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Oyenusi EE
Oduwole AO
Oladipo OO
Njokanma OF
Esezobor CI

Reliability of bedside blood glucose estimating methods in detecting hypoglycaemia in the children's emergency room

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Oyenusi EE (✉)
P.O.Box 4337, Ikeja,
Lagos, Nigeria.
Email: ebikike@yahoo.com

Oduwole AO, Esezobor CI
Department of Paediatrics,
Lagos University Teaching Hospital,
Idi-Araba, Lagos, Nigeria.

Oladipo OO
Staten Island University Hospital,
Staten Island. NY. USA

Njokanma OF
Department of Paediatrics,
Lagos State University Teaching
Hospital, Ikeja, Lagos, Nigeria.

Abstract: *Background:* Hypoglycaemia occurs in many disease states common in the tropics. Facilities and skilled manpower required for laboratory blood glucose measurement are not always available in health facilities in developing countries.
Objective: The study was carried out to determine the validity of bedside methods of blood glucose measurement in detecting hypoglycaemia.
Methods: Blood glucose was determined by two bedside methods (*Accuchek Active*® and *Betachek Visual*®) in 430 patients aged between one month and 10years and simultaneously sent for laboratory spectrophotometric analysis at a wavelength of 500nm using the hexose kinase method. Hypoglycaemia was defined as plasma glucose < 2.5mmol/L.
Results: The prevalence of hypoglycaemia was 5.6%.There was a higher correlation (r =0.84, p< 0.05) between *Accuchek Active*® results and laboratory values than was obtained with *Betachek Visual*® (r = 0.48, p=0.000).In detection of hypoglycaemia, both bedside glucose monitors were found to have a high specificity and high predictive values of a negative test (99.8% and 98.5% for *Accuchek Active*® and 89.4% and 97.8% for *Betachek Visual*® respectively) with moderate sensitivity (75.0% and 66.7% respectively). However, the *Accuchek Active*® monitor has a much higher predictive value of a positive test (94.1%) compared to the *Betachek Visual*® (27.1%).
Conclusion: The bedside glucose monitors are valid bedside tools for detecting or ruling out hypoglycemia.

Keywords: hypoglycaemia, children, bedside investigation, glucose estimation, blood glucose.

Introduction

Hypoglycaemia occurs in many disease states such as severe malaria, severe malnutrition, diarrhoea amongst others common in the tropics[1-4] and may also complicate treatment with some drugs like quinine used in the treatment of severe malaria[5]. A previous study[3] had documented a prevalence rate of 17% among children with severe malaria seen at the children's emergency centre of the Lagos University Teaching Hospital (LUTH)[3]. Significant morbidity and mortality can be associated with hypoglycaemia[6,7]. Survivors of prolonged hypoglycaemia are prone to neurological complications such as mental retardation, recurrent seizure activity, transient cognitive impairment and neurological deficits[6,7].

Clinical manifestations of hypoglycaemia include sweating, jitteriness, anxiety and nervousness. Others are headaches, visual disturbances, lethargy, restlessness, irritability, convulsions and mental confusion[8]. However, the absence of clinical symptoms does not always indicate that the glucose concentration is normal because hypoglycaemia may be frequently asymptomatic[8]. Thus it is important to investigate for hypoglycaemia in acutely ill children, more so as it complicates paediatric emergencies in Africa[9-11].

The gold standard technique of determining blood glucose level involves laboratory spectrophotometric analysis using methods involving enzymes such as glucose oxidase, hexokinase and glucose dehydrogenase. These methods require standard laboratory equipment, skilled manpower, consistent electricity and water supply. These resources required for the laboratory determination of blood glucose level are not always available in our health facilities in the developing countries, yet early diagnosis and prompt treatment of hypoglycaemia in critically-ill children minimizes hypoglycaemia-related organ damage[6,7].

In addition, the cost of laboratory determination of blood glucose level could be high when serial measures are required. Because of relatively long turn-around time results from laboratory determination of glucose may not be available in a timely fashion to affect management of a child. To overcome some of these challenges, various types of reagent test strips have been developed for bedside usage. An added advantage of these rapid bedside diagnostic tests is that less expertise/training is required prior to their usage. These strips use a method in which a dye is coloured by the glucose oxidase-peroxidase chromogenic reaction[12,13]. The resulting colour change is either visually interpreted by comparison with an accompanying colour chart or read with a reflectance meter (glucometer)[14-15].
Therefore, it is imperative to validate these bedside methods for reliability of results obtained from them. Hence, this study was conducted to determine the sensitivity, specificity and predictive values of two bedside methods of glucose determination using a laboratory-based enzymatic method (the hexokinase method) as the gold standard.

