December 1, 2013

Randomized Trial to Evaluate Nutritional Status and Absorption of Enteral Feeding after Brain Death

Georgene W. Hergenroeder, *Baylor College of Medicine*
Norman H. Ward, *Baylor College of Medicine*
Xiaoying Yu, *Baylor College of Medicine*
Antone Opekun, *Baylor College of Medicine*
Anthony N. Moore, *Baylor College of Medicine*, et al.

NIH Public Access
Author Manuscript

Randomized trial to evaluate nutritional status and absorption of enteral feeding after brain death

Georgene W. Hergenroeder, RN, MHA, CCRC, **Norman H. Ward III, BS**, **Xiaoying Yu, MD, MS**, **Antone Opekun, MS, PA-C**, **Anthony N. Moore, BS**, **Claudia A. Kozinetz, PhD, MPH**, and **David J. Powner, MD**
The University of Texas at Houston (GWH, NHW, ANM, DJP), Memorial Hermann Hospital-Texas Medical Center, Houston (GWH, NHW, DJP), Baylor College of Medicine, Houston, Texas (XY, AO, CAK)

Abstract

Context—Catecholamines and inflammatory mediators, with elevated levels after brain death, are associated with reduced function and survival of transplanted organs. Enteral nutrition reduces tissue damage and may benefit organs.

Objective—To evaluate the effects of immunomodulating enteral nutrition in organ donors.

Design—Prospective, randomized, open-label study.

Setting—Intensive care unit.

Patients—Thirty-six brain-dead organ donors.

Interventions—Donors were randomized to receive enteral nutrition containing omega-3 polyunsaturated fatty acid, antioxidants, and glutamine or standard care (fasting). Donors received hormonal replacement therapy of corticosteroid, levothyroxine, dextrose, and insulin.

Main Outcome Measures—Gastrointestinal assimilation (measured by ^{13}carbon-labeled uracil breath analysis), quantity of organs recovered, resting energy expenditure, urine level of urea nitrogen, and serum levels of albumin, prealbumin, interleukin 6, tumor necrosis factor-α, and C-reactive protein were evaluated.

Results—Thirteen patients (36%) assimilated ^{13}C-labeled uracil. Resting energy expenditure was significantly higher than predicted between 10 and 14 hours after baseline in 33 donors ($P = .007$). Other measures were not conclusively different between fed and fasting groups. No adverse events occurred that were related to the enteral feeding.

Conclusions—About 30% of donors metabolized ^{13}C-labeled uracil, although no difference in oxidation rate was found between fasting and fed donors. Corticosteroid administration lowers plasma levels of interleukin 6 and most likely contributes to greater than predicted resting energy expenditure. Thus energy needs may not be met during fasting if hormones are given. Consequences of this possible energy deficit warrant further study.

Maintaining the nutrition of organ donors is proposed to reduce toxic effects from high concentrations of catecholamines and/or proinflammatory mediators generated during the

Corresponding author: Georgene W., Hergenroeder, Vivian L. Smith Department, of Neurosurgery, 6431 Fannin Street, MSB 7.156, Houston, TX 77030 (georgene.w.hergenroeder@uth.tmc.edu).

evolution of brain death and by other complications of critical illness or injury.[1–3] Marked elevations in levels of catecholamines, interleukin 1, interleukin 6 (IL-6), tumor necrosis factor–α (TNF-α), and other cytokines or chemokines are well documented in humans after brain death[1,4–6] and are associated with reduced function and survival of transplanted organs.[7–9]

The possible benefits of immunomodulating nutrition in a variety of patient groups include reduced translocation of bacterial products from intestine to liver that may contribute to multiorgan failure[10]; provision of antioxidants, vitamins, or "nutri-ceuticals" that lower oxidative stress, cytokine levels, and apoptosis[11,12]; and improved neutrophil response to infection and inflammation.[13] Although enteral postpyloric feeding is preferred over intravenous nutrition in patients,[14,15] the intestinal absorption of enteral nutrition and the effect on transplantable organs in brain-dead organ donors have not been studied.

Increased resting energy expenditure (REE), ascribed to the release of catecholamines, occurs after traumatic brain injury. However, despite the continuing high circulating catecholamine and cytokine levels following brain death, indirect calorimetry shows lower REE (25%–80%) than predicted by traditional formulas, presumably because of hypothermia, absent brain metabolism, and flaccid musculature.[14,16,17] Although REE among donors does not increase during intravenous infusion of amino acids,[17] the effects of enteral feeding on REE are unknown.

Urinary nitrogen losses and serum level of prealbumin (transthyretin) provide estimates of protein loss or the current status of protein reserves.[18,19] A low serum level of prealbumin, as a "negative" acute phase reactant, may also reflect hypermetabolism in a systemic inflammatory response.[18,20,21] Changes in these parameters among enterally fed donors are also unknown.

The hypothesis was that providing enteral immuno-modulating nutrition to organ donors will reduce systemic inflammation and improve organ recovery. We evaluated gastrointestinal absorption, REE, the number of organs recovered, and other nutritional parameters during care of 36 donors, comparing fasting to continuous enteral feeding with commercially available nutrients Oxepa (Ross Products Division, Abbott Lab oratories) and Glutasolve (Nestle Nutrition) (Table 1).

Materials and Methods

Thirty-six (36) brain-dead organ donors were randomized in a 1:1 ratio to standard care (fasting) or to receive a nutritional intervention via naso/oro-duodenal feeding (see Figure). Inclusion criteria for study were consented brain-dead organ donors age 14 to 70 years. Donors may have received parenteral or enteral nutrition before enrolling in the study, but were excluded for prior gastric or small-bowel resections, gastrointestinal malabsorption, bariatric procedures, vagotomy, pyloroplasty, or pancreatitis. Donors were also excluded if a fraction of inspired oxygen (F_{Io_2}) greater than 60% was required when initial metabolic cart measurements of REE were made. The study was open-label, but the investigator interpreting the breath test results was blinded to the treatment arm.

