Hyperglycemia and insulin resistance are common in critically ill patients, even those without a history of diabetes mellitus.1,2 Patients in intensive care units (ICUs) experience significant physiological stress, which leads to disturbances in the endocrine axis such as changes in the levels of epinephrine, cortisol, growth hormone, and glucagon. Such changes may subsequently cause hyperglycemia.3,4 Administration of certain medications such as norepinephrine,5 corticosteroids,6 and/or high-caloric enteral or parenteral nutrition7 may also aggravate hyperglycemia in these patients.

A growing body of evidence has linked hyperglycemia and insulin resistance are common in critically ill patients, even those without a history of diabetes mellitus.1,2 Patients in intensive care units (ICUs) experience significant physiological stress, which leads to disturbances in the endocrine axis such as changes in the levels of epinephrine, cortisol, growth hormone, and glucagon. Such changes may subsequently cause hyperglycemia.

BACKGROUND Recent evidence has linked tight glucose control to worsened clinical outcomes among adults in intensive care units.

OBJECTIVE To evaluate the effectiveness and safety of a nurse-led intravenous insulin protocol designed to achieve conservative blood glucose control in patients in a medical intensive care unit.

METHODS A nurse-led intravenous insulin protocol was developed, targeting blood glucose levels at 110 to 149 mg/dL. Hypoglycemia was defined as a blood glucose level less than 70 mg/dL. Patients admitted to the medical intensive care unit who required an insulin infusion were enrolled in the study. Blood glucose levels in those patients were compared with levels in 153 historical control patients admitted to the unit in the 12 months before the protocol was implemented who required an insulin infusion.

RESULTS Ninety-six patients were enrolled and treated with the protocol. The protocol and control groups had similar characteristics at baseline. More measurements in the protocol group than in the control group (46.3% vs 36.1%, P < .001) were within the target glucose range (110-149 mg/dL). Hyperglycemia (blood glucose ≥200 mg/dL) occurred less often in the protocol group than in the control group (14.8% vs 20.1%, P = .003). Hypoglycemic events (blood glucose <70 mg/dL) also occurred less often in the protocol group (0.07% vs 0.83%, P < .001).

CONCLUSIONS Implementation of a nurse-led, conservative intravenous insulin protocol in the medical intensive care unit is effective and safe and markedly reduces the rate of hypoglycemia. (Critical Care Nurse. 2011;31[6]:27-35)
resistance to worsened clinical outcomes in various groups of patients. In particular, impaired glycemic control has been associated with increased hospital mortality in patients admitted to ICUs. The effects of blood glucose control with insulin on patients’ outcomes have been investigated in a number of studies, and results have been markedly positive. In a prospective randomized controlled trial of 1548 surgical ICU patients, hospital mortality was reduced by 34% after an intravenous insulin protocol was introduced. Following this landmark study, various intensive insulin protocols aimed at achieving inpatient glycemic control in the ICU, including the medical ICU, have been described.

The optimal target range for blood glucose level in critically ill patients remains unclear. Most researchers prefer to use tight ranges of blood glucose control (80-110 mg/dL; multiply by 0.0555 to convert to millimoles per liter) in order to prevent hyperglycemia; however, these ranges increase the risk for hypoglycemia. Others prefer to use less stringent ranges for blood glucose (eg, 100-140 mg/dL) in order to minimize the risk for hypoglycemia but still prevent hyperglycemia. Although the first randomized controlled trial showed that tighter glucose control (80-110 mg/dL) reduced morbidity and mortality, or at least did not increase mortality, the NICE-SUGAR multicenter study recently showed that tight glucose control increased mortality and increased the risk of severe hypoglycemia among adults in the ICU. These conflicting results led to the recommendation to avoid lower glucose targets in critically ill adults.

We undertook this study to develop and evaluate a nurse-led, self-adjusting, standardized intravenous insulin protocol designed to achieve safe and effective control of blood glucose levels in patients in the medical ICU by using a more conservative glucose target and a higher hypoglycemic threshold.