Subjects and methods

The study was conducted at the Olikoye Ransome-Kuti Children's Emergency Centre of the (LUTH), Lagos Nigeria. All consecutively admitted children, aged between one month and 10 years over a period of nine months (September 2009 to May 2010) were eligible for inclusion in the study. Approval was obtained from the Human Research and Ethics Committee of LUTH before commencement of the study. Written informed consent was also obtained from all parents or care –givers of participating children.

Data Collection

For each subject recruited, at the point of admission into the emergency room, before commencement of intravenous fluids, a drop of capillary blood obtained by a finger prick was applied to each of the two reagent strips according to the manufacturer's instructions[16,17] and about 1.5mls of blood was withdrawn from a convenient peripheral vein and put in a fluoride oxalate-containing bottle for laboratory spectrophotometric analysis using the hexose kinase method.

A visually interpreted test strip by *Betachek Visual*[16] and a reflectance meter, *Accuchek Active*[17] were used for the bedside determination of blood glucose because these are readily available and commonly used in our facilities. The test pad of the *Betachek Visual*® contains 0.09% glucose oxidase, 0.19% peroxidase, 1.2% TMB (3, 3', 5, 5'-Tetramethylbenzidine dihydrochloride) and 0.35% DCP (2,4-dichlorophenol 6-monooxygenase)[16]. A test strip was removed and the bottle was immediately recapped. A drop of blood was pressed onto the centre of two test pads, moving it around to ensure complete coverage. Exactly 30 seconds after application, the blood was wiped from the test pads with a folded tissue paper and repeated using a clean region of the tissue paper. It was ensured that strip was blood-free, as excess blood left on the pads usually affects the result[16]. After an additional 30 seconds, the test result was read by comparing the reacted test pad to the B*etachek Visual*® colour chart label. If the colour fell between two colour blocks, the average value was taken as the test result[16].

For the *Accuchek Active*® the test strip was held so that the application area and arrows were facing upwards. In this position the test strip was pushed into the glucometer until it clicked into place[17]. The insertion of the test strip automatically turned the monitor on and put it in test mode[17]. When the drop symbol flashed in the display, a drop of blood was applied to the middle of the orange coloured test pad. The test was complete after about five seconds and the result appeared in the display and was automatically saved with the date and time. The *Accuchek Active*® monitor measures blood glucose within a defined range (10-600 mg/dl or 0.6-33.3 mmol/L). Values outside this range are displayed as "lo" meaning the result is less than 0.6 mmol/L or "Hi" meaning the result is greater than 33.3 mmol/L[17].
The blood in the fluoride oxalate-containing bottle was sent to the Chemical Pathology Department of the hospital for plasma glucose determination. The blood sample was centrifuged for five minutes at about 1600Gy to obtain plasma not more than one hour after collection[18]. The separated plasma was frozen at -80^0C and stored in the refrigerator until analysis. Samples were analysed in batches of 25 samples using the Hitachi Automatic Analyser (Cobas- ROCHE). The analyser uses spectrophotometric analysis at a wavelength of 500nm and hexose kinase method[12]. Hypoglycaemia was defined as whole blood glucose less than 2.2 mmol/L for the bedside methods, (*Betachek Visual*® *Accuchek Active*®) and as plasma glucose less than 2.5 mmol/L from the sample analysed in the laboratory[12]. This was based on the fact that whole blood glucose concentration is approximately 8 to 15% less than plasma glucose because the water content of plasma is approximately 12% higher than that of whole blood[12].

Data management and analysis

The data was analysed using the Statistical Package for the Social Sciences (SPSS) version 20. Measures of statistical location (mean, standard deviation, median and range) were determined. Probability (p value) less than 0.05 was taken as statistically significant. The sensitivity, specificity, positive and negative predictive values of blood glucose obtained from the two reagents strips were calculated using the blood glucose from the laboratory as the gold standard[19]. For the purposes of this study, the values of sensitivity, specificity, positive and negative predictive values of blood glucose were classified as low if between 0 to <50%, moderate if between 50-80% and high if from >80 to 100%.

