E. Vincent S. Faustino, MD, MHS; Associate Professor of Pediatrics; Yale School of Medicine

Hypoglycemia and the Pediatric Brain in Survivors of Tight Glucose Control – Flying Through the Danger Zone!

Disclosures
  o I have no commercial relationships to disclose.

Presentation Overview/Summary
  Hypoglycemia is common among children admitted to the pediatric ICU. Its prevalence is increased with the use of insulin. It is also associated with prolonged duration of mechanical ventilation and stay in the pediatric ICU, and probably mortality. Insulin-induced hypoglycemia is worrisome because of its potential effect on the developing brain. Short-term outcomes may be worse with insulin-induced hypoglycemia in children but not in adults. Studies of neurodevelopmental outcomes after tight glucose control in children have produced conflicting results. Worse outcomes were seen with hypoglycemia in children after repair of their congenital heart disease.

Learning Objectives
  At the conclusion of the presentation, the learner will be able to:
  1. Characterize the prevalence of hypoglycemia in children admitted to the pediatric ICU
  2. Describe the physiologic consequences of hypoglycemia in children admitted to the pediatric ICU
  3. Understand the long-term implications of hypoglycemia from tight glucose control on neurodevelopmental outcomes in pediatric ICU survivors

Key Takeaways/Fast Facts
  1. Hypoglycemia is common among children admitted to the pediatric ICU. Its prevalence is increased with the use of insulin.
  2. Hypoglycemia is associated with prolonged duration of mechanical ventilation and stay in the pediatric ICU, and probably mortality.
  3. Short-term outcomes may be worse with insulin-induced hypoglycemia in children but not in adults.
  4. Hypoglycemia is associated with worse neurodevelopmental outcomes in children after repair of their congenital heart disease.

Learning Assessment Questions
  1. Hypoglycemia increases the plasma level of which of the following hormones:
     A. Glucagon
     B. Epinephrine
     C. Insulin
     D. Growth hormone
  2. Which of the following statement/s is/are true regarding hypoglycemia in critically ill patients:
     A. Critically ill patients have impaired counter regulatory response to hypoglycemia
     B. Warning symptoms of hypoglycemia may be missed because of ongoing illness and interventions
     C. Hypoglycemia may be a side effect of certain drugs
     D. All of the above
  3. The primary energy source of the brain during prolonged fasting is:
     A. Ketone bodies
4. Which of the following statement/s is/are true?
   A. Insulin-induced hypoglycemia is associated with increased mortality in both children and adults.
   B. Tight glucose control is associated with increased risk of hypoglycemia in both children and adults.
   C. All of the above.
   D. None of the above.

5. Which of the following statement is false?
   A. Studies of neurodevelopmental outcomes after tight glucose control in children have produced conflicting results.
   B. Hypoglycemia is associated with worse neurodevelopmental outcomes in children after repair of their congenital heart disease.
   C. Insulin-induced hypoglycemia improves neurocognition.
   D. Using propensity score matched controls, tight glucose control-induced hypoglycemia was not associated with worse IQ in children.

**Learning Assessment Answers:**
1. Answer = C; Rationale: Plasma levels of insulin decreases during hypoglycemia.
2. Answer = D; Rationale: Critically ill patients are at risk of hypoglycemia and its consequences because of the factors listed.
3. Answer = A; Rationale: Ketone bodies are the brain’s primary energy source during prolonged fasting. Insulin prevents ketogenesis depriving the brain of its primary energy source.
4. Answer = B; Rationale: Meta-analyses of RCTs of tight glucose control showed increased risk of hypoglycemia in both children and adults. RCTs of tight glucose control in adults showed lower risk of mortality with insulin-induced vs. spontaneous hypoglycemia. RCTs of tight glucose control in children did not suggest any increase in mortality with hypoglycemia, in general, or with insulin-induced hypoglycemia.
5. Answer = C; Rationale: Although studies of neurodevelopmental outcomes after tight glucose control in children have produced conflicting results, none of the studies have shown that insulin-induced hypoglycemia improves neurocognition.

