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Intensive Glycemic Management in Critically Ill Patients

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An initiative at The Stamford Hospital, a 305-bed university-affiliated community teaching hospital in Stamford, Connecticut, was undertaken to assess the effect of an intensive glucose management protocol. An increasingly robust body of literature describes the adverse consequences of hyperglycemia. Clinical situations in which impaired glycemic control has been associated with worsened outcomes include myocardial infarction and acute coronary syndromes, stroke, postoperative wound infections, and trauma. A recent review of more than 1,800 consecutive admissions to our intensive care unit (ICU) demonstrated that hospital mortality was strongly associated with glycemic control during ICU admission.[1] Patients with mean glucose level of 80–99 mg/dl during ICU admission sustained 9.6% hospital mortality; this increased to 12.5% among patients with mean glucose level of 100–119 mg/dl and rose to as high as 42.5% when mean glucose level was > 300 mg/dl. This study raised the possibility that treatment of even mildly elevated glucose levels during ICU admission may save lives.

The protocol used in this initiative was created by a multidisciplinary group between November 2003 and January 2004 (Appendix 1, page 312).[2] The process involved small-group discussions, the drafting of a preliminary protocol, retooling the protocol after reviewing its efficacy and applicability, and in-depth education of the nursing and unit medical staff regarding the protocol's details and goals.

A goal of 140 mg/dl was agreed on as both achievable and safe. The database analysis had shown that ICU patients who died before hospital discharge had a mean glucose value of 172 mg/dl during their ICU stay, whereas ICU patients who survived to hospital discharge had a

Article-at-a-Glance

Background: The effect of an intensive glycemic management protocol was assessed in a heterogeneous population of critically ill adult patients.

Methods: Patients representing 800 consecutive admissions following the institution of the protocol were compared with the 800 admissions immediately preceding the institution of the protocol in a 14-bed mixed medical-surgical intensive care unit (ICU). The protocol used intensive monitoring and treatment to maintain blood glucose values > 140 mg/dl. Continuous intravenous insulin was used if glucose values were > 200 mg/dl on two successive occasions.

Results: Mean glucose decreased from 152.3 mg/dl to 130.7 mg/dl ($p < .001$), marked by a 56.3% reduction in the percentage of glucose values ≥ 200 mg/dl, without a significant change in hypoglycemia. There were decreases in the development of new renal insufficiency ($p = .034$) and in the number of patients receiving transfusion of packed red blood cells ($p = .035$) during the protocol period. Hospital mortality decreased 29.3% ($p = .002$), and ICU length of stay decreased 10.8% ($p = .011$) after institution of the protocol.

Discussion: The 29.3% relative reduction in hospital mortality seen among the treatment patients following institution of the protocol probably exceeded the expectations of the initiative's champions. The culture of the ICU regarding glycemic control changed definitively. The protocol was extended to an intermediate care unit, resulting in improvement in glycemic control without an increase in hypoglycemia.

Table 1. A Timeline of the Initiative*

- Sep. 1998: Development of the comprehensive ICU database
- Sep. 2002: Database analysis reveals strong relationship between increasing glucose levels in the ICU and increasing hospital mortality†
- Nov. 2002–Jan. 2003: Meetings with nursing staff to design and then disseminate the protocol
- Feb. 2003: Protocol is instituted and data analysis begins
- Jan. 2004: The 800th treatment protocol patient is admitted to the ICU

*ICU, intensive care unit.

† Krinsley J.S.: Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc* 78:1471-1478, Dec. 2003.

mean glucose value of 138 mg/dl.[1] After the core group, including the medical and nursing directors of the ICU and a small group of staff nurses, completed the first iteration of the glycemic management protocol, it was released to the entire ICU staff for further discussion, modification and orientation. By the time that the protocol was initiated on February 1, 2003 enough discussion had ensued to ensure the nursing staff's consensus and buy-in regarding the goals of the protocol and the means to achieve them.

A timeline for the initiative can be found in Table 1 (above). The initiative, which required minimal additional funding and resources, was championed by the director of critical care and the nursing director of critical care services—the medical and nursing directors of the ICU. The database used to support the project was already operational when the project was conceived, and data input during the initiative continued without change. The initiative's success depended on the strong data management system developed in the ICU and on its tight integration with the numerous multidisciplinary protocols in use.

