Does insulin treatment during and after acute stress have advantage beyond the lowering effect of blood glucose?

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Decreased survival in diabetic patients

![Graph showing decreased survival over age at diagnosis for male and female diabetic patients.]
Consequences of diabetes
Risk of perioperative complications in diabetic patients

- Hyperglycemia, ketoacidosis
- Neuroglycopoenia (drugs, unadequate supervision)
- Perioperative complications (wounds’ infection, MI, healing)
Metabolic deterioration at acute stress

- **Hormonal disorders:**
  - ↑ cortisol
  - ↑ somatotropin
  - ↑ catecholamines;
  - ↑ sympathetic overactivity;
  - ↓ endogenous insulin secretion;
  - ↓ peripheral insulin sensitivity;

- **Metabolic disorders:**
  - ↑ glicogenolisis
  - ↑ glukoneogenesis
  - ↑ proteolisis
  - ↑ lipolisis
  - ↑ ketogenesis

Elliott M Clin Anaesthesiol 1983;1: 527
Interaction between glucose toxicity and insulin deficiency in critical illness

Glucose toxicity

Lack of insulin effect

Critical illness

Hypoxia/reperfusion, iNOS activation, increased GLUT-1 and GLUT-3, cytokines, etc.

Intensive insulin infusion at ICU (surgical)
(goal 110 mg/dl)
Insulin in critically ill
(glycemia < 110 mg/dl)

↓ 42% mortality

↓ 20% duration of intensive care

↓ 34% in-hospital mortality

↓ 46% septicemia

↓ 41% dialysis

↓ 50% red cell transfusion

↓ 44% critical illnes polyneuropathy

Intensive insulin infusion at ICU (medical)
(goal 110 mg/dl)

Additional metabolic effects of insulin

- Anti-inflammatory effect
- preventing endothelial dysfunction
- preventing hypercoagulation
- anabolic effect
- improvement of dyslipidemia
- anti apoptotic effect

Van den Berghe J Clin Invest 2004;114:1187
Original Article
Survival Benefits of Intensive Insulin Therapy in Critical Illness
Impact of Maintaining Normoglycemia Versus Glycemia-Independent Actions of Insulin
Björn Ellger,1,2 Yves Debrayve,1 Ilse Vanhorebeek,1 Lies Langouche,1 Annapaula Giulietti,3 Evelyne Van Etten,3 Paul Herijgers,4 Chantal Mathieu,3 and Greet Van den Berghe1

Subjects

Normal insulin / normoglycemia
High insulin / normoglycemia
Normal insulin / hyperglycemia
High insulin / hyperglycemia

Survival
Other parameters

Ellger B Diabetes 2006; 55:1096
INSULIN OR HYPERGLYCEMIA

- Maintaining normoglycemia, independent of insulin levels, prevented endothelial dysfunction, liver and kidney injury.

- Benefits of intensive insulin therapy required mainly maintenance of normoglycemia.

- Glycemia-independent actions of insulin exerted only minor, organ-specific impact.

Ellger B Diabetes 2006;55:1096
INSULIN TREATMENT IN ACUTE MI
(aim: insulin infusion)

- ECLA- Circulation 1998; 98:2227
- CREATE-ECLA JAMA; 2005:293:435
- Pol-GIK Caremużyński Cardiosurg Drugs Ther 1999;13:191
- Dutch GIK J Am Cardiol 2003:42: 784

Glucose/Insulin constant proportion irrespective of glycemia

No therapeutic effect
INSULIN TREATMENT IN ACUTE MI
(aim: glucose control)

- DIGAMI- Am J Cardiol 1995; 26:57-65- 29% reduction of mortality
- DIGAMI-2 Eur Heart J 2005; 26:650- no effect
The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) Study

A randomized controlled trial of insulin infusion therapy for myocardial infarction

N. Wah Cheung, PhD
Vincent W. Wong, PhD
Mark McLean, PhD

Table 2—Mortality when cohort divided into those with a mean glucose level in first 24 h above and below 8 mmol/l.

<table>
<thead>
<tr>
<th></th>
<th>24-h mean blood glucose level ≤8 mmol/l</th>
<th>24-h mean blood glucose level ≥8.1 mmol/l</th>
<th>Significance</th>
<th>Adjusted odds ratio (95% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient mortality</td>
<td>0%</td>
<td>7%</td>
<td>0.05</td>
<td>7.2 (0.9–58.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>3-month mortality</td>
<td>2%</td>
<td>9%</td>
<td>0.05</td>
<td>4.7 (1.0–22.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>6-month mortality</td>
<td>2%</td>
<td>11%</td>
<td>0.02</td>
<td>5.6 (1.2–26.1)</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, and cardiac intervention (PTCA or thrombolysis).

