Comparison of Glycemic and Surgical Outcomes After Change in Glycemic Targets in Cardiac Surgery Patients

DOI: 10.2337/dc14-1199

OBJECTIVE
To compare perioperative glycemic and long-term surgical outcomes in patients undergoing cardiac surgery before and after the recommended 2009 changes in inpatient glycemic targets.

RESEARCH DESIGN AND METHODS
We performed a retrospective review of patients who underwent cardiac surgery between 4 September 2007 and 30 April 2011. Comparison was made of blood glucose (BG) outcomes 3 days after surgery, and 30-day cardiac outcomes before and after a change in insulin protocol that took place on 1 September 2009, which consisted of raising the glycemic targets during intravenous insulin infusions from 80–110 mg/dL (80–110 group) to 110–140 mg/dL (110–140 group).

RESULTS
When compared with the 80–110 group (n = 667), the 110–140 group (n = 658) had higher mean postoperative BG levels during the intravenous insulin infusion (141 ± 15 vs. 121 ± 15 mg/dL, P < 0.001) and the subcutaneous insulin period (134 ± 24 vs. 130 ± 23 mg/dL, P < 0.001), and for 3 days postoperatively (141 ± 17 vs. 127 ± 15 mg/dL, P < 0.001). Fewer patients in the 110–140 mg/dL group experienced moderate hypoglycemia (BG <70 mg/dL) (177 vs. 73, P = 0.04). Severe hypoglycemia (BG <40 mg/dL) occurred in only one patient in the 80–110 group and three patients in the 110–140 group. There were no significant differences in mortality or surgical complication rates (with the exception of reintubation) between the groups.

CONCLUSIONS
The higher glycemic target of 110–140 mg/dL resulted in similar mean glucose values, with significantly less hypoglycemia and no significant differences in mortality/morbidity compared with the more strict target of 80–110 mg/dL.

Hyperglycemia is common in hospitalized patients, and multiple studies have established that it is an independent risk factor for poor clinical outcomes in patients with and without diabetes (1–9). Intensive management of hyperglycemia, particularly in the intensive care unit (ICU) setting, has been implemented in hospitals with the goal of decreasing the number of adverse outcomes. Several, but not all, clinical trials have shown morbidity and mortality benefits from intensive inpatient hyperglycemia management (blood glucose [BG] goal 80–110 mg/dL), even in individuals

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Received 10 May 2014 and accepted 12 August 2014.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-1199/-/DC1.

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Outcomes after Glycemic Target Change

The American Association of Clinical Endocrinologists and the American Diabetes Association for higher targets for glycemic control in inpatients (21). This new guideline recommended a BG target of 140–180 mg/dL, with 110–140 mg/dL being marked as acceptable in certain centers with considerable experience with such management. Because of our prior extensive experience and studies at Northwestern Memorial Hospital (NMH) demonstrating the safety of intravenous insulin protocols with a BG target of 80–110 mg/dL (22,23), we decided to change to the 110–140 mg/dL target. As a result, the intravenous insulin infusion and subcutaneous injection protocols used by our Glucose Management Service (GMS) at NMH were modified in 2009, so that the target BG levels for the intravenous protocol would be 110–140 mg/dL instead of 80–110 mg/dL, and the fasting and preprandial glucose levels during the subcutaneous insulin protocol would be 110–180 mg/dL instead of 80–150 mg/dL.

There was a paucity of data reported on glycemic and clinical outcomes after these changes in glycemic control recommendations. The goal of this study is to examine retrospectively glucose and cardiac outcomes before and after this glycemic target management change in patients undergoing cardiac surgery.