Methods

Patients and Setting

This prospective study with a retrospective control group was performed in a 9-bed medical ICU at the Hadassah Hospital in Jerusalem, Israel. The medical ICU staff includes intensive care specialists, rotating medical residents in training, and ICU-trained and non–ICU-trained nurses. Approval for access to patients’ data and a waiver of informed consent were obtained from the institutional review board. Patients. All adult patients admitted to the medical ICU during the 12 months after the initiation of the nurse-led intravenous insulin protocol who required insulin infusion for blood glucose control were enrolled in the prospective group. Patients admitted with diabetic ketoacidosis, hyperglycemic hyperosmotic nonketotic coma, or who were being fed orally were excluded. Patients enrolled in the retrospective control group were those who had been admitted to the medical ICU during the 12 months preceding implementation of the protocol who required intravenous insulin therapy. Patients with ketoacidosis and hyperglycemic hyperosmotic nonketotic coma were excluded from the control group. Patients with a history of diabetes mellitus were included in both groups.

Oral Hypoglycemic Agents. As a routine, oral hypoglycemic agents are withheld during insulin administration in the medical ICU. Therefore, none of the patients in the protocol group or the control group received oral hypoglycemic agents during the study.

Standard Insulin Therapy (Control Group). Before development of the protocol, elevated blood glucose measurements were often untreated until they reached 180 mg/dL or higher. When patients consistently had blood glucose levels of 180 mg/dL or greater, an insulin infusion was ordered. A typical order was to adjust insulin to maintain blood glucose levels between 90 and 140 mg/dL. Orders of this type did not direct the nurses when and how much to increase or decrease the insulin infusion; this resulted in glucose control that varied with nurses’ experience and comfort level.

Development and Implementation of the Intravenous Insulin Protocol

The development of an insulin infusion protocol was initiated by key
contributors from a team of nurses and physicians from various disciplines. The protocol was written in a logarithm format table that allowed shifting between several algorithms horizontally and vertically, depending on changes in capillary blood glucose values from the previous blood glucose measurement (see Appendix—online only). No special adjustments were made for the use of corticosteroids, parenteral nutrition, or substitution solutions with glucose-containing infusions. All patients who received an insulin infusion also were receiving 1 or more of the following: glucose infusions, total parenteral nutrition (TPN), or enteral feeding.

For measurement of blood glucose levels, nurses used bedside glucometers or undiluted heparinized arterial blood (if systolic blood pressure was <80 mm Hg). Capillary blood glucose levels were measured hourly in the first 8 hours of use of the protocol, and then decreased to every 2 hours until the glucose level had been within the target range (110-149 mg/dL) for 8 hours. Subsequently, the frequency of capillary blood glucose measurements was changed to every 4 hours. Insulin was administered by continuous intravenous infusion through a peripheral or a central venous catheter with a 50-mL syringe pump. The standard concentration of the infusion was 1 IU/mL (50 IU of regular insulin in 50 mL of 0.9% saline).

In an effort to provide the nurses with as much support as possible before the protocol was implemented, a plan was created to facilitate acceptance and correct use of the protocol. Initially, the protocol and updated literature about the importance of glycemic control in critical care patients were presented in our bimonthly staff meeting. The meeting involved all members of the medical ICU (30 nurses and 4 physicians), and lasted approximately 1½ hours, including time for questions and feedback. Subsequently, all nursing staff in the medical ICU received informal education for 2 weeks from the key project developers and contributors. The educational sessions lasted approximately 30 minutes and included explanations about the proper use of the protocol and its bedside implementation. In addition, during the study period, a bedside chart containing the protocol guidelines was available. This chart also was used to fill in the date, hour, blood glucose measurements, protocol number, and the corresponding rate of the insulin infusion.

Evaluation of the Protocol

The protocol was evaluated with respect to effectiveness and safety. Effectiveness was evaluated by calculating the percentage and mean percentage of blood glucose values within the target range (110-149 mg/dL) during implementation of the protocol. The different blood glucose levels were defined as hypoglycemic (<70 mg/dL), low (≥70 but <110), target (≥110 but <150), acceptable hyperglycemic (≥150 but <200), and severely hyperglycemic (≥200). The higher the mean percentage of blood glucose measurements within the target range, the better the effectiveness. Safety was assessed by determining the mean percentage of blood glucose measurements less than 70 mg/dL and the percentage of patients with at least 1 hypoglycemic episode.

