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ORIGINAL RESEARCH

Differences in hospital glycemic control and insulin requirements in patients recovering from critical illness and those without prior critical illness

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Introduction: Hospital patients recovering from critical illness on general floors often receive insulin therapy based on protocols designed for patients admitted directly to general floors. The objective of this study is to compare glycemic control and insulin dosing in patients recovering from critical illness and those without prior critical illness.

Methods: Medical record review of blood glucose measurements and insulin dosing in 25 patients under general ward care while transitioning from the intensive care unit (transition group) and 25 patients admitted directly to the floor (direct floor group).

Results: Average blood glucose did not differ significantly between groups (transition group 9.49 mmol/L, direct floor group 9.6 mmol/L; $P = 0.83$). Significant differences in insulin requirements were observed between groups with average daily doses of 55.9 units in patients transitioning from the intensive care unit (ICU) versus 25.6 units in the direct floor group ($P = 0.004$).

Conclusions: Patients recovering from critical illness required significantly larger doses of insulin than those patients admitted directly to the floor. Managing insulin therapy in patients transitioning from the ICU may require greater insulin doses.

Keywords: hyperglycemia, glycemic control, insulin, critical illness

Introduction

While much attention has been paid to determining optimal targets for critically ill patients, the process of transitioning patients from insulin therapy in the intensive care unit (ICU) to general ward care has not been studied and previously has been ignored by clinicians. The association between high blood glucose and poor patient outcomes in a variety of hospital care settings has prompted institutions to develop protocols to optimize glycemic control in various patient care areas.[1] In patients recovering from critical illness, these protocols use previous intravenous insulin rates to calculate subcutaneous insulin dosing.[2] In contrast, subcutaneous insulin doses for patients admitted directly to general wards are based on either previous home insulin doses or weight.[3,4] While controlled evidence is lacking, the American Diabetes Association recommended blood glucose targets are fasting readings of 6.99 mmol/L and maximal readings of 9.99–11.1 mmol/L in noncritically ill inpatients.[4]

A number of factors contribute to hyperglycemia and complicate blood glucose management in critically ill and noncritically ill patients. The stress of either injury or illness leads to insulin resistance, glucose intolerance, and hyperglycemia, and has been termed

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'diabetes of injury'.[5,6] Illness and trauma stimulate hepatic gluconeogenesis even in the presence of hyperglycemia and increased insulin production. Uptake of glucose into skeletal muscles is impaired. The level of hyperglycemia stimulated by these mechanisms is related to the severity of illness.[6] Critically ill patients have more profound insulin resistance and have greater insulin requirements than noncritically ill patients.[2] As patients recover from illness, increased glucose production and insulin resistance subside.

While the physiological mechanisms of hyperglycemia in critically ill and noncritically ill patients are similar, the degree of hyperglycemia and insulin requirements are different due to the variation in disease process severity.[2] Several issues related to the care of patients recovering from critical illness distinguish them from those patients not recovering from critical illness, including resolution of severe stress-related hyperglycemia, the use of glucocorticoids for adrenal insufficiency, and the use of continuous enteral or parenteral nutrition.

Despite these differences, there are no studies comparing glycemic control and insulin requirements between patients recovering from critical illness and those who are not. Therefore, the primary objective of this study was to compare inpatient glycemic control in patients recovering from critical illness and those admitted directly to a general floor (in other words, those not recovering from critical illness). The secondary objective was to compare insulin requirements between these two populations. We hypothesize that patients recovering from critical illness will have less optimal glycemic control and greater insulin requirements than those not recovering from critical illness.

