Results of a multicenter prospective pivotal trial of the first inline continuous glucose monitor in critically ill patients

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BACKGROUND: We have previously demonstrated that tight glycemic control (80–120 mg/dL) improves outcome in critically injured patients. However, many centers have gotten away from aggressive glucose control due to the workload and risk of hypoglycemia. The objective of this pivotal trial is to evaluate the first in human continuous inline glucose monitor (OptiScanner) in critically ill patients.

METHODS: A multicenter pivotal trial was conducted over a 1-year period (2014–2015) at four major academic centers in 200 critically ill patients. Three thousand seven hundred thirty-five glucose measurements were obtained and measured. A paired blood sample was then collected to coincide with the OptiScan measurement. The OptiScanner withdraws 0.13 mL of blood every 15 minutes from a central venous line, centrifuges the sample, and uses midinfrared spectroscopy to directly measure glucose levels in blood plasma. We plotted a Clarke Error Grid, calculated mean absolute relative difference (MARD) to analyze trend accuracy, and population coefficient of variation (PCV) to measure deviations. OptiScanner and Yellow Springs Instrument values were "blinded" from clinicians. Treatment was guided by the standard point of care meters.

RESULTS: 95.4% of the data points were in zone A of the Clarke Error Grid and 4.5% in zone B. The MARD was 7.6%, the PCV 9.6%. The majority of data points achieved the benchmark for accuracy. The MARD was below 10%, which is the first inline continuous glucose monitor to achieve this result in a clinical trial. The PCV was less than 10%. We confirmed that the OptiScanner outperformed every 1- to 3-hour glucose measurements using point of care meters which prevents glucose excursions and variability and achieves a higher amount of time the patient's glucose values remain in range.

CONCLUSION: This pivotal multicenter trial demonstrates that the first inline CGM monitor is safe and accurate for use in critically ill surgical and trauma patients. (*J Trauma Acute Care Surg.* 2017;82: 1049–1054. Copyright © 2017 American Association for the Surgery of Trauma. All rights reserved.)

LEVEL OF EVIDENCE: Diagnostic study, level I.

KEY WORDS: Glucose; hyperglycemia; glucose monitoring; ICU.

Glucose control is associated with improved outcome in trauma[1–3] and critically ill patients.[4,5] The positive effect of glucose control has been observed in trauma patients especially during the first week of hospitalization.[2] Perioperative glucose control has also been associated with improved outcome in postoperative[6–8] and transplant patients.[9,10] The ideal target for glucose is 80 to 120 mg/dL;[11] however, because of the untoward effects and dangers of hypoglycemia, targeted ranges have drifted upward.[8] The need to maintain glycemic control safely in the ideal target range is balanced by the risks of hypoglycemia. Glucose variability is also harmful;[12] therefore, excursions require prompt and effective treatment because they have a bearing on prognosis.

Current practices of glucose measurements rely on point of care meter testing, which involves the use of handheld glucometers. These are known to be fraught with inaccuracies and add considerable workload to the nursing staff.[13–19] Attempts at tight glycemic control are limited by the accuracy of available equipment and the number of feasible measurements. A near continuous glucose monitor would provide multiple measurements without intervention. The information would be available and visible to clinical staff such that it would guide therapy as the need arises, theoretically increasing the time in range of ideal glucose levels and thereby improving outcomes.

The goal of this study is to investigate the first human use of an inline near continuous glucose monitor for safety and accuracy in measuring glucose levels in the critically ill surgical and trauma patients. We recently reported our initial findings of the first 23 patients that were connected to the OptiScanner.[20] These initial patients were considered "roll ins" to train the study team make any necessary modifications to the protocol in addition to evaluating for potential safety concerns. During this "roll in" phase, there were no serious adverse events reported or any logistical or safety concerns identified, and thus the study continued and moved into a "general enrollment" phase. We now report on the entire study cohort (N = 200) in this FDA-regulated pivotal trial.

