Should Insulin be added to Parenteral Nutrition?

Jay M Mirtallo
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Insulin Indications for PN

- Manage hyperglycemia
- Protein accretion (anabolism)
- Anti-inflammatory activity
Insulin in PN: Outline

- Indication: Manage Hyperglycemia
  - Frequency of hyperglycemia in PN patients
  - Association of adverse outcomes with hyperglycemia in PN patients
  - Variables associated with poor glucose control in PN patients
  - Issues with insulin in PN
    - Criteria for adding medications to PN
# PN: Frequency of Hyperglycemia

<table>
<thead>
<tr>
<th>Reference</th>
<th>Criteria</th>
<th>N (%)</th>
<th>Comment</th>
<th>NSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dodds et al. NCP 2001</td>
<td>@ least 1 value &gt; 200 mg/dl</td>
<td>762 (28)</td>
<td>Only 2 pts developed symptoms complication</td>
<td>Yes</td>
</tr>
<tr>
<td>Weinsier et al. JPEN 1982</td>
<td>&gt; 300 mg/dl after at least 48 hrs of PN</td>
<td>47 (47)</td>
<td>No symptoms observed</td>
<td>Yes but not used, guidelines, flow sheets, order sets in place</td>
</tr>
<tr>
<td>ChrisAnderson et al J PEN 1996</td>
<td>As per Weinsier</td>
<td>23 (22)</td>
<td>No effect of NSS in prospective trial</td>
<td>Yes, consult with recommendations only(64% compliance), substantial staff education</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Non NSS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- NSS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Use of 3 in 1 (TNA)</td>
<td></td>
</tr>
<tr>
<td>Rosmarin et al, NCP 1995</td>
<td>&gt; 200 mg/dl</td>
<td>0 (0)</td>
<td>- Dext infusion &lt; 4</td>
<td>Yes, dextrose based diet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 (7)</td>
<td>- Dext infusion 4-5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>18 (43)</td>
<td>- Dext infusion &gt;5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No risk factors present</td>
<td></td>
</tr>
<tr>
<td>Pleva et al, NCP 2009</td>
<td>&gt;200 mg/dl</td>
<td>22 (44)</td>
<td>Resulted in 1.4 events per patient course</td>
<td>Yes, pharmacist management</td>
</tr>
<tr>
<td></td>
<td>&gt;150 mg/dl</td>
<td>45 (90)</td>
<td>Risk factors: diab, pancreatitis, Steroids</td>
<td></td>
</tr>
</tbody>
</table>

*Same institution*
PN and Hyperglycemia: Adverse Outcomes

- Relation between blood glucose levels and outcomes
  - Myocardial infarction
  - Stroke
  - Cardiothoracic surgery
  - Critical illness
  - General hospitalized patients

Cheung NW et al Diabetes Care 2005; 28: 2367-2371
PN and Hyperglycemia: Adverse Outcomes

- Risk of any complication 1.58 (p < 0.01)
  - Infection
  - Septicemia
  - Acute renal failure
  - Cardiac complications
  - Death

- Quartile analysis
  - Risk level increased at high quartile vs low quartile group
    - OR of 4.3 for complication, 10.9 for death

Cheung NW et al Diabetes Care 2005; 28: 2367-2371
Severity of Hyperglycemia

- Stronger predictor of adverse outcomes than history of diabetes
  - Majority of PN patients who become hyperglycemic are not diabetic
    - Excluded from Rosmarin study
    - 12% of Pleva study population
    - 27% of Wah Cheung study population

- Evidence that hyperglycemia in itself is harmful.

Cheung NW et al Diabetes Care 2005; 28: 2367-2371
Quartile Values for Patient Population

Blood glucose, mg/dl

Mirtallo PN

Pleva et al Nutr Clin Pract 2009; 24:626-634
Variables Associated with PN Hyperglycemia

- Caloric dose
  - Type of calorie provided
  - ‘Hidden’ Sources of CHO
- Target glucose range
  - Impact of controlling glucose to this range
- Responsibility for glucose management
- Use of sliding scale insulin
- FEAR of hypoglycemia
Variables Associated with PN Hyperglycemia

- No one method known to be effective in achieving target glucose
- Lack of consensus for insulin use
  - Long-acting insulin
  - Sliding scale insulin
  - Insulin drip
  - Insulin in PN
  - Any combination of the above
- Practice varies widely among patient populations, disciplines and individual clinicians
- Overall, management of hyperglycemia is most important
  - Interdisciplinary nutrition care
  - Experience and skill of staff managing PN
  - View as a process
Insulin in PN