Feeding tubes were placed by intensive care unit (ICU) personnel and placement was confirmed with abdominal radiography. Blood, urine, calorimetric, and breath test data were obtained at baseline (T1) and 12 ± 2 hours after baseline (T2) for all donors, and blood samples were obtained again just before transfer to the operating room. Oxepa infusion was initiated at 20 mL/h for 2 hours and, if gastric residual was less than 150 mL, was advanced to deliver 1.0 g of protein per kilogram (ideal body weight) in 24 hours. Glutasolve was administered before the Oxepa infusion and again every 8 hours. The head of the donor's

bed was elevated to 30°, enteral input and gastric outputs were monitored, and a naso/oro-gastric tube was maintained on suction (clamped during breath testing) to minimize risk of aspiration.

Donor care was provided by coordinators from our regional organ procurement organization (OPO), LifeGift (Southeast Region, Texas). Standardized best practice treatment guidelines were used throughout care. Euthermia was maintained to minimize temperature effects on organ function, breath testing, and indirect calorimetry. Treatment included hormone replacement therapy of 50% dextrose (bolus 25 g), a 20-unit bolus of regular insulin, levothyroxine (bolus of 20 ug followed by 20 ug/h) and corticosteroids (methylprednisolone 1000-mg bolus followed by 100 mg every 8 hours or hydrocortisone sodium succinate 100-mg bolus followed by 50 mg every 6 hours).[22]

^{13}C-Uracil Breath Test

Gastrointestinal absorption and assimilation was measured by using standardized ^{13}C-labeled uracil breath tests performed at T1 and T2.[23] During each test the indicator substrate, ^{13}C-uracil 113 mg (99atom%) [^{13}C-uracil, ^{13}C-pyrimidine-2,4(1H,3H)-dione], was administered in 113 mL of water by postpyloric bolus. Breath samples were collected every 10 minutes for 60 minutes. $^{13}CO_2$ gas enrichment of exhaled gas was analyzed by an infrared spectrophotometer (POCone, Otsuka Electronics). An exhaled gas concentration of 9% cumulative percent dose recovery was defined as assimilating the ^{13}C-uracil.

Sufficient indicator dosing was ensured by analyzing the plasma concentration of ^{13}C-uracil by gas chromatography-mass spectrometry (Metabolic Solutions) in a subset of samples. A relationship between pulmonary $^{13}CO_2$ excretion and the blood $^{13}CO_2$ concentration has been shown.[24] Gas chromatography-mass spectrometry was used to measure the ratio of labeled to unlabeled uracil in blood samples from 16 subjects and confirmed adequate dosing.

Indirect Calorimetry

The REE was assessed at T1 and T2 by using standardized hospital procedures for measuring oxygen consumption and carbon dioxide production (Direct Connect preVent Pneumotach, MedGraphics Cardiorespiratory Diagnostic System) and calculated from the Weir equation: REE = $[V_{O2} (3.941) + V_{CO2} (1.11)]$ 1440 min/d].[25] Predicted energy expenditure as basal energy expenditure (BEE) was calculated from the Harris-Benedict formula: BEE_{men} = 66.4730 + (13.7516 × weight in kg)+(5.0033 × height in cm) − (6.7550 × age in years); BEE_{women} = 655.0955 + (9.5634 × weight in kg)+(1.8496 × height in cm) − (4.6756 × age in years). No modifications to the BEE-based predicted REE were made. Donors were euthermic, immobile and showed no evidence of infection. Metabolic "stress factors" due to elevated catecholamines and/or pro-inflammatory mediators after brain death were assumed to be present, but their documentation and potential impact on metabolic energy requirements of donors are goals of this protocol.

REE testing was performed after donor ventilation was optimized to OPO guidelines, but was omitted if the F_{IO2} was greater than 60% or positive end-expiratory pressure exceeded 12 cm H_2O. AVEA ventilators (Care-Fusion Corporation) were used during donor care.

Urine Urea Nitrogen

Urine level of urea nitrogen (UUN), measured by the hospital laboratory (Dimension Vista, Siemens), was used to estimate protein catabolism. Urine samples were collected for two 2-hour periods (T1 and T2). Twenty-four hour UUN was extrapolated from the 2-hour measurements on the basis of the actual urine output. If the donor transferred to the

operating room in less than 24 hours, the averaged hourly output was extrapolated for unrecorded urine output to estimate the 24-hour value.

Blood Sample Analysis

Prealbumin (transthyretin), albumin, creatinine, serum urea nitrogen, alanine aminotransferase, aspartate aminotransferase, blood glucose, and C-reactive protein (CRP) serum concentrations were measured by the hospital laboratory (Dimension Vista). Blood samples for IL-6 and TNF-α concentrations were taken at T1, T2, and just before transfer to the operating room. IL-6 and TNF-α plasma concentrations were measured by sandwich enzyme-linked immunosorbent assays (R&D Systems) as previously described.[26]

Transplant Results

The numbers of solid organs transplanted from fed versus fasting groups were compared. Six-month posttransplant recipient outcome, defined as deceased (including retransplant) or alive, was obtained from the United Network for Organ Sharing database.