PATIENTS AND METHODS

A prospective interventional study was conducted at 4 major academic centers in which patients were admitted to the intensive care unit (ICU). Patients were eligible for inclusion if they were 18 years or older, admitted to the ICU with an expected minimum ICU stay of 18 hours after enrollment, and required blood glucose monitoring. Patients must also have had a nontunneled central venous catheter (CVC) where the OptiScanner could exclusively occupy the most proximal port without any infusion running more proximal and a paired site to draw blood whether it was an arterial line, another central venous line, or a peripheral line. Patients were excluded if they were pregnant or nursing, could not tolerate the amount of saline associated with being connected to the OptiScanner or the blood draws, had a hematocrit less than 15% or greater than 60%, or a medical condition whereby, if additional vascular access was required, they would not have a site free of disease. Further, patients were excluded if, in the investigator's opinion, they had a medical condition that would warrant exclusion, such as previous complications with vascular access, a heightened predisposition to complications with vascular access, or a reason that they cannot safely tolerate the study procedures. No exclusion was made based on disease type or severity. Patients were also excluded if they were in any other investigational drug or device study within the last 30 days up to and including time enrolled in the study. We obtained institutional review board approval before the conduct of this study and obtained informed consent from patients or their legally authorized representative before enrollment.

OptiScanner

The OptiScanner5000 Glucose Monitoring System (OptiScanner) from OptiScan Biomedical Corporation (Hayward, CA) is a bedside blood glucose monitoring system that provides plasma-based, automated monitoring of ICU patient's glucose levels. The OptiScanner can be wheeled into a patient's

room and connects to the patient's proximal port of a CVC via intravenous tubing. It draws the patient's blood, retains 0.13 mL and returns the rest of the sample with a saline flush (total saline per day is up to 360 mL). Sampling is done every 15 minutes and within 7 to 8 minutes after each draw, the corresponding glucose value is displayed on the monitor's screen. However, in this study, the glucose values remained blind to the study team, patient, and clinicians but the data were saved for safety and accuracy testing. For each sample drawn, the machine internally spins the blood to create plasma and examines it via mid-infrared spectroscopy to determine glucose levels. The software controls for known interferents with plasma processing and with glucose measurement at the spectral bands at which glucose absorbs light. Interferents in plasma include, certain medications, and extreme levels of triglycerides.

Study Procedures

Before connecting the OptiScanner to the patient, baseline data including medical history was gathered from the patient's medical chart. Enrollment was defined as the time of the OptiScanner's initial connection to the patient. Patients could remain connected up to 72 hours from initial enrollment, until transfer out of the unit, loss of the CVC connection site (e.g., mechanical failure of the central line, decision to discontinue the central line by the clinical care team, and so on) or by investigator decision to protect patient interests. Blood draws were automatic and occurred every 15 minutes while the patient was connected. A comparative paired sample was taken for analysis as close as possible during the time of the OptiScanner draw (within a 2-minute window) at an interval of at least 1 hour apart, with a maximum of 12 paired samples collected per day. Comparative samples were drawn from an existing arterial line, central line, or by peripheral venous stick. No capillary blood was used. The OptiScanner draw time period starts when the device initiates a blood draw via negative pressure through a thin capillary line that is connected to the proximal port of a CVC or multipurpose access catheter and ends when the device has acquired the sample and returned unused blood in the line to the patient with a saline flush. The paired blood samples were then spun down for plasma within 15 minutes by the study team and analyzed twice via Yellow Springs Instrument (YSI) 2300 STAT Plus Glucose and Lactate Analyzer ("YSI Analyzer"; YSI Life Science, Yellow Springs, OH), which is the criterion standard for measuring blood glucose levels on a remote basis. At the end of a patient's participation, the data were collected from the OptiScanner device and transferred electronically for analysis. Any potential device related adverse events were reported by the study team. Device-related adverse events were defined as an untoward event with any potential relation to the device that has impacted the patient, for example, air embolism, heparin-induced thrombocytopenia, allergic reactions, and blood hemolysis.

