

Benefits and Risks of Tight Glucose Control in Critically Ill Adults: A Meta-analysis. *JAMA*. 2008;300(8):933-944. Sara Handy and Scott Sherr – September 2, 2008.

Background:

- 2001 Study Berghe Et Al concluded that tight glucose control (<110) in the ICU decreased hospital mortality by one third, decreased blood stream infections by 47%, decreased ARF requiring HD by 41%, decreased RBC transfusions by 50%, and decreased critical illness neuropathy by 44%
- The subgroup of patients with sepsis and multisystem organ failure showed the greatest decrease in death from this intervention.
- As a result, the Surviving Sepsis Campaign in 2004 and again in 2008 recommended tight glucose control for all patients with sepsis and multiorgan failure (Glucose <150)
- 16 other professional societies have also endorsed these recommendations.
- The 2001 study however, only included critically ill surgical patients in a Surgical ICU (mostly post cardiac surgery) and these results were then generalized to all patients with sepsis and multiorgan failure.
- Other controversies with this study were the use of early glucose infusion and parental nutrition, both of which can induce hyperglycemia and are non-standard practices in most ICU settings.
- Most significantly, subsequent studies in medical and mixed medical-surgical ICU environments have had mixed results.
- One recent cohort study of over 10,000 ICU patients showed a trend towards increased mortality with the use of tight glucose control when adjusted for disease severity.
- The major complication to tight insulin control in all studies on this issue has been hypoglycemia with rates much higher than the initial Berghe et al reported 5% incidence, some as high as 30% to 40% range.

Hypothesis: Tight glucose control reduces mortality in the ICU setting.

Study Design

Study Type: Meta-Analysis of 29 RCTs

Setting: Surgical, Medical and mixed med-surg ICUs.

Time period: Search included 1950-2008

Inclusion Criteria:

- Setting = adult ICU
- Intervention group received tight glucose control defined as glucose goal < 150 obtained using insulin infusion
- Comparison group received usual care (allowed the usual care glucose goal and route/method of insulin administration to vary)
- Primary or secondary outcomes included hospital or short term mortality (<= 30 days), septicemia, new need for dialysis, or hypoglycemia

Exclusion Criteria:

- Inability to obtain adequate details of study methodology or results
- Tight glucose intervention conducted during intraoperative period rather than during ICU stay

Randomization: Each of the included 29 studies were randomized controlled trials with the intervention as defined by inclusion criteria above. A total of 8432 patients contributed data.

Patient characteristics: This is more difficult to describe in a meta-analysis study.

The authors performed subgroup analyses on the variables of:

- glucose goal (very tight control and moderately tight control)
- type of ICU setting (surgical, medical, or mixed ICU).

In addition they performed sensitivity analyses on the prespecified clinically relevant variables:

- Proportion of diabetics
- Use of insulin-only infusions (as opposed to glucose-insulin-potassium infusions)
- Achieved mean glucose level

Outcomes

Primary outcome

- Hospital mortality defined as death occurring during the hospital stay or within 30 days following admission.

Secondary outcomes

- Rate of septicemia defined as sepsis, septicemia, bacteremia, or a description of positive blood

cultures

- New need for dialysis defined as patients without a preexisting dialysis requirement who subsequently developed acute renal failure that required dialysis.
- Hypoglycemia defined as a patient with 1 or more recorded blood glucose measurement of 40 mg/dL or lower. Of note, this was not PER EPISODE, but by number of patients having at least one episode of hypoglycemia, and it did not require that any hypoglycemia symptoms be present. Conversely, patients may have had symptomatic hypoglycemia at a higher blood glucose measurement that did not meet this definition.

Meta-analysis Validity

- 1) Was a focused clinical question asked? Yes.
- 2) Were exclusion and inclusion criteria appropriate and explicit? Arguably yes, with room for improvement in defining "usual care."
- 3) How likely is it that important, relevant studies were missed? Included all languages, several databases searched, made extensive efforts to find unpublished studies and data, therefore fairly unlikely, however there is always the publication bias factor.
- 4) How was the validity of included studies appraised? Yes. Formal assessment of each trial using Jadad scale.
- 5) Were reviewers blinded? Is agreement reported? Reviewers not blinded, but there was independent assessment and abstraction of each study, no calculation of agreement was reported.
- 6) Were the results similar from study to study? Was variation analyzed? They did assess variability using 2 thresholds: "statistically significant heterogeneity" (P value of less than 0.10) and effect of variability "meaningful heterogeneity" (I² greater than 50%). They also compared fixed-effects model and random-effects model analyses. Finally, a funnel plot of study size vs. effect size was constructed to evaluate the impact of publication bias.

Comments:

- There was no significant difference in hospital mortality between tight glucose control and usual care strategies even when the data was stratified by ICU type (medical, surgical, or mixed) or by glucose goal (very tight vs. moderately tight)
- Absolute reduction in mortality was 1.7%, thus 58 patients would have to be treated to prevent one death.
- The relative risk of death in the tight glucose control group was 1.03, a small increase in mortality, however.
- Tight glucose control decreased rates of septicemia (positive blood cultures, sepsis, bacteremia) in Surgical ICU patients only when stratified by ICU type.
- There was also nearly significant reduction in the moderately tight glucose group when stratified by glucose goal.
- There was no significant association between glucose control and new need for dialysis with any data stratification
- Hypoglycemia risk was higher when using either the very tight or moderately tight glucose goal parameters vs. usual care as expected.
- After sensitivity analysis, the only change to these results was a statistically significant reduction in septicemia in the very tight glucose control subgroup and loses statistical significance in the moderately tight glucose control group.

Can we trust these results?

- The standard for glycemic control (i.e. the "usual" control group) was not well defined.
- The effect of blood glucose variability and inaccurate bedside measurement of blood glucose remain unclear.
- Each of these studies included in the meta-analysis used different treatment regimens, different methods of blood glucose monitoring, and variable levels of quality control.
- However, overall, if there is a mortality benefit that exists that was not detected in the meta-analysis, it almost certainly is not of the magnitude found in the van den Berghe study.

The next step?

- NICE SUGAR, a study of tight glycemic control, being conducted in 41 hospitals with 6100 participants was due to be completed last month and results should be available by early 2009.