Methods

Data Analysis

The analysis compared the baseline group (800 consecutive admissions to a 14-bed mixed medical-surgical ICU immediately preceding the institution of the protocol) and the treatment group (the first 800 admissions to the ICU following the institution of the protocol). Glycemic control was assessed using (1) mean glucose level (the mean of all glucose levels obtained in the ICU population), calculated twice monthly; and (2) a histogram showing the percentage of glucose values at discrete mg/dl intervals for the baseline and treatment populations. This second measure provided monitoring of the occurrence of hypoglycemia (defined as glucose < 40 mg/dl) and gave the staff a powerful visual image of the increase in euglycemia and profound decrease in marked hyperglycemia that occurred as a result of the protocol.

The comprehensive ICU database, consisting of the core dataset entered on a daily basis on all admissions by the director of critical care, with linkages to numerous hospital data repositories, allowing complex queries, was used for all analyses reported in this application. The baseline and treatment periods each lasted approximately 11 months.

Results

Comparison of Baseline and Treatment Groups

The baseline and treatment groups were well matched; there was no significant difference between the two populations in age, sex, race, the percentage of patients with diabetes, severity of illness at ICU admission (as defined by the APACHE II score), or the percentage of patients admitted to the medical versus surgical service. Nor were there significant difference between the baseline and treatment groups in the number of patients, age or APACHE II scores in each of the major diagnostic categories.

Effect of the Protocol on Glycemic Control

The glycemic management protocol led to significantly improved glucose levels without a significant increase in hypoglycemia. Figure 1 (page 310) displays the distribution of glucose values in the baseline and treatment periods. The mean and median glucose levels during the baseline period were 152.3 mg/dl and 131 mg/dl, which decreased to 130.7 mg/dl and 119 mg/dl during the treatment period ($p < .0001$). There was a 56.3% decrease in the percentage of glucose values ≥ 200 mg/dl, from 16.2% during the baseline period to 7.1% during the treatment period ($p < .001$). The percentage of patients with marked hypoglycemia, defined as glucose values < 40 mg/dl, was comparable in the baseline (0.35%) and treatment (0.34%) periods. The percentage of patients with mild

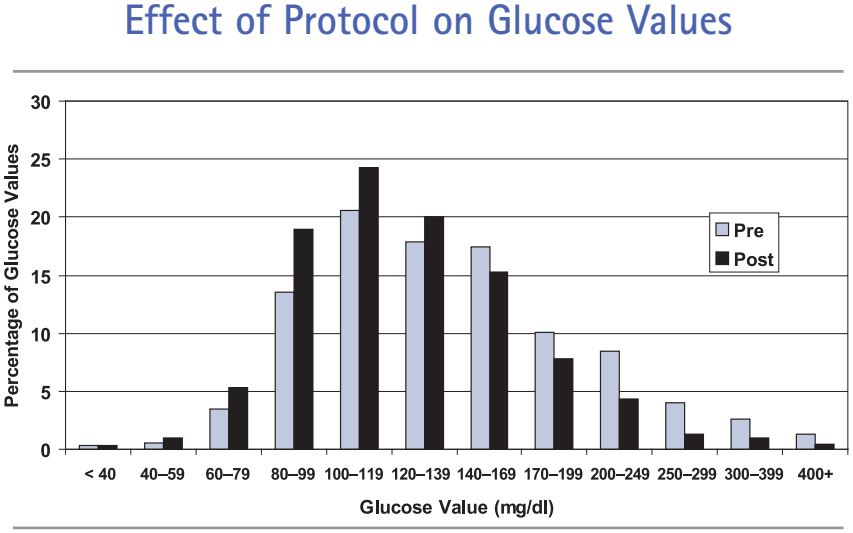

Figure 1. *The distribution of glucose values in the baseline and treatment periods is displayed.*

hypoglycemia, defined as glucose values 40–59 mg/dl, increased from 0.54% to 1.02% (p = .023; Chi-square test). There were no associated adverse clinical sequelae associated with hypoglycemia during either period.

Mortality Rates

Hospital mortality decreased by 29.3% during the protocol period (168 baseline patients [20.9%] versus 119 treatment patients [14.8%], p = .002). The improved survival among patients undergoing the glycemic management protocol was notable regardless of acuity of illness, except among the 5%–6% of the patients with the most profound illness (APACHE II scores ≥ 35) at ICU admission.

