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Medscape Medical News

Tight Glucose Control May Increase Mortality in Critically Ill Patients CME/CE

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Learning Objectives

Upon completion of this activity, participants will be able to:

1. Identify outcomes improved with intensive glucose control vs standard glucose control in a meta-analysis of critically ill patients.
2. Describe the effects of intensive glucose control vs standard glucose control in the current randomized trial.

Authors and Disclosures

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Disclosure: Marlene Busko has disclosed no relevant financial relationships.

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Disclosure: Charles Vega, MD, FAAFP, has disclosed no relevant financial relationships.

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Disclosure: Laurie Scudder, MS, NP, has disclosed no relevant financial information.

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Disclosure: Brande Nicole Martin has disclosed no relevant financial information.

From Heart*wire* — a professional news service of WebMD

March 26, 2009 — Ninety-day mortality was 14% higher in hyperglycemic patients in general intensive-care units (ICUs) who received insulin to meet intensive vs conventional blood glucose targets, in a large, multinational trial [1].

Findings from the **Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation** (NICE-SUGAR) study are published in the March 26, 2009, issue of the *New England Journal of Medicine*.

The study showed that "intensively lowering blood glucose to a target of 81 to 108 mg/dL does not benefit critically ill patients and may well increase their risk of dying," lead author **Dr Simon Finfer** (the George Institute for International Health, Sydney, Australia) told **heart*wire***. "There is no benefit to be gained beyond a target of less than 180 mg/dL."

Cardiovascular failure was seen in 57% of patients at study entry, and cardiovascular causes accounted for most of the increased mortality in the intensive-glucose-control group, he noted. "This raises the possibility that intensive glucose control has adverse effects on the cardiovascular system, but our study was not designed to study this in detail," he said.

Inconsistent Findings

Patients in ICU commonly have hyperglycemia, which is associated with increased morbidity and mortality, the authors write. In 2001, Van den Berghe et al reported that in a study of over 1500 surgical-ICU patients, intensive glucose control reduced mortality. However, three subsequent studies in medical- and general-ICU patients did not demonstrate a mortality benefit with tight glucose control.

Intensive glucose control has been recommended by the **American Diabetes Association** (ADA), the **American Society of Clinical Endocrinologists** (ASCE), and the **Institute for Healthcare Improvement**, and it is widely practiced in ICUs, said Finfer.

To test the hypothesis that intensive blood glucose control lowers 90-day mortality, the researchers randomized 6104 patients to intensive glucose control with a target of 81 to 108 mg/dL or conventional glucose control with a target of 180 mg/dL or less.

Average blood glucose was 115 mg/dL with intensive control and 144 mg/dL with conventional control. Among patients who received intensive vs conventional blood glucose control, 90-day mortality was higher (27.5% vs 24.9%; odds ratio 1.14; p=0.02), as was severe hypoglycemia (6.8% vs 0.5%). Length of stay in the ICU or hospital, time spent on mechanical ventilation, and need for dialysis were similar in the two groups.

Caution Against Overreaction

In an accompanying editorial [2], **Dr Silvio E Inzucchi** and **Dr Mark D Siegel** (Yale University School of Medicine, CT) stress: "We would caution against any overreaction to the NICE-SUGAR findings."

The study showed that lowering blood glucose levels below about 140 to 180 mg/dL for patients in a general ICU did not provide added benefit, and levels below this may cause harm, they note. This does not imply that efforts to optimize glucose control should be abandoned.

"Until further evidence becomes available, it would seem reasonable to continue our attempts to optimize the management of blood glucose in our hospitalized patients, especially to avert the extremes of hyperglycemia (which have acute effects on renal function, hemodynamics, and immune defenses) and also hypoglycemia (with its own, often more immediate and serious, consequences)," they write.

Similarly, in a joint statement, the ADA and the ASCE caution that the NICE-SUGAR results "should *not* lead to an abandonment of the concept of good glucose management in the hospital setting," since uncontrolled blood glucose can lead to serious problems such as dehydration and increased risk of infection.

The two organizations are preparing joint recommendations for treating hyperglycemia in inpatients, to be published this spring. "Until more information is available, it seems reasonable for clinicians to treat critical-care patients with less intensive — yet good — glucose control strategies used in the conventional arm of the NICE-SUGAR trial," they write.

Conservative Targets Warranted

Commenting on the results for **heart*wire***, **Dr Darren McGuire** (University of Texas Southwestern Medical Center, Dallas) concurs: "Part of the take-home message is this is just another warning signal that we should pause in our zeal for normalization of blood glucose and adopt more conservative targets until additional data become available."

The findings appear to strongly support the **American Heart Association** position paper published in *Circulation* in February 2008, which "dramatically backtracked from zeal in recommending [tight] glucose control in ACS patients and recommended that it would be reasonable to have a blood glucose target of less than 180 mg/dL — coincidentally, the conservative-management arm in this trial," he said.

It is noteworthy that the bulk of the mortality difference in this study is driven by cardiovascular events, McGuire added.

