Challenges in Detection of Adolescent Anaemia: Validation of Point-of-Care Device (Mission® plus) for Haemoglobin Measurement among Tribal Residential School Children of Selected Districts of Odisha, India

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Abstract

Background: Screening for anemia among tribal school children has been a challenge. **Objectives:** To validate a point-of-care (POC) device (mission® plus hemoglobinometer) to the gold standard method, spectrophotometry. **Study Design:** Cross-sectional study. **Participants:** The representative sample of 953 tribal adolescents from the residential schools of Odisha. **Methods:** Hemoglobin was measured simultaneously by the POC and gold standard method during January to July 2019. The validity of the POC device was measured by sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The area under the curve was calculated using receiver operating characteristic (ROC) analysis. Concordance of the POC device with the gold standard method was determined by the Bland–Altman plot. The intraclass correlation coefficient (ICC), precision (ρ), a bias correction factor (C_b), and the concordance correlation coefficient were also calculated. Deming regression analysis was performed, and a linear equation was established. **Results:** The mean age of the study participants was 13.07 ($\pm$1.48) years. The prevalence of anemia was 45.54% by the gold standard method. The sensitivity and specificity of the POC device were 94.9% and 56.1%, respectively. PPV and NPVs were 64.4% and 93.0%, respectively. The area under the ROC curve was found to be 0.856. The ICC was 0.887 (95% confidence interval: 0.872–0.901). **Conclusions:** Very good reliability/absolute agreement for hemoglobin measurements existed between the POC device and the gold standard method making it suitable as a screening device.

Keywords: Adolescent, anemia, erythrocyte indices, point-of-care testing, population, validation

Introduction

Iron deficiency anemia has major health and economic consequences. In adults, it leads to a substantial loss of productivity. During pregnancy, it is associated with low birth weight, preterm labor, infant, and maternal mortality.[1] Anemia in children may lead to low cognition level, faltered growth and development, weakened immune system, a decline in school performance and reduced ability to live a productive adult life. Severe cases, if not detected and treated appropriately may even result in fatality.[2]

The National Family Health Survey-IV revealed the prevalence of anemia to be 53% among females (15–49 years), 23% among males (15–49 years) with still a higher proportion (59%) among children (6–59 months).[3] Odisha is one among the eight empowered action group states with relatively poor socioeconomic and demographic indicators. The Clinical, Anthropometric, and Biochemical survey in Odisha (2014) showed a prevalence of 71% and 81% of anemia among under 5 and 5–9-year-old children, respectively.[4]

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Screening is the first step to combat anemia. Among the several methods available, automated analyzers are considered the gold standard method,[5] although several limitations make them unsuitable for deployment in outreach areas.[6] Point-of-care (POC) devices to detect anemia may be an alternative method because of their low cost, portability, ease of use, nondependence on electricity, and providing results immediately.

The government of Odisha took the initiative to detect and treat cases of anemia among the tribal school students. Close to 75,000 students from 395 residential schools under scheduled caste and scheduled tribe department were planned to be screened through a POC device. However, data to support or refute the use of these POC devices for the screening were lacking. We, therefore, conducted this study to validate the currently used Mission® plus hemoglobinometer and generate evidence for its use for detecting anemia among school-going adolescents.

METHODS

Study setting and participants
Residential school students under Scheduled Caste and Scheduled Tribe department in three selected districts, namely Keonjhar, Kandhamal, and Rayagada constituted our study population. These districts were selected because of having predominantly tribal population and poor health indicators compared to other districts.

Study duration
The study duration was January to July 2019.

Study design
The study design was cross-sectional study.

Sample size
Sample size was calculated[7] based on the prevalence of anemia of 50% from previous studies.[8] With a sensitivity and specificity of 90% each, considering a marginal error of 4% at 95% confidence interval (CI), 864 samples were needed. The sample size was raised (12%) to 968 to compensate for the wastage during blood collection and transportation.

Sampling method
Probability proportionate to size sampling method was used to choose a representative sample from a total of 61,981 students from three districts. Eight schools from each district were selected randomly. Sample from each school was also drawn proportionate to the total number of students in the school. During the school visit, students from the 5th to 10th standard were chosen randomly from each class.

Mission® plus hemoglobinometer
This is a portable, electric or battery-operated POC device that uses disposable test strips, manufactured by the ACON biotech. It detects azide-methemoglobin level at a wavelength of 525 nm using reflectance photometry. Both capillary and venous blood can be used, and the test results are displayed on a digital display panel.