- Criteria for medications added to PN
  - Stable and compatible
  - Evidence supports clinical value of medication administered in PN
    - Frequency of dosage adjustment no more than every 24 hours
  - Insulin is associated with frequent harmful events in PN

Mirtallo et al. JPEN 28 (suppl) S39-S70, 2004
# Management of Hyperglycemia: Alternative to Insulin-Hypocaloric PN

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</tr>
</thead>
<tbody>
<tr>
<td>Choban PS et al Am J Clin Nutr 1997</td>
<td>Hypocaloric 75 Cal:g nitrogen Normal 150 Cal: g nitrogen 2 g Pro/kg IBW/d</td>
<td>Obese patients 12 pts received insulin (11/12 diabetic) Less insulin days in NIDDM hypocaloric group</td>
</tr>
<tr>
<td>McCowen KC et al Crit Care Med 2000</td>
<td>Study: 1000 kcal, 70 g pro Control: 25 kcal/kg, 1.5 g/kg pro</td>
<td>No difference in □ Frequency of hyperglycemia – non diabetics □ insulin use □ Average glucose □ worse nitrogen balance in hypocaloric group</td>
</tr>
<tr>
<td>Ahrens CL et al Crit Care Med 2005</td>
<td>Low Cal: 20 NPC/kg/d Standard Cal: 30 NPC/kg/d</td>
<td>□ Excluded underweight/morbid obese □ Used sliding scale insulin □ Insulin in PN if &gt;50% values &gt; 200 □ Fewer hyperglycemic events and lower severity □ Mean glucose lower (118 vs 172)</td>
</tr>
</tbody>
</table>
Insulin Availability from PN

- Range: 10-95%
  - Composition of PN
    - Lipids, trace elements, vitamins
  - Final concentration of insulin
  - Assay for insulin
  - Laboratory simulation of clinical practice

- Adequate monitoring of patient clinical response

Seres DS; NCP 1990;5: 111-116
Evidence Supporting Insulin Use Diabetic Patients

- Pre hospital insulin dose
- Reduced daily dextrose dose to start
  - 100 g – Type 1
  - 150 g – Type 2
- Accept modest hyperglycemia to avoid hypoglycemia
  - Sliding scale insulin: glucose > 250
- Mean glucose around 200 mg/dl
  - No hypoglycemic episodes
- Insulin in PN
  - Significant calories from enteral nutrition or tube feeding
    - Insulin separate from PN
- Source of dextrose determines route of insulin
  - Dialysis

Hongsermeier T et al. JPEN 17:16-19, 1993
Evidence Supporting Insulin Use:
Insulin protocol

- NSS: primarily pharmacist
- Capillary Blood glucose (CBG) every 6 hrs
  - Criteria: glucose > 140 mg/dl
- Insulin dose per g Carbohydrate (CHO)
  - PN induced hyperglycemia
    - 1 U/20 g CHO
  - Diabetes/glucocorticoids
    - CBG < 11.1 mmol/L (200 mg/dl)
      - 1 U/10 g CHO + 0.15 U/kg/d
    - CBC > 11.1 mmol/L
      - 1 U/5 g CHO + 0.25 U/kg/d
  - 2/3 insulin dose in PN, 1/3 separate as long-acting insulin

Jakoby MG et al. JPEN @
http://pen.sagepub.com/content/early/2011/08/06/0148607111415628
Evidence Supporting Insulin Use: Insulin protocol

- Mean CBG < in protocol group by 21 mg/dl
  - Higher CBG in diabetic group but better control with protocol

- Hypoglycemia (CBG < 80)
  - more frequent in protocol group (3 vs 1%)
  - No episodes of severe hypoglycemia (CBG < 40)

Jakoby MG et al. JPEN @ http://pen.sagepub.com/content/early/2011/08/06/0148607111415628
Evidence Supporting Insulin Use: Computer-assisted, Critically Ill

- Nurse centered computerized decision support for insulin administration
  - “step-up” rule
    - Graded increases in amount of PN administered
    - For glucose < 10 mmol/L (180 mg/dl)
  - End-point: achieve full PN at 24 hours along with glucose control during introduction period
    - Goal: 25 kcal/kg/d, max = 2500 kcal
- Use of insulin drip
- Desired caloric intake achieved within 24 hr
- Glucose levels
  - 6.6 (119 mg/dl) to 7.6 (137 mg/dl) mmol/L (ave – 7.4 (133))
  - Insulin drip rate of 1.1-2.0 U/h

