original research

CME

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# Basal/Bolus Insulin Is Superior to Prevalent Methods of Diabetes Management on the General Medicine Service at a Regional Medical Center


## ABSTRACT

**Background:** Diabetes mellitus (DM) is a common comorbid condition of patients on the hospital general medicine service. This study evaluated the impact of a basal/bolus insulin protocol utilizing insulin glargine (Lantus) and insulin aspart (Novolog) on glycemic control and clinical outcomes for diabetic patients admitted to the general medicine service at Carle Foundation Hospital.

**Methods and Results:** Patients admitted to the medicine service for at least 24 hours from June 1 to August 31, 2004 were used as historical controls (N = 176, 94.3% Type 2 DM). The protocol began July 2005 and concluded when sufficient patients had been treated (N = 116, 93.1% Type 2 DM) to detect a 20 mg/dL difference in finger-stick glucose with 80% statistical power. Hyperglycemia managed with the basal/bolus insulin protocol showed significant improvement at 24 hours ($P$ <.001) and discharge ($P$ <.001) compared to admission in protocol-treated patients. No improvement was observed in the control population. Protocol patients were significantly more hyperglycemic at admission than controls ($P$ = .005). Hypoglycemia (FS-glucose <70 mg/dL), though infrequent, occurred more frequently in protocol-treated patients than control patients ($P$ = .0002). Length of stay was significantly shorter for protocol-treated patients ($P$ = .02).

**Conclusions:** From the start of hospital admission, diabetes management with prandial and basal insulin analogs significantly improved hyperglycemia—compared to historical and *ad hoc* therapy—and shortened length of stay for diabetic patients on the medicine service. These results confirm the superiority of basal/bolus insulin therapy to typical management for diabetic patients on the hospital medicine service, and suggest a need for additional study of diabetic patients on other hospital services such as general surgery and rehabilitation.


## Introduction

Diabetes mellitus (DM) is a common comorbid condition of patients admitted to the hospital general medicine service. A recent study of over 2000 consecutive admissions to Georgia Baptist Medical Center, a community teaching hospital in Atlanta, Georgia, found a 26% prevalence of known diabetes and 12% prevalence of new hyperglycemia, defined as fasting plasma glucose of ≥126 mg/dL or random glucose ≥200 mg/dL on at least two occasions.[1] Admissions data from Carle Foundation Hospital, Urbana, Illinois, also confirm an approximate 25% prevalence of diabetes among patients admitted to the general medicine service.[2]

Hyperglycemia and diabetes have significant and negative impacts on hospital outcomes. Diabetic patients are more likely to die of myocardial infarction than diabetic patients, and diabetic patients are also more likely to die or suffer serious neurological disability when presenting with stroke.[3-7] Diabetes and hyperglycemia increase morbidity and mortality for patients admitted to Intensive Care Units (ICU) and who undergo cardiothoracic surgery.[8-9] Patients with diabetes or new hyperglycemia admitted to the general hospital wards at Georgia Baptist Medical Center had significantly increased length of stay (LOS), risk of mortality, and odds of discharge to an extended care facility than non-diabetic patients.[1]

Intensive insulin therapy and tight glycemic control has been demonstrated to reduce morbidity and mortality for cardiothoracic surgery and intensive care unit patients with diabetes.[10-13] The growing evidence that good glycemic control improves clinical outcomes has prompted many medical centers to develop diabetes management protocols, but little has been published regarding the impact on glucose control and clinical outcomes for general hospital service patients. A small study (N = 20) at St. Joseph's/Chandler Health System in Savannah, Georgia showed improved glycemic control with a 70/30

insulin protocol compared to sliding scale insulin alone.[14] A more recent and much larger study by investigators at Northwestern University demonstrated that insulin drip and subcutaneous insulin protocols implemented by a Glucose Management Service in the surgical ICU (N = 276) and general surgical wards (N = 922) significantly improved glycemic control compared to previous management strategies.[15] This study investigated the effects of a basal/bolus insulin protocol utilizing recombinant human insulin analogs on both glycemic control and clinical outcomes for patients admitted to the general medicine service at Carle Foundation Hospital (CFH).

