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GLUCOSE CONTROL IN SEVERELY THERMALLY INJURED PEDIATRIC PATIENTS: WHAT GLUCOSE RANGE SHOULD BE THE TARGET?

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INTRODUCTION

Hyperglycemia is a common pathophysiological phenomenon in burn and critically ill patients. During the early phases of postburn, hyperglycemia is due to an increased rate of glucose appearance along with an impaired tissue extraction of glucose leading to an increase of glucose and lactate^{1, 2} associated with impaired insulin receptor signaling and endoplasmic reticulum stress.³⁻⁵ The clinical relevance of hyperglycemia after a severe burn was shown in recent studies in which the authors showed that burn patients with poor glucose control had a significantly higher incidence of bacteremia/fungemia and mortality.⁶⁻⁸ These data indicate that hyperglycemia, associated with insulin resistance, represents a significant clinical problem in burn patients similar to insulin resistance in critically ill patients. Tight euglycemic control as published by van den Berghe and colleagues⁹ changed ICU practice. They showed that insulin administered to maintain glucose at levels below 110 mg/dl decreased morbidity and mortality in surgically critically ill patients and morbidity in medically critically ill patients.¹⁰ In another study, the authors showed that tight euglycemic control improved mortality in pediatric ICU patients¹¹ and insulin given during the acute phase not only improved acute hospital outcomes but also improved long-term rehabilitation and social reintegration of critically ill patients over a period of 1 year^{12, 13}, indicating the advantage of insulin therapy.

Various unicenter and multicenter studies followed the Leuven trials to determine whether tight euglycemic control, in fact, improves outcomes of critically ill, septic, trauma, and medical patients. Results of these studies were mixed with some showing a benefit with the use of euglycemic control^{14, 15}, while others failed to show improved outcomes; in contrast, some of these studies even demonstrated detrimental effects associated with tight euglycemic control and a dramatically increase in the incidence of hypoglycemia.¹⁶ A large multicenter trial was initiated: the NICE SUGAR trial, which failed to show beneficial outcome for critically ill patients with intensive insulin therapy¹⁷. This trial on the other hand delineated risks and problems associated with tight euglycemic therapy. Given all these controversial findings, current recommendations which glucose range should be targeted, are now based on opinions and not on scientific evidence.

We, therefore, designed this trial in severely burned patients to answer the question which glucose levels are associated with improved morbidity and mortality. We hypothesized that

hypoglycemia as well as hyperglycemia are detrimental for severely thermally injured patient outcome and that an ideal glucose range exists that is associated with improved morbidity and mortality.

PATIENTS AND METHODS

Thermally injured children with burns over 30% of their total body surface area (TBSA) who consented to an IRB-approved experimental protocol between 2002 and 2009 and who were randomized to control (patients did not receive any anabolic or anti-catabolic experimental drug) or randomized to tight euglycemic or conventional insulin, requiring at least one surgical intervention were included in this study.

Glucose levels were checked as needed by using a laboratory hexokinase assay. A total of 208 patients were included into this trial. For these 208 patients, daily average and 6 a.m. glucose levels were collected and a statistical analysis performed (see below) that divided these patients into good glucose control vs. poor glucose control and subsequent parameters were determined. Daily average glucose measurements are all glucose measurements obtained in one day in the same patient. The amount of glucose measurements varied for each patient from 6 measurements per day to 24 measurements per day depending on the acuity of the burn injury and the patient's critical condition. Daily 6 a.m. glucose levels were glucose levels that were determined every day at 6 a.m. during the hospitalization of the patient resulting in one daily value.

If needed, patients were resuscitated according to the Galveston formula with 5000 cc/m² TBSA burned + 2000 cc/m² TBSA lactated Ringer's solution given in increments over the first 24 hours. Within 48 hours of admission, all patients underwent total burn wound excision and the wounds were covered with autograft. Any remaining open areas were covered with homograft. After the first operative procedure, patients were taken back to the operation theater when donor sites were healed. This procedure was repeated until all open wound areas were covered with autologous skin. All patients underwent the same nutritional treatment according to a standardized protocol. The intake was calculated as 1500 kcal/m² body surface + 1500 kcal/m² area burn as previously published.^{18–20} The nutritional route of choice in our patient population was enteral nutrition via a duodenal (Dobhof) or nasogastric tube.

