Clinical Results of an Updated Insulin Infusion Protocol in Critically Ill Patients

Philip A. Goldberg, MD; Maureen G. Roussel, APRN, MSN; and Silvio E. Inzucchi, MD

Editor’s note: In the Winter 2005 issue of Diabetes Spectrum, we published an article titled “Selling Root Canals: Lessons Learned From Implementing a Hospital Insulin Infusion Protocol” by Goldberg and Inzucchi. The following article reports on an updated version of the same insulin infusion protocol, setting lower glycemic standards to reflect the euglycemic glucose ranges set in the American Diabetes Association recommendations for managing hyperglycemia in the hospital setting. We believe that the care of hospitalized patients with diabetes is an area in which continuing research is needed to develop the safest and most effective protocols for glycemic management. In keeping with this belief, we have decided to publish this follow-up to stimulate and promote discussion in this important area of diabetes care. — Geralyn Spollett, MSN, C-ANP, CDE, guest editor, From Research To Practice: Moving Toward Excellence in the Care of Hospitalized Patients With Diabetes. Diabetes Spectrum 18:18–50, 2005.

Strict glycemic control has recently been shown to improve clinical outcomes in critically ill patients. In the February 2004 issue of Diabetes Care, we reported our early experience implementing an insulin infusion protocol (IIP) in a medical intensive care unit (MICU). To facilitate early acceptance by our critical care physicians and nurses, we initially selected a conservative blood glucose target of 100–139 mg/dl. We subsequently published similar (indeed, slightly better) results using this same IIP in two cardiothoracic intensive units (CTICUs).

Following this work, based on the primary literature, a position statement from the American College of Endocrinology (ACE), and a technical review by the American Diabetes Association (ADA), we decided to lower our target further into the normal range. Rather than abruptly drop to the 80–110 mg/dl target espoused by both the ACE and ADA, we elected to gradually lower our blood glucose target range in order to carefully study the impact of lowering the target on both glycemic control and rates of hypoglycemia.

To this end, we present here our updated experience with a new, more stringent IIP, which differs from our old protocol in three fundamental ways:

1. Target blood glucose levels are lowered to 90–119 mg/dl.
2. To facilitate more rapid glycemic control, the initial insulin bolus is increased by ~40%, and,
3. The protocol language is now in compliance with the Joint Commission on Accreditation of Healthcare Organizations.

The complete, updated IIP is shown in Figure 1.

We first studied 54 consecutive patients receiving intravenous (IV) insulin in our CTICU, who, because of their typically brief lengths of stay in the unit, remained on the IIP for a median of just 15 hours. From a mean initial blood glucose level of 189 ± 44 mg/dl, the median time required to achieve our new target level of 80–119 mg/dl was 6 hours (interquartile range [IQR] 5–9 hours).

At first glance, this median time-to-target seems slightly delayed compared with our initial IIP (median 5 hours, IQR 3–8 hours). However, this is not unexpected, because it should take longer for blood glucose levels to drift < 120 mg/dl than < 140 mg/dl. In fact, our new IIP took the same amount of time to reach the old blood glucose target of 80–139 mg/dl (median 5 hours, IQR 3–7 hours).

Additional comparisons between the old and new IIPs in our CTICU are shown in Table 1. To summarize, mean blood glucose levels obtained using the new IIP were 12–13 mg/dl lower than with the old IIP (depending on how mean blood glucose levels were analyzed), and the percentage of blood glucose levels within any given desirable range was superior using the new protocol.

In the CTICU, these benefits surprisingly occurred with no changes in observed rates in hypoglycemia. Among 679 blood glucose levels obtained after target levels were achieved, just 2 (0.3%) were < 60 mg/dl; specifically, two readings of 57 and 58 mg/dl were recorded. No clinically relevant sequelae of hypoglycemia were apparent.