## Methods

Adult patients ages 18 years and older with either Type 1 or Type 2 DM admitted to the general medicine service at CFH, a 300-bed facility with level one trauma center, in Urbana, Illinois, were eligible for management with an Institutional Review Board (IRB) approved basal/bolus subcutaneous insulin protocol (Appendix 1) at the discretion of the admitting physician. Patients had to be admitted for at least 24 hours and receive an oral diet to be included in the study. Patients receiving enteral or parenteral nutrition were excluded. Study enrollment began in July 2005 and ended in October 2005. The study concluded when enough patients had been managed with the insulin protocol to detect a 20 mg/dL difference in finger-stick glucose from admission and compared to historical controls with 80% statistical power.

Historical controls were drawn from adult patients with Type 1 or Type 2 DM admitted to CFH from June to August 2004. Patients had to be admitted for a minimum of 24 hours and be written for an oral diet to be included in the control group. Patients managed with enteral or parenteral nutrition were excluded. The control period was chosen to overlap the months of the study period to insure similar experience with diabetes management for Internal Medicine Residents managing the study and control patients.

All patients managed with the insulin protocol received insulin glargine (Lantus) as basal insulin and insulin aspart (Novolog) as prandial and supplemental insulin. Insulin glargine was administered either in the morning or before bedtime, and insulin aspart was administered within 15 minutes of a patient's meal. The protocol provided explicit instructions for calculating insulin doses for patients with either Type 1 or Type 2 DM. All ambulatory diabetes medications were held unless the patient was already managed with insulin glargine and insulin aspart at home. For patients with tight ambulatory glycemic control, total home insulin doses were used as initial total hospital insulin doses. Weight-based dosing algorithms were provided for patients with poor ambulatory glycemic control or who were not managed with basal/bolus insulin in the outpatient setting. Half the total initial insulin dose was ordered as basal insulin, and the other half was ordered as prandial insulin divided evenly between the patient's meals. Standardized daytime and nighttime supplemental insulin orders were also part of the study protocol. Insulin dosing adjustments after admission were made at the discretion of the managing hospital team. Finger-stick glucose was monitored before meals, at bedtime and as needed using Precision PCx glucometers.

The primary end point of the study was the difference in change in finger-stick glucose from admission at 24 hours and hospital discharge between the control and protocol-treated patients. Secondary end points included direct comparisons of admission, 24 hour, and discharge finger-stick glucose between the control and protocol patients, frequency of hypoglycemia (finger-stick glucose <70 mg/dL), proportion of finger-stick glucose values meeting American College of Endocrinology targets, hospital LOS, disposition at hospital discharge, hospital charges, and mortality.[16] In addition, other prognostic variables such as age, gender, type of DM, mode of outpatient DM therapy, most recent hemoglobin A1c within six months of admission, mode of inpatient DM therapy in the control group, reason for admission, and frequency of finger-stick glucose monitoring were also considered. Finger-stick glucose data for all patients were obtained from electronic records maintained by the CFH pharmacy. Other study parameters were obtained by chart review.*

## Results

Clinical demographics of the control and protocol patients are summarized in Table 1. Both groups were well matched for age, gender, and proportion of patients with Type 1 or Type 2 DM. There were trends toward higher pre-admission HbA1c and proportion of patients with HbA1c ≥8% among protocol-treated patients that fell slightly short of statistical significance. Protocol-

*Statistical analyses were performed using InStat Version 3.0 for Windows statistical software (GraphPad Software Inc., San Diego, CA). Means were compared by Student's two-tailed t-test, and proportions were compared by Fischer's exact test.

treated patients were much less likely to be diet-managed ($P$ = .02) and more likely to be managed with insulin ($P$ = .02) prior to admission than control patients. The proportion of patients managed with oral diabetes medications alone or oral medications in combination with insulin was no different between the two patient groups.

