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Estimating Center Effects Using Multiple Methods in a Pediatric Glycemic Control Study

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Estimating Center Effects Using Multiple Methods in a Pediatric Glycemic Control Study

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2013

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An abstract of
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Abstract

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By Samantha Shepler

Blood sugar levels can increase to unsafe levels following trauma through injury or illness resulting in prevalent hyperglycemia in pediatric ICUs. This condition has been associated with many negative health outcomes including longer lengths of stay and increased mortality. Glycemic control protocols have been presented as a treatment for critical illness hyperglycemia. This multi-center study created a group of six pediatric ICUs to implement this type of protocol. The protocol consisted of blood glucose checks every 12 hours, if the initial blood glucose reading was >140 mg/dl an additional reading was done within two hours. If the second reading was also >140 mg/dl then insulin was delivered. This analysis aims to assess the relationship between the ICUs and length of stay and mortality for the hyperglycemic pediatric ICU patients. Log-normal, gamma, and Cox proportional hazards models were proposed to model length of stay with random intercepts to allow for variation by ICU. The gamma regression model was selected as the principle method for modeling length of stay due to the distribution of the data and easy interpretation. Emory CICU, the single pediatric cardiac ICU in the study, had significantly shorter estimated length of stay adjusting for pediatric logistic organ dysfunction (PELOD) score, a measure of baseline severity. Weight and if the patient was an infant were also found to be significantly associated with length of stay. Additionally, a logistic model was created to model mortality with random intercepts to allow for variation between ICU. The results showed no significant differences in odds of mortality across the ICUs but showed a significant association between mortality and PELOD score. Our results suggest there is a difference at the ICU level that our data set is unable to ascertain which is driving significantly different lengths of stay for pediatric ICU patients.

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Chapter I: Introduction

Background

Added stress on the body due to severe illness or injury can result in high blood sugar. This complication termed hyperglycemia has been shown to be associated with negative health outcomes, including longer hospital stays and increased mortality (Preissig, Rigby, & Maher, 2009). Glycemic control procedures have been presented as an option to reduce these outcomes in intensive care unit (ICU) patients. A typical protocol for controlling hyperglycemia for critical illness consists of repeatedly checking blood glucose levels and administering insulin if those levels exceed a threshold specified a priori. Since the protocol is using insulin to lower blood glucose levels, there is a risk of lowering the levels too far, which could result in a number of adverse reactions such as seizures or hypoglycemia. Hypoglycemia, or low blood sugar, is a very serious condition that could result in death; this serious side effect is one of the main arguments against this type of protocol.

Foundational studies implementing glycemic control protocols have been principally focused on adult ICU patients; however, more recent projects have now shown similar favorable health outcomes (i.e. lower mortality and shorter length of stay) in pediatric ICU patients treated with these protocols (Kandil, Miksa, & Faustino, 2013). Even so, these results have been inconsistent, with some studies indicating significant differences in mortality and length of stay and others demonstrating no decreases in negative outcomes, while concurrently citing the risk

for hypoglycemia as too large (Agus et al., 2012; Kandil et al., 2013; Macrae et al., 2014). Reducing rates of negative outcomes in ICU patients, especially children, would be beneficial for all parties involved; therefore, it is imperative to determine what is driving these results.

A multi-site clinical study was federally funded with two specific aims: (1) to create a consortium of pediatric ICUs that would treat eligible patients according to the critical illness hyperglycemia (CIH) protocol proposed by Preissig et al. (2009) and (2) test the hypothesis that outcomes from the hospitals with prior experience using the CIH protocol would show similar patient results to de novo hospitals.

Problem Statement

Glycemic protocols may seem straightforward to implement, but patient care in an ICU can be extremely complex. Specifically, in a pediatric ICU there are diverse groups of children with a variety of conditions at differing levels of severity. Nurses and healthcare staff are responsible for a vast amount of medical procedures, on which they are expertly trained and practice routinely. Glycemic control protocols are not universally required in either adult or pediatric ICUs, and therefore, many healthcare workers lack the necessary experience to implement these protocols, while ensuring high quality of care.

It is unknown how experience with the protocol, clinical center, and disparate patient populations are related to the different health outcomes of individuals whom receive glycemic control treatment. It could be possible that nurses with less experience with this type of treatment have less optimal results and

potentially higher occurrences of hypoglycemia, resulting in the inconsistency that we have seen in the studies.

Purpose Statement

Our primary aim is to investigate the relationship in glycemic care between individual hospitals (i.e. nursing care, nurse experience, and patient population) as they relate to the adverse outcomes, prolonged length of stay and patient mortality. Specifically, we want to determine if patients receiving glycemic care from a protocol-experienced clinic have statistically shorter ICU lengths of stay and decreased risks of mortality relative to patients receiving treatment from hospitals newly instituting a hyperglycemia protocol. Secondly, we want to determine the superior statistical method for modeling the association between hospital ICUs and adverse outcomes (i.e. length of stay, and mortality), while adjusting for data obtained from multiple hospital sources.

Significance Statement

This research will provide foresight into the efficacy of the CIH protocol. Additionally, this work aims to address incongruences in the literature by identifying means of improving patient care (i.e. glycemic control training programs) and reducing drivers for inconsistent results.

