COMPARISON OF THREE PROTOCOLS FOR TIGHT GLYCEMIC CONTROL IN CARDIAC SURGERY PATIENTS

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Additional information for this article can be found in an online appendix at

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**Objective:** We performed a randomized trial to compare three insulin-titration protocols for tight glycemic control (TGC) in surgical ICU: an absolute glucose (Matias) protocol, a relative glucose change (Bath) protocol, and an enhanced model predictive control algorithm (eMPC).

**Research Design and Methods:** 120 consecutive post-cardiac surgery patients were randomized to the three protocols with a target glycemia range from 4.4 to 6.1 mmol/l. Intravenous insulin was administered continuously or in combination with insulin boluses (Matias protocol). Blood glucose was measured in 1-4 hour intervals as requested by protocols.

**Results:** eMPC algorithm gave best performance as assessed by time to target (8.8±2.2 vs. 10.9±1.0 vs. 12.3±1.9 hours; eMPC vs Matias vs Bath; P<0.05), average blood glucose after reaching the target (5.2±0.1 vs. 6.2±0.1 vs. 5.8±0.1 mmol/l; P<0.01), time in target (62.8±4.4 vs. 48.4±3.28 vs. 55.5±3.2 %, P<0.05), time in hyperglycemia >8.3 mmol/l (1.3±1.2 vs. 12.8±2.2 vs. 6.5±2.0 %, P<0.05), and sampling interval (2.3±0.1 vs. 2.1±0.1 vs. 1.8±0.1 hours, P <0.05). However, time in hypoglycemia risk range (2.9-4.3 mmol/l) in eMPC group was longest (22.2±1.9 vs. 10.9±1.5 vs. 13.1±1.6; P<0.05). No severe hypoglycemic episode (< 2.3 mmol/l) occurred in eMPC group compared to 1 in Matias and 2 in Bath groups, respectively.

**Conclusion:** eMPC algorithm provided best TGC without increasing risk of severe hypoglycemia while requiring fewest glucose measurements. Overall, all algorithms were safe and effective in the maintenance of TGC in cardiac surgery patients.
The landmark Leuven study [1] demonstrated that intensive insulin therapy targeted to maintain normoglycemia between 4.4 to 6.1 mmol/l reduced mortality at the surgical intensive care unit (ICU) and markedly decreased the frequency of organ complications associated with critical illness. Other studies confirmed these findings, particularly in cardiac surgery patients [2-5] while others questioned safety and universality of beneficial effect of tight glycemic control (TGC) in different subgroups of critically ill patients [6-9].

Principally, the need to maintain euglycemia in ICU has been widely accepted. Numerous insulin protocols of variable effectiveness have been developed [5, 10-12]. Most of these protocols require considerable ICU staff training and experience and some call for intuitive decisions. In consequence, some protocols may lead to inconsistent application, mistakes or misinterpretation. Furthermore, frequent glucose measurements, essential for TGC, may markedly increase the workload of ICU nursing staff [13, 14].

Most newly developed glucose management protocols are compared against the so called standard protocols that usually do not reach adequate glucose control. Head-to-head comparison of specifically-designed TGC protocols [15-18] is not available although such information is of the highest importance from the practical point of view.

We carried out such a direct comparison of three different, effective, and published TGC management protocols with a major focus on TGC effectiveness and safety. We performed a mono-centre randomized trial and compared a protocol based on the absolute glucose value - Matias protocol (Matias) [15, 17], a protocol based on the relative glucose change - Bath protocol (Bath) [19] and a computer-based model predictive control algorithm with variable sampling rate (eMPC) [16] developed within the 6th Framework European Project CLINICIP.

RESEARCH DESIGN AND METHODS

Patients: Patients, aged 18 to 90 years, admitted to the postoperative ICU after elective cardiac surgery, were included. A written informed consent was signed by all participants before being enrolled in the study. The study was approved by the Human Ethical Review Committee, 1st Faculty of Medicine and General University Hospital, Prague, Czech Republic, and was performed in accordance with the guidelines proposed in the Declaration of Helsinki. Exclusion criteria were insulin allergy, mental incapacity, and language barrier.

