Dear Colleague:

We invite you to participate in a survey on the use of insulin for glycemic control of critically ill patients in the intensive care unit. With the controversy and questions of safety arising from recent randomized control trials, we suspect that different doctors may have different approaches to glycemic control in the intensive care unit.

Much thanks for your time and help,

Medicine Department of Medicine
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Lecture Content

- Definitions
- “Old” School of Thought
- New Theories
- Current Practice
- Causes of Stress-Induced Hyperglycemia
- Multi-system Effects of Hyperglycemia
- Effects of Insulin in Critical Illness
- Literature on Tight Glucose Control/Hypoglycemia in Adults
- Pediatric Studies on Glycemia and Outcomes
- Unpublished data

Definitions

- Hyperglycemia: glucose elevation above normal parameters
  - Caused by relative lack of insulin
  - Insulin resistance

- Normal plasma glucose levels:
  - University Hospital: 60-100 mg/dL
  - Christus Santa Rosa Children’s Hospital: 60-100 mg/dL.

- ADA definitions of diabetes
  - Fasting plasma glucose >125 mg/dL.
  - OGTT: 2 hr plasma glucose ≥200 mg/dL.

“Old” School of Thought

- Hyperglycemia in the face of illness…a natural stress response important for providing nutritional substrate to vital organs.

- Tampering with this natural rise in glucose was considered detrimental especially in the pediatric population given the risk of hypoglycemia w/ insulin treatment.

New Theories Emerging

- Adult studies have shown decreased mortality associated with tight glucose control in critically ill patients.

- Pediatric studies have shown an association between hyperglycemia and mortality. But, concerns regarding the methods of controlling for severity of illness have been raised.

- Are the protective effects seen in adult patients being treated with intensive insulin therapy due to non-glycemic insulin effects and not glucose control?
Current Practice in the PICU

- Treatment w/ insulin common only once renal threshold for glucose resorption is exceeded (200-250 mg/dL)...preventing osmotic diuresis
- Most pediatric intensivists treat hyperglycemia in critically ill children.
  - Significantly less stringent parameters as followed by our adult counterparts.

Causes of Hyperglycemia in Critical Illness (Stress-induced hyperglycemia)

- Excessive counter-regulatory hormones
  - Glucagon
  - Growth Hormone
  - Catecholamines
  - Glucocorticoids
- High circulating levels of cytokines (TNF-alpha, IL-1/IL-6)
- Leads to:
  - Failure of insulin to suppress hepatic gluconeogenesis
  - Insulin resistance/ decreased skeletal-muscle glucose uptake

Multi-system Effects of Hyperglycemia

- Neurologic effects
- Cardiovascular effects
- Electrolyte imbalance
- Fluid status
- Immunological deficiency
- Oxidative stress
- Nutrition

Neurologic Effects

- Increased cerebral ischemia and edema
- Disruption of the blood-brain barrier
- Increased mortality after neurological insult
- More likely to suffer severe disability after an acute CVA
- Critical-Illness Polyneuropathy

Cardiovascular effects

- Nitric oxide-mediated myocyte damage
- Myocardial apoptosis
- Increased systemic vascular resistance
- Decreased CO, cardiac index, and stroke volume
- Increased risk of CHF
- More likely to require CABG
- Increased risk of cardiogenic shock
- Increased mortality post-AMI

Electrolyte imbalance

- Lactic acidosis due to poor tissue perfusion
Fluid status

- Osmotic diuresis w/ glucose > 200 mg/dL can lead to dehydration, poor perfusion, and augment acidosis

Immunologic effects

- Decreased immune function
- Pro-inflammatory effects
- Impaired macrophage and neutrophil function
  - Leukocyte chemotaxis
  - Opsonization
  - Phagocytosis

Immunologic effects

- Impaired cell-mediated immune response
- Decreased tissue perfusion leading to increased risk of infection
  - Wound infections
  - Sepsis associated with central line infections

Nutritional Abnormalities

- Dysregulation of lipid homeostasis
  - Increased triglycerides
  - Increased VLDL
  - Decreased LDL and HDL

Oxidative stress…Cellular Damage

- Hyperglycemia
  - Polyol Pathway
  - Advanced Glycation Pathway
  - Receptor Oxygen Pathway
  - Protein Kinase C Pathway
  - Activation Of Cell Signaling Molecules
  - Altered Gene Expression and Protein Function
  - Cellular Dysfunction and Damage

Systemic Effects of Insulin in Critical Illness (Attenuation of the Catabolic State of Critical Illness)

- Modulate inflammation via:
  - Mannose binding lecithin pathway
  - Nuclear factor-κB
  - Alteration in proinflammatory and anti-inflammatory cytokines
- Regulate apoptosis
- Prevent endothelial dysfunction
- Decrease neutrophil chemotaxis and leukocyte adhesion
- Prevents excessive NO
Adult Literature Promoting Tight Glucose Control With Intensive Insulin Therapy (IIT)

- Van den Berghe et al. 2001. NEJM. Intensive Insulin Therapy in Critically Ill Patients.
- Van den Berghe et al. 2006. NEJM. Intensive Insulin Therapy in the Medical ICU.

