A Randomized Trial of Supplemental Parenteral Nutrition in Under and Over Weight Critically Ill Patients: The TOP UP Trial

Co Principal Investigators: Daren K. Heyland1,2, Naomi E. Jones1,2, Paul E. Wischmeyer5
Co-investigators: Cathy Alberda3, Leah Gramlich4, Khusreend Jeejeebho5, John Drover5, Jean Charles Preiser6, Mette Berger7, Gunnar Elke8

Queen’s University and Clinical Evaluation Research Unit, Kingston General Hospital, Kingston, ON Canada; 2Royal Alexandra Hospital, Edmonton, Alberta, Canada; 3St Michael’s Hospital, University of Toronto, Toronto, Ontario, Canada
4University of Colorado, Denver, Colorado, US 5Centre Hospitalier Universitaire Liege, Belgium; 6Centre Hospitalier Universitaire Vaudois, Lusanne, Switzerland; 7University Medical Center Schleswig-Holstein, Campus Kiel, Germany

OVERALL OBJECTIVE

- Initiate a prospective, randomized, blinded multi-center trial of a strategy to prevent protein-energy deficit.
- Experimental Group: Supplemental parenteral nutrition (PN) plus enteral nutrition (EN) in first 7 ICU days.
- Control Group: EN with placebo PN addition
- Only Lean (BMI<25) and Obese (BMI>35) where we have shown display significant risk of mortality from underfeeding are eligible
- We will perform an initial multi-center pilot study in 160 patients to demonstrate feasibility
- Assuming feasibility, a large-scale 2000 patient multi-center trial will then be undertaken

HYPOTHESIS

Increased early energy and protein delivery to underweight (BMI < 25) and obese (BMI>35) critically ill patients will result in improved survival at 60 day versus usual care

BACKGROUND

- Accumulated calorie deficit in critically ill patients results in increased mortality and morbidity (1,2)
- Unintentional feeding deviation (49-70%) of calculated energy requirements is universal worldwide(3)
- It is likely critically ill patients exhibit differences in risk from calorie deficit and malnutrition based on admission nutritional status
- Some patients may be placed at great risk from mortality from this underfeeding, while others are not
- Supplemental PN is uncommon in U.S. and around the world without evidence to support use in all patients
- No trials have examined targeted calorie deficit replacement in at risk patients or use of PN in selected nutritionally at risk population who would be likely to benefit.

PRELIMINARY DATA: WHO IS AT RISK?

1. 2772 consecutively mechanically ventilated patients expected to stay in ICU > 12 hours enrolled
2. Body Mass Index (BMI) used as surrogate marker of pre-ICU nutritional status
3. Regression models developed to explore relationship between nutrition received and 60-day mortality and how BMI modifies this relationship.

RESULTS: WHO IS AT RISK?

- Overall, a significant inverse linear relationship between odds of mortality and total daily calories received (Table 1 and Figure 1)
- Beneficial treatment effect of increased calories and protein intake and its effect on mortality in different BMI groups
- No benefit for patients in the BMI 25-33 group. (Table 1 and Figure 1)

SYSTEMATIC REVIEW OF TRIALS: COMPARING EN+PN VERSUS EN ALONE

- Five RCTs identified
- Combination EN+PN showed no benefit with regard to mortality (RR 1.27 [95% CI 0.82-1.94, p = 0.3])
- However, limited inferences can be made from this data due to:
  - Very small sample size of trials
  - Heterogeneous patient populations
  - Practice changes since trials completed such as: Hyperalimentation (30-35 kcal/kg/day) no longer practiced

EVIDENCE FROM RCTS THAT MORE PROTEIN-CALORIES IMPACTS OUTCOMES: EARLY VersUS LATER CALORIC DELIVERY

- Data reveals statistically significant (p<0.05) benefit of early calorie delivery via enteral route (see figure 2)
- However, our International Nutrition Survey data reveals unintentional hypocaloric enteral feeding (38-55%) of calculated energy requirements is universal worldwide(3)
- 33% (mean) of prescribed calories are delivered in United States Centers (36 centers total)
- Thus, it is clear caloric needs of critically ill patients are not being met in existing ICU practice of enteral nutrition

STUDY POPULATION

- Multicenter, randomized, double-blinded clinical trial
- Randomization will be stratified on the basis of admission BMI: C25, 20-25, and 35-40 and >46, presence of sepsis on admission, and by site
- Sample: 2000 patients
- Primary Outcome: 60 day mortality

PROPOSED PILOT TRIAL

- Purpose:
  1. >18 years old in ICU
  2. Not expected to survive > 48 h
  3. Expected to stay > 72 h
  4. Initiates on enteral nutrition within 48 h of ICU admit
  5. Patients with a BMI < 25

- Estimate recruitment rate i.e. number of eligible/eligible patients per month per site.
- Confirm feasibility/safety of blinding intervention.
- Establish adequate compliance with study protocols/completion of case report forms.

STUDY INTERVENTIONS

- Patients receive EN plus placebo PN (standard care) or EN+PN
- Upon enrollment, study dietitians will calculate the total volume/24 hours of either EN or PN required to receive goal calories and protein. Suggested target dose of protein/energy based on BMI category (Table 1)
- Both EN and PN will be continued for 7 days post randomization or until death, whichever comes first. In the event that the patient is discharged from ICU prior to day 7, we will continue the study intervention on the hospital wards.
- The study and placebo PN solution will be started at 1 ml/hr and increase by 20 ml/hr increments every 4 hours till 100% of goal calories are reached.
- In both groups, the volume of PN will be titrated up or down according to the volume of EN received over a 24 hour period to ensure that the patient receives 100% of their prescription.
- Both enteral and parenteral solutions will be provided continuously for a 24 hour period. Both the EN and PN will be continued for 7 days post enrollment, inclusive of the intervention period. The study PN will be dispensed by the pharmacy as MCT/LCT lipid lipid solution (10 mg/ml lipid/L, 20% of energy provided). The study PN will be dispensed by the pharmacy as MCT/LCT lipid lipid solution (10 mg/ml lipid/L, 20% of energy provided). The study PN will be dispensed by the pharmacy as MCT/LCT lipid solution (10 mg/ml lipid/L, 20% of energy provided).

STUDY OUTCOMES

- Primary outcomes:
  1. 60 day mortality
  2. Secondary outcomes: 28 day mortality, hospital mortality, duration of stay (ICU and hospital), incidence of infections (SFOA, SPOA, and POCUS), duration of mechanical ventilation, development of ICU-related infections (SFOA and POCUS), duration of ICU-related infections and 3 and 6 month survival and health-related quality of life.

OUTCOMES

- Pilot study: Differences in the effects of different calorie-delivering protocol on mortality
- Secondary outcomes: Compliance with study intervention, reasons for interruptions, adverse events, and completion of case report forms.
- Usability of the study protocol: Feasibility and acceptability of the study protocol.