Original Article

Are blood glucose monitors for home use and hospital use interchangeable?

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Objective: To assess the analytical performance of Accu check Active®, One Touch Ultra®, On Call Plus® and Nova Stat Strip® glucose monitoring point of care devices, when compared to each other and with Roche ® Hexokinase method on Hitachi 902 ® automated chemistry analyzer in the presence of interferants like hematocrits and ascorbic acid.

Methodology: The study was conducted at Dr. Ziauddin Hospital, Karachi from May 2014 to September 2014. Venous blood samples were modified pre-analytically to generate varying hematocrits. Samples were glycolyzed or spiked to achieve various glucose levels. Similarly, different levels of ascorbic acid were also added and glucose tested on blood glucose monitoring devices and automated chemistry analyzer. This process generated 18 different combinations of glucose with hematocrit or ascorbic acid.

Results: Differences in hematocrit and ascorbic acid levels brought about significant changes in glucose measurements in the glucometers. The Nova Stat Strip® displayed results close to the analyzer in the presence of interfering substances. The Accucheck Active® and One Touch Ultra® had a similar performance, while the On Call Plus® showed the most variability of results.

ISO 15197:2013 requirements were fulfilled by Nova Stat Strip® and Accucheck Active® while the One Touch Ultra® and On Call Plus® did not reach the acceptable limits.

Conclusion: Hospitalized patients have a multitude of interfering substances in their blood, which bring about a significant difference in glucose readings. Glucose monitoring devices designed with additional strips to minimize interference by interfering agents are more accurate and should be preferred over other devices for use in hospitals point of care testing and self monitoring. (Rawal Med J 201;42:390-395)

Keywords: Glucose, blood glucose self monitoring, point of care systems.

INTRODUCTION

Poor glycemic control is a well recognized hurdle on the road to recovery of critically ill patients. A lot of emphasis has been laid on strict blood glucose monitoring in diabetic patients, leading to the introduction and development of advanced point of care glucose testing, but the analytical accuracy of these handheld devices has not able to parallel that of the laboratory reference methods due to varying methodologies and the difference between venous and capillary blood sampling.[1] A study conducted in Pakistan, compared bedside glucose monitoring with centralized laboratory testing and showed that although point-of-care testing had a faster turnaround time and lower cost, laboratory testing was more accurate in acutely ill patient, with very high or very low glucose testing.[2]

Glucometers function under the principle of oxidation of glucose through enzyme based strips. Reflectance photometry measures the amount of light reflected from the test strip, which contains the reagent. This produces a color change, which is then measured. The process was initially manual or automated, but studies have shown that sample temperature can influence the results of manual (wiping) reflectance glucometers,[3] which resulted in the introduction of automated devices. Most glucometers today have glucose oxidase or glucose dehydrogenase based biosensors, which produce an enzymatic reaction. Colorimetric meters have now been widely replaced by meters, which are amperometric and generate electrons, which are transferred from the blood to the electrodes. The magnitude of the resultant current is proportional to

the concentration of glucose in the specimen and the signal is converted into a readout displayed on the screen of these devices. The major disadvantage of these enzyme based strips is that along with glucose, other substances such as maltose, galactose and ascorbic acid also interfere with electrochemical strips as they are oxidized at the electrode surface, resulting in the generation of more electrons and current, leading to falsely elevated glucose readings.[4]

These interfering substances are of utmost importance in the management of critically ill patients who are frequently subject to a combination of therapeutic drugs, intravenous fluids, dialysate solutions, etc. Breakdown of these chemicals leads to the presence of other substances in their blood. These factors along with fluctuating hematocrits, temperatures and blood pressure, produce a confounding effect on glucometer readings. While Dungan et al proved that glucose dehydrogenase based devices have the advantage of not being disturbed by low oxygen tension and low pH,[5] Eastham et al showed that pyrroloquinolinequinone (PQQ)-glucose dehydrogenase-based technologies give inaccurate reading in the presence of interfering substances due to cross reactivity with other substances.[6]

Initially, clinicians underestimated the magnitude of the problem, but then studies showed that over a 12-month period, substances such as high serum uric acid, bilirubin, acetaminophen, triglycerides, etc were identified in 1.2% of patients admitted to a community hospital. Substances remained at interfering concentrations until the time of discharge in 30% of the patients. Thirty-six percent of those patients had an active order for an insulin product during the interference time interval.[6]