Insulin Therapy in Surgical/Medical Patients: Study Design

- Prospective, randomized, control study of 1548 adult pts admitted to ICU receiving mechanical ventilation
  - Treatment group: intensive insulin therapy maintaining blood glucose 80-110 mg/dL
  - Control group: conventional insulin treatment maintaining glucose 180-200 mg/dL

Van den Berghe et al. 2001. NEJM. Intensive Insulin Therapy in Critically Ill Patients.

Insulin Therapy in Surgical/Medical Patients: Results

- Mortality rate from 8% to 4.6% in primary group (32% risk reduction)
- Mortality rate in pts w/ ICU stay >5 days: 20.2% to 10.6% (48% risk reduction)
- IIT group had decreased morbidity:
  - LOSICU
  - LOMV
  - Renal Replacement Therapy
  - Sepsis
  - Inflammatory markers
  - Critical illness polyneuropathy

Insulin Therapy in Medical Patients: Study Design

- Prospective randomized control trial of 1200 non-surgical patients admitted to ICU. Patients randomized to receive:
  - Intensive insulin therapy: maintaining blood glucose 80-110 mg/dL
  - Conventional insulin treatment: maintaining glucose 180-200 mg/dL

Van den Berghe et al. 2006. NEJM. Intensive Insulin Therapy in the Medical ICU.

Insulin Therapy in Medical Patients: Study Design

- Primary Outcome: In-Hospital Death

- Secondary Outcomes:
  - ICU and 90 day mortality
  - Duration of mechanical ventilation
  - ICU and hospital LOS
  - Acute Kidney Injury (creatinine doubling or peak Cr > 2.5 mg/dL)
  - Initiation of dialysis
  - Days of inotropic or vasopressor support
  - Hyperinflammation (CRP >150 mg/dL)
  - Bacteremia
  - Antibiotics > 10 days
  - Hyperbilirubinemia
Insulin Therapy in Medical Patients: Results

- No difference in mortality in primary group (negative study)
- In-hospital mortality rate: 52% to 43% in pts w/ IIT and ICU stay ≥ 3 days (17% risk reduction)
- Increased mortality in pts w/ IIT and ICU stay < 3 days
- Decreased morbidity in primary group ≥ 3 days ICU stay:
  - New AKI
  - LOMV
  - LOSICU/Hosp
  - Hyperbilirubinemia

Intensive vs. Conventional Glucose Control in Critically Ill Patients: Study Design

- Prospective, RCT of 6104 medical/surgical patients from 42 hospitals
- Patients randomized to receive:
  - Intensive Insulin Therapy: Goal glucose 81-108 mg/dL
  - Conventional Therapy: Glucose goal 144-180 mg/dL


Intensive vs. Conventional Glucose Control in Critically Ill Patients: Results

- Decreased 90-day mortality in conventional group (24.9% vs 27.5%; 9.3% risk reduction)
- No difference in LOSICU or hosp
- No difference in LOMV
- No difference in need for CRRT


Hypoglycemia and Risk of Mortality

Conclusions!

• Even in the adult population, we have not confirmed the optimal level of glycemia to impart the best patient outcomes.

• The evidence relating to hypoglycemia and risk of mortality is also varied.

• However, tight glucose control due to intensive insulin therapy does impart increased risk of hypoglycemia.

How about the kids...

• Children are definitely not little adults… despite what they sometimes think!

• We cannot presume that hyperglycemia in children, as in adults, is a negative prognostic indicator…leading to increased morbidity/mortality in the intensive care setting.

• Children differ significantly from adults in many physiologic processes as well as the prevalence of underlying disease. Thus, their response to hyperglycemia may also differ.

Pediatric Retrospective Studies

• In the last 10 years, there have been relatively few pediatric studies evaluating the association between hyperglycemia and mortality in different critically ill patient populations:
  – Head trauma
  – Neonates with NEC
  – Post-op cardiac patients
  – Medical/Surgical patients (3)

Hyperglycemia in Head Trauma

• 50 children
  – 29 w/ isolated head injury
  – 21 w/ multi-organ trauma

• Hyperglycemia > 150 mg/dL associated with lower GCS @ presentation and with poor outcomes

• Sustained hyperglycemia (>24 hrs) was present in all patients who died or who survived w/ poor outcome


Hyperglycemia in Neonates with NEC

• Peak glucose level >215 mg/dL associated w/ mortality and increased LOS in neonates w/ necrotizing enterocolitis.

