The Impact of Intensive Insulin Protocols and Restrictive Blood Transfusion Strategies on Glucose Measurement in American Burn Association (ABA) Verified Burn Centers

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The prevalence of intensive insulin and restrictive blood use protocols in burn centers is unknown, which may be problematic as the combined impact of these therapies is to concomitantly increase the prevalence of anemia and hypoglycemia in intensive care unit patients. Such a development is important because point-of-care (POC) glucometers report erroneously high values in the presence of low hematocrit (HCT), potentially masking the presence of hypoglycemia. We hypothesized that most American Burn Association (ABA) verified burn centers have adopted intensive insulin therapy while simultaneously restricting blood transfusions potentially increasing risk of hypoglycemia. All ABA verified burn centers (N = 44) were contacted. Clinical practices regarding intensive insulin therapy, restrictive transfusion practices, and the use of POC glucometers were evaluated. Intensive insulin protocols were implemented at 73% of ABA centers (defined as upper glucose target of ≤120 mg/dl) and POC glucometers measurement was nearly universal; 95% of ABA centers use them routinely. Anemia is prevalent in intensive care units and may be increasing because of recent changes in practice. Defined hemoglobin and HCT levels trigger blood transfusion at 84% of centers, and of these, 51% restrict transfusion to hemoglobin <7 g/dl or HCT <22%. Most ABA centers now use intensive insulin protocols, many in combination with restrictive transfusion strategies. The combination of a higher prevalence of hypoglycemia in the presence of near universal anemia is concerning, particularly given the pervasiveness of glucometer use among burn centers. (J Burn Care Res 2008;29:718–723)

The prevalence of anemia in critical illness was demonstrated in several well-conducted studies.1–3 The average hemoglobin (HBG) before transfusion in two of these, one by Vincent et al,2 and another by Corwin et al,1 was 8.4 to 8.6 mg/dl. Similar findings were reported for burned patients beginning in the 1940s and are common to this day.4,5 Recently, Hebert et al5 showed that blood transfusion can safely be withheld until HBG is less than 7 g/dl, and these results were confirmed in burn patients by Kwan et al.6 Burn surgeons are influenced by both studies, as was demonstrated by a survey conducted by Palmieri and Greenhalgh7 in which multiple centers reported using low transfusion thresholds for the treatment of patients within five different age groups. Shortly after publication of the Hebert et al study,3 Van den Berghe et al8 reported that the use of intensive insulin therapy in critically ill surgical patients significantly improved morbidity and mortality. The recommendation from this single center trial that blood glucose be maintained between 80 and 110 mg/dl has met with much debate; however, its impact on intensive care unit (ICU) practice around the world is indisputable. Many institutions, including

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our own, adopted the glucose target proposed by Van den Berghe et al and tight glucose control has even become a measure of excellence used by the Joint Commission on Accreditation of Healthcare Organizations. In less than a decade the Van den Berghe et al study has so changed the practice of critical care that few institutions today would consider glucose of 200 mg/dl to be an acceptable threshold of correction, a practice that was common in the not too distant past.

Although seemingly unrelated, the simultaneous adoption of intensive insulin therapy and lower hematocrit (HCT) triggers has inadvertently led to increased potential for error in values obtained with point-of-care (POC) glucometers. HCT effect is the name given to the phenomenon of inappropriately high or low POC glucose measurement of anemic and polycythemic blood samples, respectively.9–14 HCT effect is widely reported in the pathology literature,9–14 yet some clinicians remain unaware of this phenomenon, whereas others continue to use glucometers because of the lack of a viable alternative.

Our hypothesis for this survey was that most American Burn Association (ABA) verified burn centers use POC glucometers to implement intensive insulin therapy, often in combination with restrictive transfusion practices, inadvertently increasing risk of undetected hypoglycemia because of HCT effect.

METHODS

All ABA verified burn centers were identified via a website query (www.ameriburn.org) conducted in August of 2006. Every center was contacted by telephone (N = 44) and responses were obtained from the nurse in charge of the unit, when that person could be identified, or a staff nurse. A three-question survey was formulated and responses obtained in 100% of cases. The questions were as follows: 1) Is intensive insulin therapy used, and if so, what is the glucose range targeted in titrating insulin infusions? 2) Is a POC glucometer used to monitor glucose during insulin infusion, and if so, what brand is in use? 3) Does the center have a defined HBG and HCT threshold at which blood transfusion is initiated? Results were tabulated and responses calculated as a percent of the whole.