Control and protocol patients were assigned to disease categories based on admission ICD-9 codes. Results are presented in Table 2. There were no significant differences in frequency of presenting disease based on admission codes, though there was a trend toward increased rate of admission for decompensated DM among protocol-treated patients.

Diabetes treatment regimens for control patients are presented in Table 3. Basal/bolus insulin was used infrequently to manage control patients. Only four patients (2%) in the control group were managed with insulin glargine and a rapid-acting insulin analog at meals. The most common treatment regimens were supplemental insulin alone (31%), supplemental insulin with basal and/or mealtime insulin other than a basal/bolus regimen (31%), and supplemental insulin with oral diabetes medications (21%).

Glycemic control results for the control and protocol-treated patients are presented in Table 4 and Figure 1. Protocol-treated patients were over 30 mg/dL more hyperglycemic at admission than controls, a highly and statistically significant difference ($P$ = .0051). Average finger-stick glucose improved by over 40 mg/dL from admission at 24 hours among protocol-treated patients ($P$ = .0002), a significant improvement that persisted to hospital discharge ($P$ = .0009). There were no significant changes in glycemic control from admission at 24 hours or discharge among control patients. Average finger-stick glucose at 24 hours and discharge in the protocol-treated group was slightly better than corresponding values for thecontrol group, though the differences were not significant. As anticipated from the between group comparisons at 24 hours and discharge, there was no significant difference in the proportion of finger-stick glucose values in the 70–109 mg/dL category between the two groups. (Figure 1) Hypoglycemia, defined as a finger-stick glucose <70 mg/dL, occurred with 4.5% frequency in the protocol-treated patients and 2.2% frequency in the controls ($P$ = .0002).

**Table 1. Patient Characteristics at Admission**

| | Control | Protocol | *P* |
|---|---|---|---|
| N | 176 | 116 | — |
| Age (years) | 69 ± 16 | 66 ± 15 | .10 |
| Men:Women | 79:97 | 53:63 | .90 |
| Type 2 DM (%) | 94.3 | 93.1 | .80 |
| HbA1c (average) | 7.4 ± 1.8 | 7.8 ± 2.0 | .08 |
| HbA1c ≥8% (%) | 23.6 | 35.2 | .06 |
| Outpatient treatment (%) | | | |
| Diet | 9.7 | 2.6 | .02 |
| Oral drugs | 37.5 | 37.9 | 1.00 |
| Insulin | 34.7 | 49.1 | .02 |
| Oral + insulin | 13.6 | 8.6 | .26 |
| Unknown | 4.5 | 1.7 | .32 |

**Table 2. Hospital Diagnosis by ICD-9 Defined Disease Category**

| | Control % | Protocol % | *P* |
|---|---|---|---|
| Cardiovascular | 26 | 35 | .11 |
| Infectious | 19 | 15 | .35 |
| GI | 17 | 12 | .32 |
| Neurological | 11 | 6 | .21 |
| Renal | 9 | 5 | .36 |
| Diabetes | 4 | 10 | .08 |
| Other | 15 | 17 | .62 |

**Table 3. Control Patient Diabetes Treatment Regimens**

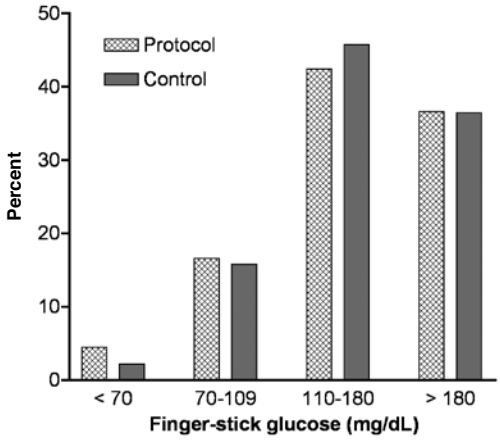
| | |
|---|---|
| Supplemental insulin only | 31% |
| Supplemental and routine insulin | 31% |
| Supplemental insulin and oral drugs | 21% |
| Supplemental insulin, routine insulin, and oral drugs | 8% |
| Oral drugs only | 4% |
| Routine insulin only | 2% |
| Oral drugs and routine insulin | 1% |
| Diet only | 1% |

