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ORIGINAL ARTICLE

Analytic Evaluation of a New Glucose Meter System in 15 Different Critical Care Settings

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Abstract

Background:

Maintaining appropriate glycemic control in critically ill patients reduces morbidity and mortality. The use of point-of-care (POC) glucose devices is necessary to obtain rapid results at the patient's bedside. However, the devices should be thoroughly tested in the intended population before implementation. The use of POC glucose meters in critically ill patients has been questioned both in the literature and by regulatory agencies. The aim of this study was to determine if the ACCU-CHEK® Inform II system (Roche Diagnostics) POC glucose meter demonstrated the desired accuracy and precision, as defined by Clinical and Laboratory Standards Institute guideline POCT12-A3, in a large number of critically ill patients from multiple intensive care settings at two academic medical centers.

Methods:

A total of 1200 whole blood meter results from 600 patients were compared with central laboratory plasma values. Whole blood aliquots from venous samples were used to obtain duplicate meter results with the remaining sample being processed to obtain plasma for central laboratory testing within 5 min of meter testing.

Results:

A total of 1185 (98.8%) of the new meter's glucose values were within ±12.5% (±12 mg/dl for values ≥100 mg/dl) of the comparative laboratory glucose values, and 1198 (99.8%) were within ±20% (±20 mg/dl for values <100 mg/dl).

Conclusions:

Considering the large number of patients from numerous critical care units examined, the new glucose meter system appears to have sufficient analytic accuracy for use in critically ill patients.

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Abbreviations: (ED) emergency department, (FDA) Food and Drug Administration, (ICU) intensive care unit, (NICE-SUGAR) Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm, (POC) point of care, (TGC) tight glycemic control, (UVA) University of Virginia, (WU) Washington University

Keywords: critical care, glucose meters, point-of-care devices

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Introduction

Stress-induced hyperglycemia is common in critically ill hospitalized patients whether or not they have preexisting diabetes.[1] Adverse outcomes due to hyperglycemia have been observed in numerous critically ill patient populations, including those from cardiac, neurological, surgical, burn, and trauma care units.[2–5] Maintaining near-normal glucose concentrations (80–110 mg/dl) by tight glycemic control (TGC) emerged as a potential approach to reduce morbidity in surgical,[6,7] medical,[8] and pediatric[9] intensive care units (ICUs) in the seminal studies from Van den Berghe and coauthors.[6,8] Because of these and other studies, TGC became standard of care in critical care medicine in the mid-2000s.[10–13]

In 2012, the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm (NICE-SUGAR) studies, a multinational trial involving 6104 patients, showed that patients undergoing TGC had increased mortality and more frequent hypoglycemic events.[14,15] In addition, a meta-analysis of 27 studies involving critically ill adults and TGC showed that there was no benefit in mortality or morbidity from TGC and a 3–5-fold increase in hypoglycemia events.[16] As a result of these findings, professional organizations now recommend less stringent glycemic control in critically ill patients, generally targeting 140–180 mg/dl.[17–20]

The different outcomes in the earlier versus the later studies may be attributed to a variety of factors, including differences in study design, settings, clinician compliance with protocols and the target glucose values for the treatment and control groups. Another possibility for the discrepant outcomes is how glucose was measured.[21] For instance, in the original Van den Berghe study,[6] a precise blood gas analyzer using a glucose electrode was used for glucose measurement in arterial blood samples; whereas glucose meters were often used in the NICE-SUGAR study and in 8 of the 10 studies in the meta-analysis for which the method of glucose measurement was provided in the methods sections.[21] Numerous factors that are particularly variable and common in critically ill patients can also influence the accuracy of glucose meters including pH, blood oxygen, and hematocrit. Changes in microcirculation and vasopressor therapy can also affect the clinical relevance of glucose meter values when certain sample types (especially capillary fingertip or skin-puncture samples) are used.[22]

Taken together, the controversies and analytic questions about the use of meters in TGC protocols for critically ill patients led the Food and Drug Administration (FDA) to call a public meeting regarding the use of glucose meters in critical care settings in March 2010.[23] Shortly afterward, the FDA required manufacturers of newly cleared glucose meters to add the limitation "not for use in critically ill patients" to their product labeling. Interestingly, this revised limitation was not retroactively required for meters cleared prior to 2010. In November 2012, the FDA modified the this limitation statement for newly cleared meters to "not evaluated in critically ill patients." Based on this limitation, we evaluated the accuracy of the new ACCU-CHEK® Inform II system (Roche Diagnostics) glucose meter using venous samples from a large number of patients in a variety of critical care settings at Washington University (WU) and at the University of Virginia (UVA). Use of a large number of samples from 15 different critical care units should include the vast majority of drugs and potential interfering substances that might be encountered in these complicated patients.