Methods

This retrospective, observational pilot study was conducted at a 649-bed, tertiary, community, academic medical center. The local institutional review board approved this study, and a waiver of informed consent was granted. A standardized protocol based on guidelines from the American Diabetes Association to enhance the use of subcutaneous insulin had been previously implemented.[7] Primary outcome measures for this study were average daily blood glucose and average daily insulin dose. Secondary outcomes included the proportion of readings above the recommended goal (9.99 mmol/L) and the proportion of readings in the hypoglycemic range (defined as a blood glucose reading $\leq$3.33 mmol/L).[8]

Patients receiving subcutaneous insulin between December 2007 and July 2008 were screened for study inclusion. Patients in the group transitioning from a critical care unit (transition group), had previously received $\geq$24 hours of intravenous insulin therapy in either the medical or surgical ICU and received subcutaneous insulin using the standard protocol when transitioned to either general medical or surgical wards. An abbreviated version of this protocol is found in Figure 1. For inclusion in the direct floor admission group, patients received subcutaneous insulin using the standard protocol and were admitted to either general medical or surgical floors during the study period. Patients admitted for diabetic ketoacidosis or hyperosmolar coma, patients receiving oral or intravenous corticosteroid therapy, patients with type I diabetes, patients who were pregnant, and patients who were immediately postoperative from cardiac surgery were excluded from this study.

Paper and electronic medical records of patients while on the general floor were reviewed for data collection. Demographic data collected included age, gender, height, and weight. History of type 2 diabetes and admitting diagnosis (categorized as medical or surgical) were collected. In the transition group the number of ICU days was also obtained. Factors affecting blood glucose, including orders for dextrose-containing IV fluids and dietary orders were recorded. All available point-of-care blood glucose measurements, scheduled insulin doses administered, and correction factor (as needed) insulin doses administered were documented. Insulin doses were also calculated on a unit per kilogram basis. Data were recorded for the patient's stay on the floor, up to 10 days. If a patient's length of stay exceeded 10 days, blood glucose and insulin data were not collected after the 10th day. This cut-off was established because in both patients transitioning from the ICU and those admitted directly to the floor, stabilization in blood glucose and insulin doses was expected by day 10.[8]

Previous studies were not available for sample size analysis; therefore a convenience sample size of 25 patients per group was selected to provide pilot data in this area. Demographic variables such as age, height, and weight, and outcome variables including average blood glucose measurements and insulin doses were compared using an unpaired Student's *t*-test. Data on past medical history of diabetes, use of enteral nutrition and dextrose-containing IV fluids, and proportion of readings outside goal range were assessed using Chi square analysis.

All statistical analyses were performed using SPSS version 17.0 (StataCorp, College Station, TX) and Excel 2003 (Microsoft, Redmond, WA). A P value of <0.05 was set to indicate statistical significance.

Results

Patients in the direct floor group (n = 25) were admitted between November 2007 and March 2008; and patients in the

Institutional Insulin Protocol

Goal Blood Glucose: Fasting less than 6 mmol/L OR Random less than 10mmol/L

1. **Discontinue all previous insulin orders**
2. **Check fingerstick blood glucose** (at least one choice must be selected)
   Before meals and at bedtime every 6 hours (0000, 0600, 1200, 1800)
   At 0300 _____ Hours after meals other: _____
3. **Basal and Prandial Insulin** – Check agent(s) to be used

New start: Consider 0.5 unit/kg of body weight then divide total daily dose such that ½ doses is basal and other ½ is divided to cover meals.

	Breakfast	Lunch	Dinner	Bedtime
Basal Long Acting Insulin **Lantus** (glargine) (once daily **or** divided for large dose)	_____ units			_____ units
Prandial Rapid Acting Insulin **Novolog** (aspart) **Administer with meals** (may give with first bite)	_____ units	_____ units	_____ units	

4. **Correction Insulin – Novolog** (aspart) **-** Check desired algorithm

Blood Glucose (mmol/L)	Low Dose Algorithm (suggested if patient receiving less than 40 units/day)	Medium Dose Algorithm (suggested if patient receiving 40 – 80 units/day)	High Dose Algorithm (suggested if patient receiving greater than 80 units/day)	Individualized Algorithm
8.32 – 11.0	1 unit	2 units	3 units	
11.1 – 13.8	2 units	4 units	6 units	
13.9 – 16.6	3 units	6 units	9 units	
16.7 – 19.4	4 units	8 units	12 units	
> 19.5	5 units	10 units	15 units	

Diabetes Education Consult.
Draw HgbA1c with next a.m. labs if not already obtained this admission.
Notify MD for blood glucose less than _____ mmol/L or greater than _____ mmol/L.

