Association Between Intraoperative and Early Postoperative Glucose Levels and Adverse Outcomes After Complex Congenital Heart Surgery

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Background—This study sought to determine whether associations exist between perioperative glucose exposure, prolonged hospitalization, and morbid events after complex congenital heart surgery.

Methods and Results—Metrics of glucose control, including average, peak, minimum, and SD of glucose levels, and duration of hyperglycemia were determined intraoperatively and for 72 hours after surgery for 378 consecutive high-risk cardiac surgical patients. Multivariable regression analyses were used to determine relationships between these metrics of glucose control, hospital length of stay, and a composite morbidity-mortality outcome after controlling for multiple variables known to influence early outcomes after congenital heart surgery. Intraoperatively, a minimum glucose \( \leq 75 \) mg/dL was associated with greater adjusted odds of reaching the composite morbidity-mortality end point (odds ratio [OR], 3.10; 95% confidence interval [CI], 1.49 to 6.48), but other metrics of glucose control were not associated with the composite end point or length of stay. Greater duration of hyperglycemia (glucose \( > 126 \) mg/dL) during the 72 postoperative hours was associated with longer duration of hospitalization (\( P < 0.001 \)). In the 72 hours after surgery, average glucose \( < 110 \) mg/dL (OR, 7.30; 95% CI, 1.95 to 27.25) or \( > 143 \) mg/dL (OR, 5.21; 95% CI, 1.37 to 19.89), minimum glucose \( \leq 75 \) mg/dL (OR, 2.85; 95% CI, 1.38 to 5.88), and peak glucose level \( \geq 250 \) mg/dL (OR, 2.55; 95% CI, 1.20 to 5.43) were all associated with greater adjusted odds of reaching the composite morbidity-mortality end point.

Conclusions—In children undergoing complex congenital heart surgery, the optimal postoperative glucose range may be 110 to 126 mg/dL. Randomized trials of strict glycemic control achieved with insulin infusions in this patient population are warranted. (Circulation. 2008;118:2235-2242.)

Key Words: cardiopulmonary bypass ■ glucose ■ heart defects, congenital ■ hyperglycemia ■ insulin ■ pediatrics ■ surgery

Hyperglycemia occurs commonly in critically ill patients, partly because of elevated hepatic glucose production, release of counterregulatory hormones, and peripheral insulin resistance.1–3 Hyperglycemia has been associated with increased morbidity and mortality in critically ill adults, including those undergoing cardiac surgery.4–6 Mechanistically, in the setting of critical illness, hyperglycemia causes mitochondrial dysfunction and disturbances in neuronal, endothelial, and immune function, leading to end-organ injury, prolonged mechanical ventilation, and sepsis.7 Observational studies and randomized trials have found that the use of insulin to achieve strict glycemic control can decrease morbidity and mortality in critically ill adults, particularly those undergoing cardiac surgical procedures.8–11 Preliminary studies examining the relationship between perioperative glucose levels and outcomes after congenital heart surgery are limited and have yielded conflicting conclusions.12,13

Clinical Perspective p 2242

The aims of the present study were to determine whether associations exist between intraoperative or early postoperative glucose levels and adverse outcomes after complex congenital heart surgery. The primary hypothesis was that higher 72-hour postoperative average glucose levels would be associated with a longer duration of hospitalization. We also hypothesized that larger disturbances in other metrics of glucose control, including peak and minimal glucose levels, glucose variability, and duration of hyperglycemia, would be associated with a greater incidence of morbid events and a longer duration of hospitalization.
Methods

Data were obtained in part from a larger data set created to study severity of illness scores in all 1113 children admitted to the cardiac intensive care unit (ICU) during the 2003 calendar year. Additional covariates and all glucose exposure variables were collected by a single investigator (A.P.) for the present study. The Committee on Clinical Investigation at Children’s Hospital Boston approved the study and waived the requirement for written informed consent.

Setting and Patients

This retrospective cohort study was conducted in the 21-bed pediatric cardiac ICU at Children’s Hospital Boston. We included all patients undergoing cardiac surgery at our institution during the 2003 calendar year who could be assigned to a Risk Adjustment in Congenital Heart Surgery (RACHS-1) category ≥3.14 RACHS-1 is a validated risk adjustment method that groups cardiac surgical procedures with similar expected in-hospital mortality rates into 6 predefined risk categories; category 1 has the lowest risk for death (eg, secundum atrial septal defect closure) and category 6 has the highest risk for death (eg, stage 1 Norwood operation). We excluded patients undergoing a cardiac surgical procedure that could not be classified with the RACHS-1 method.