Statistical Analysis

Power calculations based on previous donor IL-6 levels yielded an estimate for sample size of 18 subjects in each group. Repeated-measures analysis of variance using Wilks Lambda approximate F test was applied to generate the estimates by PASS 2008 (NCSS, LLC). The study was powered at 86% to detect a group by time interaction (effect size 0.52) with an alpha of 0.05 based on changes in IL-6 levels between the intervention (fed) and the control (fasting) group. Study randomization codes were generated by the statistician using a computer program. The codes were placed in sealed, numbered, opaque envelopes that were opened by the clinicians sequentially to determine subjects' assignment.

Descriptive statistics were calculated for all donors by treatment group based on intent to treat, by as treated, and by those with positive breath test results compared with others. The distributions of the variables were examined. The 2-sample t tests for continuous variables and χ^2 tests for categorical variables were performed. Fisher exact tests were used for variables that had a small expected cell number. Wilcoxon rank sum tests were used for comparison between 2 groups, and Spearman correlation coefficients were used to assess the correlation for the continuous variables not normally distributed. Additionally, paired t tests were used to compare the differences between the REE and the predicted REE for the 33 subjects with data available for both tests. Cytokine data were analyzed by using a linear mixed model based on log-transformed values. For transplant results, Poisson regression compared the number of "alive organs" between fed and fasting groups accounting for the number of organs transplanted, which was treated as an offset in the model. P values less than .05 were considered statistically significant. Data analyses were conducted with SAS Version 9.2 (SAS Inc).

Approval was received and procedures were followed in accordance with the ethical standards of the Committee for the Protection of Human Subjects at The University of Texas Health Science Center at Houston and the Institutional Review Board for Human Studies at Baylor College of Medicine and Affiliated Hospitals. Informed consent was obtained from the legally authorized representatives of organ donors after the nature of the procedures had been explained. The study was registered on ClinicalTrials.gov as NCT00858390.

Results

Enrollment was completed from February 2009 through April 2011. One donor did not receive intended feeding because the naso/oro-duodenal tube could not be placed. He was

analyzed as fed in the intent-to-treat analysis. The mean time that the fed group received nutrition was 12.6 (SD, 4.4) hours. Descriptive data are in Tables 2 and 3. No significant differences were found for variables examined in the intent-to-treat analysis. Serum creatinine, serum urea nitrogen, alanine aminotransferase, and IL-6 levels in the fed group at T1 are approximately 1.5 times higher than in the fasted group owing to inclusion of 1 donor with preexisting chronic renal failure. All donors required vasoactive drugs for blood pressure support. Two subjects received enteral feeding within 24 hours before the study started: one was randomized to feeding and did not assimilate, and the other was randomized to fasting and assimilated. No subject received parenteral nutrition before or during the study. Regarding safety assessments, no adverse events related to the intervention were observed. No donor showed apparent aspiration of feedings; none had a bowel movement or diarrhea, although bowel sounds were heard. Residual gastric volumes were not different between the fed and fasting groups (fed patient mean, 168 [SD, 193] mL; fasting patient mean, 243 [SD, 363] mL; P=.44).

^{13}C Breath Test and ^{13}C Level in Plasma

Thirteen donors (36%) assimilated ^{13}C-uracil at 1 or both testing intervals (Table 3). No significant difference in breath test results was apparent between the fed and fasting groups at either testing interval (at T1, P= .46, at T2, P= .72). Blood test analysis confirmed that absorption occurred and that the dose of ^{13}C-uracil was sufficient for oxidation to occur if the donor had the capacity.

Indirect Calorimetry

Indirect calorimetry results were not available for 3 subjects because of high F_{IO_2} requirements or equipment malfunction. Paired t tests from the 33 subjects with T1 and T2 measures showed significantly higher measured REE than predicted at T2 (2039.8 [SD, 821.9] vs 1691.6 [321.1]; P=.007) regardless of group assignment. The fed and fasted groups did not differ in either predicted or measured REE.

Urine Urea Nitrogen

The calculated Spearman correlation (ρ = 0.26; P =.16) showed no relationship between nitrogen loss estimated by the UUN and REE.

Subjects Who Assimilated Versus Others

Additional analyses were performed to identify variables associated with gastric assimilation of the ^{13}C-uracil. No demographic parameter was identified that was associated with the donor's ability to assimilate. Only a lower serum albumin concentration before transfer to the operating room showed a statistically significant difference between assimilators and nonassimilators (2.2 [SD, 0.6] g/dL vs 2.7 [SD, 0.4] g/dL; P = .009), but was unrelated to whether donors were fed or fasted.

Inflammatory Markers

Median plasma concentrations of IL-6, TNF-α, and CRP were not different between fed and fasting groups at any time point. When feeding status was controlled for, all cytokine values changed significantly across time and followed a quadratic time trend (markers changed at a faster rate earlier and then the rate of change slowed down).

In those donors who assimilated the ^{13}C-uracil at T2, median plasma IL-6 concentrations before transfer to the operating room were significantly lower in 5 fed donors than in 6 fasting donors (Table 4). Because of the small number of subjects, this finding should be interpreted cautiously.

Transplant Results

There was no effect of feeding on recipient all-cause mortality at 6 months after transplant. Seventeen (15%) of the 117 recipients of organs from the 36 donors had a poor outcome within 6 months after transplant: 15 died and 2 required retransplant. Deaths/retransplant included recipients of lungs (7), hearts (3), livers (3), and kidneys (4). Nine of the recipient deaths received organs from fed donors and 8 from fasted donors. The average number of organs procured and transplanted by feeding status (Table 2) and by bowel absorptive function as measured by ^{13}C-uracil breath test was not significantly different between groups (3.8 [SD, 2.3] vs 3.8 [SD, 1.9] assimilated vs others; $P = .93$). Data comparing detailed graft function (eg, laboratory tests) among recipients were not available from United Network for Organ Sharing.