RESEARCH DESIGN AND METHODS

Study Design

A retrospective electronic medical record (EMR) review of patients who underwent cardiac surgery that involved coronary artery bypass grafting and/or cardiac valve repair/replacement and had undergone postoperative glucose management by the GMS between 4 September 2007 and 30 April 2011 at NMH was performed with approval by the Northwestern University Institutional Review Board. Aspects of glycemic control, rates of hypoglycemia, and surgical outcomes after this change in BG management targets were evaluated. All patients 18–90 years of age surviving for >24 h after cardiac surgery were eligible. EMRs were reviewed during the following two periods: 4 September 2007 to 30 April 2009 (target 80–110 mg/dL); and 1 September 2009 to 30 April 2011 (target 110–140 mg/dL); these dates were selected because of the availability of data electronically after 4 September 2007 and because full implementation of the protocol change across all hospital units took place after 1 September 2009. With the protocol change, intravenous administration of insulin was initiated postoperatively according to standardized protocols if the postoperative BG level was >110 or >140 mg/dL, respectively, for the 80–110 and 100–140 groups (see Supplementary Appendix). With these protocols, a bolus followed by a continuous infusion of regular insulin was given when the postoperative glucose levels were found to be greater than these thresholds, the doses being proportional to the level of glucose. Insulin doses were increased or decreased at hourly intervals for changes in glucose levels according to the protocol directions. Patients were converted to subcutaneous insulin when transferred to the floor from the ICU and when eating. Generally, the steady-state rate of insulin infusion at the time of conversion was converted into a daily rate, the intravenous infusion was stopped, and 80% of this amount of insulin was given as insulin glargine subcutaneously and 10% as lispro or aspart insulin subcutaneously as a bridging dose. On the day of conversion, this same 10% dose of rapid-acting insulin was given subcutaneously preprandially. On subsequent days, the doses of insulin glargine and lispro/aspart were generally reduced by ~20% per day, depending upon the clinical situation of the patient as judged by the GMS (22,23). The fasting and premeal targets during subcutaneous treatment were 80–150 mg/dL for the 80–110 group and 110–180 mg/dL for the 110–140 group.

Patients undergoing procedures that included glucocorticoid administration intraoperatively and postoperatively (including, but not limited to, cardiac transplantation, aortic arch repair, and MAZE procedure) were excluded. Data for 1,340 patients were obtained from the EMR of patients seen by our GMS and the Cardiovascular Research Database (CARD) in the Clinical Trial Unit of the Bluhm Cardiovascular Institute at NMH. CARD was approved by the Northwestern University Institutional Review Board, and only subjects consenting to participation in CARD were included in the analysis.

Of the initial 1,340 potential participants identified with complete data, 15 were excluded prior to comparison between the two groups, as follows: 11 for receiving steroids equivalent to >20 mg of prednisone, and 4 for surgery times that were considered outliers (2 for surgery lasting >12 h, and 2 for surgery lasting <100 min).

Glucose (laboratory and point-of-care) and insulin data were collected using the Northwestern Medicine Enterprise Data Warehouse. Ten percent of charts were manually reviewed by a medical provider to verify the accuracy of both glucose and outcome data. Mean daily BG levels, mean BG levels on the intravenous insulin drip, and mean BG levels on the first 3 days of subcutaneous insulin administration were calculated. Moderate hypoglycemia was defined as BG levels <70 mg/dL, and severe as BG levels <40 mg/dL.

The primary analysis was a comparison of the mean glucose levels for the first 3 days postoperatively (mean 3 day glucose) between the two groups studied: before (the 80–110 group) and after (the 110–140 group) the change in glycemic control targets. Secondary analyses were before/after group comparisons involving the following: 1) the number of patients in whom hypoglycemia developed (BG <70 mg/dL and BG <40 mg/dL) each day; and 2) postoperative complications (within 30 days of the date of surgery) (e.g., postoperative mortality; deep sternal wound infections; other infections; pulmonary, renal, cardiac, or neurological complications; and hospital readmission within 30 days of the initial surgical procedure).