We enrolled 120 consecutive patients, 40 patients were randomized into Matias, Bath and eMPC protocol treatment groups regardless of the preoperative or admission glycemia levels. The TGC protocols were started after patients’ admission to the ICU after arrival from the operating theatre and lasted until the end of ICU stay. Since the duration of ICU stay and the total monitoring time differed among patients, only data for up to 48 hours were used for the comparison of the protocols. 48 hours of ICU stay was accomplished in 109 from 120 patients included to the study. The mean follow-up time was 46.7±0.5 hours for Matias, 45.7±0.7 hours for Bath, and 47.2±0.3 hours for eMPC protocol, respectively.

Target glucose range: The target glucose range was 4.4 to 6.1 mmol/l, which has been demonstrated to reduce mortality and morbidity [1]. No routine protocol was used for perioperative glycemia control.

Blood glucose monitoring, insulin treatment regimens and nutrition: Blood glucose was monitored and insulin was administered according to each protocol rules/suggestions. Undiluted arterial blood for measurement of BG was drawn from an
Comparison of protocols for glycemic control

arterial line, inserted for routine monitoring procedures. Whole blood glucose (BG) was analyzed by a standard point of care testing device (ABL 700, Radiometer Medical A/S, Copenhagen, Denmark). Insulin (Actrapid HM, Novo Nordisk, Baegsvard, Denmark) was given into a central venous line as a continuous infusion (Bath and eMPC protocols) or as a combination of a continuous infusion and boluses (Matias protocol). A standard concentration of 50 IU of insulin in 50 ml of 0.9% NaCl was used. In all patients, infusion of 10% glucose solution was initiated upon admission to ICU with glucose dose of 2.5 g/kg of ideal body weight (height in centimeters minus 100) per hour and lasted for 18 hours, when normal oral food intake was started. In ventilated patients, the glucose infusion lasted for 48 hours, and then standard enteral nutrition was initiated.

Clinical parameters and patients’ clinical history data including age, sex, race, height, weight, BMI, EuroSCORE (The European System for Cardiac Operative Risk Evaluation that identifies a number of risk factors which help to predict mortality from cardiac surgery), history of diabetes and type of surgery were collected prospectively. Adverse events, medication and nutrition were continuously monitored and documented.

Outcome measures: Parameters for the assessment of the effectiveness of different TGC management protocols were as follows: entire study average glycemia level; time to the target range of 4.4-6.1 mmol/l (80-110 mg/dl); average glucose level after reaching the target range; number of hypoglycemic episodes (BG <2.9 mmol/l); time within the target range; time between 2.9-4.3 mmol/l (54-70 mg/dl) with no clinical manifestations of hypoglycemia but indicating risk for hypoglycemia; time between 6.2-8.3 mmol/l (110-150 mg/dl) indicating risk of hyperglycemia; time in >8.3 mmol/l (150 mg/dl) indicating hyperglycemia; sampling interval indicating workload. The percentage of time in the target range was calculated as number of values in the target range in each patient / number of measurements *100.

The three TGC management protocols were implemented by the ICU nursing staff with supervision by ICU doctor as required. Protocol training was carried out by the ICU physician and a departmental nurse, usually individually, at bedside. A three months period was devoted to the implementation of Bath insulin protocol, while Matias and eMPC protocols have been used in the ICU previously.

Statistical analysis: Statistical analysis was performed using STATISTICA software (StatSoft, USA). The protocols were compared using ANOVA followed by Holm-Sidak test, Student t-test or Mann-Whitney U-test as appropriate. The significance level was set at P=0.05.

Description of TGC glucose management protocols: See appendices 1-3 in the online appendix available at http://care.diabetesjournals.org.

RESULTS

The baseline characteristics of study patients at the time of admission to ICU are listed in Table 1. The study groups did not differ with respect to age, BMI, EuroSCORE, type of surgery, baseline blood glucose level or occurrence of diabetes. Blood glucose control characteristics are shown in Table 2 and Figures 1 and 2, respectively.

Table 2 demonstrates a significantly better BG control in the eMPC group compared to both the Matias and the Bath groups: entire study average glucose (5.9±0.2 vs. 6.7±0.1 vs. 6.5 ±0.2 mmol/l; P<0.05) and percentage of time within the target range (46.6±3.0 vs. 38.2±2.9 vs. 39.7±3.1 %, P<0.05). To better describe and compare TGC associated with each protocol, we divided glucose profiles into the period before
reaching the target range (Table 2 and Figure 1) and the period after reaching the target range (Table 2). With respect to the time to target range, eMPC performed significantly better than Matias and Bath protocols (Table 2, Figure 2).