We then performed the same data analysis in 47 consecutive patients receiving IV insulin in our MICU. Since 11 of our MICU patients were placed on the IIP more than once, 63 individual insulin infusions were analyzed, consistent with the format of our initial publication. Because the average length of stay in our MICU is significantly longer than in the CTICU, our MICU patients remained on IV insulin for a median of 63 hours. From a mean initial blood glucose level of 238 ± 76 mg/dl, the median time required to achieve a target of 80–119 mg/dl was 6 hours.
YALE INSULIN INFUSION PROTOCOL 2005

The following insulin infusion protocol is intended for use in hyperglycemic adult patients in an ICU setting, but is not specifically tailored for those individuals with diabetic emergencies, such as diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar states (HHS).

When these diagnoses are being considered, or if BGs 500 mg/dL, an MD should be consulted for specific orders. Also, please notify an MD if the response to the insulin infusion is unusual or unexpected, or if any situation arises that is not adequately addressed by these guidelines.

Initiating an Insulin Infusion

1.) INSULIN INFUSION: Mix 1 unit Regular Human Insulin per 1 cc 0.9 % NaCl. Administer via infusion pump (in increments of 0.5 unit/hr.)
2.) PRIMING: Flush 50 cc of infusion through all IV tubing before infusion begins (to saturate the insulin binding sites in the tubing.)
3.) THRESHOLD: IV insulin is indicated in any critically ill patient with persistent BG ≥ 140 mg/dL; consider use if BG ≥ 110 mg/dL.
4.) TARGET BLOOD GLUCOSE (BG) LEVELS: 90-119 mg/dL
5.) BOLUS & INITIAL INSULIN INFUSION RATE: If initial BG ≥ 150 mg/dL, divide by 70, then round to nearest 0.5 units for bolus AND MD if the response to the insulin infusion is unusual or unexpected, or if any situation arises that is not adequately addressed by these guidelines.

Blood Glucose (BG) Monitoring

1.) Check BG hourly until stable (3 consecutive values within target range). In hypotensive patients, capillary blood glucose (i.e., fingersticks) may be inaccurate and obtaining blood sample from an indwelling vascular catheter may be preferable.
2.) Then check BG q 2 hours; once stable x 12-24 hours. BG checks can then be spaced to q 4 hours IF:
   a.) no significant change in clinical condition AND b.) no significant change in nutritional intake.
3.) If of the following occur, consider the temporary resumption of hourly BG monitoring, until BG is again stable (2-3 consecutive BG values within target range):
   a.) any change in insulin infusion rate (i.e., BG out of target range)
   b.) significant changes in clinical condition
   c.) initiation or cessation of pressor or steroid therapy
   d.) initiation or cessation of renal replacement therapy (dialysis, CVVH, etc.)
   e.) initiation, cessation, or rate change of nutritional support (TPN, PN, tube feedings, etc.)

Changing the Insulin Infusion Rate

If BG < 50 mg/dL:
   D/C INSULIN INFUSION
   Give 1 amp (25 g) D50 IV; recheck BG q 15 minutes.
   ⇒ When BG ≥ 90 mg/dL, wait 1 hour, recheck BG. If still ≥ 90 mg/dL, restart infusion at 50% of most recent rate.

If BG 50-69 mg/dL:
   D/C INSULIN INFUSION
   If asymptomatic (or unable to assess), give 1 amp (25 g) D50 IV; recheck BG q 15 minutes.
   ⇒ When BG ≥ 90 mg/dL, wait 1 hour, recheck BG. If still ≥ 90 mg/dL, restart infusion at 75% of most recent rate.

If BG ≥ 70 mg/dL:

STEP 1: Determine the CURRENT BG LEVEL - identifies a COLUMN in the table:

| BG 70-89 mg/dL | BG 90-119 mg/dL | BG 120-179 mg/dL | BG ≥ 180 mg/dL |

STEP 2: Determine the RATE OF CHANGE from the prior BG level - identifies a CELL in the table - Then move right for INSTRUCTIONS:

[Note: If the last BG was measured 2-4 hours before the current BG, calculate the hours rate of change. Example: If the BG at 2PM was 150 mg/dL, and the BG at 4PM is now 120 mg/dL, the total change over 2 hours is -30 mg/dL; however, the hourly change is -15 mg/dL.]

