NUTRITIONAL AND IMMUNE EFFECTS OF EARLY ENTERAL FEEDING SUPPLEMENTED BY ARGININE, GLUTAMINE AND OMEGA 3 FATTY ACID IN CRITICALLY ILL PATIENTS

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ABSTRACT

***Objective**: This study was performed to evaluate nutrition, immune cell respond and clinical outcomes of early enteral feeding enriched with arginine, glutamine and omega 3 fatty acid. **Material and method**: Study design: Preliminary prospective, one center. Twenty eligible ICU patients were involved to this study by consecutive sampling from March 2003 - September 2004, age between 25-65 years, no previous infection, APACHE II score 10 -15. They were randomized to receive either standard or immune enhancing formula enriched with glutamine, arginine, omega 3 fatty acids, and high protein. Formula was given with the concentration 0.5 kcal/cc on the day one and increased to meet the target calories 25-30 kcal/kg/day and 1 - 1.5 g protein/kg/day. The laboratory measurement was made on the day one and seventh. Beside the routine measurement prealbumin and transferrin level were measured as nutritional indicator, total lymphocytes count, CD4 and CD8 cell count were used as immune function indicators. Major complication, mortality, aspiration and GI adverse reaction were observed. **Results**: The standard group received more calories (33.3 kcal/kg/day) and less protein (0.98g/kg/day) compared to immune enhancing group which received less calories b (24.9 kcal/kg/day) but more protein (1.51 g/kg/day). Prealbumin significantly increased in the treatment group, but no difference in ICU length of stay and ventilator days. The ICU mortality is higher in standard subgroup which use ventilator more than 1 week, compared to the same subgroup in immune enhancing group (3/10 vs 0/10). All of deaths were caused by severe pneumonia. Statistically, there was no significant change of TLC and CD4, CD8 cell count in both groups, but there was an inclination tendency of CD4 count and declination tendency of CD8 count in immune enhancing group. The two formulas were tolerated well since only one diarrhea in standard group. **Conclusion**: Early enteral feeding with immune enhancing in critically ill scored APACHE II 10-15 have beneficial effects for clinical outcome, nutrition and immune cell response as well.*

***Keywords**: immune cell response, nutritional and clinical outcome, immune enhancing early enteral feeding, critically ill patients*

INTRODUCTION

Most of critically ill patients, including those with major surgery, protein calorie malnutrition, injury, and burn, have immune defense dysfunction that is related to general depression of both cellular and immune function. Failure to provide nutritional support my lead to unopposed loss of lean body mass, subsequent organ dysfunction and immune depression. Recently, the line of research has focused on the use of nutrients that have the potential of altering cellular responses to mediators and improve immune function in laboratory and clinical trials. The dose of the nutrients necessary to produce this effect is higher than dose for usual nutritional support.

Result of clinical trials showed that enteral nutritional support with arginine, glutamine and omega 3 fatty acids have immune enhancing effects that improve host immune defense through different mechanism. To evaluate the clinical outcomes, nutritional and immune effects of early enteral feeding with combined arginine, glutamine and omega 3 fatty acid in critically ill patients, a preliminary prospective study was performed on this nutrient effects compared to commonly used standard enteral formula.

METHOD

An open randomized trial with consecutive sampling was done from March 2003 - September 2004 in Intensive Care Unit. Eligible patients were men and women between 20-65 years of age who referred to intensive care unit. Twenty members of the eligible patients were divided in two groups, i.e., immunoenhancing group and standard group. Patients had to fulfill the following criteria: normal renal, hepatic function, no previous evidence of infection (rectal temperature > 37.5 and or WBC > 10.000 cell/mm3), serum albumin >2.5 g%, no history of IDDM. The APACHE II score was between 10 - 15.

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Table 1. Sex, age distribution and APACHE II score

Immune Enhancing Group

No	Sex	Age(year) /BW(kg)	Diagnosis	APACHE II
1	M	61 / 70	Bulbar Palsy	11
2	F	45 / 44	Trauma Capitis	11
3	F	65 / 44	Decomp Cordis	11
4	F	66 / 50	CVA	10
5	M	49 / 70	ICH	12
6	F	59 / 50	Acute Lung Odema	14
7	M	58 / 60	Trauma capitis, op	12
8	M	33 / 65	Acute respiratory failure	11
9	M	58 / 60	Trauma Capitis	16
10	F	63 / 60	CVA	14

Standard Group

No	Sex	Age(year) /Bw(kg)	Diagnosis	APACHE II
1	M	47 / 68	CVA,	10
2	M	55 / 60	IMA †	12
3	F	32 / 60	Acute lung Odema †	13
4	F	47 / 60	COPD, respiratory failure	10
5	M	60 / 70	CVA	11
6	M	55 / 65	COPD, respiratory failure	13
7	M	46 / 60	CVA	15
8	M	48 / 65	CVA	10
9	M	60 / 50	Corpulmonale †	13
10	F	35 / 50	Acute lung Odema	11

They were expected need enteral feeding more than one week and had no contraindication to the use of enteral nutrition. The patients received enteral feeding by nasogastric tube intermittent bolus within 24 hours after admission. They were randomized to receive either standard formula or immunonutrition supplemented by L arginine, glutamine and omega 3 fatty acids.