Other Outcomes

The number of patients with new renal dysfunction after ICU admission, defined as initial serum creatinine < 1.5 mg/dl with maximum serum creatinine > 2.5 mg/dl or initial serum creatinine > 1.5 mg/dl with maximum serum creatinine two or more times the initial value, decreased from 12 during the baseline period to 3 during the treatment period (p = .034 by Fisher's exact test). There was a reduction in the number of patients requiring transfusions of packed red blood cells (PRBC) during the protocol period. Excluding patients admitted to the ICU with a primary diagnosis of acute upper or lower gastrointestinal bleeding (50 in the baseline group and 44 in the treatment group), 25.2% of the baseline patients and 20.5% of the treatment patients (p = .035) received a mean of 3.77 and 3.30 units of PRBC (p = .169) respectively.

ICU Length of Stay

Mean and median ICU length of stay (LOS) decreased during the treatment period. The median LOS decreased from 1.9 (1.0–3.9) to 1.6 (0.9–3.3) [median and interquartile range] days (p = .011). The mean ICU LOS decreased from 3.6 (3.2–3.9) to 3.2 (2.9–3.5) [mean ad 95% CI] days (p = .107). There was no change in the hospital LOS following discharge from the ICU.

Comparison of Mortality Results with a Second Baseline Period

To exclude the possibility that the decreased mortality rate of the patients in the protocol group was due to a temporal trend in the improvement of ICU care within the institution in general, an additional group of 800 patients, admitted to the ICU just before the patients in the baseline group, was abstracted from the database. The APACHE II score and age of the patients was not significantly different than those of the baseline or treatment groups; values for hospital mortality and mean ICU LOS were comparable to those of the baseline group.

Table 2 (page 311) describes the stability of glucose control in this ICU during the three years before institution of the intensive glycemic management protocol. There was no significant difference in the mean glucose value or the percentage of glucose values ≥ 200 mg/dl during this period. The mean value and percentage of glucose values ≥ 200 mg/dl decreased dramatically after institution of the protocol (p < 0.0001 for all comparisons).

Data Dissemination

The creation of the comprehensive ICU database in 1998 and its subsequent growth and maturity helped to create a data-conscious, data-driven culture in the unit. Nurses, medical and surgical house staff, respiratory therapists, pharmacists, and attending physicians were

Table 2. Temporal Trends in Glucose Control (mg/dl)*

One-Year Period Beginning	Mean (SD) Glucose	% Glucose Values ≥ 200 mg/dl
Feb. 2000	154.7 (85.9)	18.8
Feb. 2001	152.9 (78.8)	19.1
Feb. 2002	152.5 (93.2)	16.4
Feb 2003	130.7 (55.1)	7.3

* SD , standard deviation.

used to regular reporting of data relating to ongoing quality and resource utilization projects.

The data resulting from this initiative were reviewed regularly at many different levels. The nurses and house staff received glycemic control data on a twice-monthly basis to ensure that the goals of the protocol were being achieved. Mortality and other outcome data were generated after two months of the protocol had been completed. The methods of data dissemination within the ICU included informal discussions, distribution of colorful charts and tables into the decentralized nursing stations scattered within the unit, and posting of numerous data in the multidisciplinary conference room in the unit.

Data generated from the initiative were also reported monthly or bimonthly at the critical care committee meeting and the clinical leadership council meeting, as well as to larger gatherings of physicians and nurses within the hospital.

Discussion

The 29.3% relative reduction in hospital mortality seen among the treatment patients following institution of the protocol certainly met, and, frankly, probably exceeded the expectations of the initiative's champions. The decrease in new renal insufficiency, the decrease in red blood cell transfusions, and the decreased LOS during the treatment period compared with the baseline period were all welcome findings.

