Validity of non-invasive hemoglobin measured by pulse co-oximeter in neonates - An observational study

Swapna Lingaldinna, Anitha M, Mangalabharathi Sundaram

From Associate Professor, Department of Neonatology, Institute of Child Health and Hospital for Children, Madras Medical College, Chennai, Tamil Nadu, India

Correspondence to: Dr. Mangalabharathi Sundaram, Department of Neonatology, Institute of Child Health and Hospital for Children, Madras Medical College, Chennai, Tamil Nadu, India. E-mail: drmangalabharathi@gmail.com

ABSTRACT

Background: Hemoglobin is a frequently ordered investigation in neonatal intensive care units. There is a need for hemoglobin estimation by point of care methods to reduce iatrogenic anemia and to alleviate pain associated with repeated venous sampling. Pulse co-oximeters have been developed to measure hemoglobin non-invasively based on spectrophotometric method. We compared hemoglobin measured by pulse co-oximeter with reference venous hemoglobin in neonates admitted to a tertiary care newborn unit. **Design:** This was an observational study. **Duration:** The study duration was from November 2016 to December 2016. **Setting:** Department of Neonatology, Institute of Child Health and Hospital for Children, Egmore. **Methods:** Neonates admitted in nursery who warranted hemoglobin estimation underwent both invasive venous hemoglobin estimation by automated hematology analyzer and non-invasive hemoglobin estimation by pulse co-oximeter (Masimo SET radical 7). **Results:** Of 158 newborns enrolled, the device failure rate was 12.5%. The bias between transcutaneous and venous hemoglobin was 1.66±2.26 g/dl (mean ± standard deviation). Transcutaneous and venous hemoglobin showed moderate agreement on Bland Altman plot with intraclass correlation coefficient of 0.56. At lower levels of hemoglobin, we noted higher bias. It was 2.69±1.87 g/dl at hemoglobin <13 g/dl and 3.29±1.86 at hemoglobin ≤10 g/dl. On regression analysis, only the level of hemoglobin influenced bias and device failure rate. **Conclusion:** Non-invasive hemoglobin measured by pulse co-oximeter shows only a moderate agreement with reference venous hemoglobin in neonates admitted to nursery. We report a high device failure rate of 12.6%. Level of hemoglobin is the single most determinant of device failure and degree of agreement. With high device failure rates and poor agreement at low hemoglobin levels, the clinical utility appears negligible.

Key words: *Neonate, Non-invasive hemoglobin, Pulse co-oximeter*

Anemia is a common morbidity seen among neonates admitted to intensive care units. Frequent blood sampling is often required for repeated monitoring of various blood parameters to measure the extent of multiorgan dysfunction and response to the treatment [1,2]. The most common cause of anemia reported in sick neonates is iatrogenic due to frequent blood sampling [1]. Venous sampling is associated with various drawbacks such as invasiveness, pain, discomfort, risk of hospital-acquired infections, and need of transport to laboratory for processing which further delays the process of diagnosing and planning interventions [3]. This iatrogenic anemia often results in need of blood transfusions. Among the various methods known to reduce iatrogenic anemia, point of care devices such as glucometers and transcutaneous bilirubinometers is found to play a major role [1,4]. The gold standard for hemoglobin estimation is venous hemoglobin measured by automated hematology analyzer [5]. A non-invasive method has been developed for rapid point of care estimation of hemoglobin using pulse co-oximeter. Pulse co-oximeters measure hemoglobin non-invasively using multiple wavelength spectrophotometry technology [6]. Few studies in the past have attempted validating transcutaneous hemoglobin in stable neonates, but studies are very limited in sick babies. With this background, we conducted a study to compare non-invasive hemoglobin measured by Masimo radical 7 pulse co-oximeter with invasive venous hemoglobin estimated by automated hematology analyzer in neonates admitted to a tertiary level neonatal care unit.

MATERIALS AND METHODS

We conducted this prospective observational study at a tertiary care neonatal unit in Chennai, South India, from November 2016 to December 2016. After getting institutional ethical committee approval, we included all babies who needed hemoglobin estimation as warranted by management protocol during the study period irrespective of their birth weight, gestational age, postnatal age, or sickness level. After obtaining informed written consent from parents, demographic characteristics of included babies such as birth weight, gestational age, sex, and postnatal age were recorded.

