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Priority Updates from the Research Literature from the Family Physicians Inquiries Network

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Glucose control: How low should you go with the critically ill?

Being too aggressive in lowering blood sugar levels of ICU patients may increase their risk of death, a new study shows.

Practice changer

For hyperglycemic patients admitted to an intensive care unit (ICU), the target blood glucose level should be ≤180 mg/dL, not 81 to 108 mg/dL. More aggressive glucose lowering is associated with a higher mortality rate.[1]

Strength of recommendation:
B: Based on a single, high-quality randomized clinical trial.

Finfer S, Chittock DR, Su SY, et al; NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* 2009;360:1283-1297.

How to implement less aggressive goals
Author Adam Zolotor provides implementation tips at jfponline.com

PURLs methodology
This study was selected and evaluated using FPIN's Priority Updates from the Research Literature (PURL) Surveillance System methodology. The criteria and findings leading to the selection of this study as a PURL can be accessed at www.jfponline.com/purls.

ILLUSTRATIVE CASE

A 71-year-old woman with diabetes and coronary artery disease has just been admitted to the ICU, where she'll receive treatment for sepsis, multilobar pneumonia, and respiratory failure requiring mechanical ventilation. Her blood sugar is 253 mg/dL. In writing her admission orders, you contemplate targets for glycemic control. How low should you go?

Hyperglycemia is common in patients admitted to intensive care, whether or not they have diabetes. Elevated blood sugar is associated with stress and trauma and affects both postoperative and critically ill medical patients. A wealth of evidence has demonstrated that hyperglycemia is associated with poorer outcomes and increased mortality in this patient population, including those with myocardial infarction, stroke, trauma, and other medical conditions.[2-5] Thus, intensive glucose control is the standard of care in the ICU, based on consensus guidelines from such groups as the American Diabetes Association (ADA) and the Surviving Sepsis Campaign—an initiative developed by 3 critical care organizations and endorsed by 16 specialty groups.[6-8]

Is intense therapy better? Study results differ

The association between hyperglycemia and an increased risk of death led investigators to study the effectiveness of aggressive treatment with insulin in decreasing morbidity and mortality. A 2004 meta-analysis of 35 trials comparing insulin vs no insulin in critically ill hospitalized patients demonstrated a 15% reduction in short-term mortality among patients treated with insulin.[9] A 2008 meta-analysis of 29 randomized trials, including data from 8432 adult ICU patients, compared intensive insulin

therapy with conventional therapy—and found that intensive therapy did not lower hospital mortality rates compared with conventional therapy. In addition, this meta-analysis revealed a marked increase in severe hypoglycemia (blood sugar ≤40 mg/dL) in the intensive therapy group.[10] (The intensive therapy group included studies with glucose goals of ≤110 mg/dL and <150 mg/dL in about equal numbers; conventional therapy goals were generally between 180 and 200 mg/dL.)

The studies included in both the meta-analyses, however, were mostly small, single-center trials, and of low-to-medium quality. In addition, methods for achieving glycemic control varied. Nonetheless, current consensus guidelines set a goal for glucose levels of 80 to 110 mg/dL for all critically ill hospitalized patients.[6-8] But because of the lack of sufficient high-quality evidence from a single large RCT, Finfer et al conducted the large study described here to clearly establish that intensive glycemic control decreases all-cause mortality. Given their hypothesis, the results were surprising.

STUDY SUMMARY

Intensive therapy does more harm than help

NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation) was a large-scale, multicenter, multinational trial comparing aggressive blood sugar control (goal 81-108 mg/dL) with conventional therapy (goal ≤180 mg/dL) in 6104 critically ill hospitalized patients with hyperglycemia. Patients were followed for 90 days. The primary end point was death from any cause 90 days after randomization. Secondary outcomes included survival time during the first 90 days, specific cause of death, duration of mechanical ventilation, renal replacement therapy, and length of stays in the ICU and in the hospital. Other outcomes included death from any cause within 28 days, place of death, new organ failure, positive blood culture, blood transfusion, and units of blood transfused.

The study was conducted in 42 hospitals in Canada, Australia, and New Zealand. Patients had to have an anticipated ICU admission of 3 days or more and randomization had to occur within 24 hours of admission. The study protocol was discontinued when patients began eating or were discharged from the ICU; if they were readmitted to the ICU within 90 days of randomization, the study protocol was resumed.

Treatment assignment was revealed to clinical staff after randomization, and was determined by a specific algorithm (https://studies.thegeorgeinstitute.org/nice/). Blood sugar levels were managed with insulin infusions.

In the conventional group, insulin was started at 1 unit/h for glucose levels >180 mg/dL, and decreased or stopped when levels were <144 mg/dL, depending on previous glucose value and current rate of drip. In the intensive therapy group, insulin was initiated for lower levels (blood sugar >109 mg/dL) and at a higher rate (2 units/h). The insulin rate was decreased or maintained for glucose levels from 64 to 80 mg/dL, depending on previous glucose value and current rate of drip. Insulin was withheld for blood sugar levels of <64 mg/dL.

Contrary to the hypothesis, intensive therapy spelled trouble. Patients with intensive glycemic control had an all-cause mortality rate of 27.5%, compared with a rate of 24.9% for patients in the conventional therapy group (P=.04, number needed to harm [NNH]=38). Severe hypoglycemia (glucose ≤40 mg/dL) occurred in 6.8% of those in the intensive therapy group, compared with 0.5% in the conventional therapy group (P=.03, NNH=16).

Most of the deaths in both groups occurred in the ICU or in the hospital. Deaths from cardiovascular causes were more common among those in the intensive therapy group. There were no

FAST TRACK

Nearly 7% of patients receiving intensive therapy developed severe hypoglycemia, vs 0.5% of those in the conventional therapy group.

significant differences in any other outcomes. The mean glucose level in the intensive therapy group was 118, vs 145 mg/dL in the conventional therapy group.

For multivariate and subgroup analyses, the patients were assigned strata (Canada or Australia/New Zealand; operative vs nonoperative admission) or classified into groups (traumatic vs atraumatic; diabetes vs no diabetes; corticosteroids in previous 72 hours or not; high vs low critical illness symptom severity) based on predefined characteristics. No subgroups had significantly improved outcomes with intensive therapy.[1]

WHAT'S NEW

Now we know: Don't go too low

This study, in contrast to a number of smaller studies of lower quality, demonstrates a higher all-cause mortality rate at 90 days for critically ill patients receiving intensive glucose therapy. It is now clear that, among critically ill hospitalized patients, aiming for intensive glucose control (81-108 mg/dL) is associated with an increased rate of severe hypoglycemic events and all-cause mortality at 90 days. The previously used goal of conventional therapy (≤180 mg/dL) is safer.

CAVEATS

Study population may not reflect primary care

There are 2 caveats to this study. The first is that because of the nature of the research, it was impossible to maintain blinding of the clinical staff to patient assignments. The second important caveat pertains to the severity of illness among participants in this multicenter study: Most of these patients were in ICUs at tertiary care medical centers and had an expected ICU length of stay of 3 or more days. Although many family physicians manage patients in ICUs, the patients randomized in this study may represent a sicker than average patient population for some hospitals.

CHALLENGES TO IMPLEMENTATION

Some may doubt validity of this outcome

Less aggressive glycemic control for critically ill patients should be easier to achieve, not more difficult. However, a change in glucose targets may require new admission order sets and, notably, reeducation of physicians and nurses who have been convinced by earlier studies that more intensive glucose control is superior. ■

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