Statistical Analysis

Data points were included if there was a valid measure of glucose by the OptiScanner and by the reference standard (YSI). The data are presented on a Clarke Error Grid. Zone A represents glucose values that deviate by no more than 20% from the reference or are in the hypoglycemic range (<70 mg/dL) when the reference is also in the hypoglycemic range. Zone B values are outside zone A and are predicted to have no untoward effect toward the patient if considered for clinical care. Zone C values would result in overcorrection of acceptable blood glucose values which could lead to hypoglycemia or to hyperglycemia. Zone D represents a dangerous failure to treat zone. Zone E values would result in the opposite of the intended treatment. All of zones C, D, and E are potentially dangerous. In addition, the percentage of glucose values within 10%, 10% to 20%, 20% to 30%, and more than 30% from the reference are reported. A Bland-Altman plot will be derived to show the agreement between the device glucose measurements and the standard.

The primary endpoint is to achieve an overall mean absolute relative difference (MARD) of less than 10%.

$$\text{MARD} = 100 \times \mu \frac{(|\text{OS}-\text{YSI}|)}{\text{YSI}} \text{ where } \mu \text{ is the average.}$$

MARD is considered a measure of trend accuracy, and it has been reported to be a predictor of improved glucose control in the ICU by reducing hypoglycemia and hyperglycemia, reducing glucose variability, and by increasing the time in range.[14,15] 97.5% confidence interval (CI) were reported for the MARD.

The population coefficient of variation (PCV) is calculated.

$$\text{PCV} = \sigma \frac{(\text{OS}-\text{YSI})}{\mu(\text{YSI})} \text{ where } \sigma \text{ is the standard deviation and } \mu \text{ is the average.}$$

PCV is the coefficient of variation for the entire group of glucose samples and is reported as a measure of trend accuracy. All data analysis was carried out through Microsoft Office Excel 2013, or SAS 9.4 Cary North Carolina 2015. The study was

TABLE 1. Demographics and Characteristics of the Study Population

Demographics	Total
No. patients	200
Age, y	
Mean (SD)	61.6 (16.4)
Sex	
Male	137 (68.5%)
Female	63 (31.5%)
Race	
White	165 (82.5%)
Black	18 (9%)
Hispanic/Latin American	7 (3.5%)
Other	10 (5%)
Apache II score	
Mean (SD)	15.1 (6.3)
Minimum (first quartile)	3 (10)
Median (third quartile)	14 (19)
Maximum	35
Conditions	
Hypotension	132 (66%)
Diabetes	69 (34.5%)
Vasopressors	51 (25.5%
Septic shock	23 (11.5%)
Sepsis	16 (8%)

powered at the 97.5% level to show a MARD of less than 10%, but done so with assumed less accuracy than demonstrated during the trial. The actual 97.5% *p* value for MARD has been subsequently calculated.

RESULTS

A total of 243 critically ill patients met inclusion/exclusion criteria and were enrolled into the study. Three patients were excluded due to labeling (Hetastarch usage, > 500 mL; ibuprofen overdose; triglycerides, > 500). Forty patients were excluded due to either an inability to obtain the minimum number of six samples or they were unable to be attached to the OptiScanner for the minimum number of hours (18 hours).

Of the 40 patients, the largest reason for exclusion was the inability to maintain the line for blood draws for the YSI reference analyzer, totaling 13 (32.5%). The second largest reason for exclusion was that 11 (27.5%) patients were transferred to another unit before 18 hours. The OptiScanner could not pull blood initially in six (15%) patients and had difficulty in doing so while monitoring in another four (10%) patients. There were two patients who were either disconnected for medical emergency or who voluntarily withdrew from the study (10%). There was one patient where no CVC line was available and one where the CVC was removed before 18 hours (5%). We analyzed the paired OptiScan/YSI data from these 40 patients (n = 155) for potential bias. One hundred forty-four (92.9%) were in zone A of the Clarke Error Grid, with the remainder in zone B, similar to the results of the included data. The MARD for the excluded data was 8.7%, and remained below 10% at the 97.5% CI, also in alignment with the included data.