Chapter II: Review of the Literature

The following literature review provides necessary information and justification for this study and the associated analyses. First, the review defines stress hyperglycemia and explains its physiologic effects to demonstrate the need for effective glycemic control treatment. Second, the review summarizes previous ICU glycemic control studies to understand the protocols, results, and safety of the treatments. Third, the review explores the use of length of stay as the outcome of interest, specifically pertaining to the different methods of statistical modeling. Last, the review investigates the use of random effects to adjust for variation between hospital ICUs.

Stress Hyperglycemia

Hyperglycemia is defined as a blood glucose level greater than 7.7 mmol/l or 140mg/dl (Preissig, et al., 2009). High blood glucose levels during critical illness is called stress hyperglycemia because it is thought to be the body's response to a stressor such as an injury or illness (Kandil et al., 2013). While this biological response might be beneficial throughout the acute phase of illness or injury, chronic high blood glucose levels has been linked with negative health outcomes. Preissig et al. (2009) showed that pediatric postoperative cardiac patients in the ICU that developed hyperglycemia had longer hospital stays and increased mortality when compared to patients that did not develop hyperglycemia. Furthermore, this study pointed out the ubiquity of stress hyperglycemia in pediatric ICU patients, with incidence rates reaching 84% in this study and others. Patients needing vasopressor

infusions (i.e. deliverance of a drug to constrict blood vessels and raise blood pressure) had an even higher incidence of hyperglycemia (reaching 90%), indicating a population that might benefit most from glycemic control protocols.

ICU Glycemic Control Protocols

Glycemic control protocols have been implemented as a possible solution for stress hyperglycemia in both adult and pediatric ICU populations. Since this type of treatment is not yet universal and still somewhat controversial, medical associations do not agree on blood glucose-level parameters for determining when insulin should be delivered in critically ill adults (Kandil et al., 2013). For adults, the Society of Critical Care Medicine recommends a target blood glucose range of 100-150 mg/dl; whereas, the American Diabetes Association calls for a target blood glucose range of 140-180 mg/dl. Glycemic control treatment is even more contentious in pediatrics, as there are no consensus standards on target blood glucose ranges for critically ill children at present, resulting in differing blood glucose ranges for pediatric glycemic control studies. This discord is evidenced in the following trial descriptions. Vlasselaers et al. (2009) conducted the first randomized control trial (RCT) implementing glycemic control in critically ill children. This study set their target blood glucose range to be 50-80 mg/dl for children less than 1 year old, and 70-100 mg/dl for children 1 to 16 years old. Conversely, Safe Pediatric Euglycemia after Cardiac Surgery (SPECS) trial, a RCT using postoperative children older than 36 months, set their target blood glucose range to be 80-100 mg/dl (Agus et al., 2012). Also, the Control of Hyperglycaemia in Paediatric Intensive Care (CHiP) trial, a RCT using pediatric ICU patients under the

age of 16, set their target blood glucose range to be 72-126 mg/dl (Macrae et al., 2014).

Different protocols make comparing the pediatric ICU glycemic control studies increasingly difficult. Even so, it is apparent that results across these studies have been inconsistent. The Vlasselaers RCT showed promising results implementing glycemic control in critically ill children (Kandil et al., 2013). For the children randomized to the glycemic control treatment, researchers found a 3% reduction in mortality, a decrease in the risk of secondary infection, and a shorter length of stay overall. The SPECS trial did not find any significant differences between the treatment (i.e. glycemic control) and control (i.e. standard of care) groups for mortality, healthcare associated infections, or length of stay (ICU or hospital) (Agus et al., 2012). The CHiP trial demonstrated benefits for glycemic control treatment for very specific outcomes and subgroups (Macrae et al., 2014). Compared to the control group, the patients that received the glycemic control treatment had lower rates of renal-replacement therapy. Also, for those patients that had not undergone cardiac surgery, length of stay was 13.5 days shorter on average for the patients that received the glycemic control treatment compared to the control group.

A significant concern pertaining to these studies was the safety of glycemic control protocols. Hypoglycemia is a potentially serious side effect of this treatment, occurring when too much insulin is delivered and blood glucose levels are lowered to unsafe levels. Definitions varied slightly by study, but the CHiP trial defined moderate hypoglycemia as a blood glucose level between 36 and 45 mg/dl and

severe hypoglycemia as a blood glucose level below 36 mg/dl (Macrae et al., 2014). The Vlasselaers RCT using the glycemic control protocol had a 25% incidence of hypoglycemia in the treatment group versus 1% incidence in the control group (p-value <0.001) (Kandil et al., 2013). Hypoglycemia was more common in the treatment group, but their analysis showed no significant association with hypoglycemia and mortality. The SPECS trial had a total hypoglycemia incidence of 19%, with a severe hypoglycemic incidence of 3% in the treatment group compared to 9% and 1% in the control group, respectively (p-value <0.001; p-value = 0.030) (Agus et al., 2012). None of the episodes of hypoglycemia resulted in any associated complications. The SPECS trial had a mortality rate of 2% for both their treatment and control groups. The CHiP trial also found higher rates of hypoglycemia in the treatment group compared to the control group (Macrae et al., 2014). The proportion of the treatment group that had moderate hypoglycemia was 12.5% compared to 3.1% in the control group (p-value <0.001) and the proportion of the treatment group that had severe hypoglycemia was 7.3% compare to 1.5% in the control group (p-value <0.001). The investigators noted that 5.9% of the patients that had an episode of hypoglycemia also had a seizure the same day, and that in the subgroup of patients that had undergone cardiac surgery, hypoglycemia was significantly associated with mortality. The researchers also noted that 5.1% of the patients in the glycemic control treatment died within 30 days of entering the trial, and that 10.5% died within a year of entering the trial. Preissing et al. (2009) showed that glycemic control in a pediatric setting could be done without an increased risk of hypoglycemia. Their project of 20 postoperative cardiac patients