Discussion

In this randomized, open-label study organ/recipient survival and several measures of organ function were evaluated in 36 brain-dead organ donors to determine the effect of enteral feeding with an omega-3 polyunsaturated fatty acid, antioxidant, and glutamine-enhanced nutritional intervention. None of the laboratory parameters evaluated improved or worsened significantly after 12.6 (SD, 4.4) hours of enteral feeding. No pulmonary aspiration or increased gastric residual volumes occurred during postpyloric feeding with standard ICU preventive therapy. Similarly, no benefit to or worsening of graft or recipient survival was associated with the nutritional protocol, but a detailed comparison of specific graft function was not available.

Earlier investigations after brain death documented REE as a mean of 30% (SD, 11%) below Harris-Benedict equation predictions, most likely because of reduced cerebral oxygen consumption and hypothermia.[16] Reduced REE and cardiac output after traumatic brain injury were also observed in patients treated with experimental hypothermia[27] and among normothermic organ donors receiving parenteral alimentation.[17] Euthermia was maintained by OPO protocols, and the REE of our donors was higher than predicted. Recent studies in critically ill patients indicate that the Harris-Benedict equation yields underestimates of actual energy expenditure,[28,29] findings similar to our data. However, our data are not consistent with previous organ donor results. Although the reason for an elevated REE is unclear, the hormonal replacement therapy may have contributed. Corticosteroid infusion increases nitrogen loss and REE in normal males, perhaps because of increased protein oxidation,[30,31] and hydrocortisone is known to increase gluconeogenesis and nitrogen loss.[32,33] The administration of thyroid hormone and insulin as a part of the replacement protocol may have also increased cellular metabolism. The increased energy expenditure documented here, with hormone replacement as part of donor care, may represent an unsuspected "energy deficit" within organs awaiting removal if donors fast, as commonly practiced. This potential deficit may metabolically stress donor organs or tissues and warrants further study.

Approximately 30% of these organ donors metabolized uracil after its enteral administration, as evidenced by metabolic isotope recovery from exhaled gas. None of the parameters listed in Table 3 was predictors of donors who would demonstrate this ability, and it is unclear if this finding might be useful when selecting donors for liver or intestinal transplant. Although serum albumin before transport to the operating room was higher in donors who did not assimilate uracil ($P = .009$), the significance of this finding is unclear and unlikely to reflect improved nutritional status as the prealbumin level did not change.

Intolerance of enteral feeding in patients with a brain injury most likely results from damage of the central nervous system, elevated intracranial pressure,[34] intestinal barrier

dysfunction,[11] catecholamine infusions,[35–37] impaired gastric emptying due to vagus nerve damage, and other medications.[14] Although these earlier findings also suggest loss of bowel motility, supported here by our findings of minimal bowel sounds and absent bowel movements, we have shown with ^{13}C-uracil breath analysis that physiologic absorption and metabolism of enteral feeding does occur in some donors. Therefore, some nutrients can be available to possibly benefit transplantable organs. Benefits would be a function of the nutrient selected and the length of time it is available. Continuation of donor feeding that has already begun may, therefore, be more valuable than beginning new nutrition. The time-of-feeding variable may also warrant further investigation.

Elevated blood concentrations of inflammatory mediators, especially IL-6 and CRP, present after brain death and in early acute respiratory distress, decline after corticosteroid administration.[5,38–40] Suppression of IL-6 after corticosteroid administration is confirmed here, although the persistent elevation of serum CRP and requirement for vasoactive drugs possibly suggest continuing inflammation. Sequential laboratory tests, however, did not show other evidence of progressive inflammation, such as glucose intolerance, abnormal liver or renal function, change in respiratory quotient or increased TNF-α level. Median plasma IL-6 concentration was further reduced in fed donors who absorbed uracil at T2 and may suggest that although further reduction in IL-6 beyond that obtained from steroids did not occur immediately, some additional benefit might accrue from sustained nutrition even for the relatively short duration of 12 hours. However, because of the small number of subjects, we must interpret this result cautiously.

Limitations

Several limitations of the study must be considered. Our study was not designed to detect differences in clinical graft outcomes, so we are limited to reporting organ survival at 6 months. No intestinal transplant was included in the organs donated from this small group. Therefore, the direct effect of our enteral feeding on that organ is unknown. Donor care by our local OPO complies with national standards of "best donor care" through detailed comprehensive protocols, but may not be generalized to other OPOs, where different protocols might be used. Routine hormonal replacement for all donors was adopted as standard practice before we started using this protocol, but may be considered controversial by some.[39,41,42] If hormone replacement had been withheld, a greater effect of nutrition might have been detected. Finally, although early enteral nutrition is standard practice in our ICU, often the time between a neurological incident and the evolution of brain death may be short and thus the potential for nutritional benefit is limited. Although the time dedicated to donor care may be extended to achieve optimal cardiovascular function, data are currently insufficient to justify a delay in organ recovery to gain a possible benefit from nutritional support. As more sophisticated biomarkers of nutritional benefit become available, however, such coordination between nutritional supplementation and organ removal may be justified.

Conclusions

In conclusion, enteral feeding is safe in donors. Although no increased gastrointestinal absorption of nutrients or reduction of inflammatory cytokines was documented in fed compared with fasting donors, these data demonstrate that about 30% of donors absorb and metabolize enteral feedings. All donors in this study received hormonal replacement therapy, which is a proposed factor in these donors' elevated REE. The higher than predicted REE may suggest that energy expenditure requirements may not be met in fasting donors awaiting organ removal. The consequences of this energy imbalance remain unclear. Data here and from other sources show that corticosteroid administration lowers serum levels of proinflammatory mediators.