5. **Nursing :**
   - **If two consecutive non-fasting glucose readings are10 mmol/L or greater,** advance to next higher Correction Algorithm. If patient is receiving the High Dose Correction Algorithm and has two consecutive non-fasting glucose readings greater than 180 mg/dL, **notify MD.**
   - Hold prandial if patient NPO or not taking a meal; notify MD if patient not eating. DO NOT HOLD BASAL.
   - If pre-meal FSBG (finger stick blood glucose) is:
     4.4 mmol/L or greater, give full-dose of prandial insulin, as long as patient is eating meals
     Below 4.4 mg/dL, do NOT give prandial insulin
   - Correction insulin may be added to prandial insulin dose (if ordered) and administered in same syringe with meal.
   - Initiate Hypoglycemia Protocol for finger stick blood glucose **less than** 3.33 mol/L.

6. **Titration of Basal Insulin [Lantus (glargine)]: Adjust every other day from start of most recent order.**

Average a.m. (fasting) glucose for today and yesterday	Basal (Lantus) Insulin
Less than 4.4 mmol/L	Decrease by 2 units
4.4 - 6.0 mmol/L	**No change**
6.1 - 7.2 mmol/L	Increase 2 units/day
7.3 - 8.3 mmol/L	Increase 4 units/day
8.4 - 10 mmol/L	Increase 6 units/day
> 10 mmol/L	Increase 8 units/day

Figure 1 Insulin protocol for inpatients

transition group (n = 25) were admitted between November 2007 and July 2008. The extended interval for inclusion of ICU transition patients was needed because of a low number of ICU patients receiving intravenous insulin for ≥24 hours. Patient characteristics are shown in Table 1. Age and history of diabetes differed statistically between groups. There was also a trend toward significance in weight and body mass index (BMI) with transition patients having greater weight and BMI. A total of 805 and 534 blood glucose readings were collected in the transition and direct floor groups, respectively. Data were collected over an average of 7.3 days in the transition group and 5.1 days in the direct floor group.

Table 1 Patient characteristics

	ICU transition	Direct floor	*P*-value
Age (years)	57 ±10	64 ± 12	0.023
Gender (males) (no.)	14	14	1
Weight (kg)	99.5 ± 35.4	83.7 ± 18.9	0.055
Body mass index (kg/m^2)	35.4 ± 15.9	28.5 ± 5.7	0.052
ICU stay (days)	12.1 ± 7.9	–	–
Medical admitting diagnosis (no.)	16	18	0.544
Past medical history of diabetes (no.)	19	24	0.041

Types of nutrition varied among ICU transition and direct floor admit patients with 20 patients in the transition group receiving supplemental enteral nutrition via tube compared with one patient in the direct floor group. Other patients received an oral diet. There was no difference between groups with respect to dextrose-containing IV fluids.

Average daily blood glucose did not differ significantly between groups (Table 2). The ICU transition group had an average of 9.49 ± 1.89 mmol/L, and the direct floor group had an average of 9.6 ± 2.1 mmol/L ($\alpha = 0.05$, $\beta = 94.6$, $P = 0.83$). Patients in the direct floor group had a greater proportion of readings greater than or equal to the recommended target ≥9.99 mmol/L, with 37.6% in the ICU transition group versus 44% in the direct floor group ($P = 0.02$). There was a low incidence of hypoglycemia (blood glucose ≤ 3.33 mmol/L) in the study with a nonsignificant difference in hypoglycemic readings in each group (transition 0.87%, direct floor 1.31%, $P = 0.43$).

Significant differences in blood glucose were observed among average blood glucose for individual days (Figure 2). On study day 1, ICU transition patients had significantly lower average blood glucose than direct floor admit patients. Groups were similar on days 2–7. As the study progressed on days 8–10, ICU transition patients had higher average blood glucoses.

There were significant variations in insulin doses between groups (Table 3). Patients transitioning from ICU care received total average daily insulin doses of 55.9 units compared with 25.6 units in patients admitted directly to the floor ($P = 0.004$). These differences remained statistically significant on a unit per kilogram basis with an average daily dose of 0.58 units/kg in the transition group and 0.32 units/kg in the direct floor group ($P = 0.02$). These differences were observed in both scheduled and correction factor insulin doses. In addition, total average daily insulin dose for each day of the study period was examined. There were no changes in average insulin doses over time.