Unfortunately, there are no strict criteria to monitor the accuracy of point-of-care devices and many international organizations have resorted to vague guidelines for clinical use. According to the ISO 15197:2013, 95% of results provided by blood glucose meters should be within± 15mg/dl (for glucose concentrations <100mg/dl) and within 15% (for glucose concentrations >100mg/dl), whereas CLIA 88 requires external proficiency testing results to be within 10% of target values or <0.3 mmol/liter (6 mg/dl), whichever is larger in the results.[7] Other studies have suggested that error tolerance limit for bedside glucose testing in critical patients should be within 5mg/dl.[8] In a large multicenter European study, Tack et al compared five commonly used blood glucose monitoring devices and proved that only two of the five fulfilled the ISO 15197 requirement.[9]

This study assesses the effects of different hematocrits on point-of-care blood glucose measurements. Ascorbic acid was also chosen among many other interfering factors, as it is a common supplement taken by in-patients. Gan et al showed that 60% of hospitalized patients in a Canadian teaching hospital were found to have a subnormal Vitamin C concentration,[10] whereas 30.8% of parturients were deficient in ascorbic acid, as seen in a Brazilian study.[11] Vitamin C is rapidly gaining popularity for its antioxidant properties and is now being used in trauma patients and as part of total parenteral nutrition.[12-14] Therefore, the aim of this study was to assess the analytical performance of four commonly used glucose monitoring devices, in the presence of different hematocrits and varying levels of ascorbic acid and compare them to the reference clinical chemistry analyzer, which is considered the gold standard of glucose testing

METHODOLOGY

The study was conducted at Dr. Ziauddin Hospital, Karachi from May 2014 to September 2014.

Four glucometers used comprised of J&J OneTouch Ultra® (Life Scan Inc., Milpitas, CA) and the On Call Plus® (Acon Laboratories Inc., San Diego, CA), both of which use a glucose-oxidase based amperometric system. The Nova Stat Strip®, (Nova Biomedical Corporation, Waltham, MA) also functions with a glucose-oxidase based amperometric system, but has been modified for hematocrit correction. Accu chek Active® (Roche Diagnostics, Mannheim, Germany) differs in its method as it uses photometric determination of glucose by means of glucose-dye-oxidoreductase (PQQ-dependent glucose dehydrogenase mediator reaction). Comparison was made with reference to

glucose estimated by hexokinase method on plasma through Roche reagents on Automated Chemistry Analyzer Hitachi 902®.

For the interference studies, 4 tubes (20 ml) of freshly drawn, heparinized venous blood drawn from a single healthy donor were placed on a blood rotor mixer at room temperature for 24 h to promote glycolysis. The samples were then centrifuged and a micropipette was used to proportion plasma and erythrocytes and generate hematocrits of the target ranges: Low (22%), Intermediate (45%), and High (62%). Prior to testing, the blood samples were mixed and aerated for 10 minutes to ensure adequate oxygenation and equilibration.

Samples were then spiked with concentrated solutions of glucose to bring the glucose levels in the target ranges: Low (20-60mg/dl), Intermediate (200-275 mg/dl) and High (325-400 mg/dl). The addition of 7.5 ul of concentrated glucose solution to a 1 ml whole blood sample increases the glucose concentration by 150mg/dl. This process generated nine samples, which were tested in duplicate with the glucometers and then the automated chemistry analyzer.

In the next phase of testing, ascorbic acid was added to see its effect on glucose readings. The addition of 5 ul of ascorbic acid to a 1 ml whole blood sample increases the ascorbic acid concentration by 5mg/dl and the addition of 10ul to a 1ml blood sample increases the ascorbic acid concentration by 10mg/dl. This process also generated nine samples which were tested in duplicate with the glucometers and then the automated chemistry analyzer.

Results obtained were expressed as mean of two values and analyzed using independent sample t-test, with the null hypothesis that the glucometer readings were not different from the reference method. $p<0.05$ was considered as significant. All statistical analysis was performed with the SPSS version 19.