Methods

Both institutions followed Clinical and Laboratory Standards Institute guideline POCT12-A3.[24] There was no input from the manufacturer in study design or data analysis; there was strict adherence to the POCT12-A3 standard, and all results are reported. Venous samples were collected in lithium heparin tubes for routine clinical chemistry testing from adult patients in seven different ICUs at WU, and six critical care units at the UVA were used in the study. In addition, 13 samples from patients with diabetic ketoacidosis were collected in the emergency department (ED) at WU, and 3 from the ED at the UVA were included to obtain samples with high glucose values. The meter is an electrochemical method that uses a mutant variant of quinoprotein glucose dehydrogenase from *Acinetobacter calcoaceticus*.

Upon receipt in the laboratory, a small aliquot (~200 µl) of whole blood was removed for meter testing. A trained medical technologist immediately used the whole-blood aliquot to perform duplicate meter testing on the new glucose meter system. The original tube was processed within 5 min of the meter testing. We compared these results with standard laboratory measurements of blood glucose using either the Abbott Architect c16000 (UVA) or the Roche Modular P system (WU). Both laboratory methods use hexokinase. In addition to glucose values, hematocrit (from a complete blood count drawn within 1 h of the chemistry sample) and sodium were available for each patient sample. If a concurrent hematocrit from a complete blood count was not available, hematocrit was measured on a whole blood aliquot at WU. At the UVA, all samples had measured hematocrits from complete blood counts.

Within-run imprecision studies were performed using a single vial of strips (n = 20) by one technologist within a 1 h period. Between-run imprecision was determined using two levels of quality control material during the course of the study (20–25 days). Mean patient results from the laboratory methods were compared with the individual meter results (two per subject) and analyzed by Deming regression analysis and Bland–Altman difference plots. Acceptable accuracy criteria were from POCT12-A3, which states that 95% of meter results should be within ±12.5% for glucose values ≥100 mg/dl or ±12 mg/dl when glucose is <100 mg/dl and that 98% of values should be within 20% (±20 mg/dl when <100 mg/dl).

Results

Within-run imprecision (n = 20) of the new glucose meter system was 1.8% at 42.9 mg/dl and 1.9% at 296.3 mg/dl, and between-run imprecision (n = 38) was 2.5% at 44.3 mg/dl and 3.7% at 305.8 mg/dl at WU. At the UVA, within-run imprecision (n = 20) was 2.3% at 43.0 mg/dl and 1.5% at 296.9 mg/dl, and between-run imprecision (n = 75) was 2.6% at 44.9 mg/dl and 1.7% at 306.3 mg/dl. The mean imprecision of the 600 duplicate meter values was 1.8% ± 1.6%, which compared favorably to a mean imprecision 1.0% ± 0.9% for the 295 central laboratory Roche Modular duplicate values and 1.0% ± 0.7% for the Abbott Architect c16200 305 duplicates.

A total of 600 patients were examined from 15 different critical care settings including two EDs (**Table 1**). Laboratory glucose values ranged from 19 to 542 mg/dl, and the mean blood glucose concentrations in this entire group of critically ill patients was 137.1 mg/dl by the laboratory methods and 137.8 mg/dl with the glucose meter system [combined bias 0.71 mg/dl (0.52%),WU bias -0.87 mg/dl (-0.62%), and UVA bias 2.24 mg/dl (1.67%)]. Deming regression analysis between the laboratory and glucose meter values is shown in **Figure 1**.