In the period after reaching the target range, eMPC algorithm showed superior performance relative to Matias and Bath protocols with respect to average glycemia (5.2±0.1 vs. 6.2±0.1 vs. 5.8 ±0.1 mmol/l; P<0.05), time in target range (62.8±4.4 vs. 48.4±3.2 vs. 55.5±3.2 % of time; respectively, P<0.05), time in risk of hyperglycemia (13.7±2.6 vs. 27.5±2.2 vs. 24.5±2.4 % of time; P<0.05) and time in hyperglycemia (1.3±1.2 vs. 12.8±2.2 resp. 6.5±2.0 % of time; P<0.05) (Table 2).

The average insulin infusion rate and the total insulin dose throughout the entire study were significantly higher in the eMPC compared to the Matias and Bath algorithms (mean insulin rate 5.1±1.0 vs. 3.7±0.4 vs. 4.1±0.5 IU/h; P<0.05). The average sampling interval, as an indicator of workload, was significantly shorter in the Bath vs. both Matias and eMPC groups (Table 2). Two episodes of severe hypoglycemia defined as glycemia lower than 2.3 mmol/l were observed during the study in the Bath protocol group and one episode in the Matias protocol group while no such episode occurred in eMPC group. All three hypoglycemic episodes were classified as "asymptomatic" and were not related to established major risk factors of ICU hypoglycemia such as nutritional interruption, delayed glucose measurement or drug administration.

DISCUSSION

In the present study we compared the performance and safety of three insulin-titration protocols for tight glycemic control in postoperative period in cardiac surgery patients. We showed that the most satisfactory glucose control was achieved with computer-based enhanced model predictive control algorithm (eMPC) while the use of relative glucose value-based Bath protocol resulted in less satisfactory glucose control. The absolute glucose value-based algorithm – Matias protocol – showed the least satisfactory performance. Importantly, all three protocols were reasonably safe. Only three severe hypoglycemic episodes (blood glucose bellow 2.3 mmol/l) occurred throughout the entire study. Strikingly, no such episode was noted in the eMPC group that achieved the best glucose control among the three protocols.

The results of our study further underscore that the ability to correctly implement glucose management protocol is the key prerequisite to successful and safe glucose control in critically ill patients. Our ICU has over six years experience with the use of the Matias protocol and 4 years experience with testing the eMPC algorithm, while the Bath protocol has never been used in our center before. However, after a three months implementation period, our ICU staff was able to successfully use all three protocols without any major problems and safety concerns. This experience markedly differs from the two large multicenter studies with TGC that were discontinued due to excessive risk of hypoglycemia - the Glucontrol Study and the VISEP study. It is possible that insufficient time for insulin protocol implementation and the lack of previous experiences with TGC markedly influenced the outcome of both studies [7, 9, 20, 21].

To our knowledge, our study is the first to compare head-to-head three well-documented and widely used TGC protocols. We used the simplest and possibly the most straightforward way to analyze the data and calculated the average BG and the percent of time within the target range. For the sake of clarity and transparency we did not use any data interpolation and/or other more sophisticated data analysis tools.
Each protocol tested in our study represented a principally different approach to glucose control. The Matias algorithm differs from the other two protocols by combining continuous intravenous insulin infusion with intravenous insulin boluses. This approach might bear a possible advantage in the ability to quickly achieve the target range. Interestingly, while the Matias protocol achieved the target range in about 1.5 hours earlier than the Bath protocol, it was still significantly worse compared to computer-based eMPC algorithm that achieved the target range 2 hours earlier than the Matias protocol without using insulin i.v. boluses. The superior performance of the eMPC algorithm was not accompanied by higher risk of hypoglycemia. In fact, the opposite was true since no severe hypoglycemia was detected in the eMPC algorithm group (see Tab 2).