Sysmex XN 3000 (manufactured by Sysmex GmBH)
It uses spectrophotometry technique to detect S-lauryl sulfate, thus considered as the gold standard test for hemoglobin measurement in a laboratory set-up. The XN series has low sample turnaround time giving more sensitive, precise, and accurate results especially on low cell counts.[9]

Data collection procedure
The team, comprising of a doctor, qualified laboratory personnel, a lady staff nurse and an attendant, were trained on all the relevant procedures. The training included data collection on basic demographic profile, counselling before blood collection, capillary blood collection procedure, venipuncture procedure, operation of the POC device, recording of the results, quality check, postprocedural observation for any untoward event, and bio-medical waste handling. A sterile lancet was used for pricking. The first drop of blood was discarded using a sterile cotton swab. Pressure on the finger was avoided to prevent hemodilution. A pipette was used to collect blood and dropped it on the test strip connected to the POC device. The reading was then documented.

A minimum of 2 ml of blood was collected through venipuncture following standard guidelines. The blood sample was transported in cold boxes to the institute's NABL accredited laboratory and tested within 24 h for hemoglobin estimation using the gold standard method, Spectrophotometry. Both the POC device and the spectrophotometer were standardized for quality control, every day, before initiating the testing procedure. The bio-medical waste generated and segregated at the site was also transported back to the institute for appropriate disposal.

Statistical analysis
The qualitative variables were expressed in terms of number and percentages. The quantitative variables were expressed in terms of mean and standard deviation. A cutoff value of 12 g/dl was taken to classify an individual as anemic or nonanemic according to the World Health Organization classification for anemia among adolescents.[10] The validity of the screening test (POC) device was measured by sensitivity, specificity, positive predictive value and negative predictive value (NPV). The receiver operating characteristic curve (ROC) and area under the curve (AUC) was calculated to find out the performance of the POC device as a screening test. Youden's J index was used to find out the ideal cutoff value of hemoglobin at which the POC device provided optimum sensitivity and specificity. Concordance of the POC device with the gold standard method was determined by the Bland–Altman plot. The analysis was performed using SPSS software v27.0 (IBM Corp., Armonk, NY) licenced to the institute. The intraclass correlation coefficient (ICC), precision (ρ), a bias correction factor (C_b), and the concordance correlation coefficient (CCC) were also calculated. Deming regression analysis was performed for method comparison (POC vs. Gold standard) to consider the measurement errors by both the methods, and a linear equation was established. These

analyses were performed using the trial version of MedCalc software MedCalc Statistical software version 19.2 (MedCalc bv, Ostend, Belgium).

Ethical issues

Ethical guidelines for medical research involving human participants were followed. Ethical approval was obtained from the Institutional Ethical Committee. Written informed consent was obtained from the legally accepted representative or head of the school before the enrollment. Confidentiality was maintained, and students were informed about the study before the sample/data collection. Further, the results were shared with the participants and those found to have anemia received appropriate treatment.

RESULTS

A total of 968 students were enrolled in the study. After data cleaning, 15 students were excluded from the study because of missing/incomplete information or wastage of blood sample with a nonresponse rate of 1.5%. The mean age of the participants was 13.07 (±1.48) years, with a range from 10 to 18 years. Gender distribution showed a slightly higher proportion of males (54.4%) as compared to females (45.6%). Almost equal proportion participants were from 6th (24.7%), 7th (24.7%), 8th (22.6%), and 9th (21.0%) class. Participants from 5th (3.7%) and 10th class (3.5%) were less due to a fewer number of students in the class and ongoing board examination of students, respectively. The prevalence of anemia was 45.54% by the gold standard method. The sensitivity and specificity of the POC device was 94.9% and 56.1%, respectively. Similarly, positive and NPVs were 64.4% and 93.0%, respectively [Table 1].

The ROC curve [Figure 1] estimated the effectiveness of the POC device in differentiating the diseased and nondiseased population. The AUC was found to be 0.856 (95% CI: 0.83–0.88), suggesting the hemoglobin measurement by the POC device was good in segregating anemic and nonanemic students. Youden's J index (0.55) suggested that at a cutoff hemoglobin value of 11.50 g/dl, the test performed better with a sensitivity of 87.8% and specificity of 67.4%.

Figure 2 shows the Bland–Altman plot, illustrating the association between the bias (difference in hemoglobin measurements) and the average between the POC method and the gold standard hemoglobin value. Bland and Altman's limit of agreement was from −2.9 to 1.14 with a mean difference of −0.87.

The ICC was 0.887 (95% CI: 0.872–0.901) indicating a good reliability/absolute agreement for hemoglobin measurements between the POC device and the gold standard method. There was a strong positive linear correlation (precision) between both the measurements with a correlation coefficient of 0.802 (ρ) with a $P < 0.001$. The bias correction factor which measures the accuracy was found to be 0.867 (C_b). CCC ($\rho \times C_b$) was found to be 0.695 (95% CI: 0.666–0.722). Deming regression model established the equation $y = -2.437 + 1.121x$, where "y" denotes POC measurements and "x" denotes gold standard measurements [Figure 3].