Patient demographics (age, date of burn and admission, sex, burn size and depth of burn) and concomitant injuries such as inhalation injury, sepsis, morbidity, and mortality were recorded. Inhalation injury was diagnosed by bronchoscopy along with a consistent history. Wound infection was defined as >10⁵ colony forming units per gram tissue in a wound biopsy with the identification of a pathogen. Repeated counts of the same bacteria in the same location were counted as the same infection. Sepsis and infection were defined by the American Burn Association and Society of Critical Care Medicine guidelines.^{18, 21, 22} Multi-organ failure (MOF) was defined as previously published.²³

Ethics

The study was reviewed and approved by the Institutional Review Board of the University Texas Medical Branch, Galveston, Texas. Prior to the study, each subject, parent or child's legal guardian had to sign a written informed consent form.

Statistics

We used several statistical methods (backward stepwise regression, factor analysis, and principal component analysis) to determine which independent variables contribute to predicting mortality, and compared their results to best fit the mortality model. Robust

estimation techniques were used to estimate the covariance matrix of the data. Based on the output of the backward stepwise regression and principal component analysis, there were independent variables that appeared to be highly correlated with other independent variables or had no variability and therefore these variables were removed from the regression model. We used two glucose markers: daily average glucose and glucose level at 6:00 a.m. for each patient to determine association between patient outcome and glucose levels.

In both cases (daily average and 6:00 a.m.), TBSA%, %good140 and %good130, were significant parameters respectively in developing the prediction model for mortality, other variables did not significantly add to the ability of the equation to predict the mortality and were not included in the final equation because of the multicollinearity, or collinearity, relationships among the independent variables. We modeled mortality using the multivariate logistic regression. In our multiple logistic regression, we used Hierarchical forward with switching model with max 50 iterations.

To calculate a probability from the logistic equation, the logit was transformed using $\text{Probability [survive]} = 1/[1 + \text{Exp} \{-\text{Logit P}\}]$. To assess the regression fit for the analysis, the likelihood ratio test statistic and the mean, standard error, and Wald statistic for each parameter were examined. The sensitivity and specificity of the resulting logistic regression was depending upon the Logit P value, which is considered to be predictive of mortality. The relationship between sensitivity and specificity was presented as a receiver operating characteristic (ROC) curve. These analyses were performed using several statistical analysis system packages (SigmaStat, and NCSS). Analysis of variance with post hoc Bonferroni correction, paired and unpaired Student's t-test, Chi-square analysis, and Mann-Whitney tests were used where appropriate. Data are expressed as means $\pm$ SD or SEM, where appropriate. Significance was accepted at $p < 0.05$.

Hypermetabolism and insulin resistance

Glucose metabolism and Insulin resistance: During acute hospitalization, we determined daily average blood glucose levels, daily 6 a.m. blood glucose levels, daily maximum glucose levels, and daily minimum glucose levels. Glucose concentration was determined in our clinical laboratory by hexokinase assay (Siemens Healthcare Diagnostics, West Sacramento, CA). We further determined the number of patients requiring insulin administration during acute hospitalization and the daily amount of insulin needed per patient, as well as serum insulin levels during acute hospitalization.

Indirect calorimetry: All patients underwent resting energy expenditure (REE) measurements within one week following hospital admission and weekly thereafter during their acute hospitalization. All measurements of REE were performed between midnight and 5 a.m. while the patients were asleep and receiving continuous feeding. Resting energy expenditure was measured using a Sensor-Medics Vmax 29 metabolic cart (Yorba Linda, CA) as previously published.²⁰ REE was calculated from oxygen consumption and carbon dioxide production using equations described by Mlcak and colleagues.²⁰ Measured values were compared to predicted normal values, based upon the Harris-Benedict equation, and to body mass index.²⁰

Cytokines, hormones, and proteins—Blood and urine were collected from each burn patient at admission, preoperatively, and 5 days postoperatively for 4 weeks and were used for analysis of serum hormone, protein, cytokine, and urine hormones. Blood was drawn in a serum-separator collection tube and centrifuged for 10 minutes at 1320 rpm; the serum was removed and stored at -70°C until assayed. Serum hormones and acute phase proteins were determined using HPLC, nephelometry (BNII, Plasma Protein Analyzer Siemens Healthcare