Acknowledgments

References

1. Adrie C, Monchi M, Fulgencio JP, et al. Immune status and apoptosis activation during brain death. Shock. 2010; 33(4):353–362. [PubMed: 20407403]

2. Singer P, Cohen J, Cynober L. Effect of nutritional state of brain-dead organ donor on transplantation. Nutrition. 2001; 17(11–12):948–952. [PubMed: 11744347]

3. Singer P, Shapiro H, Cohen J. Brain death and organ damage: the modulating effects of nutrition. Transplantation. 2005; 80(10):1363–1368. [PubMed: 16340775]

4. Barklin A. Systemic inflammation in the brain-dead organ donor. Acta Anaesthesiol Scand. 2009; 53(4):425–435. [PubMed: 19226294]

5. Kellum JA, Venkataraman R, Powner D, Elder M, Hergenroeder G, Carter M. Feasibility study of cytokine removal by hemoadsorption in brain-dead humans. Crit Care Med. 2008; 36(1):268–272. [PubMed: 18090355]

6. Perez Lopez S, Otero Hernandez J, Vazquez Moreno N, Escudero Augusto D, Alvarez Menendez F, Astudillo Gonzalez A. Brain death effects on catecholamine levels and subsequent cardiac damage assessed in organ donors. J Heart Lung Transplant. 2009; 28(8):815–820. [PubMed: 19632578]

7. Murugan R, Venkataraman R, Wahed AS, et al. Increased plasma interleukin-6 in donors is associated with lower recipient hospital-free survival after cadaveric organ transplantation. Crit Care Med. 2008; 36(6):1810–1816. [PubMed: 18496370]

8. Ogliari AC, Caldara R, Socci C, et al. High levels of donor CCL2/MCP-1 predict graft-related complications and poor graft survival after kidney-pancreas transplantation. Am J Transplant. 2008; 8(6):1303–1311. [PubMed: 18444915]

9. Venkateswaran RV, Dronavalli V, Lambert PA, et al. The proinflammatory environment in potential heart and lung donors: prevalence and impact of donor management and hormonal therapy. Transplantation. 2009; 88(4):582–588. [PubMed: 19696643]

10. De-Souza DA, Greene LJ. Intestinal permeability and systemic infections in critically ill patients: effect of glutamine. Crit Care Med. 2005; 33(5):1125–1135. [PubMed: 15891348]

11. Bansal V, Ryu SY, Blow C, et al. The hormone ghrelin prevents traumatic brain injury induced intestinal dysfunction. J Neurotrauma. 2010; 27(12):2255–2260. [PubMed: 20858122]

12. Khorana J, Rerkasem K, Apichartpiyakul C, et al. Immunonutrition and cytokine response in patients with head injury. J Med Assoc Thai. 2009; 92(2):188–194. [PubMed: 19253793]

13. Giger U, Buchler M, Farhadi J, et al. Preoperative immunonutrition suppresses perioperative inflammatory response in patients with major abdominal surgery-a randomized controlled pilot study. Ann Surg Oncol. 2007; 14(10):2798–2806. [PubMed: 17632760]

14. Cook AM, Peppard A, Magnuson B. Nutrition considerations in traumatic brain injury. Nutr Clin Pract. 2008; 23(6):608–620. [PubMed: 19033220]

15. Kreymann KG, Berger MM, Deutz NE, et al. ESPEN Guidelines on Enteral Nutrition: Intensive care. Clin Nutr. 2006; 25(2):210–223. [PubMed: 16697087]

16. Bitzani M, Matamis D, Nalbandi V, Vakalos A, Karasakalides A, Riggos D. Resting energy expenditure in brain death. Intensive Care Med. 1999; 25(9):970–976. [PubMed: 10501754]

17. Cankayali I, Demirag K, Kocabas S, Moral AR. Thermogenic and metabolic response to amino acid solution in brain-dead patients. Ulus Travma Acil Cerrahi Derg. 2009; 15(1):39–44. [PubMed: 19130337]

18. Jackson AA, Phillips G, McClelland I, Jahoor F. Synthesis of hepatic secretory proteins in normal adults consuming a diet marginally adequate in protein. Am J Physiol Gastrointest Liver Physiol. 2001; 281(5):G1179–G1187. [PubMed: 11668026]

19. Motil KJ, Opekun AR, Montandon CM, et al. Leucine oxidation changes rapidly after dietary protein intake is altered in adult women but lysine flux is unchanged as is lysine incorporation into VLDL-apolipoprotein B-100. J Nutr. 1994; 124(1):41–51. [PubMed: 8283293]

20. Devakonda A, George L, Raoof S, Esan A, Saleh A, Bernstein LH. Transthyretin as a marker to predict outcome in critically ill patients. Clin Biochem. 2008; 41(14–15):1126–1130. [PubMed: 18655780]

21. Gao C, Zhang B, Zhang W, Pu S, Yin J, Gao Q. Serum prealbumin (transthyretin) predict good outcome in young patients with cerebral infarction. Clin Exp Med. 2011; 11(1):49–54. [PubMed: 20535523]

22. Rosendale JD, Kauffman HM, McBride MA, et al. Aggressive pharmacologic donor management results in more transplanted organs. Transplantation. 2003; 75(4):482–487. [PubMed: 12605114]

23. Opekun AR, Gotschall AB, Abdalla N, et al. Improved infrared spectrophotometer for point-of-care patient 13C-urea breath testing in the primary care setting. Clin Biochem. 2005; 38(8):731–734. [PubMed: 15963485]

