Hypercglycemia During Total Parenteral Nutrition (TPN): An Important Marker of Poor Outcome and Mortality in Hospitalized Patients.

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Short title: TPN-induced hyperglycemia and mortality


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Objective: To determine the effect of TPN-induced hyperglycemia on hospital outcome.

Methods: To determine whether blood glucose (BG) values prior to, within 24-hours, and during days 2-10 of TPN are predictive of hospital complications and mortality.

Results: A total of 276 patients receiving TPN for a mean duration of 15±24 days (±SD). In multiple regression models adjusted for age, sex, and DM status, mortality was independently predicted by pre-TPN BG 121-150 mg/dl (OR 2.2, 95% CI 1.1-4.4, p=0.030), 151-180 mg/dl (OR 3.41, 95% CI 1.3-8.7, p=0.01) and >180 mg/dl (OR 2.2, 95% CI 0.9-5.2, p=0.077), and by BG within 24h >180 mg/dl (OR 2.8, 95% CI 1.2-6.8, p=0.020). A BG within 24h >180 mg/dl was associated with increased risk of pneumonia (OR=3.1, 95% CI: 1.4-7.1) and acute renal failure (OR=2.3, 95% CI: 1.1-5.0).

Conclusion: Hyperglycemia is associated with increased hospital complications and mortality in patients receiving TPN.
The beneficial effect of TPN in improving the nutrition status of hospitalized malnourished patients is well established (1). Recent randomized trials and meta-analyses; however, have raised questions about its safety, and the increased rate of TPN-associated complications and mortality in critically ill patients (2-4). The increased risk of complications during TPN therapy can be related, among other factors, to the development of hyperglycemia, which occurs in 10% to 88% of hospitalized patients receiving TPN therapy (4-6). Despite the high frequency of TPN-induced hyperglycemia, it is not known if the severity of hyperglycemia and/or the timing of hyperglycemia prior to initiation or during TPN therapy lead to hospital complications. Accordingly, we determined i) the impact of TPN-induced hyperglycemia on survival, and ii) whether BG value prior to, shortly after initiation (within 24 hours), and/or during TPN therapy can serve as predictive markers of in-hospital complications and mortality.

METHODS
Retrospective study of medical and surgical patients receiving TPN during the period of 1/01/06 to 12/31/06 at Grady Memorial Hospital in Atlanta, Georgia. Patients were managed following the hospital TPN nutrition protocol aimed to provide 25-35 kcal/kg/day and 1-2 g protein/kg/day. We collected information on demographics, BG on admission, pre-TPN, within 24 hrs, and during days 2-10 of TPN, APACHE II score, length of hospital stay, hospital complications and mortality.

Data analysis: For comparison of baseline demographics and clinical characteristics between groups, we used two-sample Wilcoxon tests for continuous variables, and Chi-square test for categorical variables with Bonferroni corrections when applicable. Multiple logistic regression and adjusted odds ratios were employed to determine the influence of clinical characteristics on mortality and complications. A p-value of 0.05 was considered significant.

RESULTS
The study population included 276 consecutive medical (33%) and surgical (65%) patients (mean age: 51±18 yrs, BMI: 26±7 kg/m², known diabetes: 19.2%, ICU admission: 78.2%). TPN was started 12±12 days after admission, and was given for a mean duration of 15±24 days.

The mean BG level on admission was 139±85 mg/dl. The mean BG level prior to TPN was 123.2±33 mg/dl and increased to a mean BG of 146±44 mg/dl within 24hrs of TPN, and remained elevated (147±40 mg/dl) during days 2-10 of TPN infusion (p<0.01 from baseline).

The overall hospital mortality was 27.2%. Deceased patients were older, were more likely to be in the ICU, had higher admission APACHE II scores vs. non-deceased patients (all, p<0.01). Deceased patients had a higher pre-TPN BG (129±37 mg/dl vs. 121±32 mg/dl, p=0.08), a higher BG within 24 hr (162±55 mg/dl vs. 139±37 mg/dl, p=0.003), and a higher BG during days 2-10 of TPN (161±53 mg/dl vs. 142±34 mg/dl, p=0.013) than non-deceased patients.