RESULTS

Of the 44 ABA verified burn centers identified, 73% (n = 32) reported using intensive insulin practices, defined here as maintaining an upper limit of glucose less than 120 mg/dl (Figure 1). All centers initiate insulin treatment for glucose levels of 150 mg/dl or more. Of note, 18% (n = 8) of centers reported using 60 to 70 mg/dl of glucose as the lower limit for insulin titration, a level extremely vulnerable to the detrimental effect of low HCT on bedside glucometers. Our survey showed that 84% (n = 37) (Figure 2) of centers have defined transfusion triggers for HBG or HCT, and of these 51% (n = 19) use restrictive strategies, defined as transfusion of packed RBCs for HBG less than 7 g/dl or HCT less than 22%. The mean transfusion threshold reported by nurses in the present survey was below HBG of 8 g/dl or a HCT of 23%, demonstrating that transfusion triggers are low even in centers where restrictive policies are not in place. Centers that transfuse for HBG less than 10 g/dl or HCT less than 30% are in the minority (9%, n = 4).

Figure 1. Reported upper limit of glucose range (mg/dl) targeted during titration of insulin infusions at ABA verified centers (n = 40). Seventy-three percent of centers target upper glucose limit of 120 mg/dl or less. ABA, American Burn Association.

Figure 2. Reported hematocrit (HCT) level for pRBC transfusion at ABA verified centers (n = 37). Restrictive transfusion threshold defined as less than 22% HCT (51% of centers). ABA, American Burn Association; pRBC, packed red blood cells.
Burn ICUs where intensive insulin therapy is used in concert with restrictive transfusion practice likely have the highest prevalence of unrecognized hypoglycemia, and 32% (n = 14) of ABA centers reported simultaneously using both protocols (Figure 3). Such a finding is only of concern if POC glucometers are used at the bedside to titrate intravenous insulin infusion; however, in the overwhelming majority of centers (95%, n = 42) glucometers are the standard of care. Only 2 (5%) centers use a laboratory serum analyzer for hourly glucose measurement; all others (n = 42) use the following devices for glucose quantification: Accu-Chek Inform™ (Roche Diagnostics, Indianapolis, IN); Accu-Chek Advantage™ (Roche Diagnostics, Indianapolis, IN); LifeScan SureStep Flexx™ (LifeScan, Milpitas, CA); LifeScan SureStepPro™ (LifeScan, Milpitas, CA); and Medisense Precision PCx™ (Abbott Diabetes Care, Alameda, CA) (Figure 4).

**DISCUSSION**

Vincent et al found in a multicenter study of Western European ICUs that 29% of patients admitted to the ICU had HBG levels less than 10 g/dl. Investigators of practice in the United States reported that within 48 hours of ICU admission, almost 70% of patients had a baseline HBG level of <10 g/dl, of whom fully half had an HBG <10 g/dl. The average HBG before transfusion in both the CRIT and ABC studies was 8.4 to 8.6 mg/dl. In burned patients, anemia has been recognized since the 1940s, a function of significant blood loss during large surgical excisions, increased protein turnover, and the relatively short life of transfused RBCs. A 2004 survey of practice in American burn centers reported a mean HBG transfusion threshold of 8.12 ± 1.7 g/dl. In addition, Palmieri et al reported in 2006 that the average HBG of burn patients receiving blood transfusions in the operating room was 10 g/dl, whereas transfusions outside the operating room were administered for a HBG of less than 9 g/dl.

The increasing prevalence of anemia reflects significant changes in clinical practice resulting from seminal work done in the area of transfusion. In 1999, Hebert et al compared a restrictive transfusion protocol (blood transfusion threshold of HBG less than 7 g/dl) to liberal or traditional practice (threshold of 10 g/dl) and found no significant increase in associated morbidity. Subgroup analysis suggested potential benefit in 30-day mortality among the less acutely ill and those less than 55 years of age, and in-hospital mortality was significantly lower in the restrictive transfusion group (P = .05). Similar analysis in patients with stable, nonischemic cardiovascular disease revealed no increase in mortality. Liberal transfusion was associated with increased incidence of myocardial infarction, pulmonary edema, and acute respiratory distress syndrome compared with the restrictive transfusion strategy. The use of restrictive transfusion practices reduced the average number of red cell transfused by 54%, and eliminated transfusion in 33%.