undergoing glycemic control resulted in no patient ever having a hypoglycemic episode, defined as a blood glucose level below 40 mg/dl. While their sample size was small, the study still showed promise in reducing hypoglycemia rates during glycemic protocol treatment.

Modeling Length of Stay

Length of stay is an advantageous outcome of interest for ICU studies, as it can serve as a proxy for both quality of care and cost to the healthcare facility (Straney, Clements, Alexander, & Slater, 2009). Since length of stay data generally fails to be normally distributed with long, skew-right tails and the bulk of the data clustered close to 0, a log-transformation is commonly utilized when modeling this characteristic (Faddy, Graves, & Pettitt, 2009). Weibull and gamma models with log-links are also employed, along with many other proposed models including Cox proportional hazards (Basu, Manning, and Mullahy, 2004). The log-link function makes the estimated outcome from the regression model equal to the exponential of the corresponding coefficients. Basu et al. (2004) gauged the performance of these four models by using simulation to examine prediction bias. The researchers determined model estimates highly depend on the data to which they are being applied. Specifically, the Cox proportional hazards model does not perform well when the proportional hazards assumption is not met; concurrently, the log-transformed model does not perform well when the data is generated using a proportional hazards assumption. Using simulated log-normal, gamma, and Gompertz data, Basu et al. (2004) found the gamma model with a log-link function to performed reasonably well relative to its counterparts (log-normal, Weibull, Cox

proportional hazards); concomitantly, this result was bolstered when applied to actual length of stay data, again providing superior model fit versus other statistical methods.

Another complication when working with length of stay data is patient mortality in the ICU. The Cox proportional hazards model allows an option to include these observations as censored events, but the other models lack this capability (Basu et al., 2004). One option to adjust for patient death is to exclude the patients that died from the model (Straney et al., 2009). This option is the most straightforward, but important information is often lost. Alternatively, the SPECS trial set the length of stay for the patients that died to 30 days, which still allows for the use of the data (Agus et al., 2012). This option penalizes the length of stay estimates for patients that die, but because the selected 30 days is an arbitrary number, the estimates may be incorrect.

Center Effect

A possible explanation for the inconsistent results of pediatric glycemic control protocols could be due to differences at the ICU level. Random intercepts allow for the quantification of variation of length of stay at the ICU level, potentially discerning where the quality of care is above or below the overall hospitals' average (Straney et al., 2009). Multilevel models require a sufficient number of groups and size of groups in order to give unbiased standard error estimates (Maas & Hox, 2005). Through simulation, Maas and Hox (2005) found that standard errors for the second-level (i.e. random-intercept) variance components are estimated too small when the number of groups is ≤ 50. Using 1,000 simulated dataset, they found when

a multi-level model has 30 groups, the non-coverage rate for the second-level intercept variance was 8.9% and for 50 groups was 7.4%. The 95% confidence interval for this parameter was therefore, not actually wide enough for 30 or 50 groups. The size of the groups did not have as substantial of an impact on this standard error as number of groups, but coverage rates still improved as group size increased. It should be noted that the estimates for the regression coefficients, the standard errors for the regression coefficients, and the variance components were not significantly affected by either the number of groups or the size of the groups.

Chapter III: Methodology

This federally-funded, prospective observational study hypothesized that the CIH glycemic protocol was simple enough to implement in non-protocol-experienced ICUs, and patients within these centers would experience similar outcomes as those in protocol-experienced ICUs. This hypothesis spurred a broader question involving ICU characteristics. Specifically, the aim of this analysis was to investigate the association between individual ICUs and the clinical outcomes of pediatric patients receiving the CIH glycemic protocol treatment.

Study Sites

The study took place at six pediatric ICUs, of which two had previous experience implementing the glycemic control protocol. The two ICUs with experience were the Medical/Surgical Pediatric ICU (Emory PICU) and the Sibley Cardiac ICU (Emory CICU), both at Children's Healthcare of Atlanta, Egleston. The other four ICUs were Riley Hospital for Children (Riley) in Indianapolis, IN, Kosair Children's Hospital (Kosair) in Louisville, KY, Medical Center of Central Georgia (Macon) in Macon, GA, and Monroe Carell Jr. Children's Hospital at Vanderbilt (Vanderbilt) in Nashville, TN.