Hyperglycemia in Post-op Cardiac Patients: Study Design

- 184 pts, < 1 yr of age: cardiac by-pass surgery
- Excluded pts:
  - <2 kg
  - Pre-op ECMO pts
  - Transplant recipients
  - Pts w/ pre-op renal (Cr >1.5 mg/dL) or liver insufficiency (AST or ALT >250 units/dL)

Yates, et al. Pediatric Critical Care Medicine. 2006. Hyperglycemia is a Marker for Poor Outcome in the Postoperative Pediatric Cardiac Patients

Hyperglycemia in Post-op Cardiac Patients: Results

- Peak glucose was significantly higher in non-survivors vs survivors (255 vs 179 mg/dL)
- Duration of hyperglycemia +/- peak glucose was significantly associated with:
  - development of liver and renal insufficiency
  - need for dialysis
  - increased risk of bacterial infection
  - CNS events
  - need for ECMO support

Yates, et al. Pediatric Critical Care Medicine. 2006. Hyperglycemia is a Marker for Poor Outcome in the Postoperative Pediatric Cardiac Patients

More Permissive Hyperglycemia Range in Surgical Cardiac Patients: Study Design

- Retrospective study of 177 post-operative congenital heart patients
- Stratification: (median glucose levels)
  - Euglycemia: 60-125 mg/dL
  - Mild Hyperglycemia: 126-139 mg/dL
  - Moderate Hyperglycemia: 140-179 mg/dL
  - Severe Hyperglycemia: >180mg/dL
- Permissive hyperglycemia group: 90-140 mg/dL


More Permissive Hyperglycemia Range in Surgical Cardiac Patients: Results

- Mortality rates were higher in the moderate (38%) and severe hyperglycemia (58%) groups compared to the euglycemic (6%) and the permissive target (4.6%) groups.
- Nonsurvivors:
  - Higher peak glucose levels (389 +/- 162 mg/dL vs 274 +/- 106 mg/dL)
  - Longer duration of hyperglycemia (3.06 +/- 1.67 days vs 2.11 +/- 0.92 days)


Hyperglycemia in Medical/Surgical Patients: Study Design

- 152 patients on mechanical ventilation and/or vasoactive infusions >24 hrs (excluding post-op cardiac and organ transplant patients
- Evaluate associations between risk of mortality with:
  - Peak blood glucose
  - Time to peak blood glucose
  - Duration of hyperglycemia >126 mg/dL
  - Median blood glucose in first 48 hrs (intensity of hyperglycemia)

Srinivasan et al. PCCM. 2004
Association of Timing, Duration, and Intensity of Hyperglycemia with Intensive Care Unit Mortality in Critically Ill Children
Hyperglycemia in Medical/Surgical Patients: Results

- Glucose >150 mg/dL @ 24 hrs associated with 3.5 fold increase in mortality
- Duration of hyperglycemia correlated with increased mortality
  - Non-survivors: 71 ± 14% of days
  - Survivors: 37 ± 5% of days
  - 6 fold increase in risk of death in pts w/ hyperglycemia > 50% of PICU stay

Srinivasan et al. PCCM. 2004
Association of Timing, Duration, and Intensity of Hyperglycemia with Intensive Care Unit Mortality in Critically Ill Children

- 6 fold increase in risk of death in pts w/ hyperglycemia > 50% of PICU stay


Hyperglycemia in Medical/Surgical Patients: Study Design

- 942 non-diabetic patients
- Assessed relationship between hyperglycemia (>120/>150/>200mg/dL) and mortality/LOS:
  - Initial glucose
  - Peak glucose in first 24 hrs
  - Peak glucose PICU stay


Hyperglycemia in Medical/Surgical Patients: Results

- Degree of peak glucose and peak in 24 hrs were both associated with an escalating increase in mortality and LOS
- Initial glucose did not significantly correlate with increased mortality or LOS.


Hyperglycemia in Medical/Surgical Patients: Study Design

- 1094 non-diabetic patients
- Identify associations between mortality/LOS and
  - Hypoglycemia
  - Degree of hyperglycemia (quintiles)
  - Glucose variability


Hyperglycemia in Medical/Surgical Patients: Results

- Increase mortality and LOS:
  - Glucose variability
  - Glucose <65 mg/dL
  - Increasing maximal glucose levels >150 mg/dL


Pediatric Prospective Studies


Hyperglycemia Associated w/ Septic Shock: Study Design

- 47 medical/10 surgical pts in Porto Alegre, Brazil diagnosed w/ septic shock refractory to fluid therapy and supported w/ mechanical ventilation and vasoactive infusions
- Excluded pts w/ DNR, DM, hepatic/renal failure, post-op cardiac pts and those having received a high glucose infusion
- Monitored initial and daily glucose measurements


Hyperglycemia Associated w/ Septic Shock: Results

- In children w/ septic shock, peak glucose levels of >178 mg/dL were associated with a 2.59-fold increased risk of death.