The multicenter retrospective study conducted by Palmieri et al demonstrated a significant increase in infection among transfused burn patients; each unit of packed RBCs transfused was associated with a 13% increase in infection. Although causation has not been established, researchers noted that blood transfusions were associated with increased
mortality risk\(^2\,^5\) and the development of infectious complications\(^1\,^6\,^7\) or sepsis in burned patients\(^1\,^6\,^7\). Evidence that blood transfusion is associated with postoperative infections,\(^1\,^8\) ICU acquired bloodstream infections,\(^1\,^9\) nosocomial infections,\(^2\,^0\) diminished organ function,\(^2\,^1\,^5\) and poor outcome in trauma patients\(^2\,^1\) is mounting. One retrospective review of transfusion practice in burned children demonstrated that restrictive transfusion practices reduce the amount of blood transfused and conserves resources without negatively impacting outcomes,\(^2\,^2\) which reflects the previously reported practice of permissive anemia in burned adults.\(^2\,^3\,^4\) Furthermore, comparison of restrictive transfusion thresholds (HBG 7.1 ± 1.2) compared with a liberal threshold (9.2 ± 2.1) in burn patients resulted in significant reduction in morbidity and mortality in the restrictive group.\(^5\) As shown by this study and others, findings such as these have led physicians to tolerate ever lower HBG levels in their burn patients.

Simultaneously, the 2001 study by Van den Berghe et al\(^8\) made a major impact in the practice of critical care because of findings that intensive insulin therapy (serum glucose goal of 80–110 mg/dl) reduces hospital morbidity and mortality compared with conventional treatment (goal of 180–200 mg/dl). In response to this single site study of over 1500 critically ill surgical patients, ICU providers around the world have instituted tight glycemic control in some form or another. Our data represents the first survey of the impact of the Van den Berghe et al trial on glycemic management practice in ABA verified burn centers. Although class I data does not exist in the burn population, multiple studies have documented the association between hyperglycemia and increased mortality; and as we show here, the burn community responded with widespread adoption of intensive insulin practices for the burn population.\(^2\,^5\)\,\(^2\,^6\)\,\(^2\,^7\) Although previous studies associating mortality and hyperglycemia are compelling, they do not eliminate the need for careful prospective research to identify the ideal therapeutic range for glycemic management. Such studies are needed not only to validate the practice of tight glycemic control in the burn population, but also to evaluate the wisdom of continuing to treat hyperglycemia expectantly. Finally, the topic of the potential risk posed by transient hypoglycemia has been much debated, and additional research is required to investigate the possibility of harm with these therapies.\(^2\,^8\)

The use of POC analyzers to measure glucose content in anemic and polycythemic blood samples leads to inappropriately high or low glucose values, respectively, a phenomenon termed “HCT effect.”\(^9\)\,\(^1\,\,\,^1\,\,\,^4\) The cause is due to differential plasma displacement by the RBC mass compared with a normal HCT sample, which results in either more (anemia) or less (polycythemia) glucose molecules being available to be detected. A fixed volume of whole blood is present on a glucose strip in the area to be analyzed, and the glucometer software assumes that the amount of plasma containing the glucose in solution, called the “plasma equivalent,” is also fixed. Analysis in the glucometers available to burn units does not adjust sample plasma equivalent volumes, thus in an anemic sample, the larger glucose sample (numerator) is correctly detected, but the device fails to account for the proportionately larger plasma volume. Instead, it divides by an inappropriately normal volume (denominator), thereby overestimating the in vivo glucose concentration. Falsely elevated glucose measurement can prevent appropriate treatment of hypoglycemia that goes unrecognized, and worse, can produce hypoglycemia in patients whose blood sugar is normal by inducing practitioners to give insulin in response to falsely high values.