Results

Four hundred and sixty one children aged 1.5 to 120 months were admitted over a six-month period. Of the 461 patients, 31 laboratory blood glucose samples obtained were not valid due to improper handling. Four hundred and thirty patients had complete data sets and were analysed.

Blood glucose (BG) patterns of the patients

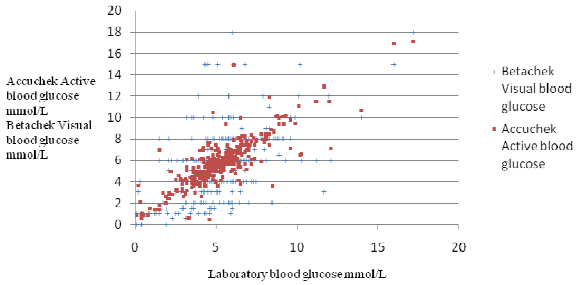
The descriptive statistics of blood glucose results by the various methods is shown in Table 1. Using the laboratory based method, the mean BG of all the study subjects was 5.19 ± 2.05 mmol/L (range of 0.1-18.0 mmol/L, median was 4.9 mmol/L).

Table 1: Descriptive statistics of the blood glucose results by the various methods

Test Method	Range (mmol/L)	Mean (mmol/L)	SD (mmol/L)	Median (mmol/L)	Total
Laboratory	0.1− 17.2	5.19	2.05	4.9	430
Accuchek Active®	0.5 −17.1	5.69	2.04	5.6	430
Betachek Visual®	0.0 −18.0	5.54	2.83	6.0	430

The scatter diagram (Fig 1) demonstrates the relationship between laboratory blood glucose and blood glucose determined by *Accuchek Active*® and by *Betachek Visual*®. Visual inspection further indicates a better positive relationship between BGs determined by laboratory and *Accuchek Active*® than between laboratory and *Betachek Visual*®.
The blood glucose values measured by the *Accuchek Active*® meter correlated better with the values from the laboratory than those measured by the *Betachek Visual*® strip (with R, 0.84 versus 0.48) and the difference was statistically significant ($p < 0.05$).

Fig 1: Scatter diagram showing the relationship between Laboratory blood glucose and blood glucose determined by *Accuchek Active*® and by *Betachek Visual*®



Correlation of *Betachek Visual*® with laboratory blood glucose, r = 0.48, p<0.05
Correlation of *Accuchek Active*® with laboratory blood glucose, r= 0.84, p<0.05

Hypoglycaemic patients

Twenty-four out of the 430 study subjects had hypoglycaemia by the laboratory method giving a prevalence rate of hypoglycaemia of 5.6%.
Sensitivity and specificity of bedside glucose monitor for the detection of hypoglycaemia: Using the laboratory values of blood glucose as gold standard, measures of diagnostic accuracy were calculated for results obtained using the bedside blood glucose monitors (Table 2 for *Betachek Visual*® strips and Table 3 for *Accuchek Active*® meter). With respect to *Betachek Visual*® strips, the sensitivity was 66.7% and the specificity was 89.4%. The positive predictive value and the negative predictive value were 27.1% and 97.8% respectively.

Table 2: Sensitivity and specificity of the Betachek Visual® strip, Laboratory based method

Test		Positive	Negative	Total
Betachek Visual ®	Positive	True Positives = 16	False Positives = 43	59
	Negative	False negatives= 8	True Negatives= 363	371
	Total	24	406	430

Sensitivity = TP / (TP + FN) = 16 / (16+8) ×100 = 66.7%
Specificity = TN / (TN + FP) = 363 / (363+43) ×100 = 89.4%
Positive Predictive Value = TP /(TP+FP)=16/(16+43)×100= 27.1%
Negative Predictive Value = TN/(FN+TN)=363/(8+363)×100 = 97.8%

The sensitivity, specificity and the positive and negative predictive values of the *Accuchek Active*® meterstrips are shown in Table 3. Measures of diagnostic accuracy were calculated for results obtained using *Accuchek Active*® meterstrips. The sensitivity was 75.0% while the specificity was 99.8%.The positive predictive value was 94.7% while the negative predictive value was 98.7%.Four out of the eight false negatives had blood glucose values ranging from 2.7 to 2.9 mmol/L.