DISCUSSION

Millions of children are affected by anemia worldwide and more than half of them due to iron deficiency. Moreover, iron deficiency sets in much before the appearance of frank anemia. Thus, the prevalence of iron deficiency is estimated to be two times higher than that of anemia.[1,10] Owing to the deficiency in laboratory methods, most patients with anemia
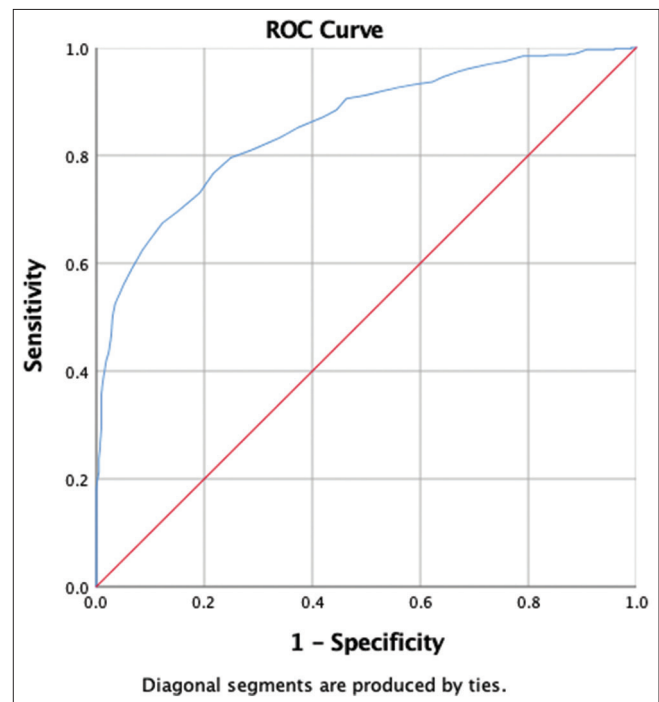

Figure 1: Receiver operating characteristic curve between the point-of-care device and the gold standard method ($n = 953$)

Table 1: Validity of point-of-care device as compared to the gold standard method ($n=953$)				
Method used	Gold standard method*		Total	Test performance (%)
	Anemic	Nonanemic		
Point of care device				
Anemic	412	228	640	PPV=64.4
Nonanemic	22	291	313	NPV=93.0
Total	434	519	953	
Test performance (%)	Sensitivity=94.9	Specificity=56.1		

*Threshold to assign anemia by the gold standard method was 12 g/dL. PPV: Positive predictive value, NPV: Negative predictive value
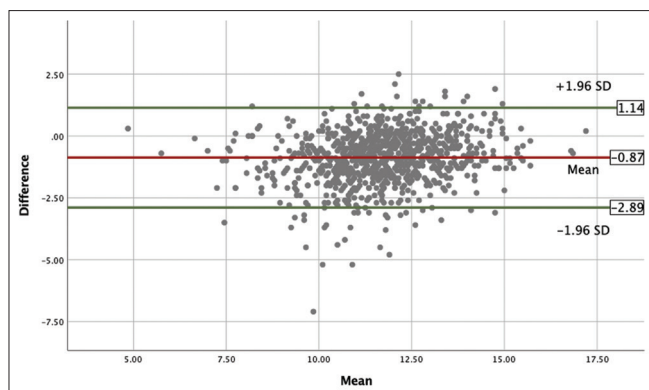
Figure 2: Bland–Altman Plot between differences in measurements and mean of point-of-care and gold standard measurements ($n = 953$)

Figure 3: Deming regression analysis between point-of-care and gold standard method ($n = 953$)

present with complications. Therefore, screening is vital for early diagnosis.

Several methods such as the copper sulfate method, Sahli's technique, Hemoglobin Color Scale, HemoCue method, and automated hematology analyzers are available for the detection of anemia.[5] Although hematology analyzers are considered a gold standard method for measuring hemoglobin, they are expensive and electricity dependence makes them unsuitable for deployment in outreach areas, where power outage is frequent. Moreover, the requirement of qualified human resource, appropriate laboratory setup, and timely maintenance make them difficult to use in resource-poor settings.[11] The search for a valid and reliable POC device alternative to a hematology analyzer is the need of the hour and our study tried to validate one of such devices at a resource-poor setting.