**Table 4. Glycemic Control for Patient Groups (finger-stick glucose, mean ± SD, mg/dL)**

| | Admission | 24 Hour | Discharge |
|---|---|---|---|
| Protocol | 197 ± 104[a,b,c] | 154 ± 67[b] | 159 ± 62[c] |
| Control | 166 ± 68[a] | 159 ± 61 | 166 ± 69 |

[a]*P* = .0051 for comparison of admission finger-stick glucose to admission
[b]*P* = .0002 for comparison of 24 hour protocol finger-stick glucose to admission
[c]*P* = .0009 for comparison of protocol discharge finger-stick glucose to admission
All other comparisons NS

Figure 1. Distribution of Finger-Stick Glucose Measurements after Hospital Admission




The frequency with which insulin orders were adjusted after hospital admission was measured to explore why glycemic control failed to improve further from 24 hours to hospital discharge in the insulin protocol group. Insulin was actively titrated after admission in only 36% (N = 42) of patients managed with the study protocol. The average initial insulin dose was 0.56 ± 0.41 U/kg/day. Finger-stick glucose was measured more frequently for protocol-treated patients (13.2 ± 15.7 measurements) than control patients (10.6 ± 8.4, *P* <.0001).

Clinical outcomes are presented in Table 5. Hospital LOS was approximately a day shorter for protocol-treated than controls (3.6 ± 3.0 vs. 4.5 ± 3.4 days, *P* = .02). LOS for all patients admitted to general medicine at CFH was the same in 2004 and 2005 (2004: 4.1 ± 5.7 days, 2005: 4.2 ± 5.9 days, *P* = NS). Shorter LOS resulted in a nearly $1700 per patient cost savings in 2005 dollars for protocol-treated patients, though the difference between groups did not reach statistical significance. There were no differences between disposition at discharge or mortality between protocol-treated patients and control patients.

**Table 5. Clinical Outcomes**

| | Protocol | Control | *P* |
|---|---|---|---|
| Length of Stay | 3.6 ± 3.0 | 4.5 ± 3.4 | .02 |
| Disposition (%) | | | |
| Home | 68 | 75 | .23 |
| Extended care | 29 | 24 | .34 |
| Deceased | 2 | 1 | .65 |
| Transfer | 1 | — | — |
| Hospital charges (2005 dollars) | 13,901 ± 18,323 | 15,561 ± 19,183 | .46 |

## Discussion

Management of hyperglycemia is a significant challenge in the care of hospitalized diabetic patients. Glycemic control may be suboptimal prior to hospital admission, and acute illness often worsens hyperglycemia by increasing insulin resistance.[17] Despite extensive investigation of intensive insulin therapy and tight glycemic control for critically ill patients, little has been published regarding the impact of diabetes management protocols on general medicine patients. This study provides insights into typical diabetes management practices at a regional medical center and how protocol-guided management with recombinant human insulin analogs can improve hyperglycemia control and clinical outcomes.

Even though management with supplement insulin alone ("sliding scale insulin") has been clearly documented to lead to poor glycemic control, slightly less than one-third of control patients were managed solely with supplemental insulin.[18] Though 31% of patients received both supplemental insulin and standing doses of basal insulin or basal and prandial insulin, in the majority of cases supplemental insulin was simply added to a patient's ambulatory insulin regimen. In one fifth of cases, supplemental insulin was added to outpatient oral diabetes medications. Review of prevalent modes of diabetes management on the general medicine service reveals that little original thought was invested in modifying outpatient diabetes therapy to account for the increased insulin requirements of acute illness or to modify failed ambulatory treatment regimens.

