

Worksheet for Using an Article About Therapy or Prevention

Journal Club Eastern Virginia Medical School

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CITATION: "Intensive versus Conventional Glucose Control in Critically Ill Patients: The NICE-SUGAR Study." New England Journal of Medicine. 360 (13). 26 March 2009, pp 1283- 1297.

I. WHAT IS BEING STUDIED?	
1. Study Objective	Determine the mortality difference (if any) between tight glucose control (81-108 mg/dl) versus a more traditional goal of <180 mg/dl
2. Study Design	International multi-center randomized study of adult medical and surgical ICU patients in a controlled trial involving 6104 patients over a 4 year period
3. Inclusion Criteria	1. Patients expected to remain in the ICU at least 2 calendar days 2. Patient has an arterial line <i>in situ</i> or the placement of an arterial line is imminent (within the next hour) as part of routine ICU management.
4. Exclusion Criteria	1. Age less than 18 years. 2. Imminent death (cardiac standstill or brain death anticipated in less than 24 hours) and the treating clinicians are not committed to full supportive care. This is confirmed by a documented treatment-limitation order that exceeds a "do-not-resuscitation" order. 3. Patients admitted to the ICU for treatment of diabetic ketoacidosis or hyperosmolar state. 4. Patients expected to be eating before the end of the day following the day of admission to the ICU. 5. Patients who have previously suffered hypoglycemia without documented full neurological recovery. 6. Patients considered at abnormally high risk of suffering hypoglycemia (e.g. known insulin

	<p>secreting tumor or history of unexplained or recurrent hypoglycemia or fulminant hepatic failure)</p> <p>7. Patient has previously been enrolled in the study.</p> <p>8. Patient cannot provide prior informed consent and there is documented evidence that the patient has no legal surrogate decision maker and it appears unlikely that the patient will regain consciousness or sufficient ability to provide delayed informed consent.</p> <p>9. Patient has been in the study ICU or another ICU for 24 hours or more for this admission.</p>
5. Interventions Compared	Intensive glucose control (81-108 mg/dl) vs target glucose <180, while in the ICU or for 90 days, whichever ended first
6. Outcomes Evaluated	<p>Primary: death from any cause at 90 days after study entry</p> <p>Secondary: survival time during first 90 days, cause of death, duration of mechanical ventilation, renal-replacement therapy, duration of stay in ICU and hospital</p> <p>Tertiary: death from any cause within 28 days, place of death, incidence of new organ failure, positive blood culture, receipt of red cell transfusion, volume of said transfusion</p>
II. Are the results of the study valid?	
1. Was the assignment of patients randomized?	Randomization was achieved by entering patients who met criteria into an algorithm along with status of operative or nonoperative reason for admission, clinicians were then provided with the patient's status as conventional versus intensive.
2. Were all patients who entered the trial properly accounted for and attributed at its conclusions?	<p>8 patients lost to 90 day follow up due to inability to locate</p> <p>74 patients were not included in 90 day data because consent was withdrawn 304 (10%) and 225 (7.4%) of the intensive and conventional groups respectively did not complete the study (i.e., the intervention was discontinued early), their data was included in the final analysis.</p>

3. Was follow-up complete?	Yes, except for as mentioned above
4. Were patients, health workers and study personnel “blind” to treatment?	No. Once randomization was given, those administering the treatments were necessarily aware of which patient received which treatment
5. Were study groups similar at the start of the trial?	Yes. Baseline characteristics were similar Intensive control: Age 60.4 +/- 17.2 Male 62.6% APACHE II 21.1 +/- 7.9 Operative Admissions 36.9% Conventional control: Age 59.9 +/- 17.1 Male 64.2% APACHE II 21.1 +/- 8.3 Operative Admissions 37.2%
6. Aside from the experimental intervention, were the groups treated equally	Intensive insulin group were treated with corticosteroids more frequently than conventional group (34.6% vs 31.7%, p= 0.02). Steroids were used more commonly in those with septic shock and there were no statistically sig. differences in the rates of septic shock between groups 36.1 % intensive control vs 34.3 in conventional (p=0.42)
III. What were the results?	
1. How large was the treatment effect? (difference between treatment and control group).	Primary Outcome – 27.5 % vs 24.9% ARR 2.6% (CI 95% 0.4-4.8) NNH: 1 death for every 38 patients treated with intensive insulin
2. What was the estimated treatment effect at a 95% confidence interval?	Primary Outcome – 0.4- 4.8
IV. Will the results help me in caring for my patients?	
1. Were all clinically important outcomes	Yes- survival to 90 days, survival to 28

considered?	days, survival to ICU discharge, survival to hospital discharge, death at home within 90 days of randomization, episodes of severe hypoglycemia (<40 mg/dl)
2. Are treatment outcomes worth the potential harms?	No. Potential harm of hyperglycemia-infection, poor long term outcome from AMI, polyneuropathy, increased vent dependence (study done on 215 mg/dl as cut off) Similar rates of time on vent, similar rates of positive blood cultures, difference previously mentioned in 90 day outcomes. 180 mg/dl appears to be a safe target glucose.

Additional Comments:

From the inception of intensive insulin protocols with Van den Berghe et al, the issue of glucose control in the critically ill has been controversial. Van de Berghe's study used higher conventional insulin goals (180-215), while using similar intensive insulin goals (80-110), and 1548 patients as opposed to 6104. Additionally, the recent meta-analysis in JAMA suggests that mortality rates are similar. However, the present study had longer follow up than most, and greater enrollment numbers and therefore statistical power.

Bottom line: According to the present study, maintenance of serum glucose <180 had an ARR of 2.6 percent over serum glucose 81<x<108. Combined with the meta-analysis showing similar mortality with both protocols, I conclude that intensive insulin therapy may pose additional harms to the patient, resource utilization from the nursing staff and additional overall costs.