Table 1.
Critical Care Settings and Numbers of Samples Tested

ICUs	WU	UVA
Medical/surgical	Not applicable at this institution	32
Medical	33	125
Surgical/trauma/burn	53	39
Cardiac care	32	51
Thoracic/cardiac post-op	30	35
Neurological	54	20
ED	13	3
Post-op critical care	53	Not done
Abdominal transplant unit	27	Not applicable at this institution

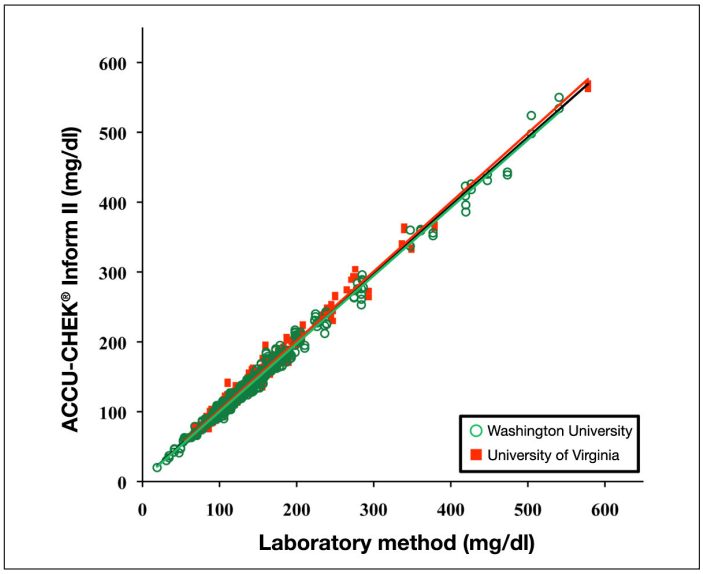

Figure 1. Scatter plot comparing the laboratory methods to the new meter. The mean blood glucose concentraon was 137.1 mg/dl determined by the labortory methods and 137.8 mg/dl determined by the new glucose meter. Deming regression data were as follows: WU (green circles), $y = 0.98x + 2.3$, $r^2 = 0.9949$ (green line); University of Virginia (red squares), $y = 1.0x + 2.2$, $r^2 = 0.9903$ (red line); and combined, $y = 0.99x + 2.7$, $r^2 = 0.9928$ (black line).

Of 1200 glucose meter results, 1185 (98.8%) were within ±12.5% (±12 mg/dl) of the mean laboratory results and 1198 (99.8%) values were within ±20% (20 mg/dl; **Figure 2**), thus meeting POCT12-A3 criteria that 95% be within ±12.5% and 98% be within ±20%. The results also meet a 10% criterion (95% of results must be within ±10% [±10 mg/dl below 100 mg/dl]), as 95.1% were within ±10% (±10 mg/dl).

There was a weak, but not clinically significant, correlation of hematocrit and sodium values on the difference between meter results and the comparative methods (**Figures 3** and **4**).

Discussion

Implementation of glycemic control in critically ill patients reduces morbidity and mortality[6–8] and has become the standard of care for critically ill patients in the intensive care and critical care settings in the United States, albeit no longer targeting normoglycemia.[20] If point-of-care (POC) glucose devices are to be used in critically ill patients to determine blood glucose levels in order to make intravenous insulin dosing decisions, it is imperative that they be accurate and have no interferences from the