Data Collection

Clinical data were obtained from patients’ charts and records. Data were collected prospectively in the protocol group and retrospectively in the control group. Patients’ baseline characteristics
included age, sex, history of diabetes, and principal reason for ICU admission. In addition, we calculated patients’ score on the Acute Physiology and Chronic Health Evaluation II (APACHE II) and the predicted mortality for every patient at admission. For each patient, data on blood glucose levels, insulin doses, duration of insulin therapy, blood glucose level at admission and when insulin was started, time to reach target glucose levels, relevant clinical interventions (corticosteroids, vasopressors, antibiotics, nutrition), and calories administered were collected from the active hospital chart and the nursing records in the medical ICU. All blood glucose measurements obtained during the period of intravenous insulin administration were documented.

Finally, data on the total duration of mechanical ventilation, length of stay in the medical ICU, dialysis after admission, and ICU mortality also were collected. All patients were followed up until discharge from the ICU or death.

**Statistical Analysis**

Descriptive statistics were generated by the SPSS Statistical Software Package Version 12 (IBM SPSS Statistics, Armonk, New York). Clinical data are expressed as median, mean (SD), or as a percentage. Subgroups of patients were compared by using χ² analysis or a Student independent t test. The mean percentage of blood glucose levels in the protocol group and the control group were compared by using a Student independent t test. Hierarchical linear regression analysis was used to detect factors that could have influenced hypoglycemia and the tightness of blood glucose control. All tests of significance were 2 tailed. P values less than .05 were considered statistically significant.

**Results**

Two hundred forty-nine patients were enrolled in the study: 96 in the prospective protocol group and 153 in the retrospective control group. Baseline characteristics, diagnoses at admission, clinical interventions, calories administered, and illness severity are presented in Table 1.

For the 96 patients in the protocol group, the median duration of insulin therapy was 7 days, with 84 (88%) continuing for more than 3 days. Overall for the protocol group, the median insulin dose used was 25.93 units per patient per 24 hours and the median blood glucose level at admission was 173 mg/dL. The median blood glucose level at protocol initiation was 212 mg/dL, and the median time required to achieve target blood glucose levels (110-149 mg/dL) was 8 hours (Table 2).

During the 12-month study period, the 96 patients had a total
of 925 protocol days. Of the 9893 measurements obtained during those 925 protocol implementation days, 649 (6.56%) were in the low range (≥70 but <110 mg/dL), 4546 (45.95%) in the target range (≥110 but <150 mg/dL), 3232 (32.66%) in the acceptable hyperglycemic range (≥150 but <200 mg/dL), and 1449 (14.64%) in the severely hyperglycemic range (≥200 mg/dL).

**Protocol Safety**

Hypoglycemia (blood glucose <70 mg/dL) in the protocol group was rare. Of the 9893 blood glucose measurements, only 11 measurements (0.11%) in 6 patients (6%) were less than 70 mg/dL. The mean blood glucose level in these measurements was 57.0 (SD, 11.5) mg/dL (Table 2). All episodes of hypoglycemia resulted in the administration of a rescue bolus of dextrose per the protocol. All episodes of hypoglycemia lasted a mean of 30 (SD, 20) minutes. None of these hypoglycemic events resulted in adverse consequences.

**Protocol Effectiveness**

To assess the effectiveness and safety of the protocol compared with our previous practice standards, we used 153 patients consecutively admitted to our medical ICU during the 12 months before the protocol was implemented. Figures 1 and 2 show blood glucose levels in the 2 groups. More samples in the protocol group than in the control group (46.3% vs 36.1%, respectively, \(P<.001\)) were within the target glucose range (110-149 mg/dL; see Figure 1). Hypoglycemic events (blood glucose <70 mg/dL) occurred less often in the protocol group than in the control group (7/10 000 measurements vs 83/10 000 measurements, respectively, \(P<.001\); see Figure 2), and fewer patients experienced 1 or more episodes of hypoglycemia (6% vs 30%, respectively, \(P<.001\)).

