Pro: We Should Use Tight Glycemic Control

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My Response…

Just a joke…
Objectives

• Review hyperglycemia in the critically ill patient
  – Pathophysiology
  – Mortality data
• Intensive insulin therapy in the ICU
  – Revisit Leuven and NICE-SUGAR trials
  – Discuss potential areas of benefit
• Attempt to reconcile conflicting evidence
• Future directions for glycemic control in the ICU
Hyperglycemia in the ICU

• “Diabetes of Injury”
  – Hyperglycemia, insulin resistance, glucose intolerance
• Very common
  – In patients admitted with AMI (Capes et al. 2000)
    • Without Diabetes: 3% - 71%
    • With Diabetes: 46-84%

Two types of Hyperglycemia:

1) Hospital-related: diabetes of injury

2) Deterioration of glycemic control in pre-existing diabetics (some of whom did not know that they had diabetes—best detected with elevated HbA1c)

Epidemiology:

Review article of pts admitted to ICU with AMI.
What causes the problem:

Interplay of catechols, growth hormone, cortisol, and cytokines.

**Insulin resistance + increased hepatic glucose production (ongoing gluconeogenesis due to glucagon, cortisol, epinephrine).** TNF may actually increase glucagon production.

**Insulin resistance:**

**Hepatic:** thus continued glucose production

**Periphery:** reduced insulin-mediated glucose uptake due to defects in post-receptor insulin signalling and downregulation of glucose transporter (GLUT-4). Also impaired non-oxidative glucose disposal probably due to decrease in skeletal muscle glycogen synthesis. Again, all of this is mediated by actions of cortisol and epi (reducing insulin mediated glucose uptake) and TNF and IL-1 (decreased insulin signalling)

Insulin resistance leads to a catabolic state in which lipolysis takes place>>increase in circulating FFA lead to more insulin resistance. Viscous cycle.

Interestingly, you actually get in increase in whole-body glucose uptake (i.e. GLUT-1 driven uptake, insulin mediated). This happens in all tissues...
Hyperglycemia: Negative Effects

![Diagram showing the relationship between hyperglycemia, oxidative stress, altered intracellular pathways and signaling, and harmful tissue effects and complications.]

Adapted from Dungan et al, Lancet 2009

Preventing glucotoxicity is key! The nervous system, hepatocytes, endothelial/epithelial and immune cells all take up glucose independent of insulin. In situations of stress, these cells experience glucose overload. In situations like this, the end result is likely increase in Reactive Oxygen Species due to increased glycolysis and oxidative phosphorylation. These may ultimately impair mitochondrial function.

Endothelial effects:

Glucotoxicity, lipotoxicity, and inflammation. Interestingly, the variability in glucose levels—we’ll get back to this later in the talk—seem to cause more endothelial dysfunction and oxidative stress response.
Adverse Effects

• Tissue Effects
  – Endothelial Dysfunction
  – Pro-inflammatory cytokines
  – Mitochondrial dysfunction
  – Catabolism
  – Procoagulation/Antifibrinolysis
  – Etc.

• Complications
  – Renal failure
  – CIP/CIM
  – Prolonged mechanical ventilation
  – Septicemia
  – Etc.

Hyperglycemia & Mortality

• Strong evidence for increased mortality:
  – Meta-analysis, acute MI (Capes et al. Lancet 2000)
    • Pts without DM: pooled RR 3.93 (2.86-5.39)
    • Pts with DM: pooled RR 1.71 (1.22-2.40)
  – Mixed ICU population (Falciglia et al., CCM 2009)
    • VA retrospective cohort study of 259,040 admissions
    • Adjusted OR of mortality increased with level of hyperglycemia
    • Increased mortality in non-diabetics

Generally speaking, there is strongest evidence that pts without DM with hyperglycemia have higher mortality that those with pre-existing dx of DM.

Many other studies also reveal the same data trend. Stroke pts without diabetes also at great risk.

Capes: meta-analysis of > 1800 pts admitted with AMI. Based on admission stress hyperglycemia.

Granted, most of this is observational data.
Increased Mortality

Mean glucose values throughout the stay. OR for mortality.

Adjusted for severity of illness.

Falciglia et al., CCM 2009
Intensive Insulin Therapy

• Historical Background
  – Glucose-insulin-potassium (GIK) trials
    • DIGAMI study (Malmberg et al. *JACC* 1995)
      – 29% relative mortality reduction in diabetic pts with AMI
    • IIT meta-analysis with sub-group analysis of 18 GIK trials (Pittas et al, *Arch Intern Med* 2004)
      – Trend toward reduced mortality: RR, 0.90; 95% CI 0.77-1.04

Intensive insulin therapy (background information):

Not all of the early GIK trials actually targeted normoglycemia.