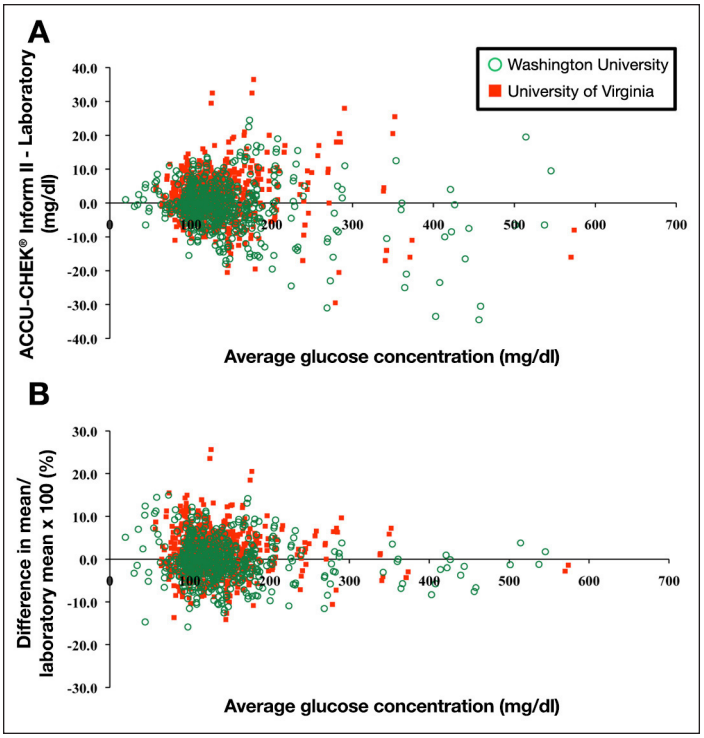

Figure 2. (A) Bland–Altman plot of the absolute difference (mg/dl) of the individual meter values and mean laboratory results. **(B)** Bland–Altman plot of the percentage difference between meter and laboratory results.

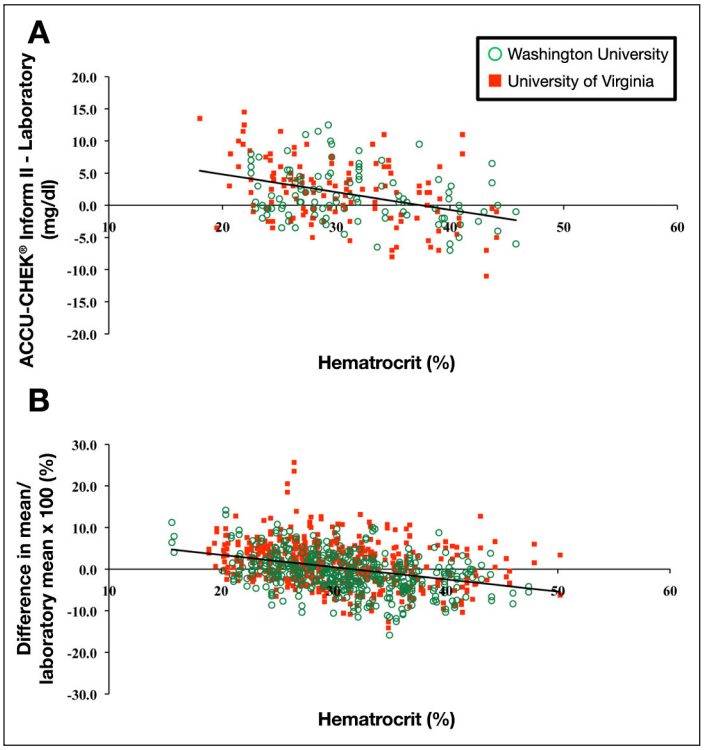

Figure 3. (A) Effect of hematocrit on the difference between the meter and the laboratory glucose results (when glucose <100 mg/dl; $r^2 = 0.15$). **(B)** Effect of hematocrit on the percentage difference between the meter and the laboratory results (when glucose ≥100 mg/dl; $r^2 = 0.11$).