Therefore, 200 patients were evaluable for the study. Table 1 shows the demographics and characteristics of the study population. A total of 3,735 glucose measurements were obtained by the OptiScanner and then compared to the criterion standard YSI.

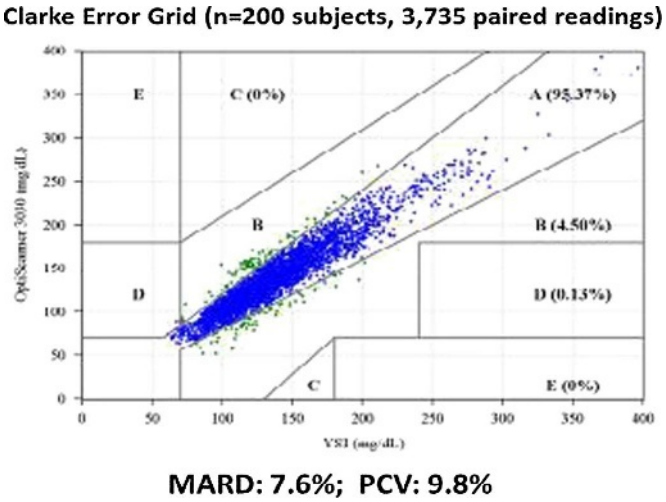

Figure 1. Clark error grid for OptiScanner results versus YSI reference of blood glucose measurements. 95.37% of measurements fall in zone A of the grid. The remaining 4.63% of blood glucose measurements fall in the other zones.

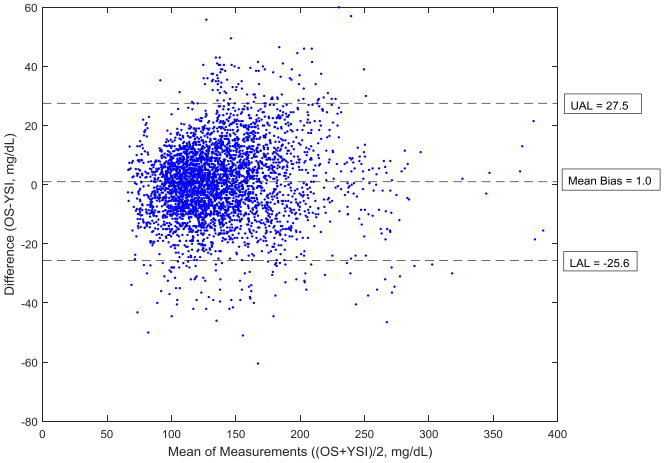

Figure 2. Bland Altman Plot shows the difference and average values of blood glucose measurements between Optiscanner and YSI reference.

The Clarke Error Grid, depicted in Figure 1, shows that 95.4% of the analyzed samples are in zone A. 4.5% were in zone B and 0.1% were in zone D. No samples were in either zone C or zone E. Furthermore, 72.5% of paired samples fell within 10% of the reference, 21.9% fell between 10% and 20%, 3.5% fell between 20% and 30%, and 1.1% have greater than 30% difference. The Bland-Altman plot demonstrates good agreement between the device and the standard (Fig. 2). The MARD was calculated to be 7.6%, upper 97.5% confidence limit of MARD was 7.8%. The PCV was 9.8%.

A total of 103 (51.5%) patients demonstrated at least one form of dysglycemia, with overlap in the categories of dysglycemia. Six (3%) patients had confirmed hypoglycemia, defined as a single reference value less than 70 mg/dL. Eighty-three (41.5%) patients had confirmed hyperglycemia, defined as a minimum of four continuous hours greater than 150 mg/dL. Eighteen (9%) patients had confirmed severe hyperglycemia, defined as a minimum of four continuous hours greater than 200 mg/dL. Forty (20%) patients had confirmed glycemic variability, defined as glucose coefficient of variation greater than or equal to 20%, measured using only the reference measurements. Strikingly, 49 (24.5%) patients exhibited at least one episode of hypoglycemia, severe hyperglycemia, and/or glycemic variability. These results are surprising because the chosen participating trial centers practiced good glycemic control overall, with a mean glucose of 137 mg/dL according to the reference method for the 200 patients in the trial. There were no device-related or potentially device-related adverse events reported.