Clinical parameters such as heart rate, saturation, capillary filling time, blood pressure, saturation, and the level of

respiratory and ionotropic support were noted. The newborns with tachycardia, temperature instability, prolonged capillary refill time, and oliguria with or without hypotension were categorized as having shock. The transcutaneous hemoglobin was estimated by attaching the probe of the Masimo Radical 7 co-oximeter adhesive sensor (R1 20L) to one thumb, and it was shielded from light by covering it with ambient shield as per the manufacturer's specifications. If hemoglobin was not picked up even at 10 min, then the site of assessment was changed to another thumb or great toe. If we could not pick up a signal from both the sites, we categorized it as device failure. Venous hemoglobin was estimated by taking 1 ml of blood in the EDTA tube and analyzing at central laboratory by Sysmex automated hematology analyzer. Laboratory technicians who estimated invasive venous hemoglobin were blinded about transcutaneous hemoglobin measurement. We labeled neonates as anemic, if invasive hemoglobin was <13 g/dl as per the WHO definition [7]. In a previous study, the reported intraclass correlation coefficient (ICC) was 0.94 between invasive and transcutaneous hemoglobin [8,9]. With confidence set at 95% and precision of 0.04, the required sample size was 132 babies.

Statistical Methods

We summarized continuous variables as mean and standard deviation if the variables are normally distributed and as median and interquartile range (IQR) if the distribution was skewed. Bland–Altman plot was used for graphical presentation of agreement between the two measurements. The mean of transcutaneous and venous hemoglobin was plotted on x-axis and the difference between these two values was plotted on y-axis. A horizontal line was drawn to represent the bias. The 95% confidence interval indicated the limits of agreement (LOA) between these values. The degree of agreement was further confirmed by estimating ICC [10]. Univariate and multivariate regression analysis were done to study the factors influencing bias and device failure.

RESULTS

Of 158 newborns enrolled, transcutaneous hemoglobin was not picked up by pulse co-oximeter in 20 babies. Hence, the device failure rate was 12.6%. Clinical characteristics of the babies are presented in Table 1. Median (IQR) gestational age was 36 (32 and 38) weeks and median (IQR) birth weight was 2190 (1175 and 2790) g. Median (IQR) postnatal age was 10 (4 and 16) days. 61.5% of our study population were male and 29.5% were female. 30% of babies required ventilation during the study period. The mean transcutaneous hemoglobin was 14.22±2.3 g/dl, whereas the mean venous hemoglobin was 12.24±3.13 g/dl.

55% of babies had hemoglobin level <13 g/dl by invasive method. Transcutaneous hemoglobin was not picked up in 17.2% of babies with hemoglobin level <13 g/dl and in 26.4% of babies with hemoglobin <10 g/dl. 13.2% of babies had shock requiring inotropes. Transcutaneous hemoglobin was not picked up in 33.3% of babies with shock. Furthermore, factors influencing the device

failure rate were analyzed by regression analysis. Although perfusion index, shock, and level of hemoglobin were found to influence the device failure rate in univariate analysis, only the level of hemoglobin influenced device failure significantly on a multivariate model (Table 2). The overall bias between transcutaneous and venous hemoglobin was 1.66±2.26 g/dl (Fig. 1), and the values showed moderate agreement with ICC of 0.56. In babies with anemia (<13 g/dl), the bias was 2.69±1.87, which was significantly higher than the bias of 0.54±2.11 in babies with hemoglobin >13 g/dl (Fig. 2). Both the values showed poor agreement with ICC of 0.284.

As blood transfusion usually would be required at lower hemoglobin levels (<10 g/dl), the agreement was estimated at venous hemoglobin level of ≤10 g/dl. Bias was 3.29±1.86 showing poor agreement with an ICC of 0.10 (Fig. 3). Bias between both the measurements in babies with shock was 2.04±3.23 g/dl, whereas in babies without shock, it was 1.62±2.13 g/dl. Factors influencing the bias were analyzed using regression methods. In univariate analysis, only the level of hemoglobin significantly influenced the bias (Table 3).