Study Glycemic Control Protocol

Physicians ordered the glycemic control protocol for patients whom were deemed high risk for developing hyperglycemia based on pre-defined criteria. High-risk patients were generally on mechanical ventilation, vasopressor infusions, and/or renal replacement therapy. Patients who received the glycemic control

protocol had their blood glucose levels checked every 12 hours by a nurse. An additional check was done within two hours if the initial reading was > 140 mg/dl. If the second reading was also >140 mg/dl, the patient was diagnosed as hyperglycemic and insulin was delivered until a target blood value was reached. The target blood glucose range for this protocol was 80-140 mg/dl.

Data

This study utilized a data registry to obtain information from the six participating pediatric ICUs. Demographic and hospital admission data were collected on all patients that were placed on the glycemic control protocol. This data included variables such as age, weight, height, admission type, and surgery type. Additionally, medical data were only collected on all patients that developed hyperglycemia while on the glycemic control protocol, and included data elements related to: adverse health outcomes, insulin delivery, length of stay, and time on mechanical ventilation. As a result of this restriction, our analytic sample only included those patients that developed hyperglycemia.

For this study, moderate hypoglycemia was defined as a blood glucose level between 40 and 60 mg/dl, and severe hypoglycemia was defined as a blood glucose level below 40 mg/dl. Pediatric logistic organ dysfunction (PELOD) scores, a measure of baseline severity, were calculated for all glycemic patients using laboratory results regarding the cardiovascular, pulmonary, neurologic, hematologic, hepatic and renal functions (Leteurtre et al., 2003).

Data Analysis

The data were managed in SAS 9.4 and analyzed in both SAS 9.4 (Cary, NC) and R Project 3.0.2 (Vienna, Austria). Categorical variables were described using frequencies and percentages. Chi-square tests of independence were used to compare the distributions of categorical variables by ICU, and an exact form of the Pearson chi-square test was used when multiple cell counts had expected values less than five (Fisher's test). Continuous variables were described using means and standard deviations. Analysis of variance (ANOVA) tests were used to compare the means of continuous variables by ICU. If the residual plots for the ANOVA model showed the normality assumption was violated, a Kruskal-Wallis test was used to compare the continuous variables across ICU.

Our primary outcome of interest was ICU length of stay. Mixed-effects regression models were used to examine the association between length of stay and the individual ICUs. Crude and PELOD-adjusted log-normal and gamma regression models with length of stay as the outcome were constructed with random intercepts to allow for variation between centers. Children that died while in the ICU were excluded from these models to avoid potential bias in the length of stay estimates. This was justified as children who died soon after being admitted likely differ in presentation as those whom were discharged soon after being admitted. Estimated mean length of stay was reported for each of the ICUs for both log-normal and gamma modeling methods. The adjusted length of stay estimates were calculated using PELOD centered at the analytic sample mean. Additionally, crude and PELOD-adjusted Cox proportional hazards models were constructed, modeling length of stay with shared frailty terms (random effects) for the ICUs. Unlike the usual Cox

proportional hazards model, the event of interest was discharge from the ICU and the censored event was death. Due to the model specification the hazard ratios provided by the Cox proportional hazards model are interpreted as chance that a patient from a specific ICU will be discharged compared to the baseline hazard rate (average patient in the study). The proportional hazards assumption was tested to determine the usefulness of the model by adding a time dependent covariate to the model and testing for significance. Hazard ratios were reported for each of the ICUs.

Based on the estimates and the proportional hazards assumption a model was selected to add additional covariates of interest to further examine the relationship between length of stay and characteristics at the patient and ICU level. The covariate selection for this multivariate model was made using stepwise selection with bidirectional elimination (i.e. after adding new a variable, the variables already included were tested again) using a 0.05 significance level. The potential additional covariates were if the patients was an infant, age, weight, sex, race, ethnicity, admission type, glycemic protocol experience, and if the patient was treated with insulin. Variance inflation factors (VIF) were calculated to assess for multicollinearity between the selected variables to ensure their need. Additionally, a covariance test was conducted to verify the need for the random intercepts for ICU after adjusting for the additional significant covariates.

Our secondary outcome of interest was death. Logistic regression models were used to examine the relationship of mortality across the ICUs. A multivariable logistic regression model was constructed including random effects for the ICUs and covariates of interest, specifically those considered in the previous length of stay

models. Stepwise selection with bidirectional elimination was employed using a significance level of 0.05. A covariance test was conducted to determine if there was need for the random intercept for ICU after adjusting for the significant covariates. Odds ratios were reported for each of the ICUs and the covariates of interest.

Chapter IV: Results

Description of Sample

The final analytic sample contained 364 patients, 49 (13.5%) from Emory PICU, 50 (13.7%) from Emory CICU, 28 (7.7%) from Macon, 159 (43.7%) from Kosair, 62 (17.0%) from Riley, and 16 (4.4%) from Vanderbilt. The average age of the patients was 8.28 (SD: 7.05) years, the average weight was 30.81 (SD: 27.55) kilograms, and 199 (54.7%) were male. Age, weight, and sex did not significantly differ between the ICUs (Table 1). The sample was principally white (64.0%) and non-Hispanic (49.3%). Race and ethnicity were found to significantly differ between ICUs (Table 1); however, ethnicity had a high rate of unknowns (44.9%), as Kosiar specified this characteristic for only 3.8% of their patients. This issue may explain the significant difference found for ethnicity across ICUs. Medical admissions made up 55.8% of the sample, with the most common type being general pediatric ICU (81.8%). Surgical admissions comprised 44.2% of the sample, with most receiving cardiovascular surgery (64.0%). Admission type and surgical type significantly differed between the ICUs potentially explained by the differing specialties of the ICUs (Table 1). Medical admission type, cardiovascular surgery type and non-cardiovascular surgical type did not significantly differ across ICUs (Table 1). The PELOD scores and risk-adjusted congenital heart surgery (RACHS) scores significantly differed by ICU, implicating the patients' baseline severity of illness differed among ICUs (Table 1).