Statistical Analyses

Continuously distributed data, including baseline patient characteristics, surgical procedures, frequency of hypoglycemia,
and postoperative complications, were summarized using means and SDs. Binary distributed variables are presented in the form of counts and percentages. Group comparisons were based on two-sample t tests with unequal variance, the Wilcoxon rank sum test (continuous data) or tests for binomial proportions (binary data). Long-term all-cause mortality was summarized using the Kaplan-Meier estimators, and groups were compared using the log-rank test. Statistical significance was declared at the two-sided 5% α-level, and there were no adjustments for multiplicity.

RESULTS

The demographic characteristics of the study population are shown in Table 1. Of the 1,325 patients, 667 were in the 80–110 group and 658 were in the 110–140 group. There were significantly higher proportions of patients with diabetes, hypertension, and dyslipidemia, but a smaller proportion with cigarette smoking in the 110–140 group. The types of cardiac surgery performed are shown in Supplementary Table 1. All patients had undergone coronary artery bypass grafting and/or valve procedures but could also have undergone other procedures that were performed concomitantly, as noted in Supplementary Table 1. There were no significant differences in the proportions undergoing elective surgery. However, the mean operative time was significantly longer in the 80–110 group (300.1 ± 92.9 vs. 281.4 ± 92.5 min, P < 0.001).

Preoperative BG values were similar for the 80–110 and 110–140 groups (117 ± 41 vs. 119 ± 41 mg/dL, P = 0.46), respectively (Fig. 1). The immediate postoperative BG levels (on ICU admission and prior to insulin infusion) were significantly higher in the 110–140 group (152 ± 48 vs. 169 ± 43 mg/dL, P < 0.001). The BG values averaged for the first 3 days postoperatively were significantly higher in the 110–140 group (127 ± 15 vs. 141 ± 17 mg/dL, respectively [P = 0.001], for the 80–110 and 110–140 groups). The mean BG levels while patients were on the insulin drip were 121 ± 15 and 142 ± 15 mg/dL, respectively (P < 0.001), in the 80–110 and 110–140 groups. The mean BG levels for patients receiving subcutaneous insulin were 130 ± 23 and 134 ± 24 mg/dL, respectively (P = 0.001), in the 80–110 and 110–140 groups.

Severe hypoglycemia (BG level <40 mg/dL) occurred in only four patients (one in the 80–110 group and three in the 110–140 group). Moderate hypoglycemia (BG level <70 mg/dL) occurred in fewer patients in the 110–140 group compared with the 80–110 group (177 vs. 73, P = 0.04), mainly due to differences occurring on postoperative day 1 (Table 2).

Postoperative complications (within 30 days of surgery) are shown in Table 3. There were no significant differences in outcomes, including mortality, between the two groups, except for reintubation rates. Kaplan-Meier curves showed no significant differences between the groups in long-term all-cause mortality (Fig. 2).

CONCLUSIONS

It is well established that hyperglycemia in hospitalized patients is associated with poor outcomes and is common regardless of diabetes status (1–9). In cardiac surgery patients, those patients who have diabetes have been found to have higher rates of complications, such as prolonged ICU stay, deep sternal wound infection, perioperative stroke, and renal dysfunction (11). Hyperglycemia per se, independent of diabetes status, has been associated with double the

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Table 1—Demographic characteristics of study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>80–110 mg/dL group (n = 667)</th>
<th>110–140 mg/dL group (n = 658)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63 ± 14</td>
<td>64 ± 14</td>
<td>0.63</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.3 ± 6</td>
<td>28.6 ± 6</td>
<td>0.34</td>
</tr>
<tr>
<td>Female</td>
<td>215 (32.2)</td>
<td>219 (33.3)</td>
<td>0.68</td>
</tr>
<tr>
<td>Diabetes</td>
<td>158 (23.7)</td>
<td>190 (28.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>463 (69.4)</td>
<td>498 (75.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>423 (63.4)</td>
<td>453 (68.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>Cigarette smoker</td>
<td>119 (17.8)</td>
<td>79 (12.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Renal failure*</td>
<td>22 (3.3)</td>
<td>25 (3.8)</td>
<td>0.67</td>
</tr>
<tr>
<td>Dialysis</td>
<td>18 (2.7)</td>
<td>25 (3.8)</td>
<td>0.49</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>88 (13.2)</td>
<td>71 (10.8)</td>
<td>0.18</td>
</tr>
<tr>
<td>Previous MI</td>
<td>144 (21.5)</td>
<td>135 (20.5)</td>
<td>0.63</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>53 (8.6)</td>
<td>49 (7.4)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or n (%), unless otherwise indicated. *History of renal failure or serum creatinine > 2.0 mg/dL.