The HCT effect phenomenon was previously recognized by neonatologists, whose patient populations often include profoundly anemic and polycythemic infants, and it was reported in the pathology literature.\(^9\)\,\(^1\,\,\,^4\) Burn care practitioners and ICU clinicians in general are only now becoming aware of this phenomenon; those that do know of it may still be using glucometers because of the lack of a viable alternative. New products are coming on the market, however, and practitioners need to familiarize themselves with the potential for HCT effect in their units; only then can they accurately assess the risks and benefits of present and future methods of glucose measurement. The number of authors raising concerns over the questionable accuracy of POC glucometers in the critical care setting is growing; however, no feasible substitute is proposed.\(^2\,\,\,^9\)\,\(^3\,\,\,^4\) At issue is the fact that practitioners need a bedside method of glucose measurement that is easy to use and provides a rapid result.

The U.S. Food and Drug Administration (FDA)\(^3\,\,\,^5\) recommends that the margin of error in glucometer performance be less than 15%, yet even this overly generous standard is not met by most manufacturers. Most report error margins of 20% or more, which translates to a range of 60 to 90 mg/dl when the reading is 75 mg/dl\(^3\,\,\,^6\)\,\(^3\,\,\,^7\) an unacceptable degree of variability given that at the low range most practitioners would administer 50% dextrose, whereas no treatment would be initiated at the high end. The FDA\(^3\,\,\,^5\) recommendation was intended for devices developed for the hyperglycemic diabetic outpatient in...
an age where the primary goal was to keep patient’s glucose under 200 mg/dl, yet currently is inappropriately applied to a clinical environment in which much tighter control is being attempted. Although the FDA has not adapted to changes in modern ICU care, other organizations have adjusted their guidelines: consensus recommendations presented at the 2000 American Association of Clinical Chemistry Meeting propose no greater than 7.9% total error in POC glucose analyzers, and the American Diabetes Association (ADA) recommends that future glucose monitoring devices should accept no more than a 5% total error in measurement.

In the absence of pressure by the FDA to improve glucometer performance, a potentially dangerous situation has arisen in which recent changes in critical care have resulted in increased prevalence of anemia and hypoglycemia among ICU populations, whereas glucometers are widely used despite performance problems. Although the problem of glucometer inaccuracy is increasingly discussed, there is a paucity of data as to causes or potential solutions. At our research institute, we have investigated the matter and determined that the major cause is HCT effect, which can be corrected at the bedside with a mathematical correction formula. The survey presented here, while offering no direct data regarding anemia and hypoglycemia at ABA centers, suggests that the prevalence could be high and such an investigation is warranted.

It remains incumbent on the users of POC glucose analyzers to demand highly reliable and accurate glucometers for management of the critically ill anemic patient. As we have demonstrated, most burn centers practice intensive insulin therapy and use of POC devices to monitor insulin infusions is nearly universal. The mounting evidence in the burn literature associating allogenic blood transfusion and infection resulting in worsening outcomes in the burn patient will undoubtedly lead to the increased prevalence of anemia in this population. Reliance on the convenience of POC glucose testing facilitates aggressive glycemic control, yet given the demonstrated error associated with HCT effect inherent in currently available technology, the chance of unrecognized hypoglycemia is of concern.

Most centers lack written guidelines to direct insulin management or have blood transfusion protocols; thus a limitation of our study was reliance on verbal reports by staff members that may erroneously represent actual medical practice. Furthermore, we only contacted the ABA verified centers.

**CONCLUSIONS**

In this survey of all verified ABA burn centers, we found that most have adopted intensive insulin protocols in response to the Van den Berghe et al trial as well as studies showing an association of hyperglycemia with poor outcomes in burn patients. This is the first report of the prevalence of intensive insulin practice in burn ICUs. We also demonstrated that many centers use restrictive transfusion practices in conjunction with intensive insulin therapy. Given the preponderance of centers that use glucometers to direct bedside glucose management, the potential for hypoglycemia masked by HCT effect is high. Restrictive transfusion therapy and intensive insulin management will likely continue to be practiced in ABA burn centers, thus practitioners should evaluate the concordance between bedside instruments and laboratory analysis in their own populations. Use of the existing technology in light of the clinical impact of HCT effect deserves critical appraisal by all burn center providers where anemia is prevalent.

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