Dextrose-containing fluids are not administered intraoperatively to patients undergoing cardiac surgery in our institution. Postoperatively, dextrose-containing intravenous fluids and infusions (10% dextrose for patients <3 months of age; 5% dextrose otherwise) are administered so that the total fluid intake is 50% (100% for patients not requiring cardiopulmonary bypass [CPB]) of the daily maintenance requirement for the first 24 hours after surgery and 100% of the daily maintenance requirement thereafter.

Definition of Variables and Outcomes

All blood glucose measurements obtained intraoperatively and for the first 72 hours after surgery were collected. Metrics of glucose control were calculated separately to reflect exposure in the operating room and during the first 72 postoperative hours in the cardiac ICU. Because the number of glucose samples obtained during a given time unit can bias the calculated average glucose level, we calculated the “area under the glucose curve,” which we designated as the time-weighted glucose average (TWGA).15 Maximum and minimum glucose values were determined. Duration of hyperglycemia was assessed by calculating the number of hours to exposure to glucose >126 mg/dL.16,17 and >200 mg/dL.1,6,8,13,18 Glucose variability was estimated by calculating the SD of blood glucose levels.19

The primary outcome variable was days of postoperative hospitalization. The study design initially included 12 secondary outcome measures: hospital mortality and a composite morbidity variable. However, an insufficient number of postoperative deaths (n=15) occurred to allow an appropriate multivariate analysis with mortality as an outcome variable. Thus, we incorporated mortality into the composite morbidity variable, which also included ≥1 of the following: nosocomial infection (defined by the Center for Disease Control and Prevention’s National Healthcare Safety Network surveillance criteria that were in use during the study time period20), cardiovascular failure requiring extracorporeal membrane oxygenation, acute renal failure requiring dialysis, hepatic injury (defined by alanine aminotransferase ≥500 U/L), and new central nervous system injury (defined by definite seizure activity, cerebrovascular accident by computed tomography scan, or new intracranial hemorrhage documented by computed tomography scan or ultrasound). This composite morbidity-mortality variable was binary; it was based on whether the patient died or had at least one of the morbidity events listed above.6 The individual components of this composite outcome variable have all been associated with glucose toxicity in other studies.8,11,12,21 To ensure that all glucose exposure occurred as the time-weighted glucose average (TWGA),15 maximum and minimum glucose values were determined. Duration of hyperglycemia was assessed by calculating the number of hours to exposure to glucose >126 mg/dL.16,17 and >200 mg/dL.1,6,8,13,18 Glucose variability was estimated by calculating the SD of blood glucose levels.19

The potential confounding variables were considered if they are believed to influence postoperative recovery after congenital heart surgery on the basis of existing literature or internal expert opinion. They included age, the presence of a genetic syndrome, the presence of at least 1 major noncardiac structural anomaly,22 prematurity (gestational age <36 weeks),23 RACHS-1 category,14 CPB time,24 need for multiple procedures during a single operation (eg, tricuspid valvuloplasty during a Fontan operation), and need for reoperation or interventional cardiac catheterization for residual cardiac defects during the same hospitalization. Given the known effect of exogenous catecholamine administration on glucose levels, a 72-hour maximal isotrope score was calculated by summing the dose of inotropic agents in micrograms per kilogram per minute: [dose of dopamine+dose of dobutamine+(dose of milrinone×10)+(dose of epinephrine×100)].

Statistical Analysis

SAS software (SAS System for Windows, version 9.1, SAS Institute, Inc, Cary, NC) was used for statistical analysis. Given the different durations of exposure and management issues and to maintain consistency with prior studies, intraoperative and postoperative glucose variables were analyzed separately. Continuous variables are reported as median (10th to 90th percentile). The primary outcome variable, days of postoperative hospitalization, was not normally distributed and thus was log transformed. For the primary analysis, linear regression was used to determine unadjusted relationships between glucose variables, potential confounders, and duration of postoperative hospitalization. Covariates with a value of P<0.10 by univariate analysis were included in multivariable analyses to explore adjusted relationships between each glucose variable and duration of postoperative hospitalization.