<table>
<thead>
<tr>
<th>BG 70-89 mg/dL</th>
<th>BG 90-119 mg/dL</th>
<th>BG 120-179 mg/dL</th>
<th>BG ≥ 180 mg/dL</th>
<th>INSTRUCTIONS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG ↑ by &gt; 40 mg/dL/hr</td>
<td>BG ↑ by &gt; 20 mg/dL/hr</td>
<td>BG ↑ by &gt; 10 mg/dL/hr</td>
<td>BG ↑ by &gt; 5 mg/dL/hr</td>
<td>↑ INFUSION by “2∆”</td>
</tr>
<tr>
<td>BG ↓ by &lt; 20 mg/dL/hr</td>
<td>BG ↓ by &lt; 10 mg/dL/hr</td>
<td>BG ↓ by &lt; 5 mg/dL/hr</td>
<td>NO INFUSION CHANGE</td>
<td></td>
</tr>
<tr>
<td>BG UNCHANGED</td>
<td>BG UNCHANGED</td>
<td>NO INFUSION CHANGE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Changing the Insulin Infusion Rate (“∆”) are determined by the current rate:

<table>
<thead>
<tr>
<th>Current Rate (units/hr)</th>
<th>∆ = Rate Change (units/hr)</th>
<th>2∆ = 2X Rate Change (units/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>3 – 6</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6.5 – 9.5</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>10 – 14.5</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>15 – 19.5</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>20 – 24.5</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>≥ 25</td>
<td>≥ 5</td>
<td>10 consult MD</td>
</tr>
</tbody>
</table>

*CHANGES IN INFUSION RATE (“∆”) are determined by the current rate:

Figure 1. The new Yale IIP.
clinically relevant consequences. In the CTICU, this hypoglycemia had no single reading of 38 mg/dl. As in the 50s, 6 readings in the 40s, and a specificly, there were 13 readings in achieved, 20 (0.4%) were < 60 mg/dl; obtained after target levels were expense of a modest increase in glycemic control was obtained at the new IIP. Using the new IIP in the MICU were less predictable and more frequent glycemia when analyzed per patient or stay in the medical unit. That is, the longer a patient remains on IV insulin, the greater the expected risk of hypoglycemia were observed, mostly due to the longer patient lengths of stay in the medical unit. This is, the longer a patient remains on IV insulin, the greater the expected risk of hypoglycemia when analyzed per patient or per patient-day (but not per blood glucose determination). In addition, less predictable and more frequent changes in both the clinical condition and nutritional status of MICU patients may predispose them to greater glycemic lability. Importantly, however, in both intensive care units, hypoglycemia was well tolerated, easily reversible, and produced no clinical complications.

Based on published outcomes data and current recommendations, despite a small increase in mild hypoglycemnic events, we believe that our new IIP is superior to its ancestor. As a result, we are now employing it throughout our hospital’s intensive care units (ICUs). In addition, the data presented in this article should be of value to other providors and hospitals actively heeding the call to lower blood glucose levels in critically ill patients.

It should be kept in mind that, as in the outpatient arena, stricter patient glycemic control will necessarily come at the cost of a greater incidence of hypoglycemia. Therefore, each hospital should weigh the risks and benefits of the various blood glucose targets and develop its own strategic approach to improving glycemic control in the ICU. These decisions should be based on available data and the unique characteristics and capacities of each institution.