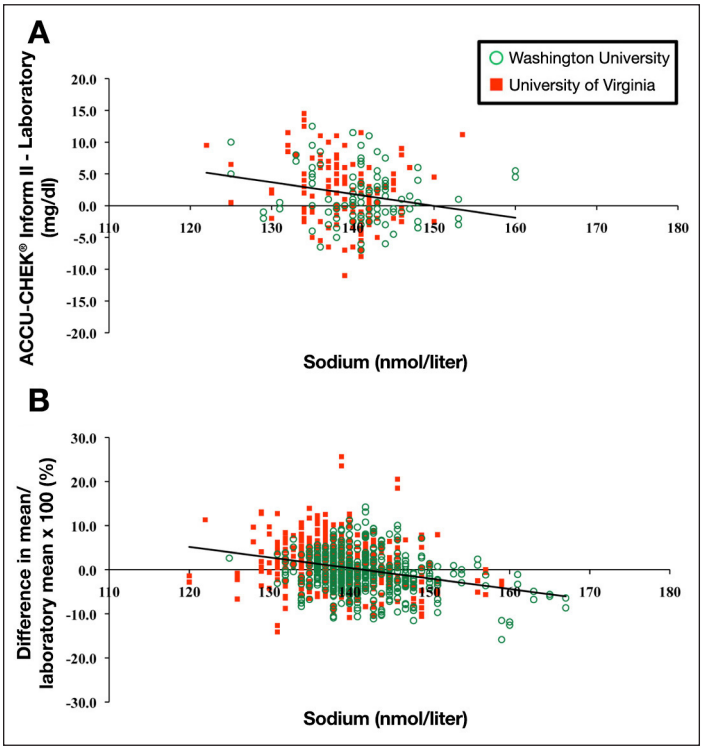

Figure 4. (A) Effect of sodium on the difference between the meter and the laboratory glucose results (when glucose <100 mg/dl; $r^2 = 0.04$). **(B)** Effect of sodium on the percentage difference between the meter and the laboratory results (when glucose ≥100 mg/dl; $r^2 = 0.08$).

hundreds of potential drugs used by these patients. A careful evaluation of the device in the critical care setting should be done before implementing any new glucose meter or other glucose monitoring devices.

This study suggests that the new meter from Roche Diagnostics has acceptable analytic accuracy as defined by CLSI POCT12-A3 when compared with two different laboratory methods for the analysis of glucose in critically ill patients. This was true across a broad range of glucose concentrations, hematocrits, and clinical care settings. The analytic performance of this meter appears to exceed any of those described in a review of 43 studies of glucose meter accuracy.[25] Moreover, the performance of the Roche meter appears to be similar or superior to that of the blood gas analyzer used in the original study of Van den Berghe and coauthors.[6] That device had day-to-day imprecision (coefficients of variation) of 2.79% and 3.49% at mean glucose concentrations of 92 and 220 mg/dl (from Bouilon via personal email to David E. Bruns, March 1, 2002). Comparison of the meter and the blood gas analyzer must be tempered, however, by the fact that Van den Berghe and coauthors[6] used the analyzer to measure glucose in central blood samples, whereas meters are frequently used to measure glucose in the less-reliable finger-stick samples. The new Roche meter does not appear to perform as well as a newer blood gas analyzer (Radiometer), for which 100% of results for samples from ICU patients were within 10% of a central-laboratory comparison (reference) method (Roche Modular).[26]

It is well-known that low and high hematocrits can affect the accuracy of glucose meter results. As anemia is common in critically ill patients, this is an important issue to evaluate in meters that may be used in this population. The new Roche glucose meter claims to correct for differences in hematocrit by measuring sample impedance. While there was a weak correlation between hematocrit and the difference between the meter and laboratory values, only 5 of the 15 meter values that exceeded the accuracy requirements of POCT12-A3 had hematocrit values < 25.

We also evaluated whether or not hyponatremia and hypernatremia, which are common electrolyte disturbances in critically ill patients, affected blood glucose determination using this POC device. Our results indicate that there was a weak correlation of sodium concentration on blood glucose concentration between the POC device and the reference method, but none of the 15 samples that exceeded POCT12-A3 accuracy requirements had a sodium concentration less than 125 mmol/liter.

We did not assess the effect of hydration or pressor status on differences in glucose results from different sample types, as the exact same venous samples were used for meter and central laboratory testing. The suitability of using different sample types for meter testing should be determined based on the clinical status of the patient, which was beyond the scope of this analytic accuracy study.

Conclusions

We conclude that the new glucose meter from Roche Diagnostics has acceptable analytic accuracy for use in critically ill patients and is not clinically affected by extreme sodium and hematocrit values. Inappropriate and improperly collected samples are likely to be much larger sources of error than the meter itself, especially when finger-stick samples are used. [27]

Disclosures:

Dr. Scott and Dr. Bruns have consulted for Roche Diabetes Care. Roche Diagnostics provided meters, test strips, and quality control material. There was no financial support of the study other than reagents.