**References**
Learning Objectives

Upon completion of this session, the learner will be able to...

1. Characterize the prevalence of hypoglycemia in children admitted to the pediatric ICU
2. Describe the physiologic consequences of hypoglycemia in children admitted to the pediatric ICU
3. Understand the long-term implications of hypoglycemia from tight glucose control on neurodevelopmental outcomes in pediatric ICU survivors

Defining Hypoglycemia

- Concentration of glucose in the blood or plasma at which the individual demonstrates a unique response to the adequate delivery of glucose to a target organ (for example, the brain)
- Use of blood glucose measurement as surrogate for symptomatic neuroglycopenia

Cornblath M et al Pediatrics 2000
Hypoglycemia in Critically Ill Patients

- Impaired counter regulatory response
  - Insufficient gluconeogenesis like relative adrenal insufficiency
  - Impaired gluconeogenesis from renal or hepatic failure
- Missed warning symptoms of hypoglycemia
- Human error
- Side effect of certain drug use
- Probably mostly transient

Response to Hypoglycemia

- Impaired Response to Hypoglycemia with Insulin

Glucose Response to Hypoglycemia

Prevalence of Hypoglycemia in Children in the ICU

HALF-PINT Study

- Eligibility criteria
  - <18 years old
  - Admitted to the pediatric ICU
  - Cardiovascular and/or respiratory failure
  - Hyperglycemia (2 consecutive BG≥150 mg/dL)
- Study design
  - Lower (80-110 mg/dL) vs higher (150-180 mg/dL) group
  - Used intravenous insulin infusion
  - Exploit protocol that included
    - Provision of carbohydrates supply
    - Computerized algorithm to dose insulin
    - CGM
Incidence of Hypoglycemia Using CGM

- 112/698 (16.0%) developed hypoglycemia
  - 79/349 (22.6%) in lower group
  - 33/349 (9.5%) in higher group
- 25/698 (3.6%) developed severe hypoglycemia
- Median time to first hypoglycemia
  - 3 days (IQR: 2-5 days)
- Median duration of hypoglycemia using CGM
  - 85 min (IQR: 35-185 min)

Faustino EV et al Crit Care Med 2019

Incidence of Insulin-Induced Hypoglycemia in Children

- 25% in treatment vs. 1% in conventional (P<0.001)
- Unadjusted OR of mortality
  - 1.7 (95% CI: 0.7-4.4; P=0.23)
- Adjusted for duration of ICU stay
  - 1.2 (95% CI: 0.4-3.3; P=0.66)
- Adjusted for other baseline risk factors
  - 1.7 (95% CI: 0.3-8.1; P=0.52)

Vlasselaers D et al Lancet 2009

Adverse Events from Hypoglycemia in Children

- Observational studies
  - Prolonged duration of mechanical ventilation
  - Prolonged duration of stay in the pediatric ICU
- Pediatric RCTs of tight glycemic control
  - Increased with insulin
  - Increased mortality

Faustino EV et al Crit Care Med 2019

Spontaneous Hypoglycemia and Mortality in Children

<table>
<thead>
<tr>
<th>Method</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griesdale et al.</td>
<td>1.7 (0.7-4.4)</td>
</tr>
<tr>
<td>Chen L et al.</td>
<td>1.2 (0.4-3.3)</td>
</tr>
</tbody>
</table>

Faustino EV and Bogue CW Pediatr Crit Care Med 2010
### Outcomes According to Hypoglycemia Status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hypoglycemia (n = 110)</th>
<th>No Hypoglycemia (n = 427)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU-free days through Day 28</td>
<td>15.3 (0–22.3)</td>
<td>20.2 (5.3–24.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Assigned zero ICU-free days, n (%)</td>
<td>33 (30)</td>
<td>96 (22)</td>
<td>0.46</td>
</tr>
<tr>
<td>Ventilator-free days through Day 28</td>
<td>17.9 (0–23.4)</td>
<td>21.1 (10.2–24.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Assigned zero ventilator-free days, n (%)</td>
<td>33 (30)</td>
<td>96 (22)</td>
<td>0.46</td>
</tr>
<tr>
<td>28-day hospital mortality, n (%)</td>
<td>17 (15)</td>
<td>54 (13)</td>
<td>0.01</td>
</tr>
<tr>
<td>90-day hospital mortality, n (%)</td>
<td>28 (10)</td>
<td>50 (12)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Faustino EV et al Crit Care Med 2019