There was a strong ICC (0.887), high precision (0.802), high sensitivity (94.9%), high NPV (93.0%), and a significant AUC in the ROC curve indicating a valid and reliable POC device. A study conducted in the adult population (15–77 years) attending primary care clinics of Selangor (Malaysia) found a comparable sensitivity (97.1%) and specificity (62.5%) for Mission® plus hemoglobinometer.[12] Our study further strengthened the evidence toward the validity of Mission® Plus hemoglobinometer, especially in the vulnerable population (tribal school-going adolescents) in the Indian context.

Although at a cutoff value for hemoglobin of 11.5 g/dL (Youden's J index in ROC analysis) yielded an optimum sensitivity and specificity (87.8% and 67.4%, respectively), the primary purpose of the study was not to provide an optimum sensitivity and specificity for the POC device. On the contrary, at a cutoff value of 12 g/dL of hemoglobin as recommended by the WHO, this POC device gave a better trade-off for sensitivity (94.9%), which is suitable for screening.

Although we did not find any study reporting ICC for Mission® plus hemoglobinometer studies comparing other POC devices, like HemoCue and a portable hemoglobin photometer, found a comparable ICC as our study (0.887).[6,13] Our study also
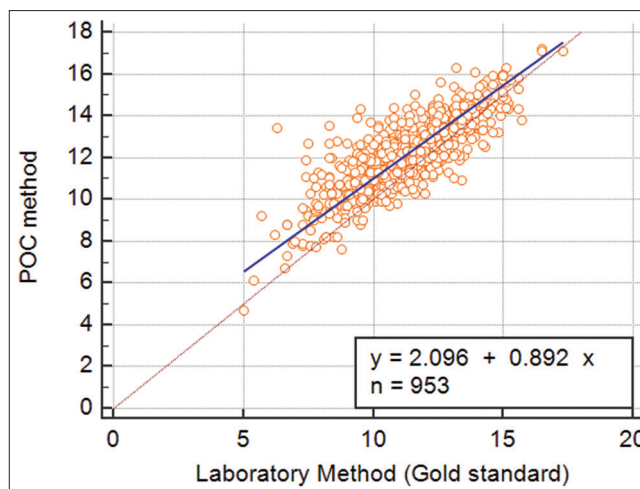
established a regression equation to calculate the values of gold standard measurements based on POC device values.

HemoCue is by far the most widely used POC device for hemoglobin measurement. Neufeld *et al.*[14] studied the validity of HemoCue using capillary blood among the adult population of Mexico and compared it with Celldyn as a gold standard method using venous blood. They found a higher specificity (93%) and a lower sensitivity (84%) as compared to our study. Similarly Sari *et al.*[15] found a higher specificity (95.2%) and a lower sensitivity (70.6%) while comparing HemoCue as a POC device using capillary blood with the direct cyanmethemoglobin method using venous blood among Indonesian mothers. Zhou *et al.*[13] in their study among pregnant women living at high altitude used a portable photometer as a POC device using capillary blood and compared its validity with Sysmex (spectrophotometry) using venous blood. They did not recommend the use of a portable photometer in detecting anemia because of a higher mean difference in hemoglobin level between the POC and gold standard method with a wide CI. These studies, however, were in contrast to our findings in terms of lower sensitivity. This could be attributed to different POC devices used in their studies and validated among the adult population living in varied geographic locations that may affect the hemoglobin concentration. However, higher sensitivity in our study favors the POC device suitable for screening programs.

To the best of our knowledge, it is the first-ever study for validating a POC device for hemoglobin measurement among the adolescent population. An adequate representative sample chosen randomly with a robust study design, enable the study findings to be generalized to other adolescent populations. Previous research has identified few bottlenecks in the use of the POC device at the grass root level such as tests were not performed according to the protocol, reagents or test strips stored improperly, routine quality controls were not performed and maintenance of these devices were lacking in the

resource-poor settings.[6,13,15] These problems are preventable with the training of field workers which was carried out in our study. Studies suggest that there was an inherent difference in the measured value of hemoglobin in capillary and venous blood. The factors such as temperature and thickness of the skin and application of pressure for milking blood during finger prick and penetration depth affected the results.[16-18] In our study, we tried to nullify these factors by choosing a specific population and carrying out the sample collection process by trained professionals.

CONCLUSIONS

Hemoglobin measurement by the Mission® plus hemoglobinometer is valid as compared to the gold standard laboratory method and has the potential to discriminate between anemic and nonanemic adolescents. POC devises may be an alternative method because of their low cost, portability, ease of use, nondependence on electricity, and provide immediate results. Further research is recommended in evaluating the current device with other such devices and among different populations, for a better candidate device deployable at the grass-root level for mass screening of anemia.

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Conflicts of interest

There are no conflicts of interest.

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