Diabetes Care 2006; 29: 765-770
INSULIN in acute MI

Overall

- Control: n=314
- Insulin iv: n=306

p = .0111

No insulin before

- Control: n=133
- Insulin iv: n=139

p = .004

Mortality in Digami 2

## Insulin use in DIGAMI 2

<table>
<thead>
<tr>
<th></th>
<th>Group 1 N=474</th>
<th>Group 2 N=473</th>
<th>Group 3 N=306</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin iv in acute phase</td>
<td>446 (94,1)</td>
<td>444 (93,9)</td>
<td>44 (14,4)</td>
</tr>
<tr>
<td>Insulin sc in hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>154 (32,6)</td>
<td>124 (40,5)</td>
<td></td>
</tr>
<tr>
<td>Insulin at discharge (%)</td>
<td>84</td>
<td>45</td>
<td>39</td>
</tr>
<tr>
<td>IU (mean ± SD)</td>
<td>36 ± 22</td>
<td>46 ± 30</td>
<td>57 ± 42</td>
</tr>
</tbody>
</table>

*Malmberg, K. et al. Eur Heart J 2005 26:650*
Postprandial hyperglycemia and macroangiopathy
(CVD, CHD, stroke)

DECODE Arch Int Med., 2001, 161
POSTPRANDIAL HYPERGLYCEMIA AND CV RISK

HEART2D Study

Acute MI

18 days

Type 2 diabetes (n=1355)

LysPro preprandially

18 months

Long-acting 1 – 2 daily

Mortality

CV events

other events

metabolic control

Milicevic, Raz, Strojek: J Diabetic Compl 2005; 19:80
Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting

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Objective: Diabetes mellitus is a risk factor for death after coronary artery bypass grafting. Its relative risk may be related to the level of perioperative hyperglycemia. We hypothesized that strict glucose control with a continuous insulin infusion in the perioperative period would reduce hospital mortality.

Methods: All patients with diabetes undergoing coronary artery bypass grafting (n = 3554) were treated aggressively with either subcutaneous insulin (1987-1991) or with continuous insulin infusion (1992-2001) for hyperglycemia. Predicted and observed hospital mortalities were compared with both internal and external (Society of Thoracic Surgeons 1996) multivariable risk models.

Results: Observed mortality with continuous insulin infusion (2.5%, n =

Insulin infusion vs subcutaneous in cardiosurgery

**J Thorac Cardiovasc Surg 2003;125:1007**

The Glucose Insulin in Stroke Trial (GIST)
Implementation of a Safe and Effective Insulin Infusion Protocol in a Medical Intensive Care Unit

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OBJECTIVE — In a recent randomized controlled trial, lowering blood glucose levels to 80–110 mg/dl improved clinical outcomes in critically ill patients. In that study, the insulin infusion protocol (IIP) used to normalize blood glucose levels provided valuable guidelines for adjusting insulin therapy. In our hands, however, ongoing expert supervision was required to effectively manage the insulin infusions. This work describes our early experience with a safe, effective, nurse-implemented IIP that provides detailed insulin dosing instructions and requires minimal physician input.

RESEARCH DESIGN AND METHODS — We collected data from 52 medical intensive care unit (MICU) patients who were placed on the IIP. Blood glucose levels were the primary outcome measurement. Relevant clinical variables and insulin requirements were also recorded. MICU nurses were surveyed regarding their experience with the IIP.

RESULTS — To date, our IIP has been employed 69 times in 52 patients admitted to an MICU. Using the IIP, the median time to reach target blood glucose levels (100–139 mg/dl) was 9 h. Once blood glucose levels fell below 140 mg/dl, 52% of 5,808 subsequent hourly blood glucose values fell within our narrow target range; 66% within a “clinically desirable” range of 80–139 mg/dl; and 93% within a “clinically acceptable” range of 80–199 mg/dl. Only 20 (0.3%) blood glucose values were <60 mg/dl, none of which resulted in clinically significant adverse events. In general, the IIP was readily accepted by our MICU nursing staff, most of whom rated the protocol as both clinically effective and easy to use.

CONCLUSIONS — Our nurse-implemented IIP is safe and effective in improving glycemic control in critically ill patients.

Diabetes Care 27:461–467, 2004
Efficacy of insulin infusion

Goldberg, Diabetes Care 2004; 27: 461
MICU nursing reaction

(anonymus survey)

Goldberg, Diabetes Care 2004; 27: 461
Cost effectiveness by insulin use

Laboratory  Pharmacy  Imaging  Total

p<0.001  p<0.099  p<0.003  p<0.001
Intensive Insulin Therapy in the Intensive Care Unit

Assessment by continuous glucose monitoring

CONCLUSIONS — GlucoDay, a well-tolerated 48-h CGM system, revealed that normoglycemia was only achieved 22% of the time in MICU patients. Further studies should investigate whether application of CGM to titrate insulin therapy can improve patient outcome.
Continuous glucose monitoring at ICU

Diabetes Care 2006;29:1750–1756
Acute stress induced by critical illness causes complex metabolic and hormonal disorders.

Maintenance blood glucose in critically ill patients (both diabetic and non-diabetic) improves survival and other outcomes.

Intravenous infusion has an advantage over subcutaneous injections.

Trained staff and precise protocol for dose titration is necessary.

Insulin application is cost effective.

Novel (and expensive) continuous glucose monitoring devices are similarly effective as standard methods.
... an unbiased opinion

is always absolutely valueless

Oscar Wilde „The Critic as Artist“ 1890