Secondary analyses assessed the relationship between the glucose variables and the composite morbidity-mortality variables. By univariate analysis, the probability of developing the morbidity-mortality end point did not change uniformly across quartiles; in most cases, the probability increased in only the most extreme quartile. Thus, these variables were dichotomized at the 75th percentile values; the 25% was used for minimal glucose level. The probability of developing the morbidity-mortality end point for TWGA had a U-shaped relationship; thus, this variable was analyzed by quartile. Logistic regression analyses were performed to seek unadjusted and adjusted relationships between glucose variables, potential confounders, and the composite morbidity variables.

Statistical Analysis

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

The 378 patients with a RACHS-1 category ≥3 who underwent cardiac surgery in our institution during the 2003 calendar year formed the study population. Demographic and selected operative characteristics for these patients are summarized in Table 1, and summary statistics of perioperative glucose levels are found in Table 2. During the study period, intraoperative hyperglycemia was not treated, and no patient received insulin during surgery. In the early postoperative period, persistent hyperglycemia (>200 to 300 mg/dL) typically was addressed by a reduction in glucose concentration in intravenous fluids, and insulin was used in only 7 of 378 patients (1.9%).
Table 1. Demographics and Selected Operative Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male, n (%)</th>
<th>Prematurity, n (%)</th>
<th>Noncardiac structural anomaly, n (%)</th>
<th>Genetic syndrome, n (%)</th>
<th>Age at surgery, y</th>
<th>Weight, kg</th>
<th>RACHS-1 category, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>378</td>
<td>26 (6.9)</td>
<td>31 (8.2)</td>
<td>62 (16.4)</td>
<td>0.61 (0.01–14.41)</td>
<td>6.2 (2.8–53.9)</td>
<td>3 (74.9)</td>
</tr>
<tr>
<td>Multiple procedures during initial operation, n (%)</td>
<td>98 (25.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPB time, min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>103 (58–184)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reoperation or interventional catheterization during the same hospitalization, n (%)</td>
<td>19 (5.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continuous variables are presented as median (10th to 90th percentile). Total patients=378.

Primary Outcome: Days of Postoperative Hospitalization

The median duration of postoperative hospitalization was 8 days (10th to 90th percentile, 4 to 21 days). By univariate analysis, several intraoperative metrics of glucose control, including higher TWGA, higher peak glucose, greater SD of glucose measurements, and greater duration of hyperglycemia, were associated with a longer postoperative hospitalization. By multivariable analysis, however, when age, prematurity, structural anomalies, genetic syndrome, RACHS-1 category, duration of CPB, 72-hour peak inotrope score, and need for reoperation or interventional catheterization during the same hospitalization were controlled for, none of the intraoperative glucose variables was significantly associated with duration of hospitalization (Table 3).

By univariate analysis, several metrics of glucose control from the first 72 hours of postoperative cardiac ICU stay, including higher peak glucose, greater SD of glucose measurements, lower minimum glucose, and greater duration of hyperglycemia, were associated with a longer postoperative hospital stay (Table 4). Using multivariable analyses, when the same variables listed above were controlled for, we found that greater duration of hyperglycemia (hours of glucose >126 mg/dL) was significantly associated with longer duration of hospitalization (Table 4).

The median duration of postoperative hospitalization for patients who died (n=15) was 14 days1–19 compared with 8 days4–21 for surviving patients. The linear regression analyses were repeated after those patients who died were excluded, and the results of the analyses were unchanged (data not shown).

