Have we gone too far?

Glycemic Control in Critical Care

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Have I got a deal for you...

- Decrease mortality
- Decrease bloodstream infection
- Decrease renal failure requiring dialysis
- Decrease transfusion rates
- Decrease critical-illness polyneuropathy
- Decrease need for prolonged ventilation and ICU care
• 1548 patients, surgical ICU
• Improved mortality (32% reduction)
• Improved morbidity
Impressive Results

• 1200 patients, medical ICU
• Decreased mortality (if in ICU > 3d)
• Decreased acute kidney injury
• Faster weaning from mechanical ventilation
• Shorter ICU and hospital LOS

Still Impressive
Devil is in the details...

- Single-center studies
- Patients received large amounts of glucose
- IIT significantly increased the risk of hypoglycemia
How much dextrose?

- 200-300g dextrose in 24 hours
- ~ 80-100cc/hr of D10

500 patients in med/surg ICU

Less than 50% of pts achieved glucose target

No difference in mortality or morbidity

Significantly increased risk of hypoglycemia
- 537 patients, multicenter trial
- Terminated early due to safety concerns (renal failure and mortality increased with HES)
- Increased risk of hypoglycemia with IIT

Brunkhorst. NEJM 358(2). 2008
• 523 patients in a med/surg ICU
• No mortality benefit
• Increased risk of hypoglycemia with IIT

• 509 patients, multicenter
• 2 x 2 factorial design evaluating steroids and IIT
• IIT did not improve mortality in patients receiving corticosteroids
• IIT increased risk of hypoglycemia
• 6104 patients, multi-center, international

• Primary outcome 90-day mortality

Intensive versus Conventional Glucose Control in Critically Ill Patients
The NICE-SUGAR Study Investigators

A

Blood Glucose Level (mg/dl)

Day after Randomization

Baseline

No. of Patients
Conventional control 2995 2233 1380 909 583
Intensive control 2989 2260 1428 908 562

Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

![Graph showing survival probability over days after randomization]

No. at Risk
Conventional control 3014 2379 2304 2261
Intensive control 3016 2337 2227 2182

P = 0.03
## Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Intensive Control (N=3010)</th>
<th>Conventional Control (N=3012)</th>
<th>Odds Ratio for Death (95% CI)</th>
<th>P Value for Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of deaths/no. with data available</td>
<td></td>
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<tr>
<td>Operative admission</td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>272/1111</td>
<td>222/1121</td>
<td>1.31 (1.07–1.61)</td>
<td>0.10</td>
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<tr>
<td>No</td>
<td>557/1898</td>
<td>529/1891</td>
<td>1.07 (0.93–1.23)</td>
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<tr>
<td>Diabetes</td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>195/615</td>
<td>165/596</td>
<td>1.21 (0.95–1.55)</td>
<td>0.60</td>
</tr>
<tr>
<td>No</td>
<td>634/2394</td>
<td>586/2416</td>
<td>1.12 (0.99–1.28)</td>
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<tr>
<td>Severe sepsis</td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>202/673</td>
<td>172/626</td>
<td>1.13 (0.89–1.44)</td>
<td>0.93</td>
</tr>
<tr>
<td>No</td>
<td>627/2335</td>
<td>579/2386</td>
<td>1.15 (1.01–1.31)</td>
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<tr>
<td>Trauma</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>41/421</td>
<td>57/465</td>
<td>0.77 (0.50–1.18)</td>
<td>0.07</td>
</tr>
<tr>
<td>No</td>
<td>788/2587</td>
<td>694/2547</td>
<td>1.17 (1.04–1.32)</td>
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<tr>
<td>APACHE II score</td>
<td></td>
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<tr>
<td>≥25</td>
<td>386/927</td>
<td>363/944</td>
<td>1.14 (0.95–1.37)</td>
<td>0.84</td>
</tr>
<tr>
<td>&lt;25</td>
<td>442/2080</td>
<td>387/2066</td>
<td>1.17 (1.01–1.36)</td>
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<tr>
<td>Corticosteroids</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>134/392</td>
<td>140/378</td>
<td>0.88 (0.66–1.19)</td>
<td>0.06</td>
</tr>
<tr>
<td>No</td>
<td>695/2616</td>
<td>611/2634</td>
<td>1.20 (1.06–1.36)</td>
<td></td>
</tr>
</tbody>
</table>

All deaths at day 90: 829/3010 vs 751/3012

Intensive Control Better

Conventional Control Better

P Value for Heterogeneity: 0.02
• Increased mortality with IIT
• Increased episodes of hypoglycemia with IIT
• No effect on duration of mechanical ventilation
• No effect on need for or duration of renal replacement therapy
• No effect on bloodstream infections
• No effect on transfusion rates