Intensive Insulin Therapy in Medical Pediatric Patients: Study Design

- 700 critically ill children (0-16 yrs) 75% were post-op cardiac patients
- Treatment group: intensive insulin therapy maintaining blood glucose:
  - Infants < 1yr: 50-80 mg/dL (317 patients)
  - Children: 70-100 mg/dL (383 patients)
- Control group: conventional insulin treatment maintaining glucose 180-214 mg/dL.

Vlasselaers, D. et al. The Lancet. 2009. Intensive Insulin Therapy for Patients in Paediatric Intensive Care: A Prospective, Randomised Controlled Study

Intensive Insulin Therapy in Medical Pediatric Patients: Results

- IIT group had:
  - Decreased LOSPICU
  - Decreased duration of vasoactive support
  - Decreased hyperinflammatory response (CRP)
  - Decreased number of secondary infections
  - Decreased mortality (5.7% vs 2.6%; 54% risk reduction)
  - No change in LOMV
  - Increased risk of profound hypoglycemia but w/o affecting mortality


What we know from the current studies in the pediatric population?

- As in adults, children have no common set point for hyperglycemia that can be confidently associated with increased risk of death.
- There seems to be a trend in pediatric data that suggests an association between hyperglycemia and mortality.
- Two prospective studies in the pediatric literature.
- Other ongoing prospective studies needed
Hyperglycemia...Cause and Effect?

- Is degree of hyperglycemia merely a reflection of more severe illness and increased risk of death?
- If one can adequately control for severity of illness, will hyperglycemia still correlate with increased risk of death?
- If hyperglycemia can be proven as an independent factor leading to increased morbidity and/or mortality, then it would be imperative to change current protocol to promote tight glucose control in all critically ill patients.

New Unpublished Study


- Historical cohort study of 2943 critically ill (mechanically ventilated or requiring CV support) patients
- Goal:
  - Evaluate the independent associations between glycemia and mortality and morbidity
  - Control for severity of illness

Study population

- 2943 patients
- 58% Mechanical Ventilation
- 37% Cardiovascular Support
- 5% MV + CS

Excluded Patients with DM or DKA

Data Collection

- Division of Critical Care Quality Control Database
  - Demographics
  - Confounding variables (severity of illness)
  - Diagnoses that impart increased mortality
  - Nosocomial infections (morbidity assessment)
  - CRRT/hemodialysis (morbidity assessment)

- Electronic Medical Records from participating hospitals
  - Glucose measurements
  - Admission and peak creatinine

Glycemic variables

- Definition:
  - Hyperglycemia: Glucose >125 mg/dL
  - Profound hypoglycemia: Glucose <40 mg/dL
- Peak Glucose 24 hrs
- Peak Glucose Stay
- Glucose Avg
- % Days Hyperglycemia Stay
Statistical Analysis

• Assessed for independent associations between glycemia
  – Mortality (Primary outcome): Cox regression survival analysis
  – Indicators of Morbidity: Multivariate logistic regression analysis
  – Length of Stay: Linear regression analysis

Study Results/Conclusions

• Duration of hyperglycemia >125 mg/dL is an independent risk factor for mortality.
• Peak glucose in the first 24 hrs as well as peak glucose and average glucose in the first 30 days of PICU stay are not independently associated with mortality when duration is considered.
• Hypoglycemia <40 mg/dL is not associated an independent risk factor for mortality.

Study Conclusions

• Development of acute kidney injury was not found to be associated with hyperglycemia >125 mg/dL.
• Average glucose and proportion of PICU stay with hyperglycemia >125 mg/dL were both associated with decreased length of stay, likely due to increased risk of death.
• Development of nosocomial bacteremia was the only infectious complication with strong statistical significance in its association with glycemia.

Summary

• Pediatric retrospective studies concur that hyperglycemia is associated with adverse outcomes.
• Additional multicenter, prospective pediatric studies will need to confirm improved outcomes of IIT before it is widely accepted. Currently, the benefit is not felt to outweigh the risk for our patients.

Summary

• Stress-induced hyperglycemia and its causes
• Multi-systemic effects of hyperglycemia
• Adult studies: association between hyperglycemia and improved outcomes. Mechanism still unclear. (insulin vs glycemic control)
• New adult study raising concerns that intensive glycemic control of 80-110 mg/dL imparts increased mortality

References

4) Association of Timing, Duration, and Intensity of Hyperglycemia with Intensive Care Unit Mortality in Critically Ill Children. Sriravasan et al. PCCM. 2004
References


Thank You!

• Questions?
• Comments?