Why would preventing a degree of hyperglycemia with insulin be helpful?

Normal cells can be protected from the effects of hyperglycemia by down-regulation of glucose transporters.

Is it the insulin itself, preventing the hyperglycemia, or both that are important?

Key points:

*Increased skeletal muscle glucose uptake.* Insulin may also have beneficial effects by itself (improved dyslipidemia, improved anabolic effects, antiinflammatory effects, prevention of endothelial dysfxn and hypercoagulability, anti-apoptosis >>>> this was the initial rationale behind GIK therapy starting 4 decadees ago.*
Key Trials Demonstrating Benefit: Intensive Insulin Therapy
Leuven I: SICU

- Prospective, randomized, single center, unblinded
- 1548 patients
- IIT (infusion for goal 80-110 mg/dl) vs. CIT (infusion for BG > 215, goal glucose 180-200 mg/dl)
- ICU mortality reduced from 8.0% to 4.6% (p < 0.04)
- Greatest benefit: pts in ICU > 5 days
- Improved morbidity: ventilatory support, septicemia, renal failure requiring dialysis, hyperbilirubinemia, CIP

Glycemic Separation: 103 vs. 153 (p < 0.001)
Mortality Benefit

**Figure 1**: Kaplan-Meier Curves Showing Cumulative Survival of Patients Who Received Intensive Insulin Treatment or Conventional Treatment in the Intensive Care Unit (ICU).

Patients discharged alive from the ICU (Panel A) and from the hospital (Panel B) were considered to have survived. In both cases, the differences between the treatment groups were significant (survival in ICU, nominal $P=0.00$ and adjusted $P=0.04$; in-hospital survival, nominal $P=0.05$; $P$ values were determined with the use of the Mantel-Cox log-rank test.)
# Study Details

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<tr>
<th><strong>Strengths</strong></th>
<th><strong>Limitations</strong></th>
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<tr>
<td>• Large study</td>
<td>• SICU pts only</td>
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<td>• Good glycemic separation between treatment and control groups</td>
<td>– &gt; 60% cardiac surgery</td>
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<td>• Control group glucose levels likely reflective of “usual” care in many ICUs</td>
<td>• Unblinded</td>
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<td>• Use of dextrose infusions</td>
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<td>• Relatively high mortality in control group</td>
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<td>• Excess use of parenteral nutrition</td>
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<td>• Reported only mean morning blood glucose variation</td>
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<td>• Study stopped early</td>
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Stopped after 4th interim analysis due to “inferior” outcomes in CIT

8% mortality in control group.

No mortality benefit in first 5 days in ICU.
Leuven II: MICU

• Prospective, randomized, single center
• 1200 MICU patients
• IIT (infusion for goal 80-110 mg/dl) vs. CIT (infusion for BG > 215, goal glucose 180-200 mg/dl)
• ICU and in-hospital mortality not significantly reduced by IIT
• However, among pts in ICU for ≥ 3 days, in-hospital mortality reduced from 52.5% to 43% (p = 0.009)
Leuven II: MICU

• Reduced Morbidity
  • Newly acquired kidney injury (8.9% to 5.9%, p = 0.04)
  • Earlier wean from mechanical ventilation (hazard ratio, 1.21; CI 1.02 to 1.44, p=0.03)
  • Earlier ICU and hospital discharge
  • Among pts in ICU >/= 3 days, additional benefits:
    – Reduced hyperbilirubinemia
    – Reduced hyperinflammation
    – Decreased costs of intensive care (reduced TISS-28)
Figure 4. Kaplan-Meier Curves for In-Hospital Survival.
The effect of intensive insulin treatment on the time from admission to the intensive care unit (ICU) until death is shown for the intention-to-treat group (Panel A) and the subgroup of patients staying in the ICU for three or more days (Panel B). Patients discharged alive from the hospital were considered survivors. P values calculated by the log-rank test were 0.49 for the intention-to-treat group and 0.02 for the subgroup staying in the ICU for three or more days. P values calculated by proportional hazards regression analysis were 0.30 and 0.02, respectively.
Study Details

• Unlike SICU study, no high dose dextrose infusions
• Increased incidence of hypoglycemia in IIT group (18.7%) vs. CIT group (3.1%)
  – Higher incidence than first Leuven trial in SICU pts (hypoglycemic events in ~ 5%)
• Hypoglycemia was independent risk factor for death.