• Retrospective analysis of SICU and MICU patients from Van den Berghe, et al

• Evaluated for blood glucose amplitude and other measures of glucose variability independent of blood glucose level

Increased blood glucose amplitude variation and pattern irregularity associated with increased mortality

This graph shows the blood glucose levels in mg/dL over the course of the day on Wednesday, May 19, 2010. The yellow line represents an average blood glucose level of 108 mg/dL, while the blue line represents an average level of 160 mg/dL. The graph indicates fluctuations throughout the day, with peaks and troughs at different times.
Table 3. Independent risk factors for mortality in the merged medical ICU and surgical ICU database: Multivariable logistic regression

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1, n = 2685 of 2748&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
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<tr>
<td>Surgical ICU vs. medical ICU</td>
<td>0.185 (0.147–0.232)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Malignancy</td>
<td>3.056 (2.412–3.873)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Female vs. male</td>
<td>1.044 (0.842–1.294)</td>
<td>.6937</td>
</tr>
<tr>
<td>Overweight, BMI &gt;25 kg/m²</td>
<td>0.667 (0.539–0.825)</td>
<td>.0002</td>
</tr>
<tr>
<td>Age per yr added</td>
<td>1.020 (1.013–1.028)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Admission blood glucose per mmol/L added</td>
<td>0.986 (0.955–1.017)</td>
<td>.3697</td>
</tr>
<tr>
<td>Measures of a blood glucose level target of 4.4–6.1 mmol/L</td>
<td></td>
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</tr>
<tr>
<td>Mean morning blood glucose &gt;6.1 mmol/L vs. ≤6.1 mmol/L</td>
<td>1.494 (1.194–1.868)</td>
<td>.0004</td>
</tr>
<tr>
<td>At least one episode of hypoglycemia &lt;2.2 mmol/L</td>
<td>3.233 (2.251–4.644)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Blood glucose amplitude variation</td>
<td></td>
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</tr>
<tr>
<td>Mean daily Δ blood glucose per mmol/L added</td>
<td>1.050 (1.003–1.099)</td>
<td>.0376</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; BMI, body mass index; OR, odds ratio; CI, confidence interval.
<sup>a</sup>63 patients were excluded because of ≥1 missing values.
A single episode of hypoglycemia is an independent risk factor for mortality
Putting it all together

Figure 2. Association of Tight Glucose Control vs Usual Care With Hospital Mortality, Stratified by ICU Setting and Glucose Goal in Tight Control Group

<table>
<thead>
<tr>
<th>Source</th>
<th>Hospital Mortality, No./Total No. of Patients</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>Favoring Tight Control</th>
<th>Favoring Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgical ICU</strong></td>
<td></td>
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<tr>
<td>Very tight control glucose goal ≤110 mg/dL</td>
<td>66/196 vs. 93/228</td>
<td>0.70 (0.50-0.96)</td>
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</tr>
<tr>
<td>Dabestani et al. 2008</td>
<td>222/695 vs. 241/568</td>
<td>0.80 (0.61-1.04)</td>
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</tr>
<tr>
<td>Moderately tight control glucose goal ≤180 mg/dL</td>
<td>3/209 vs. 1/207</td>
<td>3.08 (1.07-8.89)</td>
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<tr>
<td><strong>Medical ICU</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Very tight control glucose goal ≤110 mg/dL</td>
<td>1/12 vs. 1/16</td>
<td>0.61 (0.04-9.82)</td>
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</tr>
<tr>
<td>Dales et al. 1991</td>
<td>6/26 vs. 7/41</td>
<td>0.97 (0.36-2.72)</td>
<td></td>
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</tr>
<tr>
<td>Moderately tight control glucose goal ≤180 mg/dL</td>
<td>1/73 vs. 1/72</td>
<td>0.70 (0.32-1.52)</td>
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</tr>
<tr>
<td>All medical ICU patients</td>
<td>321/1102 vs. 389/1200</td>
<td>0.78 (0.63-0.98)</td>
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</tr>
</tbody>
</table>

Putting it all together

If that’s not enough...
What does this mean to the bedside nurse?

• 4.7 minutes per glucose measurement and insulin dose adjustment

• ~2 hours of nursing time (out of a 24 hour day) just for tight glycemic control
What we’ve learned...

• IIT associated with increased hypoglycemia
• Hypoglycemia is bad (and associated with increased mortality)
• IIT is time consuming (and expensive)
Going forward

• Indices of glycemic variability

• Better glucose monitoring modalities
Until then

- Avoid hyperglycemia
- Aim for moderate control (< 180 mg/dL)
- Avoid hypoglycemia
- Design protocols that avoid large swings in glucose levels