In multiple regression models adjusted for age, sex, and history of diabetes, the likelihood of death was independently predicted by elevated pre-TPN BG between 121-150 mg/dl (OR 2.2, 95% CI 1.1-4.4, p=0.030), 151-180 mg/dl (OR 3.41, 95% CI 1.3-8.7, p: 0.010), and >180 mg/dl (OR 2.2, 95% CI 0.9-5.2, p=0.077), or by the BG within 24hr >180 mg/dl (OR 2.8, 95% CI 1.2-6.8, p=0.020) vs. patients with a mean BG ≤ 120 mg/dl. In multivariate analysis adjusting for age, sex, and history of diabetes, the BG within 24h of TPN >180 mg/dl was
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associated with increased risk of pneumonia (OR=3.6, 95% CI: 1.6-8.4) and acute renal failure (OR=2.2, 95% CI: 1.02-4.8) compared to patients with BG <120 mg/dl. Patients with higher BG levels during TPN had a longer hospital (p=0.011) and ICU length of stay (p=0.008).

DISCUSSION

Malnutrition is reported in up to 40% of critically ill patients (1; 7) and is associated with increased risk of hospital complications, longer hospital stay and mortality (8). Despite improving the nutrition state and immunologic competence (9), TPN therapy has been associated with increased risk for infections and mortality (2; 10-13). The increased risk of complications appears to be related, among other factors, to the development of hyperglycemia (4; 14). Observational studies have reported a 33% mortality rate in TPN patients who developed hyperglycemia (15), as well as an increased risk of cardiac complications, infections, systemic sepsis, acute renal failure (3; 4; 6). In agreement with these reports, we found a strong correlation between TPN-induced hyperglycemia and poor clinical outcome. Of interest, we observed that values prior to and within 24 hours of initiation of TPN are better predictors of hospital mortality and complications than BG during the entire duration of TPN (Figure).

In multiple regression models adjusted for age, sex, and DM status, mortality was independently predicted by pre-TPN BG values between 151-180 mg/dl (OR 3.41, 95% CI 1.3-8.7, p: 0.01) and >180 mg/dl (OR 2.2, 95% CI 0.9-5.2 , p=0.077), as well as by BG within 24h of TPN >180 mg/dl (OR 2.8 , 95% CI 1.2-6.8, p=0.020) vs. patients without hyperglycemia. In addition, BG >180 mg/dl within 24h of initiation of TPN was associated with increased risk of pneumonia (OR=3.1, 95% CI: 1.4-7.1) and acute renal failure (OR=2.3, 95% CI: 1.1-5.0).

The mechanisms underlying the detrimental effects of hyperglycemia relate to alterations in immune functions and inflammatory response (16; 17). Hyperglycemia impairs leukocyte function, phagocytosis and chemotaxis (18). Hyperglycemia also increases counterregulatory hormones, inflammatory cytokines and oxidative stress (16; 17), that can lead to endothelial dysfunction and cardiovascular complications (17). In addition to hyperglycemia, the administration of Intralipid in TPN solutions may worsen clinical outcome. Intralipid infusion, a soybean oil-based emulsion rich in ω-6 polyunsaturated fatty acids (PUFAs) (19), has been associated with exaggerated inflammatory response, immunosuppression, insulin resistance, increased blood pressure, endothelial dysfunction, and oxidative stress (19).

In summary, TPN-induced hyperglycemia is associated with increased length of hospital stay, increased risk of complications, and higher mortality in hospitalized patients. Our study indicates that BG values prior to and within 24 hours of initiation of TPN are better predictors of hospital mortality and complications than the mean BG during the entire duration of TPN. These results suggest that early and aggressive intervention to prevent and correct hyperglycemia may improve clinical outcome in patients receiving TPN.

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