Table 2. Perioperative Glucose Levels for All 378 Study Patients

<table>
<thead>
<tr>
<th>Intraoperative</th>
<th>Median (10th–90th Percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose measurements, n</td>
<td>8 (5–11)</td>
</tr>
<tr>
<td>TWGA, mg/dL</td>
<td>130 (99–172)</td>
</tr>
<tr>
<td>Peak glucose, mg/dL</td>
<td>173 (127–238)</td>
</tr>
<tr>
<td>SD, mg/dL</td>
<td>29 (15–40)</td>
</tr>
<tr>
<td>Minimum glucose, mg/dL</td>
<td>86 (62–117)</td>
</tr>
<tr>
<td>Hours of glucose &gt;126 mg/dL</td>
<td>2.8 (0.2–5.1)</td>
</tr>
<tr>
<td>Hours of glucose &gt;200 mg/dL</td>
<td>0 (0–2.1)</td>
</tr>
<tr>
<td>Postoperative (first 72 h)</td>
<td></td>
</tr>
<tr>
<td>Glucose measurements, n</td>
<td>10 (4–20)</td>
</tr>
<tr>
<td>TWGA, mg/dL</td>
<td>126 (98–161)</td>
</tr>
<tr>
<td>Peak glucose, mg/dL</td>
<td>190 (130–337)</td>
</tr>
<tr>
<td>SD, mg/dL</td>
<td>34 (14–81)</td>
</tr>
<tr>
<td>Minimum glucose, mg/dL</td>
<td>86 (61–119)</td>
</tr>
<tr>
<td>Hours of glucose &gt;126 mg/dL</td>
<td>18.8 (0–47.5)</td>
</tr>
<tr>
<td>Hours of glucose &gt;200 mg/dL</td>
<td>0 (0–15.5)</td>
</tr>
</tbody>
</table>

Table 3. Linear Regression Analyses of Intraoperative Glucose Variables and Log-Transformed Days of Postoperative Hospitalization

<table>
<thead>
<tr>
<th>Intraoperative Glucose Variables</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TWGA</td>
<td>0.0248†</td>
<td>0.028</td>
</tr>
<tr>
<td>Peak glucose</td>
<td>0.0241†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SD of glucose</td>
<td>0.0857†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minimum glucose</td>
<td>-0.0228†</td>
<td>0.105</td>
</tr>
<tr>
<td>Hours of glucose &gt;126 mg/dL</td>
<td>0.07760</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hours of glucose &gt;200 mg/dL</td>
<td>0.06174</td>
<td>0.029</td>
</tr>
</tbody>
</table>

*Adjusted for age, prematurity, noncardiac structural anomalies, genetic syndrome, RACHS-1 category, duration of CPB, 72-hour peak inotrope score, and need for reoperation or interventional catheterization during the same hospitalization.
†Transformed to reflect a 10-mg/dL change in glucose variables.

Table 4. Linear Regression Analyses of Postoperative Glucose Variables and Log-Transformed Days of Postoperative Hospitalization

<table>
<thead>
<tr>
<th>72-Hour Postoperative Glucose Variables</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGWA</td>
<td>-0.0181</td>
<td>0.186</td>
</tr>
<tr>
<td>Peak glucose</td>
<td>0.0134†</td>
<td>0.002</td>
</tr>
<tr>
<td>SD of glucose</td>
<td>0.0306†</td>
<td>0.015</td>
</tr>
<tr>
<td>Minimal glucose</td>
<td>-0.0784†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hours of glucose &gt;126 mg/dL</td>
<td>0.01198</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hours of glucose &gt;200 mg/dL</td>
<td>0.01930</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for age, prematurity, noncardiac structural anomalies, genetic syndrome, RACHS-1 category, duration of CPB, 72-hour peak inotrope score, and need for reoperation or interventional catheterization during the same hospitalization.
†Transformed to reflect a 10-mg/dL change in glucose variables.
Secondary Outcome: Overall Composite Morbidity-Mortality Variable

A total of 58 patients reached the overall composite morbidity-mortality end point at some point during the entire postoperative cardiac ICU stay, including 15 deaths (4.0%), 39 nosocomial infections (10.3%), 17 patients who required extracorporeal membrane oxygenation (4.5%), 11 episodes of central nervous system injury (2.9%), 9 episodes of liver failure (2.4%), and 4 episodes of renal failure (1.1%). By univariate analysis, several intraoperative glucose variables, including TWGA ≤113 mg/dL, peak glucose ≥200 mg/dL, SD of glucose measurements ≤40 mg/dL, minimal glucose ≤75 mg/dL, and greater duration of hyperglycemia, were associated with greater odds of reaching the overall composite morbidity-mortality end point (Table 5). By multivariable analysis, when age, prematurity, noncardiac structural anomalies, RACHS-1 category, duration of CPB, and need for reoperation or interventional catheterization during the same hospitalization were controlled for, only a minimum intraoperative glucose level ≤75 mg/dL was significantly associated with greater odds of reaching the overall composite morbidity-mortality end point (Table 5).