The basal/bolus insulin protocol in this study significantly improved hyperglycemia control from admission compared to previous, *ad hoc* therapy. At 24 hours after admission, finger-stick glucose was improved by over 40 mg/dL in the protocol-treated group compared to virtually no change in the control patients. The initial improvement in hyperglycemia persisted to discharge in the protocol-treated patients while hyperglycemia remained unimproved in the control group.

There were no significant between group differences in glycemic control at 24 hours or discharge, and the proportion of post-admission finger-stick glucose measurements falling in the 70–109 mg/dL category, considered optimal by the American College of Endocrinologists, was also similar for both patient groups.[16] Potential explanations for these findings include:

1. Protocol-treated patients were significantly more hyperglycemic at admission than control patients.
2. Insulin was adjusted following admission in only about one third of protocol-treated patients.
3. Protocol-treated patients were more challenging to manage as indicated by a significantly higher proportion managed with insulin as outpatients and trends toward higher hemoglobin A1c than control patients.
4. Despite significantly shorter LOS, finger-stick glucose was monitored more frequently in protocol-treated patients, creating an element of ascertainment bias.
5. Hypoglycemia, while infrequent, was two-fold more common in protocol-treated patients, leading to more rebound hyperglycemia.

Hospital LOS was nearly a full day shorter for protocol-treated patients than for control patients. The LOS for all patients admitted to the medicine service at CFH in 2004 and 2005 was essentially identical, excluding a non-specific effect of shorter LOS for all patients in 2005 as an explanation. Admitting physicians may have been reassured by the improvement in glycemic control from admission in the protocol-group, making it less likely that patients were hospitalized for additional time to due to hyperglycemia. Insulin therapy itself may have had a therapeutic benefit; subcutaneously administered insulin improves endothelial function and parenteral insulin has anti-inflammatory effects in critically ill patients and ambulatory patients with Type 2 DM.[19-22] Control and protocol-treated patients had essentially equivalent degrees of glycemic control after admission, eliminating hyperglycemia as a potential explanation for improved LOS. This study

was not designed to identify a mechanism for the observed improvement in hospital LOS.

Basal/bolus insulin therapy with the human insulin analogs glargine and aspart has been demonstrated to be superior to prevalent modes of diabetes management on the medicine service at a mid-sized regional hospital. Despite application of the protocol to a patient population more likely to be managed with insulin as outpatients and more hyperglycemic at admission than historical controls, patients managed with basal/bolus insulin experienced a significant improvement in glycemic control from admission that persisted to discharge. Hospital LOS was also significantly shorter for protocol-treated patients. Hypoglycemia was increased two-fold in the protocol-treated group but still infrequent (4.5% of all finger-stick glucose measurements <70 mg/dL). This study has identified a need to couple a daily management algorithm to the admission orders to facilitate insulin adjustments following admission. Basal/bolus insulin therapy may also be beneficial for patients on other hospital wards such as general surgery and rehabilitation.

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## CME Questions 1a-d

Please select the best answer for the following:

1a. All of the following are common methods of hospital diabetes management **except:**
   a. "Sliding scale insulin"
   b. "Sliding scale insulin" and home oral medications
   c. "Sliding scale insulin" and home insulin regimen
   d. Basal/bolus insulin

1b. Documented benefits of the hospital basal/bolus insulin regimen for patients with Type 2 DM include:
   a. Improved glycemic control from admission
   b. Shorter hospital stay
   c. None of the above
   d. All of the above

1c. Potential reasons that glycemic control failed to improve after the initial 24 hours of basal/bolus insulin therapy include:
   a. Study patients were more likely to have cardiovascular disease
   b. Fewer than half of patients had insulin titrated after the first hospital day
   c. Insulin aspart is an inferior prandial insulin to regular insulin
   d. All of the above
   e. None of the above

1d. The most likely untoward effect of hospital basal/bolus insulin therapy is hypoglycemia:
   a. True
   b. False