All the patients in the analytic sample became hyperglycemic, but due to error, 31 (9.1%) patients did not receive insulin. The average length of stay across all hospitals was 14 (SD: 16.18) days. Average length of stay significantly differed by ICU ranging from 4.24 (SD: 7.49) days at Emory CICU to 20.56 (SD: 23.02) days at Vanderbilt (Table 2). The number of patients that died was 70 (19.2%), and mortality significantly differed by ICU (Table 2). Overall, 49 (13.5%) patients developed moderate hypoglycemia and 13 (3.6%) patients developed severe hypoglycemia. The proportion of patients that developed moderate hypoglycemia differed significantly across ICUs but severe hypoglycemia did not (Table 2), most likely due to the small proportion of patients that developed the more severe case.

Association between Length of Stay and ICU

The log-normal model, the gamma model with a log-link function, and the Cox proportional hazards model showed similar trends in length of stay by ICU for both the crude and PELOD-adjusted models (Table 3 & Table 4). The proportional hazards assumption held for the time-dependent covariate using site and the log length of stay (p-value = 0.080), therefore suggesting the log-normal model would not provide the best fit. The Cox proportional hazards model showed the only ICU where patients had a significantly higher chance of getting discharged was Emory CICU (Table 4). The patients at this ICU were estimated to be 4.91 (95% CI: 3.75 – 6.43) times more likely to be discharged compared to the average patient in the study after adjusting for PELOD. Similar effects were seen in the gamma model but due to recommendations stemming from the literature, gamma regression with a log-link was chosen as the principal means of LOS analysis. Furthermore, its

robustness for skewed data and ease of estimate interpretation over the Cox proportional hazards model better suit the aims of this investigation. Overall, the data and the analysis were most in line with the assumptions of the gamma distribution. The gamma model with a log-link estimated the overall mean length of stay to be 11.74 (95% CI: 6.56 - 21.01) days after adjusting for PELOD (Table 3). The only ICU with a significantly different length of stay from the overall mean was Emory CICU (p-value < 0.001). After adjusting for PELOD, the estimated length of stay for Emory CICU was 2.99 (95% CI: 2.19 – 4.09) days. This effect was also shown in the crude model but only became more apparent after adjusting for PELOD. The final multivariate model for length of stay additionally included weight (p-value = 0.004) and if the patient was an infant (p-value = 0.002) (Table 5). The model estimated that for every kilogram increase in weight, length of stay decreased by 0.007 (SD: 0.002) days or 9.418 minutes. The model also estimated that patients who were infants had a length of stay 0.544 (SD: 0.176) days or 13.051 hours longer than patients who were not infants. Therefore, A patient's length of stay was estimated to be longer if their weight was lower and for infants. VIFs for the three fixed-effects (PELOD, weight, and if the patient as an infant) were small and did not show signs of multicollinearity (Table 5). After adjusting for the additional covariates, the random effects for ICU were still significant in estimating length of stay (p-value <0.001).

Association between death and ICU

The final logistic model for death included the random intercept for ICU and PELOD (p-value = <0.001). The model estimated that for every one-unit increase in

PELOD, the odds of death increased by 1.07 (95% CI: 1.05 - 1.10). After adjusting for PELOD, none of the individual ICUs patients had odds of death significantly different from the average (Table 5), but the random effects were still significantly important to the model (p-value =0.001).

Chapter V: Discussion

Hyperglycemia is a common issue for the critically ill and thus is highly prevalent in ICU patients. In these populations, hyperglycemia has been shown to be associated with negative health outcomes, including longer hospital stays and increased mortality. Glycemic control protocols have been introduced as a potential solution. Research has demonstrated that this type of treatment has been beneficial in reducing mortality and length of stay for adult ICU patients but results for pediatric ICU patients have been inconsistent.

Our study intended to create a group of pediatric ICUs to implement the glycemic control protocol with the hypothesis that the treatment was simple and intuitive enough that ICUs with no previous experience with glycemic control protocols would have similar outcomes as ICUs with previous experience. For our primary and secondary outcomes, length of stay and mortality, we created random-effects models in order to allow for variation between the ICUs and to test for differences.

We found that length of stay significantly differed by ICU and that PELOD score, weight, and if the patient was an infant were significantly associated with length of stay. It is intuitive that length of stay differed by PELOD scores because it is likely that a patient that is in critical condition would need more care than a less ill patient. While weight and if the patient were an infant did not have multicollinearity issues, they seem as if they measured very similar characteristics, showing that smaller children and infants had longer lengths of stay. Our model for mortality

showed that PELOD scores were significantly associated death in pediatric ICU patients and after adjusting for PELOD, odds of death did not significantly differ by ICU. Again, it is intuitive mortality differed by PELOD scores because it is likely that a patient that is in critical condition is more likely to die that a patient with a less severe illness or injury.