Secondary Outcome: 72-Hour Composite Morbidity-Mortality Variable

Of the 58 patients who reached the overall composite morbidity-mortality end point, 48 reached the 72-hour composite morbidity-mortality end point. By univariate analysis, glucose variables derived from the first 72 hours of postoperative cardiac ICU stay, including peak glucose ≥250 mg/dL, SD of glucose measurements ≥55 mg/dL, minimal glucose ≤75 mg/dL, and hyperglycemia (glucose ≥126 mg/dL) persisting for ≥30 hours, were all associated with greater odds of developing the 72-hour composite morbidity-mortality outcome (Table 6). The TWGA quartiles of <109 or ≥143 mg/dL also were significantly associated with the

### Table 5. Logistic Regression Analyses of Intraoperative Glucose Variables and the Overall Composite Morbidity-Mortality Variable

<table>
<thead>
<tr>
<th>Operating Room Glucose Variables</th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
<th>Adjusted* OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TWGA ≤113</td>
<td>1.58 (0.61–4.06)</td>
<td>0.346</td>
<td>1.74 (0.58–5.18)</td>
<td>0.322</td>
</tr>
<tr>
<td>114–129</td>
<td>Referent</td>
<td>...</td>
<td>Referent</td>
<td>...</td>
</tr>
<tr>
<td>130–153</td>
<td>2.31 (0.95–5.60)</td>
<td>0.065</td>
<td>2.05 (0.74–5.68)</td>
<td>0.166</td>
</tr>
<tr>
<td>≥154</td>
<td>2.70 (1.12–6.48)</td>
<td>0.023</td>
<td>1.41 (0.50–3.94)</td>
<td>0.514</td>
</tr>
<tr>
<td>Peak glucose ≥200 mg/dL</td>
<td>2.67 (1.50–4.72)</td>
<td>&lt;0.001</td>
<td>1.57 (0.79–3.13)</td>
<td>0.198</td>
</tr>
<tr>
<td>SD of glucose ≥40 mg/dL</td>
<td>2.00 (1.11–3.60)</td>
<td>0.022</td>
<td>1.41 (0.69–2.90)</td>
<td>0.344</td>
</tr>
<tr>
<td>Minimal glucose ≤75 mg/dL</td>
<td>2.43 (1.36–4.36)</td>
<td>0.003</td>
<td>3.10 (1.49–6.68)</td>
<td>0.003</td>
</tr>
<tr>
<td>Glucose &gt;126 mg/dL for ≥4 h</td>
<td>2.68 (1.48–4.86)</td>
<td>0.001</td>
<td>0.95 (0.40–2.21)</td>
<td>0.895</td>
</tr>
<tr>
<td>Glucose &gt;200 mg/dL for ≥0.5 h</td>
<td>1.88 (1.03–3.44)</td>
<td>0.040</td>
<td>1.29 (0.62–2.71)</td>
<td>0.499</td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval.

*Adjusted for age, prematurity, noncardiac structural anomalies, RACHS-1 category, duration of CPB, and need for reoperation or interventional catheterization during the same hospitalization.

### Table 6. Logistic Regression Analyses of Postoperative Glucose Variables and the 72-Hour Composite Morbidity-Mortality Variable