Table 3: Sensitivity and specificity of the Accuchek Active® glucometer, Laboratory based method

Test		Positive	Negative	Total
Accuchek Active®	Positive	True Positives =18	False Positives =1	19
	Negative	False negatives =6	True Negatives = 405	411
	Total	24	406	430

Sensitivity= 18/ (18+6) ×100 = 75.0%
Specificity = 405/ (405+1) ×100 = 99.8%
Positive Predictive Value = 18/ (18+1) ×100 = 94.7%
Negative Predictive Value = 405/ (6+405) ×100 = 98.5%

Discussion

The blood glucose values measured by the *Accuchek Active*® meter correlated better with the values from the laboratory than those measured by the *Betachek Visual*® strip. The chances are very high that an increase/decrease in laboratory result will be reflected by an increase/decrease in *Accuchek Active*® meter result.

The specificity and negative predictive value of the *Betachek Visual*® strip were high, in the range of 90% and above. Sensitivity on the other hand was moderate but positive predictive value was low. This implies that the use of this technique as a screening tool confers moderate success. However, the high specificity and a high predictive value of a negative test means that a negative result can be relied upon as being truly negative. The high specificity and negative predictive value of the *Betachek Visual*® strip is comparable to a specificity of 94% and negative predictive value of 99% of a different brand of visually-interpreted reagent strip

(*ChemstripbG*) in a previous Cincinnati[14] study. However, the sensitivity and the positive predictive value of the *Betachek Visual*® strip used in the current study was lower than the reported sensitivity and positive predictive value of the *ChemstripbG* strip which was 97% and 72% respectively[14]. A possible explanation for the disparity may be the definition of hypoglycaemia as laboratory blood glucose value of <45 mg/dl (2.5mol/L) in the current study compared to the higher laboratory blood glucose value of <60mg/dl (3.3mol/L) defined as hypoglycaemia in the Cincinnati study[14]. Another possible reason for the low sensitivity of the Betachek Visual® may be because it is semi-quantitative and measures blood glucose to the nearest 1mmol/L(18mg/dl) compared to the standard laboratory method which is more quantitative measuring to the nearest 0.1mmol/L(1.8mg/dl). Furthermore, the visual reading with a colour chart used in the visually interpreted strips may introduce inter-observer bias as people may interprete colour intensity differently while visual acuity and colour blindness may be sources of bias. However, from the results in the current study, the *Betachek Visual*® strip may be more useful as a confirmatory rather than a screening test for hypoglycaemia.

The specificity and negative predictive value of the *Accuchek Active*® were nearly 100%. The positive predictive value was also very high but the sensitivity was only moderate. Sensitivity was hampered by the occurrence of false negative results in six cases but it is noteworthy that four of the six false negative blood glucose values were in the lower range of normal. The implication is that blood glucose values in the lower band of normal may require confirmation using laboratory techniques. The high specificity and negative predictive value imply that the *Accuchek Active*® meter is very useful for ruling out hypoglycaemia and a positive value can be relied upon as being truly hypoglycaemic.

The high specificity and negative predictive value of the *Accuchek Active*® meter is similar to a specificity of 96.2% and a negative predictive value of 99.7% obtained with a different brand of a blood glucose kit also interpreted by a reflectance meter (*Prestige IQ*) as documented in a previous Nigerian study[15]. However, the sensitivity of the *Accuchek Active*® meter was lower than the sensitivity of 96% of the *Prestige IQ* meter while the positive predictive value of the *Accuchek Active*® was higher than the 63.1% of the *Prestige IQ* meter. Also, in comparison with findings in a Kenyan study[20], the specificity of the *Accuchek Active*® meter in the current study was higher than the specificity of 48% but the sensitivity was lower than 84% of the *Refloflux-S* reflectance meter respectively.

The different bedside equipment for measuring blood glucose are associated with different degrees of success with identifying true positives and true negatives as well as avoiding false positives and false negatives. However, the advantages they offer in terms of low cost, immediate availability of results and the option of immediate intervention make them very attractive. There will, however, remain a need for laboratory determination of values, especially in cases where the results are borderline.

Conclusion

In conclusion, the glucose meter, *Accuchek Active*® and *Betachek visual*® are reliable in detecting or ruling out hypoglycaemia by the bedside which will enable prompt intervention while awaiting confirmatory results from the laboratory where these are available.

Author's Contributions
The research work was conceived by all the authors. OEE carried out the field work. All the authors contributed to the writing of the manuscript.
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