Two separated hierarchical multiple linear regressions were carried out to determine the extent to which the use of the protocol was predictive of 2 outcomes: (1) hypoglycemic events, and (2) the tightness of blood glucose control, after the following variables were controlled for: number of glucose measurements, the duration of insulin therapy, history of diabetes, and neurological diagnosis. Therefore, the predictors of both outcomes were entered into the model in 2 steps: (1) control variables, and (2) the use of the protocol. The first regression showed that only the use of the protocol (\(b=-.28\)) was independently associated with a lower probability for hypoglycemic events, with an adjusted \(R^2\) of 0.16 (\(P<.001\)), regardless of the effects of the control variables. The second regression revealed 2 significant predictors of the tightness of blood glucose control with an adjusted \(R^2\) of 0.18 (\(P<.001\)): use of the protocol (\(b=.35\)) and history of diabetes (\(b=-.26\), data not shown). (\(b\) indicates the relative weight of the standardized predictor variable in question. A positive value indicates a positive relationship with the outcome, whereas a negative value indicates a negative association. Adjusted \(R^2\) measures the proportion of the variation in the dependent variable that is explained by the predictor variables.)

### Table 2

Blood glucose measurements and insulin therapy in the 2 groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Protocol group (n = 96)</th>
<th>Control group (n = 153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of insulin therapy, d</td>
<td>Mean (SD)</td>
<td>Median</td>
</tr>
<tr>
<td>Mean</td>
<td>9.6 (6.5)</td>
<td>7</td>
</tr>
<tr>
<td>Median</td>
<td>10.3 (9.3)</td>
<td>7</td>
</tr>
<tr>
<td>Blood glucose level,a mg/dL</td>
<td>At admission</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Mean</td>
<td>185.9 (77.1)</td>
<td>173</td>
</tr>
<tr>
<td>Median</td>
<td>176.9 (82.3)</td>
<td>157</td>
</tr>
<tr>
<td>At start of protocol use</td>
<td>Mean (SD)</td>
<td>222.3 (52.4)</td>
</tr>
<tr>
<td>Mean</td>
<td>208</td>
<td></td>
</tr>
<tr>
<td>Time to goal, h</td>
<td>Mean (SD)</td>
<td>10.3 (11.5)</td>
</tr>
<tr>
<td>Mean</td>
<td>9.9 (7.5)</td>
<td>7</td>
</tr>
<tr>
<td>Blood glucose samples and insulin administration</td>
<td>Total No. of measurements</td>
<td>9893</td>
</tr>
<tr>
<td>Total No. of days of insulin therapy</td>
<td>925</td>
<td>1577</td>
</tr>
<tr>
<td>No. of samples per patient, mean (SD)b</td>
<td>103.10 (74.7)</td>
<td>80.11 (82.2)</td>
</tr>
<tr>
<td>Hypoglycemic values (blood glucose &lt;70 mg/dL), mean (SD), mg/dL</td>
<td>57.0 (11.5)</td>
<td>58.5 (10.8)</td>
</tr>
<tr>
<td>No. (%) of patients with at least 1 blood glucose level &lt;70 mg/dLc</td>
<td>6 (6)</td>
<td>46 (30)</td>
</tr>
<tr>
<td>Insulin dose per patient per 24 h, units</td>
<td>Mean (SD)</td>
<td>29.41 (18.98)</td>
</tr>
<tr>
<td>Mean</td>
<td>32.63 (21.1)</td>
<td>28.33</td>
</tr>
</tbody>
</table>

\(a\) Blood glucose values can be converted to millimoles per liter by multiplying by 0.0555.  
\(b\) Difference between protocol group and control group is significant (\(P = .03\)) for this variable.  
\(c\) Difference between protocol group and control group is significant (\(P < .001\)) for this variable.
Severe hyperglycemia (blood glucose ≥200 mg/dL) occurred less often in the protocol group than in the control group (14.8% vs 20.1%, respectively, \( P = .003 \)), but no significant reduction was observed in the acceptable hyperglycemia range (Figure 1). Finally, no significant reduction was observed in mortality, duration of mechanical ventilation, and dialysis after the implementation of the protocol. A significant reduction was observed in the length of stay in the ICU and in the hospital (Table 3).