Based on this analysis we cannot make a conclusion on the original hypothesis, comparing protocol-experienced and unexperienced ICUs. While one of the experienced ICUs did have a significantly shorter length of stay than the average, the other experienced ICU did not. When glycemic control protocol experience was added to the model, it did not provide significant additional information when already adjusting for the individual ICUs.

Conclusions

We found that in our glycemic control study, length of stay for pediatric patients that developed hyperglycemia differed significantly by ICU after adjusting for significant covariates (PELOD score, weight, if the patient was an infant). Specifically, Emory CICU had a significantly shorter crude length of stay compared to the other 5 ICUs in the study and this significant difference away from the mean became even more pronounced after adjusting for PELOD score, which occurred most likely because the average PELOD score was the highest at Emory CICU.

Glycemic control protocols have been previously studied in multiple pediatric ICUs citing inconsistent results (Kandil, Miksa, & Faustino, 2013). Since the previous studies have been randomized, health outcomes including length of stay and mortality have yet to be analyzed across ICUs because randomization

should remove the center effect. Even so, our results suggest that the center could help explain some of the variation in length of stay.

Safety is extremely important when implementing a treatment that is not yet standard of care, especially when working with pediatric patients. Our study reported rates of moderate and severe hypoglycemia that were comparable to both the SPECS and CHiP trials, but the mortality rate in our study may be of concern. In our study 19.2% of the patients died while in the hospital, whereas only 2% of the patients died while in the hospital during the SPECS trial. The CHiP trial does not report this exact statistic but their mortality 12 months after trial entry was 10.5%. Both of these studies had a much smaller proportion of the patients that died, this difference could potentially be explained by differing patient populations but we were unable to ascertain specifically why this outcome occurred.

Implications

Since Emory CICU's length of stay was significantly shorter than all of the other participating ICUs, it might be of interest to examine ICU specialties in relation to length of stay. Emory CICU was the only strictly cardiac ICU in the study, making is impossible to test if length of stay was shorter for patients in this type of unit or if the glycemic protocol treatment worked better for this subgroup of patients. If this relationship is true, then glycemic control protocols might be best suited for specific types of patients and therefore driving inconsistent results.

Strengths and Limitations

We were able to identify a significant difference in length of stay between the ICUs. This difference was still present even after adjusting for nurse's experience

with the glycemic control protocol, admission type, and patient characteristics. This shows that there is a fundamental difference in practice and philosophy between the ICUs that is likely causing this effect. While there are limitations to our study and the analysis, it provides a good basis for more research.

The hospitals in this study were not randomly selected and neither were the patients that received the glycemic control treatment. Therefore, the results and conclusions may not be generalizable to all hospitals but to only those that participated in the study and to the patients that received the treatment. Also, because all patients that became hyperglycemic were intended to receive the glycemic control treatment, there was no way to test the effectiveness of the treatment because there is no control group. The few patients that became hyperglycemic, but mistakenly were not given insulin, were too small of a sample to provide useful comparisons. We also were unable to compare the patients that became hyperglycemic to those who did not as no prospective data was collected on the patients that did not become hyperglycemic after admission.

An additional concern for this study is the number of hospitals and number of patients at each hospital. Our study only had six independent hospitals. Random effects analyses can be very sensitive to the number of groups present. There is concern that when the number of groups is much smaller than 100, the standard errors for the random-level (i.e. hospital) variance estimates will be too small. When there are 30 groups, the standard errors will be estimated around 15% too small (Maas & Hox, 2005), and we can assume that with six groups, the standard error estimates will be even smaller. The sample size per group is less of a concern but he

two of the hospitals that have a sample size less than 50 could have biased standard errors for the hospital-level variance estimates.

Future Recommendations

Since the difference in length of stay remained significantly different across the ICUs, even after adjusting for the significant covariates, more research needs to be done to determine why this difference still exists. One approach would be to use a latent variable for measuring quality of care. Quality of care is not something that can be ascertained directly from this dataset but could be influential in determining the association between the individual ICUs and length of stay.

It would also be interesting to analyze glycemic protocol implementation over time. We could examine the relationship between experience with the glycemic control protocol and health outcomes but since comparisons could be made for a single institution, there would be no need to balance by patient population.

References

Agus, M. S. D., Steil, G. M., Wypij, D., Costello, J. M., Laussen, P. C., Langer, M., . . . Gaies, M. G. (2012). Tight glycemic control versus standard care after pediatric cardiac surgery. The New England Journal of Medicine, 367(13), 1208 – 1209.

Basu, A., Manning, W. G., & Mullahy, J. (2004). Comparing alternative models: log vs Cox proportional hazard? Health Economics, 13, 749 – 756.

Faddy, M., Graves, N., & Pettitt, A. (2009). Modeling length of stay in hospital and other right skewed data: comparison of phase-type, gamma and log-normal distributions. Value in Health, 12(2), 309 – 314.

Kandil, S. B., Miksa, M., & Faustino, E. V. S. (2013). Control of serum glucose concentration in critical illness. Emergency and Critical Care Medicine, 25(3), 297 – 303.