References:

1. Mizock BA. Alterations in fuel metabolism in critical illness: hyperglycaemia. Best Pract Res Clin Endocrinol Metab. 2001;15(4):533–51.
2. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet. 2000;355(9206):773–8.
3. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke. 2001;32(10):2426–32.
4. Ljungqvist O, Nygren J, Thorell A. Insulin resistance and elective surgery. Surgery. 2000;128(5):757–60.
5. Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, Tress BM, Davis SM. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. Ann Neurol. 2002;52(1):20–8.
6. V an den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359–67.
7. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc. 2004;79(8):992–1000.
8. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354(5):449–61.
9. Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I, Mesotten D, Casaer MP, Meyfroidt G, Ingels C, Muller J, Van Cromphaut S, Schetz M, Van den Berghe G. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet. 2009;373(9663):547–56.
10. American Dibetes Association. Standards of medical care in diabetes. Diabetes Care. 2005;28 Suppl 1:S4–S36.
11. Mackenzie I, Ingle S, Zaidi S, Buczaski S. Tight glycaemic control: a survey of intensive care practice in large English hospitals. Intensive Care Med. 2005;31(8):1136.
12. McMullin J, Brozek J, Jaeschke R, Hamielec C, Dhingra V, Rocker G, Freitag A, Gibson J, Cook D. Glycemic control in the ICU: a multicenter survey. Intensive Care Med. 2004;30(5):798–803.
13. Hirshberg E, Lacroix J, Sward K, Willson D, Morris AH. Blood glucose control in critically ill adults and children: a survey on stated practice. Chest. 2008;133(6):1328–35.
14. Finfer S, Delaney A. Tight glycemic control in critically ill adults. JAMA. 2008;300(8):963–5.
15. NICE-SUGAR Study Investigators, Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, McArthur C, Mitchell I, Foster D, Dhingra V, Henderson WR, Ronco JJ, Bellomo R, Cook D, McDonald E, Dodek P, Hébert PC, Heyland DK, Robinson BG. Hypoglycemia and risk of death in critically ill patients. N Engl J Med. 2012;367(12):1108–18.
16. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA. 2008;300(8):933–44.
17. American Dibetes Association. Standards of medical care in diabetes--2012. Diabetes Care. 2012;35 Suppl 1:S11–63.
18. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, Inzucchi SE, Ismail-Beigi F, Kirkman MS, Umpierrez GE; American Association of Clinical Endocrinologists; American Diabetes Association. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care. 2009;32(6):1119–31.
19. Lazar HL, McDonnell M, Chipkin SR, Furnary AP, Engelman RM, Sadhu AR, Bridges CR, Haan CK, Svedjeholm R, Taegtmeyer H, Shemin RJ; Society of Thoracic Surgeons Blood Glucose Guideline Task Force. The Society of Thoracic Surgeons practice guideline series: Blood glucose management during adult cardiac surgery. Ann Thorac Surg. 2009;87(2):663–9.
20. Jacobi J, Bircher N, Krinsley J, Agus M, Braithwaite SS, Deutschman C, Freire AX, Geehan D, Kohl B, Nasraway SA, Rigby M, Sands K, Schallom L, Taylor B, Umpierrez G, Mazuski J, Schunemann H. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. Crit Care Med. 2012;40(12):3251–76.
21. Scott MG, Bruns DE, Boyd JC, Sacks DB. Tight glucose control in the intensive care unit: are glucose meters up to the task? Clin Chem. 2009;55(1):18–20.
22. Karon BS, Gandhi GY, Nuttall GA, Bryant SC, Schaff HV, McMahon MM, Santrach PJ. Accuracy of Roche ACCU-CHEK inform whole blood capillary, arterial, and venous glucose values in patients receiving intensive intravenous insulin therapy after cardiac surgery. Am J Clin Pathol. 2007;127(6):919–26.
23. U.S. Food and Drug Administration. FDA/CDRH Public Meeting: Blood Glucose Meters - March 16-17, 2010. *http://www.fda.gov/medicaldevices/newsevents/workshopsconferences/ucm187406.htm*.
24. Clinical and Laboratory Standards Institute. Point-of-Care Blood Glucose Testing in Acute and Chronic Care Facilities; Approved Guideline—Third Edition. CLSI guideline POCT12-A3. Wayne: Clinical Laboratory Standards; 2013.
25. Rebel A, Rice MA, Fahy BG. Accuracy of point-of-care glucose measurements. J Diabetes Sci Technol. 2012;6(2):396–411.
26. Poesen K, De Prins M, Van den Berghe G, Van Eldere J, Vanstapel F. Performance of cassette-based blood gas analyzers to monitor blood glucose and lactate levels in a surgical intensive care setting. Clin Chem Lab Med. 2013. Epub ahead of print.
27. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, Lernmark A, Metzger BE, Nathan DM. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem. 2011;57(6):e1–e47.