24. Sanaka M, Yamamoto T, Nakayama S, Nagasawa K, Kuyama Y. Reliability of the time to maximal [$^{13}CO2$] excretion and the half-[$^{13}CO2$] excretion time as a gastric emptying parameter: assessments using the Wagner-Nelson method. J Smooth Muscle Res. 2007; 43(5):201–209. [PubMed: 18075229]

25. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol. 1949; 109(1–2):1–9. [PubMed: 15394301]

26. Hergenroeder G, Redell JB, Moore AN, et al. Identification of serum biomarkers in brain-injured adults: potential for predicting elevated intracranial pressure. J Neurotrauma. 2008; 25(2):79–93. [PubMed: 18260791]

27. Tokutomi T, Morimoto K, Miyagi T, Yamaguchi S, Ishikawa K, Shigemori M. Optimal temperature for the management of severe traumatic brain injury: effect of hypothermia on intracranial pressure, systemic and intracranial hemodynamics, and metabolism. Neurosurgery. 2007; 61(1 suppl):256–265. [PubMed: 18813163]

28. Japur CC, Penaforte FR, Chiarello PG, Monteiro JP, Vieira MN, Basile-Filho A. Harris-Benedict equation for critically ill patients: are there differences with indirect calorimetry? J Crit Care. 2009; 24(4):628.e1–628.e5. [PubMed: 19327332]

29. Kross EK, Sena M, Schmidt K, Stapleton RD. A comparison of predictive equations of energy expenditure and measured energy expenditure in critically ill patients. J Crit Care. 2012; 27(3): 321.e5–321.e12. [PubMed: 22425340]

30. Tataranni PA, Larson DE, Snitker S, Young JB, Flatt JP, Ravussin E. Effects of glucocorticoids on energy metabolism and food intake in humans. Am J Physiol. 1996; 271(2 pt 1):E317–E325. [PubMed: 8770026]

31. Welle S, Nair KS. Relationship of resting metabolic rate to body composition and protein turnover. Am J Physiol. 1990; 258(6 pt 1):E990–E998. [PubMed: 2360629]

32. Calloway DH, Margen S. Variation in endogenous nitrogen excretion and dietary nitrogen utilization as determinants of human protein requirement. J Nutr. 1971; 101(2):205–216. [PubMed: 5540441]

33. Young VR, Taylor YS, Rand WM, Scrimshaw NS. Protein requirements of man: efficiency of egg protein utilization at maintenance and submaintenance levels in young men. J Nutr. 1973; 103(8): 1164–1174. [PubMed: 4719728]

34. Norton JA, Ott LG, McClain C, et al. Intolerance to enteral feeding in the brain-injured patient. J Neurosurg. 1988; 68(1):62–66. [PubMed: 3121807]

35. Krejci V, Hiltebrand LB, Sigurdsson GH. Effects of epinephrine, norepinephrine, and phenylephrine on microcirculatory blood flow in the gastrointestinal tract in sepsis. Crit Care Med. 2006; 34(5):1456–1463. [PubMed: 16557162]

36. Mentec H, Dupont H, Bocchetti M, Cani P, Ponche F, Bleichner G. Upper digestive intolerance during enteral nutrition in critically ill patients: frequency, risk factors, and complications. Crit Care Med. 2001; 29(10):1955–1961. [PubMed: 11588461]

37. Nguyen NQ, Besanko LK, Burgstad C, et al. Delayed enteral feeding impairs intestinal carbohydrate absorption in critically ill patients. Crit Care Med. 2012; 40(1):50–54. [PubMed: 21926614]

38. Kotsch K, Ulrich F, Reutzel-Selke A, et al. Methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver transplantation: a prospective randomized controlled trial. Ann Surg. 2008; 248(6):1042–1050. [PubMed: 19092349]

39. McKeown DW, Bonser RS, Kellum JA. Management of the heartbeating brain-dead organ donor. Br J Anaesth. 2012; 108(suppl 1):i96–i107. [PubMed: 22194439]

40. Seam N, Meduri GU, Wang H, et al. Effects of methylprednisolone infusion on markers of inflammation, coagulation, and angiogenesis in early acute respiratory distress syndrome. Crit Care Med. 2012; 40(2):495–501. [PubMed: 21983371]

41. Macdonald PS, Aneman A, Bhonagiri D, et al. A systematic review and meta-analysis of clinical trials of thyroid hormone administration to brain dead potential organ donors. Crit Care Med. 2012; 40(5):1635–1644. [PubMed: 22511141]