Until very recently, the standard of care in the treatment of ICU patients tolerated a degree of moderate hyperglycemia. Typically glucose values up to 200–225 mg/dl were not treated. It was not surprising, therefore, that there would be resistance among the nursing and medical staff to changing this paradigm. The resistance reflected uncertainty about the benefit of the new glycemic control standards, concern about the potential for increased risk of hypoglycemia, and subsequent reluctance to accept a new burden of work. These reasonable concerns were answered with data and multidisciplinary consensus about the goals of the protocol. Once the protocol was put into place the staff were provided with twice monthly report cards of glycemic control, including the incidence of hypoglycemia. These data alleviated anxieties that the protocol would increase the risk of complications and the positive feedback provided "fuel" to the staff to continue the extra work needed to keep the protocol on track. Finally, within several months of the institution of the protocol mortality data were generated. These highly favorable statistics generated more excitement and enthusiasm.

The culture of the ICU regarding glycemic control has changed definitively. Intensive glucose control is engrained in the fabric of the unit and the nurses and medical staff are becoming increasingly skilled at bedside management of glucose levels. After successful initiation of the protocol in the ICU, the question arose whether intensive glucose treatment was achievable in other patient populations within the institution. With use of the protocol extended to the special care unit (SCU), an intermediate care unit, preliminary data also indicate an improvement in glycemic control without an increase in hypoglycemia.

This institution has developed a vision of hospital-wide improved glycemic management; such a program is in the discussion phase. Nursing standards in the institution are changing. It is anticipated that adopting a 4:1 patient:nurse ratio will facilitate the adoption of a new labor-intensive glycemic management protocol.

Replication of this initiative at other institutions may depend on the following critical success factors:

- A culture of multidisciplinary cooperation and good communication between nurses and physicians
- A strong leadership bond between the nursing director and the medical director of the unit, with a shared vision for the unit
- A culture that accepts standardization of care using best available medical evidence
- The choice of achievable goals
- An ICU data management system that allows regular feedback of progress and outcomes J

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Reference

1. Krinsley J.S.: Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc* 78:1471–1478, Dec. 2003.
2. Krinsley J.S.: Effect of an intensive glucose management protocol on the mortality of critically ill patients. *Mayo Clinic Proc* 79:992–1000, Aug. 2004.

Appendix 1. Glucose Management Protocol

Rationale
Hyperglycemia is strongly associated with increased hospital mortality as well as organ system dysfunction among critically ill patients.

Goal
The goal of this protocol is to maintain serum glucose <140 mg/dl.

MD Signature
_____

Date_____

Monitoring
Glucose levels will be evaluated ***by blood testing or fingerstick testing***, using the following schedules:

Diet	Frequency of monitoring
NPO	Q6 hours: 6AM, noon, 6PM, midnight
PO diet	1 hour AC and QHS
Tube feedings, TPN	Q6 hours: 6AM, noon, 6PM, midnight

For most patients, the 6AM glucose evaluation will be obtained from the morning blood test. If glucose <140 for two consecutive days without treatment, glucose levels can be checked Q12 hours (6AM, 6PM)

Treatment of hyperglycemia

Glucose value	Action
<140	No treatment
140–169	3 units Regular insulin; Recheck glucose value in 3 hours
170–199	4 units Regular insulin; Recheck glucose value in 3 hours
200–249	6 units Regular insulin; Recheck glucose value in 3 hours
250–299	8 units Regular insulin; Recheck glucose value in 3 hours
300+	10 units Regular insulin; Recheck glucose value in 3 hours

- If glucose value exceeds 200 on two successive measurements, a continuous insulin infusion will be initiated. Hourly FSG or blood glucose measurements will be obtained in all patients receiving insulin infusions. The sliding scale noted above is a guideline; it can be modified if the patient requires more or less intensive therapy.

Management of insulin infusion

1. Initial infusion rate

Glucose value	Insulin dose
200–249	4 units/hour
250–299	6 units/hour
300–399	8 units/hour
400+	10 units/hour

2. Subsequent management, based on hourly glucose checks

Glucose value	Insulin dose
<140	Stop infusion or continue low dose to avoid "rebound"
140–169	2 unit/hour
170–199	3 units/hour
200–249	4 units/hour
250–299	6 units/hour
300–399	8 units/hour
400+	10 units/hour

Important points

- All patients receiving continuous insulin must receive a continuous source of glucose, either via IV (D5W or TPN), or enteral feeds.
- The insulin infusion is discontinued if the patient has to leave the CCU for a diagnostic test as well as upon discharge from the CCU

If this treatment plan does not lead to a decrease in the patient's glucose values, contact the house officer.