The Bath protocol principally differs from Matias protocol as the insulin dose is based on the relative change of the blood glucose between the two measurements rather than on the absolute glucose concentration itself. A major advantage of the Bath protocol might lie in the fact, that relative blood glucose change may give a better indication of the high variability of patients´ insulin resistance and nature and severity of their illness especially in comparison with the Matias protocol. A direct comparison of the Bath algorithm with absolute glucose value based Matias protocol showed slightly better performance of the former one with significantly lower mean blood glucose and time in hyperglycemia after reaching the target range. On the contrary, the time to reach the target range was longer and the sampling interval was shorter in Bath, compared to Matias protocol, respectively.

The eMPC protocol also utilises the rate of change in blood glucose although this is not carried out in an explicit manner as with the Bath protocol. Instead, the eMPC derives insulin sensitivity and other physiologically relevant parameters from up to 10-hour blood glucose profile. The eMPC algorithm reached significantly better results compared to both other protocols in the majority of the most important parameters (see Tab 2): in effectiveness (time to target range), in efficiency of glycemia management after reaching the target range (mean glycemia, time in target range, time in risk of and in hyperglycemia) and in sampling interval. Improved glucose control with the use of the eMPC algorithm was accompanied by longer time within the range at higher risk of hypoglycemia, but the occurrence of moderate or severe hypoglycemia was zero in the eMPC group suggesting high level of safety of this protocol.

Overall, compared to some of previously published studies all three protocols were able to achieve a reasonably tight glucose control without an excessive risk of hypoglycemia and/or other complications [21]. The low rate of hypoglycemic events and the overall results in our study could have been partially due to a relatively high constant rate of glucose infusion administered throughout the study. A constant high rate glucose infusion is expected to accelerate glucose turnover and the overall system response. In consequence, this feature of the protocol should improve the stability of glucose control especially under the routine protocol while the eMPC should be less affected. It is thus possible that the overall outcome of the three protocols tested would differ under the conditions of a lower parenteral glucose administration and the results thus cannot be directly applicable to other patient populations.

From the user point of view the major difference between the eMPC and other protocols is the non-fixed sampling interval of the eMPC algorithm. In typical ICU settings, there is usually a time window within which any therapeutic and/or other procedure
including the TGC should happen. In reality such a standard “fixed” interval then may vary considerably. The eMPC algorithm, with its bedside screen interface continuously showing time to next measurement, by itself emphasizes the importance of on-time sampling. The nurses then tend to adapt their activities so that they can fulfill eMPC instructions within the required timeframe. For the sake of our comparative study, we asked our nurses to be as accurate as possible in fulfilling all algorithms requirements, especially with respect to timing of blood glucose measurements. Thus, the study conditions for both Matias and Bath algorithms could have been somehow better compared to a “real life” situation.

Since two of three tested protocols were partially implemented in our ICU previously, our study does not answer the question, how difficult it is to implement the respective protocols from the very beginning. The three months period was long enough to safely implement the Bath protocol under our ICU settings. We suggest that appropriate implementation period and previous experience of our ICU staff with TGC might be the reasons why the quality and safety of glucose control in our study was significantly better than the results of most of the previously published studies [22-25].

In conclusion, we demonstrate that the computer-based eMPC algorithm with a variable sampling interval is more effective in achieving and maintaining TGC in post-cardiac surgery patients than both the relative glucose levels change based Bath protocol and the absolute glucose value based Matias protocol. Overall, all three protocols were able to achieve a reasonable blood glucose control without any major side effects.

ACKNOWLEDGEMENTS

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Disclosure: JB, PK, MM, TK, JK, ML, DR, MS, JL, MS and MH have no conflict-of-interest to declare, RH has received consultancy fees from BBraun.

Preliminary data were presented at the Annual Meeting of the European Association of Cardiothoracic Anesthesiologists, Antalya, Turkey, June 2008.
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Comparison of protocols for glycemic control

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Matias</th>
<th>Bath</th>
<th>eMPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>69.0 ± 1.7</td>
<td>67.8 ± 1.4</td>
<td>68.2 ± 1.1</td>
</tr>
<tr>
<td>Female [n]</td>
<td>14</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Ethnicity: Caucasian [%]</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>28.4 ± 0.35</td>
<td>27.3 ± 1.0</td>
<td>27.8 ± 0.8</td>
</tr>
<tr>
<td>EuroSCORE (logistic)</td>
<td>4.2±0.8</td>
<td>3.9±0.7</td>
<td>4.4±0.9</td>
</tr>
<tr>
<td>Type of surgery [n]:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>28</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>Valve replacement</td>
<td>4</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>CABG + valve replacement</td>
<td>8</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>History of diabetes [n]</td>
<td>14</td>
<td>12</td>
<td>16</td>
</tr>
</tbody>
</table>

The baseline characteristics of post-cardiac surgery patients at the time of admission at ICU (n=40 patients/protocol). Data are mean ± SEM or n.