42. Ranasinghe AM, Bonser RS. Endocrine changes in brain death and transplantation. Best Pract Res Clin Endocrinol Metab. 2011; 25(5):799–812. [PubMed: 21925079]
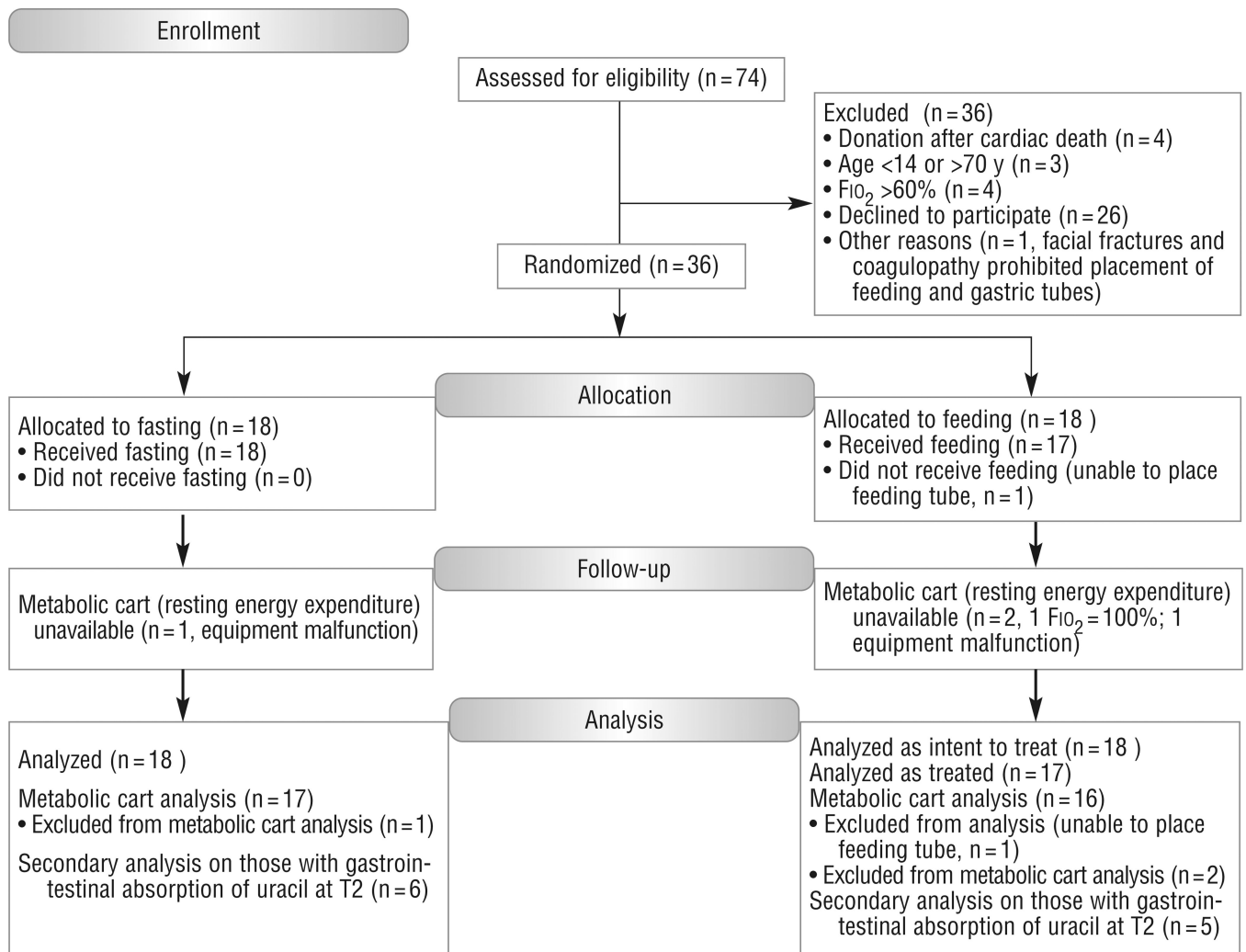
Figure.
Consort flow diagram of the progress through enrollment, intervention allocation, follow-up, and data analysis.

Table 1

Enteral nutrition: omega-3 polyunsaturated fatty acid, omega-6 fatty acid, antioxidants, and glutamine (Oxepa and Resource Glutasolve)[a]

Oxepa (Ross Products Division, Abbott Laboratories)	
	Nutrient density (per 240 mL)
Calories, cal	360
Protein, g	14.8
Carbohydrates, g	25
Fat, g	22.2
Total calories per gram of nitrogen	150:1
Nonprotein calories per gram of nitrogen	125:1
Osmolality, mOsm/kg H_2O	535
Vitamin A, IU	2840
Vitamin E, IU	75
Vitamin C, mg	205
Niacin, mg	10
Pantothenic acid, mg	5.0
Vitamin B_6, mg	1.0
Riboflavin, mg	0.85
Thiamine, mg	0.75
Folate, µg	200
Vitamin B_{12}, ug	3.0
Magnesium, mg	100
Zinc, mg	5.7
Copper, mg	0.50
Selenium, µg	18
Glutasolve (Nestlé Nutrition)	
	Nutrient density (per 22.5 g)
Calories, kcal	90
Total fat, g	0
Cholesterol, mg	0
Sodium, mg	0
Total carbohydrates, g	7
Sugars, g	0
Dietary fiber, g	0
L-Glutamine, g	15
Osmolality, mOsm/kg H_2O	310

[a]Nutritional information per manufacturers' packaging information. Manufacturers did not providing fiscal or product support for this study.

Table 2

Demographic characteristics of study participants (N = 36)

Variable	Value[a]
Male sex	25 (69)
Race	
White	34 (94)
African American	1 (3)
Asian	1 (3)
Hispanic ethnicity	15 (42)
Age, mean (SD), y	41.9 (14.7)
Body mass index[b]	27.1 (4.6)
Score on Acute Physiology and Chronic Health Evaluation II, mean (SD)	28.9 (5.1)
Primary diagnosis leading to brain death	
Traumatic brain injury	14 (39)
Subarachnoid or intracerebral hemorrhage	14 (39)
Gunshot wound to the head	6 (17)
Anoxic brain injury	2 (6)

[a]Values are number (%) unless otherwise indicated in first column. No significant results were found for any variables.

[b]Calculated as weight in kilograms divided by height in meters squared.