<table>
<thead>
<tr>
<th>72-Hour Postoperative Glucose Variables</th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
<th>Adjusted* OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TWGA ≤109</td>
<td>5.67 (1.84–17.49)</td>
<td>0.003</td>
<td>7.30 (1.95–27.25)</td>
<td>0.003</td>
</tr>
<tr>
<td>110–126</td>
<td>Referent</td>
<td>...</td>
<td>Referent</td>
<td>...</td>
</tr>
<tr>
<td>127–143</td>
<td>3.12 (0.96–10.12)</td>
<td>0.059</td>
<td>3.46 (0.88–13.67)</td>
<td>0.076</td>
</tr>
<tr>
<td>&gt;143</td>
<td>4.11 (1.31–12.87)</td>
<td>0.015</td>
<td>5.21 (1.37–19.89)</td>
<td>0.016</td>
</tr>
<tr>
<td>Peak glucose ≥250 mg/dL</td>
<td>2.56 (1.37–4.77)</td>
<td>0.003</td>
<td>2.55 (1.20–5.43)</td>
<td>0.015</td>
</tr>
<tr>
<td>Standard deviation glucose ≥55 mg/dL</td>
<td>2.15 (1.14–4.05)</td>
<td>0.018</td>
<td>2.06 (0.97–4.38)</td>
<td>0.056</td>
</tr>
<tr>
<td>Minimal glucose ≤75 mg/dL</td>
<td>2.99 (1.61–5.54)</td>
<td>&lt;0.001</td>
<td>2.85 (1.38–5.88)</td>
<td>0.005</td>
</tr>
<tr>
<td>Glucose &gt;126 mg/dL for ≥30 h</td>
<td>1.91 (1.01–3.60)</td>
<td>0.047</td>
<td>1.20 (0.55–2.63)</td>
<td>0.652</td>
</tr>
<tr>
<td>Glucose &gt;200 mg/dL for ≥7 h</td>
<td>1.59 (0.83–3.05)</td>
<td>0.164</td>
<td>1.42 (0.65–3.10)</td>
<td>0.373</td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval.

*Adjusted for prematurity, noncardiac structural anomalies, RACHS-1 category, duration of CPB, and need for reoperation or interventional catheterization during the same hospitalization.
72-hour composite morbidity-mortality outcome. By multivariate analysis, when prematurity, noncardiac structural anomalies, RACHS-1 score, duration of CPB, and need for reoperation or interventional catheterization were controlled for, TWGA <109 or >143 mg/dL, peak glucose ≥250 mg/dL, and minimum glucose ≥75 mg/dL all were significantly associated with greater odds of reaching the 72-hour composite morbidity-mortality end point (Table 6). An exploratory analysis was conducted to examine the relationship between the glucose range of 80 to 110 mg/dL targeted in adult trials of strict glycemic control and our 72-hour composite morbidity-mortality end point. With a TWGA of 111 to 140 mg/dL used as the referent group, patients with a 72-hour TWGA of <80 mg/dL had an adjusted odds of 5.93 (95% confidence interval, 0.84 to 41.90) of reaching this end point; those with a TGWA of 80 to 110 mg/dL had an adjusted odds of 2.91 (95% confidence interval, 1.14 to 7.42), and those with a TWGA >140 mg/dL had an adjusted odds of 2.13 (95% confidence interval, 0.87 to 5.23).

The primary and secondary analyses described above were repeated after the exclusion of the 7 patients who received insulin in the postoperative period, and the adjusted relationships between glucose metrics and the outcomes of interest were unchanged (data not shown).

Discussion

The study results did not support our primary hypothesis that higher average glucose levels within 72 hours of complex congenital heart surgery would be associated with a longer duration of postoperative hospitalization. However, we did find that patients whose average 72-hour glucose level was >143 mg/dL had greater odds of reaching the composite morbidity-mortality end point even after adjustment for several confounding variables known to influence postoperative recovery. Additionally, greater duration of time with glucose levels >126 mg/dL during the first 72 postoperative hours was associated with a longer duration of postoperative hospitalization, and a higher peak postoperative glucose level was associated with greater adjusted odds of reaching the composite morbidity-mortality end point. Importantly, patients whose average early postoperative glucose level was <109 mg/dL had 7-fold greater adjusted odds of reaching the morbidity-mortality end point. Optimal glucose levels in critically ill children have not been previously reported. Taken together, the associations we found between the glucose range of 80 to 110 mg/dL targeted in adult trials of strict glycemic control and our 72-hour composite morbidity-mortality end point (Table 6). An exploratory analysis was conducted to examine the relationship between the glucose range of 80 to 110 mg/dL targeted in adult trials of strict glycemic control and our 72-hour composite morbidity-mortality end point.

Several retrospective cohort studies have examined the relationship between hyperglycemia and adverse outcomes in critically ill children. In multidisciplinary pediatric ICU settings, investigators have reported that hyperglycemia is associated with increased mortality. Hyperglycemia also has been associated with mortality in children with traumatic brain injury or septic shock and in neonates with necrotizing enterocolitis. However, each of these pediatric investigations had important limitations, including small sample size, limited risk adjustment, high hospital mortality, or small number of outcomes for meaningful multivariate analysis. In studies that examined organ failure and other morbid events, some of the glucose exposure was recorded after the outcome of interest.