Table 2.

<table>
<thead>
<tr>
<th></th>
<th>Matias</th>
<th>Bath</th>
<th>eMPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline blood glucose</td>
<td>7.9±0.4</td>
<td>8.0±0.2</td>
<td>8.1±0.6</td>
</tr>
<tr>
<td>The entire study blood glucose control data (or 48 h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average blood glucose (mmol/l)</td>
<td>6.7±0.1</td>
<td>6.5 ±0.2</td>
<td>5.9±0.2*†</td>
</tr>
<tr>
<td>Sampling interval (hour)</td>
<td>2.0±0.1</td>
<td>1.7±0.1</td>
<td>2.1±0.1</td>
</tr>
<tr>
<td>Time to target range (hour)</td>
<td>10.9±1.0</td>
<td>12.3±1.9*</td>
<td>8.8±2.2†</td>
</tr>
<tr>
<td>Time in target range (%)</td>
<td>38.2±2.9</td>
<td>39.7±3.1</td>
<td>46.0±3.0*†</td>
</tr>
<tr>
<td>Blood glucose control data after reaching the target range (4.4-6.1 mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average blood glucose (mmol/l)</td>
<td>6.2 ±0.1</td>
<td>5.8±0.1*</td>
<td>5.2 ±0.1*†</td>
</tr>
<tr>
<td>Sampling interval (hour)</td>
<td>2.1±0.1</td>
<td>1.8±0.1*</td>
<td>2.3±0.1†</td>
</tr>
<tr>
<td>Time in target range (%)</td>
<td>48.4±3.2</td>
<td>55.5±3.2</td>
<td>62.8±4.4*†</td>
</tr>
<tr>
<td>Time in risk of hypoglycaemia (2.9-4.3 mmol/l; %)</td>
<td>10.9±1.5</td>
<td>13.1±1.6</td>
<td>22.2±1.9*†</td>
</tr>
<tr>
<td>Time in hypoglycaemia (&lt;2.9 mmol/l; %)</td>
<td>0.4±0.2</td>
<td>0.4±0.3</td>
<td>0.0±0.0</td>
</tr>
<tr>
<td>Severe hypoglycaemia episodes (&lt;2.3 mmol/l)</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Time in risk of hyperglycaemia (6.2-8.3 mmol/l; %)</td>
<td>27.5±2.2</td>
<td>24.5±2.4</td>
<td>13.7±2.6*†</td>
</tr>
<tr>
<td>Time in hyperglycaemia (&gt;8.3 mmol/l; %)</td>
<td>12.8±2.2</td>
<td>6.5±2.0*</td>
<td>1.3±1.2*†</td>
</tr>
</tbody>
</table>

The study blood glucose control data. Arterial blood glucose was measured as prescribed by each protocol in 1 to 4 hour interval. The patients were followed for up to 48 hours (mean follow-up time 46.7±0.5 hours for Matias, 45.7±0.7 hours for Bath and 47.2±0.3 hours for eMPC, respectively). Data are expressed as mean±SEM. The percentages of time in target range were calculated as number of in range values of each patient / number of measurements x 100.
* indicates statistically significant difference from Matias protocol, † indicates statistically significant difference from Bath protocol, (P<0.05).
Figure 1.
Blood glucose concentrations and time to target range in post-cardiac surgery patients controlled by Matias, Bath and eMPC protocols expressed as mean ± SEM.

Figure 2.
Blood glucose concentrations in post-cardiac surgery patients controlled by Matias, Bath and eMPC protocols during entire 48-hours post-operative period expressed as mean ± SEM. Average time within the target range was 38.2±2.9 % for Matias, 39.7±3.1 % for Bath and 45.98±3.0 % for eMPC, respectively.