Supplementation Of Enteral Feeds Of Critically Ill Patients In The Medical Intensive Care Unit With Glutamine

Elvin Geng

A. Study Purpose and Rationale

We intend to study whether supplementation of enteral feeds of critically ill patients in the Medical Intensive Care Unit with the glutamine improves infectious outcomes and associated morbidity.

Glutamine is a non-essential amino acid that has a variety of roles in cellular metabolism. Glutamine is an intermediate in bringing nitrogen into cellular biochemical pathways; it is an energy source as well and its metabolism into glutamate, alpha-ketoglutaric acid and into the Krebs cycles creates NAPH and ATP, and it is also has a role in salvage pathways of purine synthesis.

In vitro studies show that glutamine supplementation increases lymphocyte proliferation[1] as well as improves macrophage function.[2] In animal studies, glutamine has been shown to be an important nutrient for enterocytes. Rats with pancreatitis fed with glutamine have superior gut integrity when compared with controls.[3]

Obervational studies in humans have shown that critically ill patients with decreased plasma glutamine have an increased mortality at six months.[4] This difference remains significant even after adjustment for APACHE score and other clinical prognosticating factors.

Randomized clinical trials in humans have likewise shown impressive effects. In a double-blind trial of trauma patients randomized to glutamine supplements feeds and iso-nitrogenous, iso-caloric, iso-osmolar placebo had statistically significant that were strong: 45% of the controls developed an infection during hospitalization whereas only 17% of treatment patients did.[5] A study among bone transplantation patients lead to similarly findings and found that those randomized to glutamine had 12% in hospital infection vs. 43% in the control group. Furthermore the experimental group had an average hospital stay of 29 days vs. 39 days in the control group, -which was a statistically significant difference.[6]

Glutamine may represent a safe, low-cost, and effective agent in the management of critically ill medical pateints.

B. Study Design and Statistical Analysis.

Consecutive patients admitted to the MICU without below described exclusion criteria will be randomized to standard protein enriched feeds given currently in the Medical ICU (ProMod: Abott Laboratories, Columbus, Ohio) or the isnitrogenous, isocaloric, glutamine-supplemented feeds (Glutamine: Baxter Healthcare Corporation, Deerfield, IL) on top of regular feeds. Randomization will be accomplished by assignment of each patient's study identifier to a value generated from a random number generator. Randomization of patients will occur when the medical team decides to initiate feeds. Patients will be fed for 14 days. If transferred to the floor the study feed will be attached to their chart.

Eighty-three patients will be enrolled in each arm. This number is arrived at with an set alpha error of 0.05, power of 0.80, hypothesized endpoint of infection in the control group as 50% and endpoint of 30% in the treatment group. The infection rate in controls is taken from previous studies of bone marrow and trauma patients described above. The hypothesized proportion in the treatment group is a conservative estimate based on previous observations. Using the seconday endpont of length of stay in the ICU to calculate the number of subjects assuming the same alpha and power with hypothesized length of stay of seven days among the controls and five among the experimental group with a SD of 3.5 days yields a n=26.

Fourteen day outcomes will be defined as follows and identified on daily chart review. Pneumonia; new infiltrate with either leukocytosis or fever. UTI; urine microscopy and analysis with

greater than 3 wbc and +LE/N. Line infection; fever with positive blood cultures that resolve when line is removed. Closed space infection; fever, leukocytosis and demonstration of collection by culture and smear. Sepsis; established by four SIRS parameters and underlying infection. Length of stay will be determined by chart review.

C. Study Procedure

The study will not introduce additional procedures in the management of enteral feeding of critically ill patients. Briefly, nasogastric tubes are placed in patients requiring enteral feeds and the delivery begins after confirmation of correct placement by x-ray at a time when the primary team feels that feeding is indicated and safe. Patients receive feeds continuously and calories are calculated by a nutritionist based on body weight. No additional catheters nor instruments will be required to deliver experimental feeds. Since daily phlebotomy is indicated in every patient in the ICU and suspicion for infection is worked up promptly and aggressively, measurement of secondary laboratory and microbiologic signs of infection will not necessitate additional blood draws.

We anticipate it will take 6 months to recruit the patients necessary. Each patient will be given study drug for fourteen days.

D. Study Drugs

The experimental feeds are a glutamine-supplemented powder made by Baxter Healthcare Corporation. It is currently on formulary at New York Presbyterian Hospital.