Acknowledgments

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Table 1. Comparison of Old and New IIPs in the Yale CTICU

<table>
<thead>
<tr>
<th></th>
<th>Old IIP (100–139 mg/dl)</th>
<th>New IIP (90–119 mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (±SD) blood glucose at IIP initiation</td>
<td>218 ± 53 mg/dl</td>
<td>189 ± 44 mg/dl</td>
</tr>
<tr>
<td>Median time to &lt; 140 mg/dl</td>
<td>(IQR 3–8 hours)</td>
<td>(IQR 3–7 hours)</td>
</tr>
<tr>
<td>Median time to target range</td>
<td>5 hours (IQR 3–8 hours)</td>
<td>6 hours (IQR 5–9 hours)</td>
</tr>
</tbody>
</table>

Blood glucose values after target achieved

- within target range (%) 58 60
- 100–139 mg/dl (old target) (%) 58 66
- 80–139 mg/dl (%) 73 86
- 80–199 mg/dl (%) 94 95

Mean blood glucose level after target achieved

- Unit of analysis = patient 121 mg/dl 109 mg/dl
- Unit of analysis = blood glucose 125 mg/dl 112 mg/dl

Hypoglycemia rates (blood glucose < 60 mg/dl)

- % of blood glucose levels (n = 679) 0.2 0.3
- % of ICU patient-days (n = 66) 2.9 3.0
- % of IIPs (n = 54) 3.6 3.7

(IQR 4–9 hours). This compared favorably to our initial MICU experience (median 9 hours, IQR 7–13 hours), and even more so when comparing the new IIP’s time to reach the old target of 100–139 mg/dl (median 4.5 hours, IQR 2.5–7.5 hours). Some of these differences are certainly due to a lower clinical threshold for starting the new IIP, exhibited by a lower mean blood glucose at IIP initiation (238 ± 76 vs. 299 ± 96 mg/dl).

Additional comparisons between the old and new IIPs in our MICU are shown in Table 2. To summarize, mean blood glucose levels obtained using the new IIP in the MICU were 5–10 mg/dl lower than using the old IIP (depending on the primary unit of analysis). Again, the percentage of blood glucose levels within any given desirable range was superior using the new IIP.

In the MICU, however, improved glycemic control was obtained at the expense of a modest increase in observed rates of hypoglycemia. Among 5,109 blood glucose levels obtained after target levels were achieved, 20 (0.4%) were < 60 mg/dl; specifically, there were 13 readings in the 50s, 6 readings in the 40s, and a single reading of 38 mg/dl. As in the CTICU, this hypoglycemia had no clinically relevant consequences.

We conclude that our updated, more aggressive IIP lowers blood glucose levels approximately 10 mg/dl further than our originally published protocol. In the MICU, but not in the CTICU, modestly increased rates of hypoglycemia were observed, mostly due to the longer patient lengths of stay in the medical unit. That is, the longer a patient remains on IV insulin, the greater the expected risk of hypoglycemia when analyzed per patient or per patient-day (but not per blood glucose determination). In addition, less predictable and more frequent

Table 2. Comparison of Old and New IIPs in the Yale MICU

<table>
<thead>
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<tr>
<td>Mean (±SD) blood glucose at IIP initiation</td>
<td>299 ± 96 mg/dl</td>
<td>238 ± 76 mg/dl</td>
</tr>
<tr>
<td>Median time to &lt; 140 mg/dl</td>
<td>9 hours (IQR 7–13 hours)</td>
<td>4.5 hours (IQR 2.5–7.5 hours)</td>
</tr>
<tr>
<td>Median time to target range</td>
<td>9 hours (IQR 7–13 hours)</td>
<td>6 hours (IQR 4–9 hours)</td>
</tr>
</tbody>
</table>

Blood glucose values after target achieved

- within target range (%) 52 45
- 100–139 mg/dl (old target) (%) 52 56
- 80–139 mg/dl (%) 66 75
- 80–199 mg/dl (%) 93 94

Mean blood glucose level after target achieved

- Unit of analysis = patient 123 mg/dl 118 mg/dl
- Unit of analysis = blood glucose 130 mg/dl 120 mg/dl

Hypoglycemia rates (blood glucose < 60 mg/dl)

- % of blood glucose levels (n = 5,109) 0.3 0.4
- % of ICU patient-days (n = 267) 5.4 7.1
- % of IIPs (n = 63) 17.4 22.2

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References


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