Table 2 Blood glucose

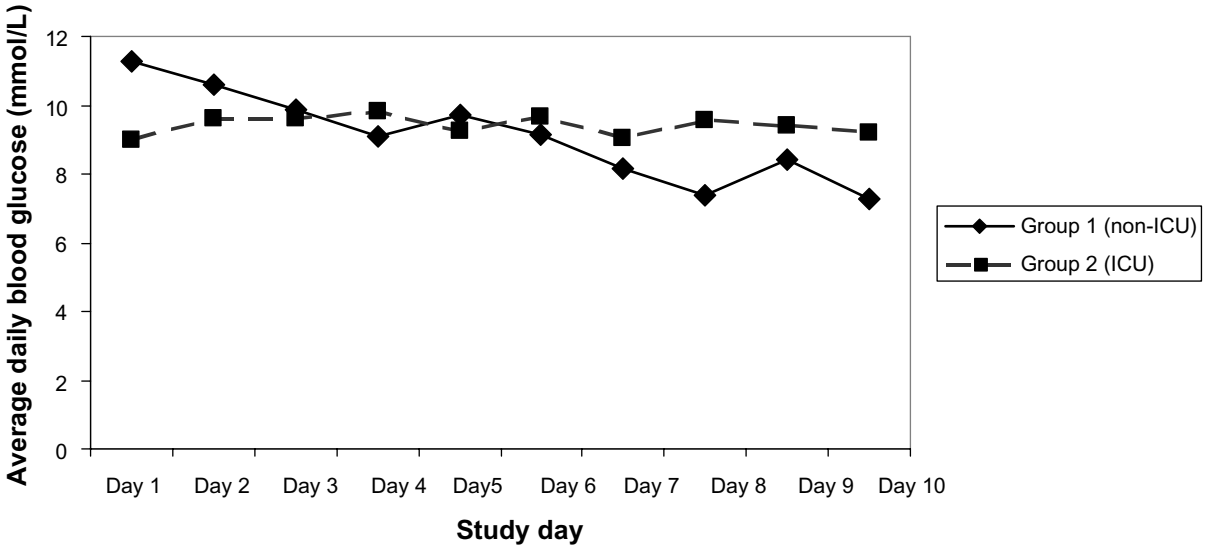
	ICU transition	Direct floor	*P*-value
Average daily blood glucose (mmol/L)	9.49 ± 2.11	9.60 ± 1.89	0.83
Readings ≥ 9.99 mmol/L	303/805 (37.6%)	235/534 (44%)	0.02
Readings ≤ 3.33 mmol/L	7/805 (0.87%)	7/534 (1.31%)	0.44

Discussion

The present study failed to find a difference in average daily blood glucose in patients recovering from critical illness and those without prior critical illness. This refutes our initial hypothesis. The key finding from this study is an increase in insulin requirements to maintain similar levels of glycemic control in patients recovering from critical illness. To our knowledge, this is the first study to compare glycemic control and insulin doses between patients recovering and not recovering from critical illness.

We hypothesized that a wide variety of factors affecting blood glucose in patients transitioning from ICU care would have led to poorer glycemic control in those patients. One expected factor is the increased use of enteral nutrition in the ICU transition group. The similarity in blood glucose between groups is explained by the increased insulin doses in ICU patients. Patients in the ICU transition group were converted to subcutaneous insulin while still in the ICU. Higher blood glucose readings were likely to occur during this initial transition period in the ICU prior to data collection while insulin doses were refined and optimized. In contrast, patients admitted directly to the floor began insulin therapy while data collection was underway. We suspect that poorer glycemic control was more likely during this period of insulin initiation. Patients in the ICU group had a similar number of daily blood glucose readings performed. The greater number of blood glucose readings performed is reflective of their increased length of stay.