Diagnostics, West Sacramento, CA), and ELISA techniques.²³ The Bio-Plex Human Cytokine 17-Plex panel was used with the Bio-Plex Suspension Array System (Bio-Rad, Hercules, CA) to profile expression of seventeen inflammatory mediators.²⁴

Organ function—Serum proteins, e.g., creatinine, bilirubin, and total protein were determined using standard nephelometry to evaluate organ function.²³

RESULTS

Demographics

Two-hundred eight patients were included in this study. Demographics are shown in Table 1. Daily average and daily 6:00 a.m. glucose levels were measured and statistical analysis were performed to determine what glucose level is associated with an improved outcome. We applied backward stepwise regression, factor analysis, and principal component analysis to determine which parameters significantly affect mortality. Based on the results from applying principal component analysis, for the daily glucose average levels, we found a daily glucose average level of 140 mg/dl to be the best glucose level with the highest weight assigned on it. We further determined how often a patient has to be in the range of 140 mg/dl to have an improved outcome. We obtained that a patient needs to be at least 70% of the entire hospitalization in that range. For the 6:00 a.m. glucose level, we found that a glucose level of 130 mg/dl to be the ideal, and a patient needs to be at least 75% of the time in that range.

Multiple logistic regressions were conducted using the most informative and significant variables, TBSA and %good140; TBSA and %good130, respectively (for the two data sets daily average and 6:00 a.m.), to develop the mortality model and the following equations were obtained:

$$\begin{aligned} \text{Logit}(p) &= -7.15 + .11 * \text{TBSA} - 6.67 * \% \text{good } 140 \text{ mg/dl (daily average)} \\ \text{Logit}(p) &= -6.89 + .10 * \text{TBSA} - 7.224 * \% \text{good } 130 \text{ mg/dl (6:00 a.m.)} \end{aligned}$$

The coefficients for %good140 and %good130 were negative, indicating that the risk of mortality decreased with the increase of these variables. The coefficients for TBSA were positive, and it indicates that patients with a bigger burn are more likely to die compared to patients with smaller TBSA. The means, SEs, and Wald statistics of the logistic regression coefficients for the daily glucose average and 6:00 a.m., respectively, are as follow:

$$\begin{aligned} \% \text{good } 140, 0.67 \pm 1.72824, p \leq 0.001 \text{ and } \text{TBSA}, 56 \pm 0.02862, p \leq 0.001; \\ \% \text{good } 130, 0.58 \pm 2.24, p \leq 0.001, \text{ and } \text{TBSA}, 58 \pm 0.027, p \leq 0.001. \end{aligned}$$

From multiple regression analysis, we identified burn size, daily average, and 6:00 a.m. glucose levels as excellent predictors for mortality (Likelihood Ratio Test Statistic 66.074; $P = <0.001$, Likelihood Ratio Test Statistic 50.877; $P = <0.001$). An ROC curve was constructed for the resulting regression equation and the area under the curve for daily average glucose was 0.96 and for 6:00 a.m. was 0.92 (Supplemental Figures 1A–B, Supplemental Digital Content 2, <http://links.lww.com/SLA/A85>). The percent correct classification rate were high for the daily average glucose level using glucose level of 140 mg/dl (94.7% total correct classification rate), and for the 6:00 a.m. measurements, glucose level of 130 mg/dl (95.7% total correct classification rate). Results show that burn patients whose glucose levels are at 140 mg/dl for 70% of their acute hospitalization have an improved outcome compared to patients with glucose levels higher than 140 mg/dl, as well

as patients whose 6:00 a.m. glucose are at 130 mg/dl for 75% of the time (Supplemental Figures 1C–J, Supplemental Digital Content 2, <http://links.lww.com/SLA/A85>).