RESULTS

Results of our study in Table 1 and Table 2 show that there were significant differences in the accuracy of the glucometers. While only 50% of On Call® results were similar to the reference method, the Stat Strip® had 93% of its results similar to the laboratory analyzer. Although both glucometers are based on the glucose oxidase method, the StatStrip® has special technology which reduces interferences by other agents, which could be the possible reason for the difference. According to our results, the Accuchek® and One Touch® had a similar performance with results being similar to the Hitachi 902® in 56% and 68% of the respective cases. The Accuchek® uses the PQQ-dependent glucose dehydrogenase mediator reaction which is known for being affected by interfering substances, but in our study, it showed a good performance with nine out of sixteen (56 %) results being statistically acceptable. As the testing procedures were standardized for this study, differences due to operator techniques, sampling issues and varying lot numbers can be ruled out.

Table 1. Mean results of glucometers compared to Hitachi 902® when glucose (mg/dl) was tested with varying hematocrit.

	Accuchek® (p value)	On call® (p value)	One touch® (p value)	Stat Strip® (p value)	Hitachi 902®
High glucose, low hematocrit	368 (0.016)	462 (0.022)	397 (0.043)	370 (0.234)	334
High glucose, intermediate hematocrit	348 (0.023)	275 (0.163)	290 (0.172)	335 (0.667)	324
High glucose, high hematocrit	230 (0.022)	138 (0.007)	169 (0.004)	382 (0.050)	304
Intermediate glucose, low hematocrit	242 (0.128)	285 (0.064)	261 (0.012)	225 (0.234)	216
Intermediate glucose, intermediate hematocrit	225 (0.128)	178 (0.054)	182 (0.021)	225 (0.033)	208
Intermediate glucose, high hematocrit	191 (0.333)	116 (0.046)	121 (0.048)	236 (0.121)	200
Low glucose, low hematocrit	Low	23 (0.044)	11 (0.667)	11 (0.667)	10
Low glucose, intermediate hematocrit	Low	21 (0.099)	11 (0.667)	Low	10
Low glucose, high hematocrit	Low	10 (0.667)	11 (0.667)	Low	10

Table 2. Mean results of glucometers compared to Hitachi 902® when glucose (mg/dl) was tested with varying levels of ascorbic acid.

	Accuchek ® (p value)	On call ® (p value)	One touch® (p value)	Stat Strip® (p value)	Hitachi 902 ®
High glucose, no ascorbic acid	364 (0.023)	334 (0.667)	358 (0.094)	357 (0.381)	340
High glucose, low ascorbic acid	364 (0.182)	330 (0.212)	358 (0.065)	343 (0.638)	332
High glucose, high ascorbic acid	372 (0.091)	333 (0.667)	367 (0.125)	345 (0.300)	336
Intermediate glucose, no ascorbic acid	244 (0.788)	220 (0.203)	229 (0.044)	235 (0.667)	241
Intermediate glucose, low ascorbic acid	252 (0.128)	225 (0.170)	242 (0.497)	237 (0.821)	235
Intermediate glucose, high ascorbic acid	259 (0.107)	230 (0.407)	248 (0.113)	235 (0.821)	233
Low glucose, no ascorbic acid	37 (0.333)	30 (0.121)	28 (0.084)	34 (0.879)	34
Low glucose, low ascorbic acid	45 (0.058)	40 (0.212)	41 (0.099)	35 (0.667)	35
Low glucose, high ascorbic acid	51 (0.031)	50 (0.033)	53 (0.055)	34 □0.667	33

Table 3. Performance of glucometers according to ISO 15197:2013 guidelines.

Glucometer	Reference method	ISO guidelines for values <100mg/dl	ISO guidelines for values > 100mg/dl
		Within +/- 15 mg/dl	Within +/- 15%
Nova StatStrip®	Hexokinase	100%	100%
Accucheck Active®	Hexokinase	96%	100%
One Touch®	Hexokinase	96%	83%
On Call®	Hexokinase	96%	90%

Both ascorbic acid and hematocrit had a negative effect on the glucose results due to interference with electron generation at the electrochemical strips. Hematocrit was seen to have a more pronounced interference when compared to ascorbic acid. This could be attributed to the oxygen diffusing from the red cells, which interfere with the strips as well as the increased viscosity which reduces the current generated. Accuchek® showed inaccuracy at high glucose levels when tested with varying hematocrits (p value of 0.016, 0.023 and 0.022 at low, intermediate and high hematocrits respectively). Accuchek ® and StatStrip® were not able to record results at lower glucose levels in the same study.