Prior studies examining the relationship between metrics of glucose control and outcomes after pediatric cardiac surgery have reached conflicting conclusions. In 184 infants recovering from cardiac surgery, Yates and colleagues found associations between early postoperative peak glucose levels, duration of hyperglycemia, and increased morbidity and mortality. In this study, the only variable used for risk adjustment was patient weight, and glucose exposure appeared to have occurred in part after the nonmortal outcomes of interest. In contrast, Rossano et al reported that infants recovering from an arterial switch operation who spent >50% of the first 24 postoperative hours with glucose levels between 80 and 110 mg/dL (n=23) were at increased risk for developing adverse events compared with those who spent the majority of the first 24 postoperative hours with glucose levels >200 mg/dL (n=13). Both of these pediatric cardiac surgical studies had small sample sizes and a limited number of outcomes for meaningful multivariate analysis and included only infants, which limit the generalizability of their findings.

We attempted to overcome these limitations with our study design. Our sample size was relatively large and included only high-risk patients. Several widely accepted covariates that predict adverse outcomes after congenital heart surgery were included in the multivariate analyses. In the logistic regression analyses, a sufficient number of patients reached the composite morbidity-mortality end point for appropriate multivariate analyses. Finally, care was taken to ensure that glucose exposure occurred before the outcomes of interest. Hypoglycemia is less common than hyperglycemia in critically ill patients, occurring in 2% to 18% of patients, depending on the definition used. Only 4 of the 378 patients (1%) in our study had a minimal intraoperative...
glucose level ≤ 40 mg/dL, and 9 of 378 (2%) had a minimal glucose level ≤ 40 mg/dL within the first 72 hours after surgery. We found that patients whose minimum glucose level was < 75 mg/dL both intraoperatively and postoperatively had a 3-fold greater adjusted odds of developing the composite morbidity-mortality end points. The occurrence of at least 1 glucose level < 40 mg/dL independently predicts mortality in patients receiving care in a multidisciplinary adult ICU, and a mean glucose < 70 mg/dL is associated with a 6-fold greater adjusted odds of death in adults hospitalized with acute myocardial infarction.15,16 In critically ill children, hypoglycemia, when defined as a glucose level < 65 mg/dL, also has been associated with increased mortality.1 Risk factors for hypoglycemia include sepsis, renal failure, liver failure, insulin use, and greater severity of illness. Whether hypoglycemia, particularly if mild and of short duration, truly causes mortality in these patients or is largely a biochemical nuisance is unknown.24 This study, like the others cited, was not designed to quantify the duration of hypoglycemia, likely a significant factor in determining its ability to produce injury. It is noteworthy that patients in this study whose average early postoperative glucose level was < 109 mg/dL were at greater adjusted odds of reaching the morbidity-mortality end point. We speculate that mat-

urational differences in glucose metabolism or toxicity threshold in children compared with adults may partly explain this observation. We found no significant relationship between higher SD of glucose measurements, as a marker of glucose variabil-

ity, and longer postoperative hospitalization. A nonsignificant trend (P = 0.061) was found, however, for an adjusted association between greater SD of glucose measurements in the first 72 hours of postoperative ICU admission and the 72-hour composite morbidity-mortality end point. Greater glucose variability was found to be a risk-adjusted predictor of mortality in critically ill adults.19 Wintergerst et al1 reported a similar finding in critically ill children, although risk adjustment in their multivariate analysis was limited. Greater fluctuation in glucose levels has been independently associated with activation of oxidative stress in adult diabetics, leading to cellular injury and apoptosis.25,26 It is plausible that this phenomenon also occurs in critically ill patients.1