Using the 6:00 a.m. cutoff, 130 mg/dl for at least 75% of the entire hospitalization, we divided patients into poor glucose controlled patients and good glucose controlled patients. At hospital admission, there were no differences in patient demographics as shown in Table 1, except good glucose controlled patients were younger than poorly controlled patients. There were no statistical differences in gender, length of ICU stay, burn size, third-degree burn, length of ICU stay per percent burn, or number of required operations (Table 1). Incidence of inhalation injury was comparable in both groups and not statistically different (Table 1) indicating that both patient groups were similar in injury severity and concomitant injuries at hospital admission. During hospital course, patients with good glucose control administration had a significantly decreased incidence of minor infections, sepsis, and MOF, $p < 0.05$ (Table 1). A reduction in infection, and sepsis was associated with improved survival. While 12% of patients died in the poor glucose group, none of the patients died in the good glucose group, $p < 0.05$ (Table 1). We would like to emphasize that these pathological events occurred during hospitalization. The Kaplan-Meier-Survival curve is depicted in Figure 1.

Glucose metabolism and Insulin resistance—Daily 6 a.m. glucose levels were significantly higher in the poor glucose group when compared to good glucose group, $p < 0.05$ (Figure 2A). We found that daily 6 a.m. blood glucose levels were lower in the good glucose control group because of a markedly lower high glucose levels, $p < 0.05$ (Figure 2B), with no effect on daily low glucose levels (Figure 2C).

To determine whether or not decreased glucose levels were the result of increased insulin administration, we determined the amounts of insulin administered throughout acute hospitalization. We found poor glucose controlled patients required more insulin when compared to the good glucose controlled patients, $p < 0.05$ (Figure 2D).

Indirect calorimetry—As previously reported, burn injury increases REE, indicating a vast hypermetabolic response. In this study, patients with poor glucose control demonstrated a significant increase in REE, as predicted by the Harris-Benedict equation, at various time points when compared to patients with good glucose control, $p < 0.05$ (Figure 3), indicating that good control was associated with a markedly attenuated hypermetabolic response.

Cytokines, hormones, and proteins—Confirming previous studies, we found that a burn injury induces a vast inflammatory response. Patients with good glucose control demonstrated a marked altered inflammatory response. Good glucose control was associated with significantly decreased IFN- γ , interleukin (IL)-10, IL-7, IL-8, IL-5, IL-6 and monocyte chemoattractant protein (MCP)-1, when compared to patients with poor glucose control, $p < 0.05$ (Figure 4A–G). Of interest is that IL-6, IL-8 and MCP-1 have been described to induce insulin resistance and that good glucose control attenuated inflammatory mediators that lead to insulin resistance.

Serum acute phase proteins, C-reactive protein, complement C3, α_2 -Macroglobulin, α_1 -antitrypsin, and haptoglobin were increased postburn. Good glucose control had no effect upon serum complement C3 and α_2 -macroglobulin, but significantly decreased serum α_1 -Antitrypsin (Figure 4H), CRP (Figure 4I), and haptoglobin (Figure 4J). Serum constitutive hepatic proteins pre-albumin, transferrin, and retinol-binding protein markedly decreased and remained low up to 60 days postburn. Patients with good glucose control had significantly increased transferrin levels at a later time point when compared to controls, $p < 0.05$ (Figure 4K).

Organ function—We further determined serum markers of organ function and homeostasis. We found that burn caused increases in ALT, AST, total bilirubin, BUN, and creatinine levels (Figure 4L-T). Patients with good glucose control had markedly decreased serum ALT (Figure 4L), AST (Figure 4M), total bilirubin (Figure 4N), total protein (Figure 4O), BUN (Figure 4P), and creatinine (Figure 4Q) levels when compared to patients with poor glucose control, $p < 0.05$.