Table 3 shows that ISO 15197:2013 requirements were fulfilled by Nova Stat Strip® and Accucheck Active® while the One Touch Ultra® and On Call Plus® did not reach the acceptable limits at high glucose levels.

DISCUSSION

The results of our study show that commonly used glucometers give inaccurate results in the presence of varying hematocrits and ascorbic acid, which can ultimately cause mismanagement.

Regulatory authorities, both internationally and locally, should recognize the impact of these interfering substances on glucose measurements and advocate the use of specially designed glucometers in hospitalized patients. Another study assessed the performance of Nova Stat Strip® on over 600 neonates in the NICU and it was seen that results of Nova Stat Strip® had better agreement with venous blood testing and critically low blood glucose levels were reported more accurately compared to other glucometers.[15]

Clinicians are often unaware of the unreliability of glucose readings from hand held devices and important management decisions are made based on the glucometer results. Hospital administration making decisions regarding purchase of glucometers should opt for devices which minimize inaccuracies due to interefering agents. Nursing staff should be trained and venous samples should also be analyzed in the laboratory at regular intervals for validation of results.

As users are becoming more aware of the ambiguity of glucose measurements from these hand held devices, newer methodologies are being introduced. Point of care analyzers for blood gases are now offering blood glucose measurements as well. These analyzers have the advantage of measuring arterial blood, which is more accurate than capillary blood taken in handheld devices. Devices measuring venous blood through central lines are also being used worldwide although research shows that

results may not be accurate.[16]

Patient education is low to begin with, as shown by Shaikh et al in a recent study conducted on type II diabetics in Karachi[17] and so an active effort should be made to provide awareness to patients on various topics, including the choice of glucometers along with safety precautions as a case of Hepatitis C transmission through glucometer lancet has been reported in literature.[18] Another novel way to measure glucose in critically ill patients is through Continuous Glucose Monitoring which works through a tiny sensor placed subcutaneously for up to a week. These devices measure the glucose level in tissue fluid and transmit the reading to a wireless monitor at 1 minute to 5 minute intervals. The concept of measuring glucose in tissue fluid was also tried by the GlucoWatch Biographer®[19] which is a watch like device based on transdermal extraction of interstitial fluid by reverse iontophoresis. Another significant advancement in the field of glucose testing is the introduction of glucose monitoring at the molecular level using molecular diagnostic biochips based on nanotechnology.[20] These products prove that glucometers are going to be changing rapidly in the near future.

Nevertheless, clinicians and users should be educated about the limitations of each device. Apart from sample interferences, there are a variety of other factors, which may affect the accuracy of the results, including operator technique, environmental exposure and volume of sample. In a review of technical challenges faced by blood glucose monitors, Tonyushkina et al stated that miscoding of the device produced errors which ultimately lead to altered clinical action. Such inaccuracies were not found on devices with automatic calibration and coding features.[21]

The easy operability, quick turnaround time and reliability of results have made glucose meters an invaluable tool for diabetics. As the need for these devices is growing, there are hundreds of new models available in the market. While home users choose glucometers based on cost and easy usage, hospitals should focus on devices, which reduce the effect of interfering substances. It is only by understanding the functioning of these instruments that we can utilize them to their maximum capacities and provide optimal patient care in diabetes management.

CONCLUSION

The results of our study show that three of the four glucometers evaluated had significant inaccuracies when tested in the presence of interfering substances. Varying hematocrits and presence of ascorbic acid are factors, which may affect a majority of hospitalized patients. Therefore, we conclude that while these glucometers are popular for home use due to their easy handling, devices designed to overcome interferences should be preferred for hospitalized patients.

ACKNOWLEDGEMENT

The authors of this study thank Dr. Nousheen Zehra, Assistant Professor of Community Health Sciences department of Dr. Ziauddin Hospital for her valuable support with the statistical analysis.