Table 3

Organ count and results of metabolic cart, breath test, and laboratory studies: treatment group vs control group

Variable	Time point[b]	Fed[a]		Fasted		
		No. of patients	Value	No. of patients	Value	P
Organ count, No. (%)						
Organs procured	—	18	4.4 (2.0)	18	4.6 (1.5)	.78
Organs transplanted	—	18	4.1 (2.1)	18	3.5 (1.8)	.36
Metabolic cart results, mean (SD)						
Resting energy expenditure (REE), kcal/d	T1	16	1773 (778.8)	17	1954 (691.9)	.47[c]
	T2	18	2098 (920.0)	17	1974 (666.1)	.65
REE predicted, kcal/d	T1	16	1727 (268.3)	17	1659 (369.3)	.55
	T2	18	1698 (267.1)	17	1659 (369.3)	.72
REE, kcal/d (values available for both tests)	T1	16	1773 (778.8)	17	1954 (691.9)	.47[c]
	T2	16	2109 (978.7)	17	1974 (666.1)	.64
REE predicted, kcal/d (values available for both tests)	T1	16	1727 (268.3)	17	1659 (369.3)	.55
	T2	16	1727 (268.3)	17	1659 (369.3)	.55
Timed urine urea nitrogen, mg/dL	T1	17	297.9 (254.7)	17	444.3 (459.8)	.35[c]
	T2	17	500.9 (468.2)	18	323.1 (296.2)	.16[c]
Body temperature, °C	T1	16	36.6 (1.5)	18	37.0 (1.3)	.39
	T2	16	37.1 (1.3)	15	36.8 (0.9)	.44
Breath test results, mean (SD)						
Positive, assimilated	T1	18	6 (33)	18	4 (22)	.46
	T2	18	5 (28)	18	6 (33)	.72
Laboratory study results, mean (SD)						

Variable	Time point[b]	Fed[a]		Fasted		
		No. of patients	Value	No. of patients	Value	P
Serum albumin, g/dL	T1	17	3.1 (0.7)	18	2.9 (0.6)	.50
	T2	16	2.7 (0.7)	14	2.7 (0.4)	.85
	OR[d]	18	2.6 (0.6)	18	2.6 (0.5)	.88
Prealbumin, mg/dL	T1	18	16.4 (5.3)	18	16.3 (6.5)	.95
	T2	18	14.0 (3.5)	18	14.2 (5.2)	.87
C-reactive protein, mg/L	T1	18	10.8 (9.3)	18	14.2 (10.3)	.31
	T2	18	17.0 (8.0)	18	17.7 (9.7)	.84
	OR[d]	18	17.3 (8.1)	18	18.3 (8.5)	.72
Creatinine, mg/dL	T1	18	2.1 (2.9)	17	1.3 (0.5)	.87[c]
	T2	16	1.4 (0.7)	16	1.2 (0.7)	.52[c]
	OR[d]	18	2.1 (3.1)	18	1.4 (0.6)	.79[c]
Alanine aminotransferase, U/L	T1	18	54.8 (82.9)	17	31.9 (12.8)	.62[c]
	T2	16	67.7 (103.3)	15	37.6 (29.4)	.77[c]
	OR[d]	18	79.0 (152.2)	18	36.4 (27.5)	.60[c]
Blood glucose, mg/dL	T1	11	160.9 (67.5)	16	133.4 (40.5)	.20
	T2	14	176.5 (63.3)	14	170.3 (38.9)	.76
	OR[d]	18	170.9 (58.5)	18	147.3 (40.8)	.17
Serum urea nitrogen, mg/dL	T1	18	21.5 (28.4)	17	14.4 (8.4)	.99[c]
	T2	16	16.3 (14.9)	16	13.7 (10.7)	.35[c]
	ORc	18	23.8 (27.5)	18	17.4 (12.6)	.57[c]
Interleukin 6, pg/mL	T1	18	2162 (3023)	18	1473 (1701)	.74[c]
	T2	18	264.9 (285.6)	18	565.5 (1010)	.48[c]

Variable	Time point[b]	Fed[a]			Fasted		
		No. of patients	Value		No. of patients	Value	P
Tumor necrosis factor–α, pg/mL							
	OR[d]	18	283.1 (581.9)		18	522.1 (1022)	.35[c]
	T1	18	22.1 (21.0)		18	20.5 (16.1)	.84[c]
	T2	18	12.6 (9.6)		18	12.6 (9.8)	.61[c]
	OR[d]	18	12.4 (9.3)		18	13.0 (10.4)	.80[c]

SI conversion factors: To convert albumin and prealbumin to g/L, multiply by 10; to convert C-reactive protein to nmol/L, multiply by 9.524; to convert creatinine to umol/L, multiply by 88.4; to convert alanine aminotransferase to ukat/L, multiply by 0.0167; to convert blood glucose to mmol/L, multiply by 0.0555; to convert serum urea nitrogen to mmol/L, multiply by 0.357.

[a] Patient (HN-06) was randomized to the group with nutritional supplement but failed to receive the intervention.

[b] T1 is before receiving the feeding intervention; T2 is 12 ± 2 hours after baseline; OR is just before transfer to the operating room.

[c] Wilcoxon rank sum test for variables not normally distributed. Fisher's exact test for variables with small expected cell number. Others: t test for continuous variables and χ^2 test for categorical variables. No significant results were found for any variables.

[d] For the patient without values at OR, the last available values were used.

Table 4

Median interleukin 6 levels of subjects who assimilated at time point 2

	Median interleukin 6 level, pg/mL		
Timing	Fed (n = 5)	Fasting (n = 6)	P^a
Time 1[b]	320.0	1231.1	.08
Time 2[c]	90.7	252.5	.05
Operating room[d]	21.4	153.2	.04

[a] Wilcoxon rank sum test for variables not normally distributed.

[b] Before receiving the feeding intervention.

[c] 12 ± 2 hours after baseline.

[d] Just before transfer to the operating room.