reported good accuracy for SpHb, which was modestly higher in patients with PI above 1.4 [16]. In preoperative children, Wittenmeier et al reported that PI has no influence on the accuracy of SpHb [17]. In a volunteer study, Miller et al. had reported different results [18]. Miller et al. had reported that higher PI (induced by digital nerve block) improved the accuracy of SpHb [18]. Peripheral nerve block induces vasodilatation; thus, it results in increased PI [19]. Our study differed from Miller’s study in number of participants (70 versus 12) as well as in type of population (patients versus volunteers). High skewness has been previously reported in PI in various types of patients [3, 20] as well as in volunteers [20, 21]; thus, low PI values could be normally found in well perfused limbs. Although our findings support the accuracy of SpHb in low PI values; we should clarify that we did not have PI values lower than 0.6. Thus; further studies should be conducted to explore the accuracy of SpHb in patients with lower PI values.

Our study has the advantage of investigating the accuracy of SpHb within the same group of patients before hypovolemia, after hypovolemia, and after restoration of euvolemia. The ventilation-induced variation in the pulse oximetry pleth signal was previously reported as a marker of fluid responsiveness in mechanically ventilated adults [22, 23]. We used a cutoff value of 13% to differentiate fluid responders and non-responders; this cutoff value was defined by Feissel et al. in septic shock patients [24].

Many factors (in addition to the accuracy) contribute to the value of non-invasive hemoglobin monitors: (1) Its value as a continuous alarming monitor in cases of sudden bleeding even within a bias of 1–1.5 g/dL (as reported by some
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previous studies), (2) Variability in measurements is present in any invasive or non-invasive device, (3) SpHb could be a good adjuvant rather than an alternative measure to Lab-Hb, (4) SpHb saves a lot of time and effort and avoids repeated sampling, (5) Upgrading of the device and its sensors in the future might increase its accuracy.

Our study has the advantage of conservative sample size calculation; moreover, it is the first report conducted in surgical patients before and after hypovolemia; however, our findings are not devoid of limitations: first, none of our patients needed vasopressor support; thus, the impact of vasopressors on accuracy of SpHb needs further research. Second, we reported the accuracy of SpHb in states with low PI; however, the lowest PI in our data was 0.6. We previously reported that critically ill patients commonly have lower values of PI [2]. Thus, we recommend future research including severely ill patients with very low PI values. Third, we excluded patients with disorders that might alter the device signals at peripheral digit site (such as diabetes mellitus and peripheral vascular disease); this might impair the generalizability of our findings. Future research is recommended to evaluate the accuracy of Masimo in these disorders.

In conclusion, SpHb showed excellent correlation with Lab-Hb in fluid responders, fluid non-responders, low-PI, and high PI states. Despite a favorable mean bias of 0.01 g/dL for SpHb, the relatively wide levels of agreement (~1.3 to 1.3 g/dL) might limit its accuracy. SpHb showed good performance as a trend monitor.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest with this work.

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