DISCUSSION

The therapeutic benefits of maintaining appropriate and normal glucose control (euglycemia) in critically ill surgical[12] and trauma patients[3] are well established. Early euglycemia[2] and maintenance within range with minimal variability is known to improve outcome. Hyperglycemia (>200 mg/dL) alone has also been linked to poor outcome in trauma patients, because it is an independent predictor of infection and mortality.[16] Conversely, hypoglycemia (<70 mg/dL) has also been associated

with poor outcomes and even mortality if not appropriately diagnosed and treated rapidly.[5] Furthermore, the recognition of excursions or variability have both a diagnostic and prognostic ability.[17] We have previously reported that AGE score (acute glucose elevation combined with glucose variability) is associated with a 91% positive predictive value for infection diagnosis. In addition, glucose variability alone has been shown to be associated with an increase in morbidity and mortality in trauma patients.[18] However, due to the fact that glucose meters are inaccurate and the workload associated with aggressive glucose monitoring is quite burdensome, many centers have backed away from a more strict level of glucose control. Therefore, to achieve a therapeutic level of control (glucose of 80–120 mg/dL), we believe that there is a critical need for an improved method of point of care glucose measurement that is more accurate and less labor intensive, thereby allowing a safer approach to aggressive glucose control. In addition, more frequent accurate glucose measurements could theoretically decrease this variability and achieve a safe level of aggressive control.

The OptiScanner is the first system that allows for realtime centrifugation of blood samples with "real time" glucose measurements every 15 minutes automatically obtained from a patient via either the proximal port of a CVC or multipurpose access catheter. The measurement is made available on a state-of-the-art electronic screen that can be readily viewed by the clinical team. Another advantage of this system is that the clinical team will be able to evaluate glucose measurement trends which we feel is a much better way to monitor for and treat dysglycemia in critically ill patients, as compared to our current standard of care which utilizes inaccurate and inconsistent meters.

We previously reported on our initial 23 patients who were connected to the OptiScanner (roll in phase of this large multicenter study) and found the OptiScanner to be safe and accurate. We now report the findings of our entire multicenter pivotal trial. All glucose measurements were appropriate on the Clarke Error Grid as 95.4% of values were within 20% of the reference. The remaining 4.8% were in the clinically benign range where the glucose estimate is not as accurate, but is not expected to have caused harm to the patient if it were applied to clinical care. The MARD for all paired glucose samples was 7.6%, 97.5% CI (7.8). A MARD of less than 10% predicts an improvement in glucose control and the prevention of glucose excursions and variability according to mathematical models of continuous glucose monitoring.[14,15] In this pivotal trial, we have achieved this benchmark with high statistical significance.

The results of this pivotal trial provide the first real solution for providing safe and aggressive glucose control in critically ill trauma/surgical patients. We have demonstrated that the OptiScanner is accurate in glucose ranges that are clinically significant especially in the lower or hypoglycemic range.

CONCLUSION

The results of our multicenter prospective study comparing the accuracy of a near continuous glucose monitoring device to the criterion standard of glucose measurement has shown that the device is safe and accurate for clinical care in critically ill and trauma patients. We feel that this technology represents the first real solution for the safe and accurate management of glucose in critically ill patients.

AUTHORSHIP

All authors contributed to the study design and conduct, data collection, data analysis, interpretation, and final revision of the article.

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DISCUSSION

Dr. Dennis Y. Kim (Torrance, California): The widespread deleterious effects of hyperglycemia on critically-injured patients are well-documented.

In addition to the negative impact of admission hyperglycemia on patient outcomes, both persistent and highly-variable hyperglycemia are also associated with increased lengths of stay, nosocomial infection, and mortality.