**Discussion**

Our data have demonstrated that a nurse-led intravenous insulin protocol with a more conservative blood glucose target is both effective and safe in medical ICU patients. When compared with historical control patients, patients in the protocol group had more blood glucose measurements within the target range, fewer blood glucose measurements in the hyperglycemic range, and significantly fewer hypoglycemic episodes. Reduced hypoglycemia was significantly associated with use of the protocol. Lengths of stay in the ICU and hospital were shorter in the protocol group.

Studies on tight glycemic control in ICU patients have shown conflicting results, with both improved outcomes and increased morbidity and mortality reported. \(^{11,22-24}\) Studies in which tight glycemic control was targeted (80-110 mg/dL) were associated with increased hypoglycemic rates even with very low hypoglycemia thresholds. \(^{21,22,25}\) Alm-Kruse et al\(^{21}\) reported that glucose targets of 80 to 110 mg/dL resulted in an increase in hypoglycemic episodes (blood glucose <40 mg/dL) from 2.4% to 8.9%. The recent NICE-SUGAR study\(^{23}\) demonstrated increased mortality in patients treated with intensive glucose control compared with patients in whom a conventional target of 180 mg/dL or less was used (27.5% vs 24.9%, respectively, \( P = .02 \)), together with an increased risk of hypoglycemia (6.8% vs 0.5%, \( P < .001 \)). That study raised pertinent questions regarding the safety of the use of intensive glucose targets; however, it did not address the safety of the use of higher glucose targets.
Use of an insulin protocol has improved glycemic control in different ICU environments and reduced the frequency of hypoglycemic events. The safety and effectiveness of such insulin protocols may be related to 2 parameters: the hypoglycemia threshold and the target range of glucose control. Although most intensive insulin protocols defined hypoglycemia as a blood glucose level of less than 40 mg/dL, significant hypoglycemic events still occurred. Our hypoglycemia threshold was defined as a glucose level of less than 70 mg/dL. Moreover, several measures were undertaken to prevent hypoglycemic episodes. Insulin rates were reduced not only according to absolute glucose levels but also according to the rate of decline. The nursing staff therefore reduced insulin administration and administered intravenous glucose earlier, thus avoiding a more extreme decrease in glucose levels and the associated symptoms. In addition, special care was taken to include guidelines for withholding insulin during periods when feeding was stopped (eg, gastric residual checks, procedures). The fact that the number of glucose measurements per patient was higher in the protocol group also may have contributed to the decreased rate of hypoglycemia. However, the results of the logistic regression did not support this idea.

A conservative glucose target range reduced the number of hypoglycemic events while still maintaining clinically desirable glucose control. Bode et al described different glucose targets for different groups of hospitalized patients receiving intravenous insulin therapy, with critically ill surgical patients requiring the most intensive glucose control. Goldberg et al used a target glucose range of 100 to 139 mg/dL and found that after the initial decrease in glucose levels, 52% of patients were within the target range and 66% were within the “clinically desirable” range of 80 to 139 mg/dL with only a minimal occurrence (0.3%) of hypoglycemic events. We opted to use a more conservative but clinically acceptable glucose target of 110 to 149 mg/dL in order to minimize the rate of hypoglycemic events but still achieve clinically acceptable glucose control.

The fact that the time to achieve glucose control was similar in both the protocol group and the control group supports the idea that our protocol was not more aggressive than standard treatment. Moreover, the increased amount of blood glucose measurements in the protocol group did not significantly influence the tightness of glucose control, as demonstrated by logistic regression; however, use of the protocol did influence the tightness of glucose control. History of diabetes mellitus was known in about half of the patients in both groups (Table 2); however, guidelines for insulin administration did not differ in our diabetic patients. Our analysis has shown that the protocol was safe in both patients with newly diagnosed hyperglycemia and in diabetic patients; however, we found a negative association between tightness of glucose control and the presence of diabetes, as glucose control in these patients was probably harder to achieve. In a recent study, mortality and inflammatory response did not differ in critically ill diabetic patients with severe sepsis and nondiabetic patients. Until further data are available, we think that glucose targets should be standard to all patients.

The use of insulin protocols in the ICU may enhance nurses’ autonomy and empowerment or it may increase nursing workload and patients’ discomfort because of the increase in the number of glucose measurements. Although using the protocol may have been more time-consuming for the nurses, as reflected in the higher mean number of glucose measurements per patient in the protocol group (Table 2), most of our ICU nurses reported that the protocol was a useful and instructive tool for glucose control in their patients. In addition, we have achieved high levels of satisfaction among nurses and physicians.
standardization of treatment among nurses, better cooperation among interdisciplinary teams, greater confidence with insulin administration, and increased empowerment of the nursing staff.