It is available commercially as a nutritional supplement to the public as well. No other experimental supplements or drugs will be used at any point. The control feeds are a protein-enriched formula which lacks the amino acid glutamine named ProMod (Ross Products Divisoon, Abbott Laboratories, Columbus, Ohio). This is the protein supplement that is currently used by the intuitionalists at the hospital for protein supplementation. It is also a commercially available.

The actual amount of protein supplementation is calculated by 0.6 gms/kg which is about 14 gms of protein supplementation three times a day. Promod is 3 gm of glutamine for 100 gms of protein.

No untoward effects of glutamine nor ProMod ingestion have been reported.

The route of administration of experimental feeds will be identical to the current standard of care feeds.

E. Medical Device

No experimental medical devices are used in this study.

F. Study Questionnaires.

No questionnaires are used in the study. Only investigators in the study will do data gathering.

G. Study Subjects.

All patients admitted to the MICU and requiring enteral feeds will be considered. Patients with conditions that contraindicate a high protein diet will be excluded. These are persons with known diagnosis of cirrhosis or clinical evidence of cirrhosis such as any of the following: gynecomastia on physical exam, both albumin <4.0 and INR > 1.1 without anticoagulation medication and without clinical evidence of DIC or vitamin K malnutrition,

Also persons with acute hepatitis will be excluded; those with total and direct bilirubin greater than 3.0 and 1.5, transaminitis twice normal limit, clinical diagnosis of acute viral hepatitis, patients admitted with suspicion of Tylenol ingestion, anyone admitted through the liver transplant service.

Also patients with creatinine clearance of less than 25 cc/min but neither on hemodialysis nor CVVHD will be restricted.

There is no restriction of gender or race for study subjects.

H. Recruitment of Subjects

All patients admitted to the MICU without above described exclusion criteria will be considered for inclusion in the study. Although the nature of patients in the ICU generally precludes informed consent in clinical research studies, the absence of any negative effects of glutamine supplementation qualify this study for a wavier of consent. We will notify the primary care physician of the protocol.

I. Confidentiality of Study Data

We will code study data by an original case number. Patient names and other unique identifiers will not be included in the final data set.

J. Potential Conflict of Interest

None of the investigators have any proprietary interest in the experimental feeds under investigation and no one stands to benefit financially from any findings.

K. Location of Study

Study will occur in the Medical Intensive Care Unit of New York Presbyterian Hospital, - Columbia campus.

L. Potential Risks

There are no known risks. The glutamine-supplemented feed will be isonitrogenous and isocaloric to the control feeds. Glutamine is a common amino acid and found in almost all foodstuffs with protein content.

M. Potential Benefits

Potential benefits include enhancement of immune function, improved barrier function of gut and reduced morbidity and perhaps mortality associated with infections.

N. Alternative therapies

There are many alternative therapies directed at preventing specific infections (for example, antibiotic impregnated catheters) but none are designed to improve systemic immune function and combat all infections.

O. Compensation to Subjects

No compensation will be provided for participation.

P. Costs to Subjects.

No costs will be incurred as a result of participation in the study.

Q. Minors as research Subjects

No minors will be a part of the study.

R. Radiation or Radioactive Substances

There are no radioactive substances used in this study.

S. References

1. Calder PC, et al. Glutamine promotes interleukin-2 production by concanavallin A-stimulated lymphocytes. Proc Nut Soc 1992; 51:105A
2. Wallace C, et al. Glutamine and macrophage function. Metabolism 1992; 41:1016-20
3. Foitzik T, M Kruschewski, AJ Kroesen, et al. Does glutamine reduce bacterial translocation? A study in two animal models with impaired gut barrier. It J Colorec Dis (1999) 14:143-9.
4. Oudesmans-van Straaten, HMP, et al. Plasma glutamine depletion and patient outcome in acute ICU admissions. Intensive Care Med 2001; 27:84-90
5. Houdijk, AP et al. Randomized trail of glutamine enriched enteral nutrition on infectious morbidity in patients with multiple trauma. Lancet 1998; 352:772-6
6. Ziegler, TR. Clinical and Metabolic Efficacy of Glutamine-supplemented Parental Nutrition after Bone Marrow Transplantation. Ann Int Med 1992; 116:821-828.