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Conflict of Interest: None declared
Rec. Date: May 8, 2016 Revision Rec. Date: Apr 23, 2017 Accept Date: May 2, 2017

REFERENCES

1. Boyd R, Leigh B, Stuart P. Capillary versus venous bedside blood glucose estimations. Emerg Med J 2005;22:177-9.
2. Baig A, Siddiqui I, Jabbar A, Azam SI, Sabir S, Alam S, Ghani F. Comparision between bed side testing of blood glucose by glucometer vs centralized testing in a tertiary care hospital. J Ayub Med Coll Abbottabad 2007;19:25-9.
3. Fazel A, Koutoubi Z, Sorg TB, Mehrotra B. Influence of Sample temperature on reflectance photometry and electrochemical glucometer measurements. Diabetes Care 1996;19:771-4.
4. Tang Z, Du X, Louie RF, Kost GJ. Effects of Drugs on Glucose Measurements With Handheld Glucose Meters and a Portable Glucose Analyzer Am J Clin Pathol 2000; 113:75-80.
5. Dungan K, Chapman J, Braithwaite SS, Buse J. Glucose measurement: Confounding issues in setting targets for

inpatient management. Diabetes Care 2007;30:403-9.
6. Eastham JH, Mason D, Barnes DL, Kollins J. Prevalence of interfering substances with point-of-care glucose testing in a community hospital. Am J Health Syst Pharm 2009; 66:167-70.
7. Krouwer JS, Cembrowski GS. A Review of Standards and Statistics Used to Describe Blood Glucose Monitor Performance J Diabetes Sci Technol 2010;4:75-83.
8. Kost GJ, Tran NK, Abad VJ, Louie RF. Evaluation of point of care glucose testing accuracy using locally smoothed median absolute difference curves. Clin Chim Acta 2008;389:31-9.
9. Tack C, Pohlmeier H, Behnke T, Schmid V, Grenningloh M, Forst T, et al. Accuracy evaluation of five blood glucose monitoring systems obtained from the pharmacy: A European multicenter study with 453 subjects. Diabetes Technol Thera 2012;14:330-7.
10. Gan R, Eintracht S, Hoffer LJ. Vitamin C deficiency in a university teaching hospital. J Am Coll Nutr 2008;27:428-33.
11. Madruga A, Rondó PH, Mastroeni SS, Oliveira JM. Plasma concentrations of ascorbic acid in parturients from a hospital in Southeast Brazil. Clin Nutr 2008;27:228-32.
12. Reddell L, Cotton BA. Antioxidants and micronutrient supplementation in trauma patients. Curr Opin Clin Nutr Metab Care 2012;15:181-7.
13. Fukushima R, Yamazaki E. Vitamin C requirement in surgical patients. Curr Opin Clin Nutr Metab Care 2010;13:669-76.
14. Berger MM. Vitamin C requirements in parenteral nutrition. Gastroenterology 2009; 137:S70-8.
15. Raizman JE, Shea J, Daly CH, Karbasy K, Ariadne P, Chen Y, et al Clinical impact of improved point-of-care glucose monitoring in neonatal intensive care using Nova StatStrip: Evidence for improved accuracy, better sensitivity, and reduced test utilization. Clin Biochem 2016 ;49:879-84.
16. Pereira AJ, Corrêa TD, de Almeida FP. Inaccuracy of Venous Point-of-Care Glucose Measurements in Critically Ill Patients: A Cross-Sectional Study. PLoS One. 2015 Jun 12;10(6).
17. Sheikh MA, Hakeem R, Asar F, Shaikh AH. Diabetes education and care in a developing country: observations from Karachi, Pakistan. Prim Care Diabetes 2015;9:48-53.
18. Inayat F, Rai AB. Acute hepatitis C virus infection related to capillary blood glucose meter. Saudi Med J 2016;37:93-5.
19. Yoo EH, Lee SY. Glucose biosensors: an overview of use in clinical practice. Sensors (Basel) 2010;10:4558-76.
20. Rauf S, Hayat Nawaz MA, Badea M, Marty JL, Hayat A. Nano-Engineered Biomimetic Optical Sensors for Glucose Monitoring in Diabetes. Sensors (Basel) 2016 Nov 17;16(11).
21. Tonyushkina K, Nichols JH: Glucose meters: A review of technical challenges to obtaining accurate results. J Diabetes Sci Technol 2009;3:971-80.