### Outcomes According to Exposure to Insulin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Insulin-Induced Hypoglycemia (n = 67)</th>
<th>No Insulin-Induced Hypoglycemia (n = 43)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU-free days through Day 28</td>
<td>15.0 (0–23.4)</td>
<td>14.6 (0–21.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Assigned zero ICU-free days, n (%)</td>
<td>24 (36)</td>
<td>9 (21)</td>
<td>0.008</td>
</tr>
<tr>
<td>Ventilator-free days through Day 28</td>
<td>18.0 (0–23.4)</td>
<td>16.6 (0–22.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Assigned zero ventilator-free days, n (%)</td>
<td>24 (36)</td>
<td>9 (21)</td>
<td>0.008</td>
</tr>
<tr>
<td>28-day hospital mortality, n (%)</td>
<td>7 (10)</td>
<td>4 (9)</td>
<td>0.60</td>
</tr>
<tr>
<td>90-day hospital mortality, n (%)</td>
<td>11 (16)</td>
<td>6 (14)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Faustino EV et al Crit Care Med 2019

### Spontaneous vs. Insulin-Induced Hypoglycemia and Mortality in Adults

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Deaths</th>
<th>Population</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-hypoglycemia</td>
<td>7/22</td>
<td>32/186</td>
<td>1.000</td>
<td>0.007</td>
</tr>
<tr>
<td>Moderate hypoglycemia</td>
<td>1/16</td>
<td>7/178</td>
<td>1.22 (0.40–3.44)</td>
<td>0.74</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>1/16</td>
<td>7/178</td>
<td>1.68 (0.62–4.62)</td>
<td>0.28</td>
</tr>
</tbody>
</table>


### Spontaneous vs. Insulin-Induced Hypoglycemia and Mortality in Adults

Kosiborod M et al JAMA 2009

### Insulin-Induced Hypoglycemia and Neurocognition in Children

Mesotten D et al JAMA 2012

### Hypoglycemia and Neurocognition with Congenital Heart Disease

Sadhwani A et al J Pediatr 2016
Key Takeaways

- Hypoglycemia is common among children admitted to the pediatric ICU. Its prevalence is increased with the use of insulin.
- Hypoglycemia is associated with prolonged duration of mechanical ventilation and stay in the pediatric ICU, and probably mortality.
- Short-term outcomes may be worse with insulin-induced hypoglycemia in children but not in adults.
- Hypoglycemia is associated with worse neurodevelopmental outcomes in children after repair of their congenital heart disease.

Learning Assessment Question 1

Hypoglycemia increases the plasma level of which of the following hormones:

A. Glucagon
B. Epinephrine
C. Insulin
D. Growth hormone

Learning Assessment Question 2

Which of the following statement/s is/are true regarding hypoglycemia in critically ill patients:

A. Critically ill patients have impaired counter regulatory response to hypoglycemia
B. Warning symptoms of hypoglycemia may be missed because of ongoing illness and interventions
C. Hypoglycemia may be a side effect of certain drugs
D. All of the above

Learning Assessment Question 3

The primary energy source of the brain during prolonged fasting is:

A. Ketone bodies
B. Glucose
C. Glycogen
D. Triglycerides
Learning Assessment Question 4

Which of the following statement/s is/are true?
A. Insulin-induced hypoglycemia is associated with increased mortality in both children and adults.
B. Tight glucose control is associated with increased risk of hypoglycemia in both children and adults.
C. All of the above.
D. None of the above.