DISCUSSION

The introduction of tight euglycemic control as a clinical concept^{9, 10} represents one of the milestones in modern medicine and changed ICU practice.^{14, 25} However, various recent studies found that tight euglycemic control worsened morbidity and mortality questioning tight euglycemic control as a paradigm.^{16, 17} In addition to the essential question whether glucose control per se is beneficial, there is a lot of discussion to which glucose level is associated with beneficial outcome. Van den Berghe and colleagues^{9, 10} studies indicate that blood glucose below 110 mg/dl is beneficial in critically ill adults and pediatric patients. However, there are several other studies indicating that 80–110 mg/dl does not improve outcomes and is associated with high risk of hypoglycemia. In a recent multi-center trial (VISEP) authors found that insulin administration did not affect mortality but the rate of severe hypoglycemia was 4-fold higher in the intensive therapy group when compared to the conventional therapy group.¹⁶ Finney and colleagues¹⁴ recommend glucose levels of 140 mg/dl and below. Preiser et al.¹⁵ summarized in their analysis recent studies on glucose modulation. The authors recommend, given the hypoglycemic risks of intensive insulin therapy and the uncertainty of the ideal glucose level, that an intermediate level of 140 mg/dl should be targeted. Following this recommendation is the Surviving Sepsis Campaign.²⁵ The authors recognized the lack of an ideal glucose range and the complications of hypoglycemic episodes but they recommend maintaining glucose levels below 150 mg/dl. As it is very difficult maintaining a continuous hyperinsulinemic, euglycemic clamp in burn patients and the risk of hypoglycemia is increased because the nutrition has to be stopped daily due to dressing changes and operations, the aim of the present study was to determine which glucose range should be targeted to improve morbidity and mortality in this patient population.

We found, using the envelope of a prospective randomized controlled trial in severely burned pediatric patients, that the most beneficial glucose 6 a.m. target is 130 mg/dl. We used statistical tools to generate a model that determined the ideal glucose levels associated with improved outcomes. We then used this glucose level to stratify the patients and to test whether this model has any validity. The weakness of this study is that it used the same patient population but the strength is that we used approximately 300,000 glucose measurements to determine the ideal glucose level. Furthermore, when we stratified the patients according to the ideal glucose target we found large differences in terms of outcomes, indicating that our statistical model has validity. By no means are we suggesting that this study replaces a prospective randomized trial determining ideal glucose target, but this is the first scientific effort to come up with a glucose level that is associated with beneficial outcomes. In this trial, we found that morbidity and mortality is improved if a severely thermally injured patient is in that range 75% of the entire acute hospitalization. We furthermore found that a daily average glucose target of 140 mg/dl for 70% of the entire hospitalization is also associated with improved morbidity and mortality. This means that in severely thermally injured patients, glucose levels should be decreased under 140 mg/dl. This finding can be associated with the underlying pathophysiology of hyperglycemia. Several studies suggested that the detrimental effects of hyperglycemia are associated in part with protein glycolysation which occurs at 150–160 mg/dl. A glucose target range below

150 mg/dl would avoid protein glycolysation and thus be beneficial in terms of postburn morbidity and mortality.

We would like to mention that daily average glucose values can entail anything from 6 glucose measurements per day up to 24 glucose measurements per day. This depended upon injury acuity and the state of critical illness of the patient. Because a different number of measurements of glucose were made in the study patients and more frequent sampling occurred in one group of patients, the results could be biased. We suggest that this is not the case because our 6 a.m. glucose values are measured once daily in all patients and, is therefore, not bias. We, therefore, propose that our results are valid and skewed.

We have recently shown that a severe burn causes endoplasmic reticulum stress and unfolded protein response in rodents and humans. The endoplasmic reticulum (ER), a membranous organelle that functions in the synthesis and processing of secretory and membrane proteins, is critical in the cellular stress response.²⁶ Certain pathological stress conditions disrupt ER homeostasis and lead to accumulation of unfolded or misfolded proteins in the ER lumen.^{26–28} The ER stress response limits unfolded protein burden in the ER lumen by inhibiting translation and inducing the nuclear transcription of additional chaperone proteins. If the unfolding protein burden cannot be reversed, apoptotic cell death ensues. To cope with this stress, cells activate a signal transduction system linking the ER lumen with the cytoplasm and nucleus, called the unfolded protein response (UPR).^{27, 28} ER stress is detected by transmembrane proteins which monitor the load of unfolded proteins in the ER lumen, and transmit this signal to the cytosol.²⁶ Two of these proteins, inositol requiring enzyme-1 and PKR-like ER kinase, undergo oligomerization and phosphorylation in response to increased ER stress.²⁶ Work in our laboratory has recently demonstrated increased phosphorylation of IRE-1 and PERK in rodents and humans after burn injury, indicating activation of ER-stress signaling pathways postburn. We now suggest that ER stress/UPR is one of the underlying causes of insulin resistance postburn. What is remarkable in this study is that patients with poor glucose control needed higher insulin doses, which failed to decrease glucose levels, indicating that patients with poor glucose control were more insulin resistant.