Hoekstra M et al. JPEN 34: 549-553. 2010
Should Insulin be Added to PN?
It depends

- Critically ill: separate insulin infusion (drip)
- Significant calories from enteral or tube feeding: separate insulin as sliding scale or long-acting
  - Minimize ‘Hidden’ sources of glucose
- Others: definitely use insulin in PN
  - Evidence that better than using sliding scale insulin
  - Reasonable glucose control with minimal hypoglycemia
  - Consider insulin dose per gram of carbohydrate in PN
    - Adjust dose daily with sliding scale insulin
      - 2/3 previous days insulin dose
Systems Issues

- Establish target glucose
  - Interdisciplinary involvement
- Assign responsibility for glucose control
- Provide algorithm or protocol to follow
  - Evaluate success in achieving target glucose values
Insulin use in PN should be done in a consistent manner according to a method that healthcare personnel have adequate knowledge.
Algorithm – Steps 1 and 2

Step 1: Risk Assessment

Does the patient have risk factors* for hyperglycemia during PN?

- **No**
  - Routine Glucose Monitoring
    - Monitor 5 AM blood glucose daily
    - Order Accuchecks Q6H
  - Does patient have >2 blood glucose >150 mg/dL in 24 hr?
    - **No**
    - **Yes**

- **Yes**
  - Order Accuchecks Q6H with sliding scale insulin
    - Start sliding scale at 150 mg/dL and correct with 2-4 units for every 50 mg/dL above 150
  - Target Serum Glucose
    - Continuous infusion: 100-150 mg/dL
    - Cyclic: 100-200 mg/dL

**Risk Factors**
- Diabetes
- Pre-existing hyperglycemia (> 150)
- Pancreatitis
- Corticosteroids
- Octreotide

Step 2: Minimize glucose from other sources

Is the patient hyperglycemic while on sliding scale insulin?

- **If yes, then minimize...**
  - Maintenance IV with dextrose
  - Medications prepared in dextrose
  - Oral diet
  - Tube feeding
Glucose Algorithm – Step 3

Step 3: Adding insulin into PN

What is the patient’s glucose level prior to initiation?

- **Euglycemic (for diabetic patients)**
  - Insulin dose: 0.1 units per gram of dextrose in formula
    (i.e. 15 units insulin per 150 grams/L dextrose)

- **Serum glucose > 300 mg/dL**
  - PN contraindicated
  - Normalize serum glucose prior to starting PN

- **Hyperglycemic**
  - If glucose is 150-200 mg/dL
    - Insulin dose: 0.1-0.2 units per gram of dextrose in formula
      (i.e. 15-30 units insulin per 150 grams/L dextrose)
  - If glucose > 200 mg/dL
    - Start PN at 100 grams/L dextrose
      Insulin dose: 0.1 units per gram of dextrose in formula
      (i.e. 10 units insulin per 100 grams/L dextrose)
Step 4: Insulin monitoring

Monitor Q6H Accuchecks
Is the patient’s blood glucose within goal range?

Yes: Continue current insulin regimen

No: Adjust insulin in PN by adding 75% of insulin dose used via sliding scale in previous 24 hours

Monitor Q6H Accuchecks
Is glucose within range?

Yes: Increase PN to goal rate (40 mL/hr)

No: Continue current insulin regimen

Monitor Q6H Accuchecks
Is glucose within range?

Yes: Increase PN to goal rate (40 mL/hr)

No: Adjust insulin in PN by adding 75% of insulin dose used via sliding scale in previous 24 hours
Glucose Algorithm - Notes

- PN may be cycled if glucose is controlled on continuous PN while at goal rate.
- Taper insulin in PN when glucose < 100 mg/dL for 3 of 4 Accuchecks in a 24-hr period.
- Insulin limit in PN is 60 units/L.
  - If patient needs more insulin, then discontinue insulin in PN and begin insulin drip.
Summary

- The use of insulin in PN is a controversial topic
  - Primary indication: hyperglycemia associated with PN
  - Original issues with bioavailability from PN
  - Little evidence evaluating outcomes of insulin use in PN
  - Considerable variability in types of patients and PN practices
Conclusion

- Evidence and clinical practice suggests insulin is clinically effective in PN when dosage adjustments are suitable on a daily basis.
References