Leteurtre, S., Martinot, A., Duhamel, A., Proulx, F., Grandbastien, B., Cotting, J., . . . Leclerc, F. (2003). Validation of the paediatric logistic organ dysfunction (PELOD) score: Prospective, observational, mulitcentre study. The Lancet, 362, 192 – 197.

Maas, C. J. M., & Hox, J. J. (2005). Sufficient sample sizes for multilevel modeling. Methodology, 1(3), 86 – 92.

Macrae, D., Grieve, R., Allen, E., Sadique, Z., Morris, K., Pappachan, J., . . . Elbourne, D. (2014). A randomized trial of hyperglycemic control in pediatric intensive care. The New England Journal of Medicine, 370(2), 107 – 118.

Preissig, C. M., Rigby, M. R., & Maher, K. O. (2009). Glycemic control for postoperative pediatric cardiac patients. Pediatric Cardiology, 30, 1098 - 1104.

Straney, L., Clements, A., Alexander, J., & Slater, A. (2010). Quantifying variation of paediatric length of stay among intensive care units in Australia and New Zealand. Quality and Safety of Health Care, 19(6).

Vlasselaers, D., Milants, I., Desmet, L., Wouters, P.J., Vanhorebeek, I., Van den Heuvel, I., . . . Van den Berghe, G. (2009). Intensive insulin therapy for patients in paediatric intensive care: A prospective, randomised control study. The Lancet, 373, 547 – 556.

Tables

Table 1: Patient Characteristics

	Total N=364	Emory PICU N = 49	Emory CICU N = 50	Macon N = 28	Kosair N = 159	Riley N = 62	Vanderbilt N = 16	P-value
Infant (age < 1)	58 (15.93%)	5 (10.20%)	16 (32.00%)	2 (7.14%)	19 (11.95%)	15 (24.19%)	1 (6.25%)	0.002
Age (years)	8.28 (7.05)	9.03 (6.24)	7.11 (6.54)	6.57 (5.53)	8.58 (6.77)	8.49 (9.31)	8.79 (5.93)	0.240
Weight (kg)	30.81 (27.55)	34.01 (25.98)	26.47 (22.56)	22.29 (22.77)	32.22 (29.32)	32.33 (30.86)	29.68 (20.43)	0.253
Male sex	199 (54.67%)	31 (63.27%)	22 (44.00%)	15 (53.57%)	97 (61.01%)	28 (45.16%)	6 (37.50%)	0.062
Race								< 0.001
African American	99 (27.20%)	27 (55.10%)	13 (26.00%)	16 (57.14%)	32 (20.13%)	8 (20.13%)	3 (18.75%)	
White	233 (64.01%)	19 (38.78%)	30 (60.00%)	12 (42.86%)	111 (69.81%)	49 (79.03%)	12 (75.00%)	
Other/unknown	32 (8.79%)	3 (6.12%)	7 (14.00%)	0	16 (10.06%)	5 (8.06%)	1 (6.25%)	
Ethnicity								< 0001
Hispanic	21 (5.79%)	5 (10.20%)	3 (6.00%)	4 (14.29%)	6 (3.80%)	1 (1.61%)	2 (12.50%)	
Not Hispanic	179 (49.31%)	41 (83.67%)	45 (90.00%)	22 (78.57%)	0	58 (93.55%)	13 (81.25%)	
Unknown	163 (44.90%)	3 (6.12%)	2 (4.00%)	2 (7.14%)	152 (96.20%)	3 (4.84%)	1 (6.25%)	
Admission type								< 0.001
Medical	203 (55.77%)	41 (83.67%)	N/A	24 (85.71%)	82 (51.57%)	43 (69.35%)	13 (81.25%)	
Surgical	161 (44.23%)	8 (16.33%)	50 (100.00%)	4 (14.29%)	77 (48.43%)	19 (30.65%)	3 (18.75%)	
Medical								0.318
General PICU	166 (81.77%)	34 (82.93%)	N/A	24 (100.00%)	63 (76.83%)	34 (79.07%)	11 (84.62%)	
Oncology	25 (12.32%)	6 (14.63%)	N/A	0	10 (12.20%)	7 (16.28%)	2 (15.38%)	
Cardiac	7 (3.45%)	0	N/A	0	5 (6.10%)	2 (4.65%)	0	
Other	5 (2.46%)	1 (2.44%)	N/A	0	4 (4.88%)	0	0	
Surgical								< 0.001
Non-CV	58 (36.02%)	8 (100.00%)	0	4 (100.00%)	36 (46.75%)	9 (47.37%)	1 (33.33%)	
CV	103 (63.98%)	N/A	50 (100.00%)	N/A	41 (53.25%)	10 (52.63%)	2 (66.67%)	
Non-CV surgical								0.261
General surgery	19 (32.76%)	4 (50.00%)	N/A	3 (75.00%)	10 (27.78%)	2 (22.22%)	0	
Trauma	28 (48.28%)	1 (12.50%)	N/A	1 (25.00%)	20 (55.56%)	5 (55.56%)	1 (100.00%)	
Liver transplant	2 (3.45%)	2 (25.00%)	N/A	0	0	0	0	
Kidney transplant	1 (1.72%)	0	N/A	0	1 (2.78%)	0	0	
Neurosurgery	6 (10.34%)	1 (12.50%)	N/A	0	4 (11.11%)	1 (11.11%)	0	
Other	2 (3.45%)	0	N/A	0	1 (2.78%)	1 (11.11%)	0	
CV surgical								0.488
CV (non-transplant)	100 (97.09%)	N/A	49 (98.00%)	N/A	40(97.56%)	9 (90.00%)	2 (100.00%)	
Heart transplant	3 (2.91%)	N/A	1 (2.00%)	N/A	1 (2.44%)	1 (10.00%)	0	
RACHS score	2.94 (1.30)	N/A	2.60 (1.123)	N/A	3.42 (1.41)	2.80 (1.32)	2.50 (0.71)	0.030
PELOD score	17.03 (12.60)	16.84 (9.88)	23.66 (10.49)	4.86 (5.47)	19.09 (12.63)	10.47 (10.84)	23.19 (16.48)	< 0.001