Although key trials, most notably Nice-Sugar, have not borne out and in fact found opposing results to those achieved by van den Berghe and colleagues in 2001, glucose control remains a key tenet of modern-day critical care.

With that said, it's difficult to ignore the numerous technical and logistical challenges involved in obtaining a rapid and accurate glucose measurement upon which protocolized management decisions can be instituted.

Reliability of point-of-care devices, the ever-increasing work demands on our ICU nurses, and lack of sufficient data points to permit analysis of trends are but a few of the issues surrounding glycemic control.

Dr. Bochicchio and his colleagues are to be congratulated on the present study which proposes a potential solution to the aforementioned problems in managing hyperglycemia in the ICU. I have several questions for the authors.

First, do you have any sense as to how many of these patients were in shock or requiring vasopressors? As you are well aware, dynamic circulatory changes and the use of vascoactive agents are known to affect accuracy of measurements of glucose and it is this patient population, in particular, that may benefit the most from aggressive glycemic control.

Second, use of this device was limited to patients who had an indwelling CVC. From a methodologic standpoint, this would seem to introduce an element of selection bias.

In the post-ProCESS, ARISE, and ProMISE era insertion of CVCs, at least in patients with severe sepsis, may be on the decline. Is a central line absolutely necessary to perform inline glucose monitoring?

Third, can you please elaborate on the paired samples which were used as the gold standard reference? There is known variability between arterial, capillary as well as venous blood samples and it would be interesting to see both the distribution and differences within and between paired samples acquired for a comparison.

Fourth, six patients were found to have a glucose less than 70 milligrams per deciliter. I am interested in knowing more about the accuracy of measurements in patients who fall into this severe hypoglycemic or less than 40 range. How accurate is the Optiscanner in this critical and potentially life-threatening scenario?

Finally, the authors report no device-related adverse events. What about device-related technical issues common to all such monitoring modalities in the ICU such as the incidence of sensor failure, line occlusion, and software malfunction?

The time and frustration dedicated to troubleshooting these issues may be difficult to quantify but are important considerations when considering the introduction of new tech into our units.

Once again, congratulations on your study. I'd like to thank the Association for the privilege of discussing this thoughtful paper.

Dr. Demetrios Demetriades (Los Angeles, California): Thank you. This is an exciting and promising methodology. Could I ask: in extreme conditions such as severe hypotension, high temperature or hypotension, would the reliability of the method be affected? Thank you.

Dr. Grant V. Bochicchio (Saint Louis, Missouri): Thank you. To answer these questions as briefly as I can, approximately 20% of the patients were on vasopressors during the trial. We estimate about 5% were truly septic at the time of the enrollment.

As far as central line placements, the Optiscanner also works on pit catheters or midlines. We also had a fair amount of patients with mat catheters because of the cardiothoracic units that were in place.

Potentially you could use a large peripheral IV, although the length of the duration of the, how long you can keep them on is variable and won't last as long as the three days that you would like it to be.

As far as alarms or accuracy of less than 40, what we do for this is we don't really look at the accuracy in that level, we look at alarms. If you are trending and you are dropping at below 90 you can set an alarm to say your trend is dropping and you should back off on your glucose.

If you have gone below 40 that means you have, you know, most likely you have not set your alarms. And the whole point of this is to prevent you from ever getting there so you should never see a 40 on an Optiscanner if you set your alarms up appropriately as per your protocol.

As far as technical issues, we calculated that the nurses needed to do one intervention per day. As far as there being troubleshooting, as far as the detail, whether it was – a pooling of blood probably was the most common factor that they had to deal with.

And I think those were all the questions. As far as Dr. Demetriades' questions, one thing about mid-infrared spectroscopy, it doesn't care how cold you are or what your blood pressure is because it measures it in plasma and, therefore, just looking at a value.

So compared to other devices we don't really care about temperature or other factors that impact this type of device which is why I think it's something that we really need.

Again, thank you.