A number of previous studies have examined inpatient glycemic control using basal-bolus insulin therapy and protocols among patients admitted directly to general medical or surgical floors.[9–12] While these studies exclude patients with prior critical illness, they do provide blood glucose data comparable to measurements observed in the present study in patients without prior critical illness. In the first, prospective, randomized study of basal-bolus insulin therapy, an average blood glucose of 9.21 ± 1.78 mmol/L was observed in the treatment group.[9] The authors also observed a decrease in blood glucose over the study period. The present study results are comparable to these findings with similar variability in average blood glucose and in the trend of a decrease in average daily blood glucose over



Number of subjects per day (corresponding to graph)

Day	1	2	3	4	5	6	7	8	9	10
ICU transition	25	25	25	22	22	19	19	17	16	13
Direct floor	25	25	25	22	17	13	11	7	6	5

Figure 2 Comparison of daily average blood glucose.

the study period. Fasting readings in the treatment group were 8.16 ± 2 mmol/L. While the retrospective nature of the present study limited the ability to record fasting readings, average first morning blood glucose readings over the study period were 8.44 ± 3.16 mmol/L. In addition, the prospective study also demonstrated a trend of decreasing average blood glucose from approximately 12.77 mmol/L on study day 1 to 7.77 mmol/L on study day 10. Our study demonstrated a similar decrease in readings over the study period with average blood glucose on day 1 of 11.27 mmol/L and 7.27 mmol/L on day 10. The parallel fasting readings and trends in blood glucose confirm the blood glucose data in direct floor admission patients in our study.

Table 3 Total insulin doses (units)

	ICU transition	Direct floor	*P* value
Average daily insulin dose per patient day	55.9	25.6	0.004
Average weight-based daily insulin dose (units/kg)	0.58	0.32	0.02
Total average scheduled insulin	142.5	59.5	0.0001
Total average correction factor	47.0	25.2	0.001

After this study was conducted, Czosnowski et al[13] evaluated glycemic control in patients following discontinuation from intravenous insulin. Mean blood glucose during the last 12 hours on an intensive insulin protocol with intravenous therapy was compared to mean blood glucose for five days following discontinuation. In a cross-over design of 65 patients, a statistically significant increase in mean blood glucose was observed when measurements from the intensive insulin period were compared with each day of the follow-up period. Also, they observed a nonsignificant trend of increasing average blood glucose over the 5-day study period with average daily blood glucose measurements between 8.99 ± 2.72 mmol/L and 9.82 ± 3.12 mmol/L. The ICU transition patients in this study also exhibited similar average daily blood glucose ranges and increases in average

daily blood glucose over the study period. The combined evidence from the present study and that of Czosnowski et al highlight problems with glycemic control in patients as they transition from intravenous insulin. This study validates the results seen in the ICU transition group of the present study.

Limitations of this study include small sample size and retrospective study design. Small sample size may have contributed to a nearly significant difference in weight between groups and large variability in blood glucose and insulin doses. The retrospective study design introduced bias as differences in nondocumented nutritional intake could not be assessed. It also led to an insufficient number of hemoglobin a1c readings for comparison between groups. Data collection occurred for more days in the ICU transition group due to a longer length of stay. However, as noted in Figure 2, blood glucose in the ICU transition group remained relatively stable throughout the hospital stay.

Despite small sample size, blood glucose readings within this study were similar to those observed in previous studies evaluating patients admitted directly to the floor and those observed in a recent study evaluating patients transitioning from ICU care. In addition, the increasing average daily blood glucose in the ICU transition group and decreasing average daily blood glucose in the direct floor admission group is similar to that of previous studies. The present study also demonstrated a statistically significant increase in insulin dosing that was maintained after standardization for weight on a unit per kilogram basis.

Conclusion

Patients transitioning from critical care units are at increased risk for hyperglycemia compared to patients without prior critical illness. We found that higher doses of insulin are required in patients recovering from critical illness to attain glycemic control similar to patients without prior critical illness. In managing blood glucose with subcutaneous insulin, larger insulin doses should be considered in patients recovering from critical illness. Future studies regarding specific insulin dosing are required to determine optimal dosing regimens for this population.

Disclosure

Financial disclosure: No financial support was received for this study

Proprietary disclosure: The authors of this study have no commercial or proprietary interests related to this study.

Institutional review board approval: Institutional review board approval was obtained prior to the completion of this study

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