Continuous variables: mean(SD); categorical variables: frequency(%)

Table 2: Patient Outcomes

	Total N= 364	Emory PICU N = 49	Emory CICU N = 50	Macon N = 28	Kosair N = 159	Riley N = 62	Vanderbuilt N = 16	P-value
Received insulin	333 (91.48%)	43 (87.76%)	47 (94.00%)	26 (92.86%)	140 (88.05%)	62 (100.00%)	15 (93.75%)	0.086
ICU length of stay (days)	14.00 (16.18)	14.39 (13.14)	4.24 (7.49)	11.29 (6.44)	15.72 (14.72)	16.68 (23.65)	20.56 (23.02)	< 0.001
Died	70 (19.23%)	12 (24.49%)	2 (4.00%)	0	45 (28.30%)	9 (14.52%)	2 (12.50%)	<0.001
Hypoglycemia								
Moderate	49 (13.46%)	3 (6.12%)	0	0	34 (21.38%)	7 (11.29%)	5 (31.25%)	< 0.001
Severe	13 (3.57%)	0	0	0	9 (5.66%)	3 (4.84%)	1 (6.25%)	0.197
Time on ventilation (days)	9.79 (13.64)	11.34 (12.08)	3.71 (13.70)	5.42 (3.54)	11.07 (12.26)	11.84 (19.02)	14.20 (17.95)	< 0.001

Continuous variables: mean(SD); categorical variables: frequency(%)

Table 3: Estimated length of stay for log-normal and gamma regression models

	Overall	Emory PICU	Emory CICU	Macon	Kosair	Riley	Vanderbilt
Crude log-normal	8.11 (3.75 – 17.54)	10.97 (7.58 - 15.88)	1.97 (1.42 – 2.73)*	9.77 (6.41 – 14.91)	11.11 (8.98 – 13.74)	9.26 (6.79 – 12.62)	13.08 (7.29 – 23.48)
PELOD adjusted log-normal	8.16 (4.20 – 15.87)	11.21 (8.55 – 14.70)	1.60 (1.25 – 2.05) *	12.61 (9.12 – 17.42)	10.96 (9.38 – 12.81)	10.51 (8.33 – 13.24)	11.36 (7.35 – 17.56)
Crude gamma	12.05 (6.23 – 23.30)	14.84 (9.52 – 23.11)	4.01 (2.71 – 5.93)*	11.36 (6.87 – 18.81)	16.12 (12.45 – 20.87)	13.70 (9.43 – 19.92)	20.52 (10.36 – 40.63
PELOD adjusted gamma	11.74 (6.56 – 21.01)	14.62 (10.40 – 20.54)	2.99 (2.19 – 4.09) *	13.70 (9.15 – 20.51)	15.68 (12.87 – 19.10)	15.41 (11.51 – 20.63)	18.05 (10.57 – 30.84)

*Significant effect (p-value <0.05)

Table 4: Hazard ratios for Cox proportional hazard model

	Emory PICU	Emory CICU	Macon	Kosair	Riley	Vanderbilt
Crude	0.77 (0.65, 0.92)	3.20 (2.70, 3.79)*	1.18 (0.98, 1.42)	0.65 (0.56, 0.75)	0.80 (0.68, 0.95)	0.66 (0.53, 0.82)
PELOD adjusted	0.76 (0.58, 0.98)	4.91 (3.75, 6.43)*	0.86 (0.68, 1.08)	0.68 (0.53, 0.87)	0.63 (0.47, 0.86)	0.73 (0.73, 0.73)

*Significant effect (p-value <0.05)

Table 5: Fixed effects for multivariate gamma regression model

	Coefficient	Standard Error	P-value	VIF
PELOD	0.020	0.005	<0.001	1.035
Weight	-0.007	0.002	0.004	1.199
Infant (age < 1)	0.544	0.176	0.002	1.213

Table 6: Odds ratios for logistic regression model

	Emory PICU	Emory CICU	Macon	Kosair	Riley	Vanderbilt
PELOD adjusted	2.36 (0.80, 6.97)	0.30 (0.09, 1.05)	0.48 (0.09, 2.41)	2.46 (0.91, 6.66)	1.79 (0.59, 5.47)	0.67 (0.17, 2.62)