"This supports a position that we should not be treating toward normal glycemic control in cardiovascular patients. Although we don't understand why, it simply is not working, and it appears to be putting people at risk."

The Australian National Health and Medical Research Council, the Health Research Council of New Zealand, and the Canadian Institutes for Health Research supported this study. Dr. Finfer has received reimbursement for travel to present research results at scientific meetings from Eli Lilly, Cardinal Health, and CSL Bioplasma and for serving on steering committees for studies sponsored by Eli Lilly and Eisai. Dr. Inzucchi has received research funding from Eli Lilly. The other study authors have disclosed no relevant financial relationships.

Sources

1. The NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283-1297.
2. 2. Inzucchi SE, Siegel MD. Glycemic control in the ICU — How tight is too tight? *N Engl J Med*. 2009;360:1346-1349.

The complete contents of **Heart*wire***, a professional news service of WebMD, can be found at www.theheart.org, a Web site for cardiovascular healthcare professionals.

Learning Objectives for This Educational Activity

Upon completion of this activity, participants will be able to:

1. Identify outcomes improved with intensive glucose control vs standard glucose control in a meta-analysis of critically ill patients.
2. Describe the effects of intensive glucose control vs standard glucose control in the current randomized trial.

Clinical Context

The collective research into the efficacy of tight glucose control in critically ill patients is mixed, as reflected in a meta-analysis by Wiener and colleagues. Their research, which was published in the August 27, 2008, issue of the *Journal of the American Medical Association*, examined randomized trials comparing intensive vs standard glucose control strategies among patients in ICUs. They found that although there was no difference between treatment strategies in the rates of overall mortality or the use of dialysis, intensive control was associated with lower rates of septicemia and higher rates of hypoglycemia.

Nonetheless, many hospitals now favor the strategy of tight glucose control for critically ill patients. The current study addresses this issue with a large cohort of randomly selected patients.

Study Highlights

- 38 academic tertiary hospitals participated in the research, along with 4 community hospitals. Patients eligible for study participation were expected to require treatment in the ICU for at least 3 consecutive days.
- Study participants were randomly assigned to tight or standard glucose control strategies. The tight control group had a glucose target of 81 to 108 mg/dL, whereas the standard control group was to have a glucose level of 180 mg/dL or less. Intravenous insulin was used to control blood glucose levels.
- The primary outcome of the study was the rate of mortality within 90 days after randomization. Secondary outcomes included the durations of mechanical ventilation and overall stay in the ICU as well as the need for renal replacement therapy. Study analysis included logistic regression to account for confounding factors affecting these outcomes.
- 6104 patients underwent randomization, and 6030 subjects had data available for analysis. The mean age of participants was 60 years, and 63% of subjects were men. Slightly more than one third of patients were surgical cases.
- The median duration of study treatment was slightly more than 4 days. The mean caloric consumption of both treatment groups was similar, and 70% of calories were given as enteral nutrition.
- The use of corticosteroids was slightly higher in the intensive-control vs standard-control groups.
- The mean time-weighted blood glucose level was lower in the intensive-control vs the standard-control groups (115 mg/dL vs 144 mg/dL, respectively).
- The 90-day mortality rates in the intensive-control and standard-control groups were 27.5% and 24.9%, yielding a statistically significant odds ratio of 1.14 favoring standard glucose control.
- Subgroup analysis based on severity of illness, operative vs nonoperative admission status, and the presence of diabetes or severe sepsis failed to alter the main outcome regarding mortality rates.
- Although the overall distribution of the cause of death was similar in comparing treatment groups, deaths from cardiovascular causes were more frequent among participants in the intensive-control group.
- There was no difference between treatment groups in the mean durations of stay in the ICU.
- Treatment groups were also similar in the duration of mechanical ventilation, the use of renal replacement therapy, and the rate of positive results of blood cultures.
- Severe hypoglycemia, defined as a blood glucose level of 40 mg/dL or less, occurred in 6.8% of participants in the intensive-control group and 0.5% of the standard-control group.

Pearls for Practice

- In a previous meta-analysis, tight glucose control reduced septicemia but increased rates of hypoglycemia vs standard glucose control in critically ill patients. There was no significant difference between glucose control strategies in the need for dialysis or overall mortality rate.
- In the current study, intensive glucose control vs standard glucose control increased the risk for mortality in critically ill patients, and the 2 treatment strategies were similar in the outcomes of duration of mechanical ventilation, overall length of stay in the ICU, and the use of renal replacement therapy.

Which of the following was an outcome of the previous meta-analysis by Wiener and colleagues comparing intensive vs standard glucose control strategies in critically ill patients?

- Intensive control resulted in lower mortality rates
- Intensive control resulted in lower need for dialysis
- Intensive control resulted in lower rates of septicemia
- Rates of hypoglycemia were similar for both strategies of glucose control

Which of the following outcomes was *worse* with intensive glucose control vs standard glucose control in the current study by Finfer and colleagues?

- Mortality rates
- Duration of stay in the ICU
- Duration of mechanical ventilation
- Use of renal replacement therapy

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