This trial was performed in an envelope of a randomized controlled trial but was not a randomized trial. The aim of this trial was to use the dataset from 208 patients and to determine which daily average and 6 a.m. glucose levels are associated with an improved morbidity and mortality. To determine which glucose target is beneficial, we analyzed approximately 300,000 glucose values and found that burn patients whose 6 a.m. glucose levels are at 130 mg/dl for 75% of their acute hospitalization has an improved outcome when compared with patients whose glucose levels are above 140 mg/dl. This data is in agreement with several studies recommending a glucose target of 140–150 mg/dl. This glucose range does not cause protein glycolysation but, furthermore, is not associated with the risk of severe hypoglycemia. Our data demonstrate that the ideal glucose target is around 130–140 mg/dl and that the glucose curve has a U-form shape, meaning that very low glucose levels are as detrimental as very high glucose levels. Given the controversy over glucose range, glucose target, risks and detrimental outcomes associated with hypoglycemia, we thus suggest that in severely burned patients, blood glucose of 130 mg/dl should be targeted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Kaplan-Meier survival curve. There were no deaths in the group with good glucose control.

*Significant difference between poor vs. good, $p < 0.05$.

Figure 2.

(A) Daily 6 a.m. glucose. Patients with good glucose control had significantly lower level compared to patients with poor glucose control. (B) Daily maximum glucose levels. Good glucose controlled patients have significantly lower peak levels of glucose compared to poor glucose controlled patients. (C) There is no difference between good and poor glucose controlled patients for daily minimum glucose levels. (D) Daily insulin administration. * Significant difference between good glucose control vs. poor glucose control, $p < 0.05$.

Figure 3.

Patients with good glucose control had a significantly attenuated hypermetabolic response at various time points when compared to poor glucose controlled patients. * Significant difference between good glucose control vs. poor glucose control, $p < 0.05$.

Figure 4.

Good glucose control significantly decreased the following cytokines: IFN- γ (A), IL-10 (B), IL-7 (C), IL-8 (D), IL-5 (E), IL-6 (F), and MCP-1 (G). Good glucose control attenuated 1-anti trypsin (H), significantly decreased CRP (I), as well as haptoglobin (J), while it significantly increased transferring (K). Good glucose control improved organ function as indicated by improved serum organ function markers ALT (L), AST (M), bilirubin (N), total protein (O), BUN (P), and creatinin (Q). Data presented as mean $\pm$ SEM. * Significant difference between control vs. propranolol at each corresponding time point, $p < 0.05$.

TABLE 1

Patient Demographics

		Poor >130 mg/dl	Good <130 md/dl
	All Patients	<75% LOS	>75% LOS
	208	148	60
Male/female	131/77	94/54	37/23
African American	8	5	3
Caucasian	17	15	2
Hispanic	178	124	54
Other	5	4	1
Age (years)	9 ± 6	10 ± 5	7 ± 5
Inhal Inj n (%)	88 (42)	68 (46)	20 (33)
Flame (n)	159	118	41
Scald (n)	35	18	17
Other (n)	14	12	2
TBSA burn (%)	58 ± 16	60 ± 17	56 ± 15
TBSA third (%)	45 ± 24	46 ± 25	43 ± 20
Operations (n)	4.4 ± 3.3	4.5 ± 3.4	4.1 ± 3.3
Time between OR's (days)	4.9 ± 2.8	4.9 ± 3.3	4.7 ± 1.4
LOS ICU (days)	30 ± 24	31 ± 25	29 ± 22
LOS ICU/TBSA (d/%)	0.5 ± 0.3	0.5 ± 0.3	0.5 ± 0.3
Minor infection (n)	5.5 ± 5	7.4 ± 6.7	3.6 ± 3.9*
Sepsis n (%)	42 (20.2)	36 (24)	6 (10.0)*
MOF n (%)	49 (24)	38 (26)	8 (13.3)*
Died n (%)	17 (8)	17 (12)	0 (0.0)*

TBSA indicates total body surface area. Data presented as means ± SEM or percentages.

* Significant difference between control vs. propranolol at corresponding time point. $P < 0.05$.