Did the episodes of hypoglycemia eliminate the mortality benefit?
Additional Evidence for Reduced Mortality

• Meta-analysis of RCTs of insulin therapy (Pittas et al., Arch Intern Med 2004)
  – 35 trials included
  – Insulin therapy decreased short term mortality 15% (RR 0.85, 95% CI 0.75-0.97)
  – Sub-group analyses revealed benefit in SICU, trials targeting normoglycemia, and in patients with DM.
Pittas et al. Meta-Analysis

• 15% reduction in short-term mortality relative to controls
Reduced Morbidity with IIT

- Renoprotection

- Decreased incidence of CIP/CIM & prolonged mechanical ventilation
  - Hermans et al., *AJRCCM* 2007

- Decreased cholestatic liver dysfunction
  - Mesotten et al., *J Clin Endocrinol Metab* 2009

Renoprotection:

Combined data from two Leuven trials: 2707 pts reviewed. IIT reduced the risk of mRIFLE injury or failure from 7.6 to 4.5%. In surgical pts, IIT also reduced the risk of oliguria and the need for RRT (7.4% to 4.0%, p = .008).

CIP/CIM:

Prospectively planned sub-analysis of LEUVEN II. All pts in ICU for at least 7 days. Independent of risk factors. Reduction in CIP/CIM from 50% to 38.9 % ( p = 0.02). Need for mech ventilation > 14 days reduced from 46.7% to 34.6% (p= 0.01)

Liver:

Preplanned analysis of LEUVEN 2, long stay pts > 5 days in ICU. IIT reduced cumulative risk of cholestasis (total bilirubin)
A role for initiating IIT in the OR?

- Supportive evidence
  - Subramaniam et al. *Anesthesiology* 2009
    - Reduction in MI and acute CHF in IIT protocol initiated intraoperatively for vascular surgery patients
- Discouraging evidence
    - No mortality benefit with IIT started intraoperatively in cardiac surgery patients
    - Increased incidence of death and stroke with IIT
- ATS recommendations
  - Insulin in OR and 24 hours post-op to maintain BG < 180.
Enthusiastic Response from Critical Care Community

- Surviving Sepsis Campaign included recommendation for glucose control (target < 150 mg/dL)
- IIT embraced by American Diabetes Association
- UCSF adopted rigorous protocol for tight glycemic control
Acknowledging the conflicting evidence…

• NICE-SUGAR *(NEJM 2009)*
• GLUCONTROL (Preiser et al. *Intensive Care Med* 2009)
• VISEP (Brunkhorst et al., *NEJM 2008*)
• Meta-analyses without benefit:
  • Griesdale et al., *CMAJ 2009*  
    – Includes NICE-SUGAR  
    – Did show mortality benefit in SICU pts  
  • Wiener et al., *JAMA 2008*

NICE-SUGAR: time-weighted blood glucose: 115 vs. 144. Statistically significant, but not enough spread, perhaps. 144 is hardly tight control. These are different studies.

Let’s acknowledge that ARDSNEt approaches previously showed no benefit.
Reconciling conflicting evidence

• IIT may be beneficial in select groups of patients but not all ICU patients
• Protocol variations possibly responsible for divergent study outcomes
  – Was there enough glycemic separation in NICE-SUGAR?
• Hypoglycemia may reduce potential mortality & morbidity benefits

Nice Sugar: Mean ~ 140 vs. 108; should we be surprised?
Is glucose variability a major factor?

• Several observational studies suggest that glycemic variability is associated with increased mortality:
  – Krinsley, *CCM* 2008
  – Egi et al., *Anesthesiology* 2006

• Leuven group’s retrospective analysis of database of two RCTs (Meyfroidt et al. *CCM* 2010):
  – Several measures of glucose variability associated with increased hospital mortality
Increasing Variability = Increasing Mortality

Egi et al., Anesthesiology 2006
Caution!

Beware the pendulum swing…
Current Recommendations: ADA/AACE Consensus Panel

• Revised glucose targets: 140-180mg/dl in critically ill patients in ICU
• Etie Moghissi, Consensus Panel Chair:
  – “Despite some inconsistencies in the clinical trial results, it would be a serious error to conclude that judicious control of glycemia in hospitalized patients is not warranted.”

ADA/AACE, May 2009
The Endocrine Society: Response to NICE-SUGAR

• Key questions related to:
  – Diabetics vs. non-diabetics
  – Effect of hypoglycemia and association with mortality
  – Potential positive impact of continuous glucose monitoring

The Endocrine Society, March 2009
The Endocrine Society

• Conclusions:
  “We believe physicians should individually tailor their approach to glycemic control in their ICU patients, perhaps targeting glucose values between 144-180 mg/dl, until we better understand the reasons for these somewhat counterintuitive findings.”
UCSF (Revised) Glycemic Control Protocol

• IV insulin infusions
• Target blood glucose: 100-160
Conclusions

• Stress hyperglycemia remains a serious concern in the ICU
• While excessively tight glycemic control appears unwarranted, a return to “usual care” would be inappropriate.
• With avoidance of hypoglycemia, better outcomes may be possible in different ICU populations
• Further studies need to evaluate new dosing algorithms and monitoring techniques