DISCUSSION

The transcutaneous hemoglobin estimation by pulse co-oximeter device has made difference in the decision-making and hemodynamic monitoring in adult ICUs and surgical units. Application of this tool

Table 1: Baseline characteristics

Variables	Median (IQR) (n=158)
Birth weight (g)	2190 (1175, 2790)
Gestational age (weeks)	36 (32, 38)
Perfusion index	0.9 (0.7, 1.2)
Saturation (%)	96 (94, 98)
Postnatal age (days)	10 (4, 16)
Heart rate (beats/min)*	149.20 (17.24)
Venous hemoglobin (g/dl)*	12.24 (3.13)
Transcutaneous hemoglobin (g/dl)*	14.22 (2.36)

*Values are represented as mean (SD). IQR: Interquartile range, SD: Standard deviation

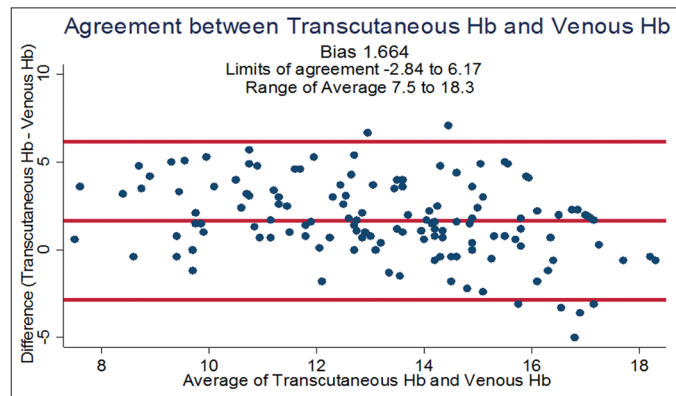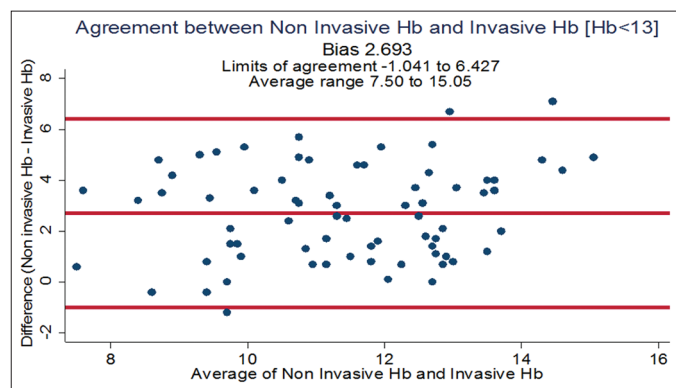**Table 2: Analysis of factors associated with device failure**

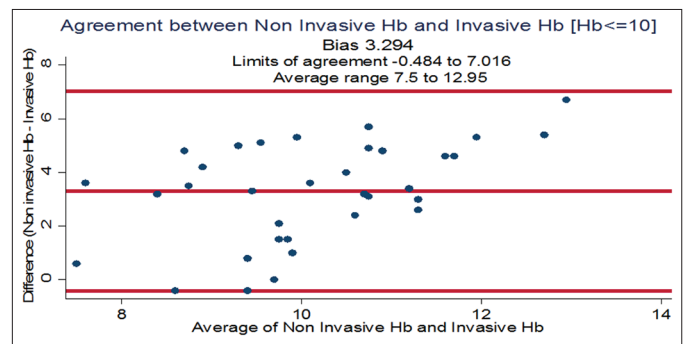| Variable	Odds ratio	95% CI	p value
Univariate analysis			
Gestational age (weeks)	1.06	0.93, 1.19	0.39
Birth weight (g)	0.68	0.07, 6.64	0.74
Heart rate (beats/min)	1.00	0.98, 1.03	0.78
Perfusion index	0.29	0.09, 0.98	0.05
Saturation (%)	0.99	0.86, 1.14	0.87
Shock (Y/N)	0.27	0.09, 0.81	0.02
Hemoglobin (g/dl)	0.81	0.68, 0.96	0.01
Multivariate analysis			
Perfusion index	0.35	0.10, 1.22	0.10
Shock (Y/N)	0.34	0.11, 1.12	0.08
Hemoglobin (g/dl)	0.83	0.70, 0.98	0.03