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Figure 1—Mean BG levels pre and postoperatively. □, 80–110 mg/dL group. □□□, 110–140 mg/dL group. Values are expressed as the mean ± SD. *P < 0.001. Postoperative glucose is the first value postoperatively prior to starting the insulin drip infusion. Post-op, postoperative; Pre-op, preoperative.
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...tality (1). Furnary et al. (11) have shown in a study of patients undergoing cardiac surgery that patients who had mean glucose levels of ≥150 mg/dL in the first 3 days after cardiac surgery have twice the infection rate and 13 times the mortality compared with normoglycemic patients. In our previous studies at Northwestern University (22, 23), using intravenous and subcutaneous insulin regimens with the previous target glucose level of 80–110 mg/dL with a GMS consultation, we have shown that the postoperative complication rates for patients undergoing cardiac surgery were similar in diabetic and nondiabetic subjects, unlike the very high levels of complications in diabetic patients found by others when glycemic control was not achieved (14).

van den Berghe et al. (10) first reported a 42% reduction in mortality in surgical ICU patients (87% without diabetes) when they were randomized to an intensive control group (BG level 80–110 mg/dL) versus a conventional group (BG level <180 mg/dL). Sepsis, ICU stay, need for dialysis, duration of ventilation, and wound infection were also significantly reduced (10). Using the same protocol, however, this group showed mortality benefits from intensive glucose control in patients requiring medical ICU care only for ICU stays of ≥3 days and not for shorter periods (24). Moreover, results from several subsequent large, randomized, clinical trials (16–18) examining intensive glycemic control in mixed or nonsurgical ICUs showed no benefit and, in some studies, even harm. A meta-analysis (25) of 29 randomized controlled trials has shown that hypoglycemia rates are fivefold higher in intensively treated patients compared with conventionally treated patients.

The results of these subsequent studies led to a change in glycemic target level recommendations by the American Diabetes Association and the American Association of Clinical Endocrinologists in 2009 (21). Following these new recommendations, our GMS changed the glycemic targets of hyperglycemia treatment during insulin infusions from 80–110 to 110–140 mg/dL. However, the question remained as to whether this change would affect hard clinical outcomes. There has been a paucity of data comparing the two targets in terms of both clinical and glycemic outcomes. This study retrospectively examined glucose and cardiac outcomes before and after this glycemic target change in cardiac surgery patients and showed that, although BG levels were slightly higher with the less strict glucose target protocol, there were no increases in 30-day mortality or other surgical complications or long-term mortality.

However, moderate hypoglycemia (BG level <70 mg/dL) occurred significantly less often with the 110–140 mg/dL protocol on the first postoperative day, but not on the second and third days. Severe hypoglycemia (BG level <40 mg/dL) was rare (one patient in the 80–110 group and three patients in the 110–140 group). A similar reduction in hypoglycemia has been shown with a change in BG target of 90–120 to 120–160 mg/dL by others (26).

Limitations of this study include that it is retrospective and was completed at a single tertiary care institution with a supporting GMS/Endocrine Service, which has been adept at the use of both insulin and subcutaneous protocols since 2004. In addition, we have amended our protocols to the acceptable goal target of 110–140 mg/dL, as opposed to a higher target of 140–180 mg/dL. Although we think that the lower rates of hypoglycemia postoperatively in the 110–140 group were due to this higher target, it is also possible that the higher BG level in the immediate postoperative period in this group contributed to that result as well. It is uncertain as to why the postoperative BG levels were different in the two groups, but it is possible that the variable intravenous bolus administration of insulin by the anesthesiologists intraoperatively may have contributed to this difference.