Learning Assessment Question 5

Which of the following statement is false?
A. Studies of neurodevelopmental outcomes after tight glucose control in children have produced conflicting results.
B. Hypoglycemia is associated with worse neurodevelopmental outcomes in children after repair of their congenital heart disease.
C. Insulin-induced hypoglycemia improves neurocognition.
D. Using propensity score matched controls, tight glucose control-induced hypoglycemia was not associated with worse IQ in children.

Key References

Presentation Title
Tight Glucose Control in Critically Ill Children – A Bitter Sweet Pill to Swallow!

Disclosures
- “I have no commercial relationships to disclose”

Presentation Overview/Summary
- Tight glucose control (TGC) emerged in the 2000s as an exciting therapy to improve outcomes in critically ill adults and children. While the first study in critically ill children demonstrated benefits from TGC, subsequent studies have failed to replicate the benefits of TGC in this population. This presentation will describe the science of TGC in critically ill children and highlight methodological differences between studies. Using the historical arc of TGC in critical illness, this presentation will evaluate the need for reproducibility of results in clinical trials before adopting widespread practice change.

Learning Objectives
At the conclusion of the presentation, the learner will be able to:
1. Discuss key studies of tight glucose control (TGC) in critically ill children
2. Evaluate methodological differences in studies of TGC in critically ill children
3. Determine the need for reproducibility of results from clinical trials before adopting widespread practice change

Key Takeaways/Fast Facts
- Pediatric studies of TGC in critically ill children have covered diverse ICU populations
- No benefit but possible harm from TGC in multi-center studies of cardiac surgery, non-cardiac surgery and mixed ICU populations
- Benefit of TGC seen in only one early single-center study and in pediatric burns population

Learning Assessment Questions
1. Question 1: Recombinant growth hormone therapy (compared to placebo) increased ICU mortality in critically ill adults.
   - A. True
   - B. False

2. Question 2: Intensive insulin therapy results in changes in the somatotropic axis characterized by:
   - A. Increase in blood glucose levels
   - B. Increase in growth hormone levels
   - C. Increase in IGF-1 levels
   - D. Increase in IGFBP-3 levels

3. Question 3: Tight glucose control with intensive insulin therapy in post-cardiac surgery critically ill children is superior to standard care
   - A. True
   - B. False
4. Question 4: Intensive insulin therapy in children with severe burns is associated with improved post-burn morbidity.
   A. True
   B. False

5. Question 5: Which of the following is correct about the HALF-PINT study of tight glucose control in critically ill children?
   A. The study enrolled cardiac surgical and non-cardiac surgical critically ill children
   B. The study emphasized the use of early parenteral nutrition
   C. The study employed several measures to minimize hypoglycemia
   D. The study observed benefits from tight glucose control to 80-110 mg/dL

Learning Assessment Answers:
1. Answer = True; Rationale: Recombinant growth hormone therapy (compared to placebo) resulted in elevated IGF-1, IGFBP-3 and IGFBP-1 levels with altered immune modulation, altered glutamine mobilization and development of hyperglycemia with insulin resistance contributing to more sepsis and multiple organ dysfunction in critically ill adults.
2. Answer = B; Rationale: Intensive insulin therapy results in changes characterized by acquired growth hormone resistance with increase in growth hormone levels. In contrast, IGF-1 and IGFBP-3 levels remain low. Blood glucose levels are lowered by intensive insulin therapy
3. Answer = False; Rationale: While the first single center study of predominantly cardiac surgery children favored tight glucose control, subsequent larger multi-center studies have not shown that tight glucose control with intensive insulin therapy is superior to standard care in post cardiac surgery critically ill children.
4. Answer = True; Rationale: In children with severe burns, intensive insulin therapy is associated with decrease in infections and sepsis, improved organ function, decrease in insulin resistance and catabolic response, dampened inflammatory and acute phase response, and trend towards lower mortality.
5. Answer = C; Rationale: While the HALF-PINT study employed several measures to minimize hypoglycemia, the study did not enroll cardiac surgical children, or emphasize the use of early parenteral nutrition, or observe benefits from tight glucose control to 80-110 mg/dL.

References