CI: Confidence interval

Table 3: Univariate analysis for factors influencing the bias between non-invasive and invasive hemoglobin

Variable	Regression coefficient	95% CI	p value
Gestational age (weeks)	0.06	−0.03, 0.15	0.20
Birth weight (g)	−0.13	−0.81, 0.55	0.70
Heart rate (beats/min)	0	−0.02, 0.02	0.78
Perfusion index	0.06	−0.62, 0.73	0.87
Saturation (%)	−0.03	−0.14, 0.08	0.57
Shock (Y/N)	−0.41	−1.67, 0.85	0.52
Level of hemoglobin (g/dl)	−0.47	−0.57, −0.38	<0.001

CI: Confidence interval

Figure 1: Bland–Altman plot between non-invasive and venous hemoglobin (n=138)

Figure 2: Bland–Altman plot between non-invasive and venous hemoglobin at hemoglobin level <13 g/dl (n=72)

Figure 3: Bland–Altman plot between transcutaneous and venous hemoglobin at hemoglobin level ≤10 (n=34)

and the level of hemoglobin. Only the level of hemoglobin was found to have statistically significant influence independently on the mean difference. The greater bias in our study could be due to more number of babies with lower levels of hemoglobin in our study. However, in the study by Aditya *et al.*, the bias was significantly higher in babies with shock as compared to healthy ones (−2.31±2.21 vs. −0.77±1.2 g/dl). However, in our study, shock was not found to influence the bias. This could be due to small numbers of babies with circulatory dysfunction in our study.

Gayat *et al.* also found that the bias was influenced by true hemoglobin levels and the oxygen saturation of the patient [12]. In a study by Khalafallah *et al.* for screening in pre-operative patients, the differences between both venous and transcutaneous hemoglobin appeared to be even across the range of hemoglobin values [13]. In a study conducted by Vora and Desai in neonates, the average bias was −0.2 with hemoglobin <12 and −0.1 at hemoglobin >12 [14]. In a study by Jung *et al.*, the laboratory hemoglobin correlated well with transcutaneous hemoglobin at levels <18 g/dl. At hemoglobin levels >18 g/dl, the correlation was not good [15]. Since blood transfusion would be required at lower hemoglobin levels (<10 g/dl), there should be good agreement, but the weak agreement in our study could limit its utilization for deciding on blood transfusion.

In our study of 158 newborn babies, the device failure rate was 12.6%. Among the various factors which could influence the pickup rate such as gestational age, weight, heart rate, saturation, perfusion index and shock, the level of hemoglobin, and perfusion index, and shock showed significant association with device failure rate on univariate analysis. However, on regression analysis, only the level of hemoglobin was found to influence the device failure rate significantly. Previous studies by Jung *et al.* and Bhat *et al.* have documented device failure rate of 1.3% and 17%, respectively [8,15]. The adhesive sensor supplied by the Masimo SET rainbow (R1 20L) sensor for infant's weighing between 3 and 10 kg is used in all the studies due to the non-availability of an appropriate sensor for babies <3 kg.

CONCLUSION

Non-invasive hemoglobin measured by pulse co-oximeter shows only a moderate agreement with reference venous hemoglobin in neonates admitted to nursery. We report a high device failure rate of 12.6%. Level of hemoglobin is the single most important

in clinical decision-making is being evaluated in neonates admitted to the NICU. In our study, there was only moderate agreement between venous and transcutaneous hemoglobin (ICC=0.56). The LOA were wide apart. Our bias (1.66±2.26) was more when compared to that in the study by Nicholas *et al.* (−0.09±1.67 g/dl) [11]. Bhat *et al.* studied healthy and sick children and reported an excellent positive correlation between the measurements [8]. However, their LOA were also wide apart similar to our study. In our study, we found the bias between the measurements to be higher at lower levels of hemoglobin when compared to babies with normal levels of hemoglobin. We analyzed the various factors which could influence the bias between these measurements such as gestational age, weight, saturation, perfusion index, heart rate,

determinant of device failure and degree of agreement. With a high device failure rate and poor agreement at low hemoglobin levels, the clinical utility appears negligible. Further, research should focus on developing better devices or technology to apply this much-needed tool in neonatal intensive care units.

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