In conclusion, our results support the higher glycemic target of 110–140 mg/dL as being safer, with significantly

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Table 2—Patients experiencing moderate hypoglycemia (BG <70 mg/dL)

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>80–110 mg/dL group (n = 667)</td>
<td>106 (15.9)</td>
<td>31 (4.6)</td>
<td>40 (6.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>110–140 mg/dL group (n = 658)</td>
<td>22 (3.3)</td>
<td>20 (3.0)</td>
<td>31 (4.7)</td>
<td></td>
</tr>
</tbody>
</table>

Data expressed as n (%), unless otherwise indicated.

Table 3—Complications in the 30-day postoperative period

<table>
<thead>
<tr>
<th>Variable</th>
<th>80–110 mg/dL group (N = 667)</th>
<th>110–140 mg/dL group (N = 658)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any complication</td>
<td>258 (38.7)</td>
<td>259 (39.4)</td>
<td>0.80</td>
</tr>
<tr>
<td>Sternal deep infection</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>0.99</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15 (2.2)</td>
<td>24 (3.6)</td>
<td>0.13</td>
</tr>
<tr>
<td>Postoperative stroke &gt;24 h</td>
<td>12 (1.8)</td>
<td>10 (1.5)</td>
<td>0.69</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>4 (0.6)</td>
<td>2 (0.3)</td>
<td>0.42</td>
</tr>
<tr>
<td>Coma</td>
<td>2 (0.3)</td>
<td>0 (0)</td>
<td>0.16</td>
</tr>
<tr>
<td>Prolonged ventilation &gt;24 h</td>
<td>54 (8.1)</td>
<td>66 (10.0)</td>
<td>0.22</td>
</tr>
<tr>
<td>Renal failure*</td>
<td>16 (2.4)</td>
<td>26 (4.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Dialysis required</td>
<td>9 (1.3)</td>
<td>10 (1.5)</td>
<td>0.79</td>
</tr>
<tr>
<td>Perioperative MI</td>
<td>16 (2.4)</td>
<td>10 (1.5)</td>
<td>0.25</td>
</tr>
<tr>
<td>Postoperative atrial fibrillation</td>
<td>168 (25.2)</td>
<td>180 (27.4)</td>
<td>0.37</td>
</tr>
<tr>
<td>Postoperative heart block (pacemaker)</td>
<td>15 (2.2)</td>
<td>13 (2.0)</td>
<td>0.73</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>14 (2.1)</td>
<td>12 (1.8)</td>
<td>0.72</td>
</tr>
<tr>
<td>Readmission within 30 days</td>
<td>81 (12.1)</td>
<td>62 (9.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>30-Day mortality</td>
<td>9 (1.3)</td>
<td>10 (1.5)</td>
<td>0.79</td>
</tr>
<tr>
<td>Reintubated</td>
<td>24 (3.6)</td>
<td>41 (6.2)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Data expressed as n (%), unless otherwise indicated. MI, myocardial infarction. *History of renal failure or serum creatinine > 2.0 mg/dL.
fewer instances of hypoglycemia, and no significant differences in mortality/morbidity compared with the stricter target of 80–110 mg/dL.

Acknowledgments. The authors thank the many nurses and physicians who participated in the care of these patients.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. I.M. wrote the manuscript and researched the data. K.S. researched the data, and reviewed and edited the manuscript. J.C. researched the data, performed statistical analyses, and reviewed and edited the manuscript. A.W. contributed to the discussion, and reviewed and edited the manuscript. A.-C.A. researched the data, performed statistical analyses, and reviewed and edited the manuscript. C.L. researched the data and performed statistical analyses. M.E.M. researched the data, contributed to the discussion, and reviewed and edited the manuscript. M.E.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 74th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 13–17 June 2014.

References