The adjusted associations we identified between various metrics of glucose control and the outcome measures are insufficient to prove causality. Evidence for causality can be derived in part from clinical trials. In the randomized trial involving 1548 adult surgical ICU patients, van den Bergh and colleagues4 reported that patients assigned to receive intensive insulin therapy to maintain strict glycemic control (glucose target, 80 to 110 mg/dL) had a 42% risk reduction for death (4.6% versus 8.0%; P < 0.04). In this study, bloodstream infections, acute renal failure requiring dialysis, number of red-cell transfusions, and critical illness polyneuropathy also were decreased by 40% to 50%. These findings support the hypothesis that hyperglycemia is most toxic to organ systems with non-insulin-dependent glucose uptake, including the endothelium, nervous system, innate immune system, and liver.21,26,26 Although benefits of strict glycemic control have been reported subsequently in other critically ill adult patient populations,9–11 it is notable that 2 recent multicenter trials of strict glycemic control in critically ill adults were stopped prematurely, largely because of an excessive occurrence of hypoglycemia in the intervention groups.37,38

The existing literature and findings of our present study support the need for a randomized controlled trial of strict glycemic control after cardiac surgery in children. Patients in such a study would likely benefit from continuous glucose monitoring to minimize the risk of hypoglycemia.39 Data from the present study and a prior report from our center do not support the need for strict glycemic control for children in the cardiac operating room.40

Study Limitations

This study is retrospective, and the timing of blood glucose measurements was not standardized. Although we did not measure glucose infusion rates, the administration of glucose-containing fluids in the immediate perioperative period is standardized in our program. As discussed, the adjusted relationships that we identified between glucose variables and outcomes do not prove causality, and residual unmeasured confounding cannot be entirely excluded. The composite morbidity-mortality outcome variable has not previously been validated, and its individual com-

ponents do not have equal clinical implications. Our findings may not be generalizable to patients who undergo low-risk cardiac surgical procedures. Finally, this study was not designed to determine whether intraoperative or early postoperative hyperglycemia or hypoglycemia predicts adverse long-term outcomes. Preliminary investigations of infant cardiac surgery patients have found no relationship between intraoperative or early postoperative glucose levels and neurodevelopmental outcomes.40,41 However, conflicting data exist as to whether hyperglycemia induces neuronal injury in immature animal models of ischemic brain injury or deep hypothermic circulatory arrest.42–44 The relationship between perioperative glucose levels and neurodevelopmental outcomes in children is not well understood and warrants further investigation.

Conclusions

This study identified associations between perioperative glycemic derangement and poor outcomes after complex congenital heart surgery. Intraoperative hyperglycemia does not appear to be harmful, although glucose levels < 75 mg/dL are associated with adverse outcomes. In the early postoperative period, a greater duration of exposure to glucose levels > 126 mg/dL was associated with a longer hospital stay, and patients with an average glucose level < 110 or > 143 mg/dL, higher peak glucose levels, and lower minimum glucose levels were at greater adjusted odds for reaching the composite morbidity-mortality end point. The ideal glucose level after pediatric cardiac surgery may be 110 to 126 mg/dL. A clinical trial is needed to determine whether strict glycemic control is beneficial in this patient population.
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CLINICAL PERSPECTIVE

Hyperglycemia occurs commonly and has been associated with increased morbidity and mortality in critically ill adults,
including those undergoing cardiac surgery. The use of insulin to achieve strict glycemic control may improve outcomes
in these patients. The aim of this cohort study was to determine whether adjusted associations exist between intraoperative
or early postoperative metrics of glucose control and longer hospitalization or adverse outcomes after complex congenital
heart surgery. After multivariate analysis, we found that none of the intraoperative glucose variables were associated with
duration of hospitalization, but a minimum glucose \( \leq 75 \) mg/dL was associated with greater adjusted odds of reaching the
composite morbidity-mortality end point. Postoperatively, greater duration of glucose levels >126 mg/dL during the first
72 hours after surgery was associated with longer hospital stay. Patients with average glucose levels <110 or >143 mg/dL,
higher peak glucose levels, and lower minimum glucose levels all have greater adjusted odds for reaching the composite
morbidity-mortality end point. Taken together, the associations we found between the various metrics of glucose control
and adverse outcomes suggest that the ideal postoperative glucose range after complex congenital heart surgery is 110 to
126 mg/dL, which is higher than the target range that some experts recommend for critically ill adults. The associations
we identified between various metrics of glucose control and the outcome measures are insufficient to prove causality.
Randomized controlled trials are needed to determine whether achieving strict glycemic control with an insulin infusion
is beneficial for children recovering from congenital heart surgery.
Association Between Intraoperative and Early Postoperative Glucose Levels and Adverse Outcomes After Complex Congenital Heart Surgery
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