Recent developments have introduced computerized systems, such as the Glucommander\textsuperscript{22} and the Clarion\textsuperscript{23} systems, in which insulin doses and measurement intervals are calculated on the basis of glucose measurements and multipliers. Although they are effective in reaching blood glucose targets with acceptable rates of hypoglycemia, such computerized systems are potentially expensive and have not been shown to be superior to other noncomputerized protocols.

**Limitations**

Our study has several limitations. We used retrospective historical control patients, admitted to the medical ICU during the 12 months preceding implementation of the protocol, who required insulin therapy. The number of patients in the control group (n=153) was higher than the number in the protocol group (n=96). This difference may have stemmed from a more liberal and nonstandardized approach to the administration of intravenous insulin in the control group, as well as the inclusion of patients taking oral nutrition, who were excluded from the protocol group (because of safety considerations). Power calculation for a difference of 0.76 in the mean percentage of the hypoglycemic level (blood glucose <70 mg/dL) between the protocol group and the control group (Table 2), with a standard deviation of 0.3 in the protocol group and 1.7 in the control group, and a sample size of 96 patients for the protocol group and 153 patients for the control group, provides a power of 99%.

Moreover, both groups were clinically similar in terms of the history of diabetes, disease profiles, severity of illness, and interventions used (Table 1). The greater percentage of neurological patients in the protocol group than in the control group (10% vs 1%, \(P=.002\)) was attributed to the implementation of a new protocol for treatment of cerebrovascular accidents that required admission to the ICU during the protocol period. The presence of a neurological diagnosis, however, did not influence the safety and effectiveness of the protocol. We therefore think that the historical control group is suitable for comparison with our protocol group.

Our population of patients consisted of complicated medical patients with a relatively high APACHE II score, with about half requiring inotropic support and more than 60% treated with corticosteroids. It is therefore difficult to compare these patients with patients in other trials in which insulin protocols were studied. Our study was not powered for end points such as patients’ outcome and length of stay. We therefore cannot attribute a shortened stay in the ICU or hospital in the protocol group to the use of the protocol alone, because other factors, such as changes in overall patient selection, discharge policies, and optimization of hospital facilities and resources may have been involved. We did not find differences in mortality between the 2 groups. However, randomized controlled trials should be performed in order to detect significant changes in mortality when such protocols are used.

**Conclusion**

Results of this study indicate that using a nurse-led intravenous insulin protocol with a conservative blood glucose target is effective in controlling blood glucose levels in critically ill medical patients and is associated with a significantly lower hypoglycemia rate than standard practices. Our protocol can assist nurses and physicians in safely targeting blood glucose levels in an ICU and can improve standardization and optimization of continuous intravenous insulin administration by the nursing staff. Randomized controlled trials should be done to determine whether such a protocol will result in improved outcomes for medical ICU patients.


32. Davidson PC, Steed RD, Bode BW, Glacomeomar: a computer-directed intravenous insulin system shown to be safe, simple, and effective in 120,618 h of operation. Diabetes Care. 2005;28(10):2418-2423.
Nurse-Led Implementation of a Safe and Effective Intravenous Insulin Protocol in a Medical Intensive Care Unit
Rabia Khalaila, Eugene Libersky, Dina Catz, Elina Pomerantsev, Abed Bayya, David M. Linton and Sigal Sviri

Crit Care Nurse 2011;31 27-35.10.4037/ccn2011934
©2011 American Association of Critical-Care Nurses
Published online http://ccn.aacnjournals.org/

Personal use only. For copyright permission information:
http://ccn.aacnjournals.org/cgi/external_ref?link_type=PERMISSIONDIRECT

Subscription Information
http://ccn.aacnjournals.org/subscriptions/

Information for authors
http://ccn.aacnjournals.org/misc/ifora.xhtml

Submit a manuscript
http://www.editorialmanager.com/ccn

Email alerts
http://ccn.aacnjournals.org/subscriptions/etoc.xhtml