Table 2. Formula Composition

	Standard	Immune Enhancing
Protein (g/l)	30	62.5
(% Calories)	(12%)	(25%)
Free Glutamine (g/l)	-	10.6
Free Arginine (g/l)	-	14.1
Fat (g/l)	50	28
(% Calories)	(44%)	(25%)
ω-3 fatty acids (g/l)	-	1.8
Carbohydrate (g/l)	107	125
(% kcal)	(44%)	(50%)
Fiber (g/l)	-	10 (Polydextrose)
Osmolaritym (Osm/L)	320	400

The day of entrance to the study was defined as day one. The observation was made on the day one and day seventh, based on the previous recommendation to use of immune enhancing diet for at least 7 days postoperatively. Moreover, the total energy expenditure during second week after admission will increase to 50-

60 kcal/kg BW/day (Uehara, 1999). Formula was given with the concentration 0.5 kcal/cc on the day one and increased to 1-1.5kcal/cc to meet 25 - 30 kcal/kg and 1-1.5 g/kg BW protein in next days with no more than 2000 cc/day. All patients received 5% Ringer Dextrose or 0.9% Saline to complete the water and electrolyte requirement in first days.

Measurement

Routinely laboratory measurements were done on the day one and seventh, including complete blood count, plasma electrolytes, glucose, albumin, renal and hepatic function indices. Prealbumin and transferrin level were measured as nutritional indicators as well total lymphocyte, CD4, CD8 cell count for immunological indicators. Major infection complication, mortality in the first week after admission, days on ventilator, length of stay in ICU were observed. Bronchial aspiration, gastric retention and adverse gastrointestinal symptoms i.e., nausea, vomiting, diarrhea, abdominal distension and cramping, were also recorded daily.

RESULT

A total of 20 patients were involved in this study from March 2003 - September 2004, 1 patient was excluded because of acute myocardial infarction. There were no significant demographic and APACHE II score differences between both groups. The calorie intake in standard group was 1824 kcal/day compared to 1435 kcal/day in immune enhancing group. Protein intake was 0.98 g/kg BW in standard group compared to 1.5 g/kg BW in immune enhancing group.

Clinical outcome

Initial prealbumin and transferrin level showed mild to moderate level of malnutrition. Improvement of nutritional parameter, i.e., prealbumin level, was significantly increased at the day seventh in the immune enhancing group.

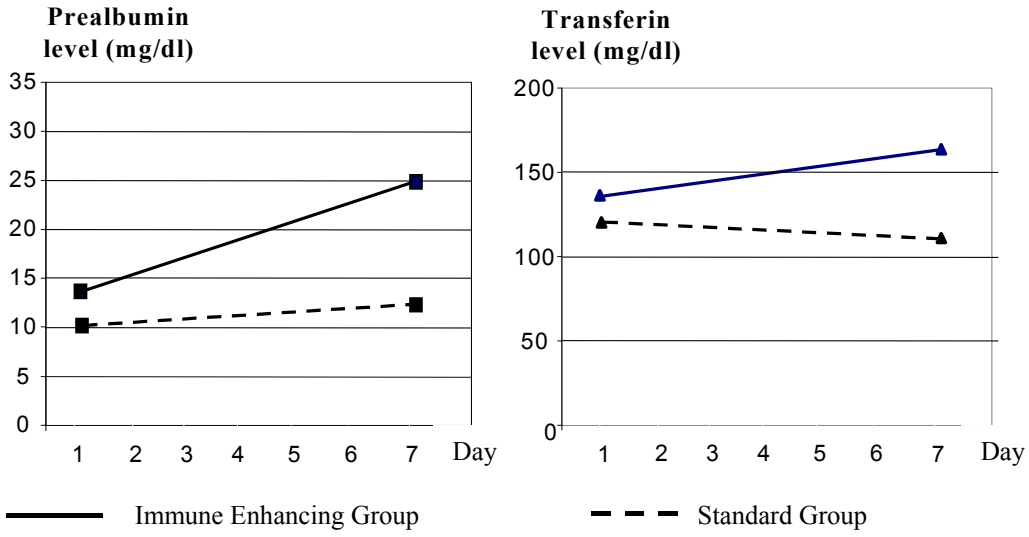

Figure 1. Nutritional Parameter

The ICU length of stay was slightly higher in standard group (12.30 + 4.99 vs. 11.10 + 3.45) as well the number of days in ventilatory support (8.30 + 4.37 vs. 7.70 + 3.34). The ICU mortality was higher in standard group (3 /10 vs. 0/10), and all deaths were caused by severe pneumonia. This mortality happened in the standard subgroup which used ventilator more than 7 days compared to no mortality in the same immune enhancing subgroup. The two formulas were tolerated well since only one diarrhea that subsided after first day in the standard group.

Table 3. Clinical Result

	Standard	Immune Enhancing	P
ICU Length of stay	11.1 ± 3.4	12.3 ± 4.9	0.734
Ventilator day	7.7 ± 3.3	8.30 ± 4.3	0.539
Mortality*	3 / 10	0 / 10	
Intolerance	1 / 10	0 / 10	

* Ventilator > 7 days
Severe pneumonia

Immunologic parameter

Statistically, there was no significant change of TLC and CD 4, CD8 cell count in both groups, but in the immune enhancing group there was an inclination tendency in CD4 count and declination tendency of CD8 cell count compared to standard group.

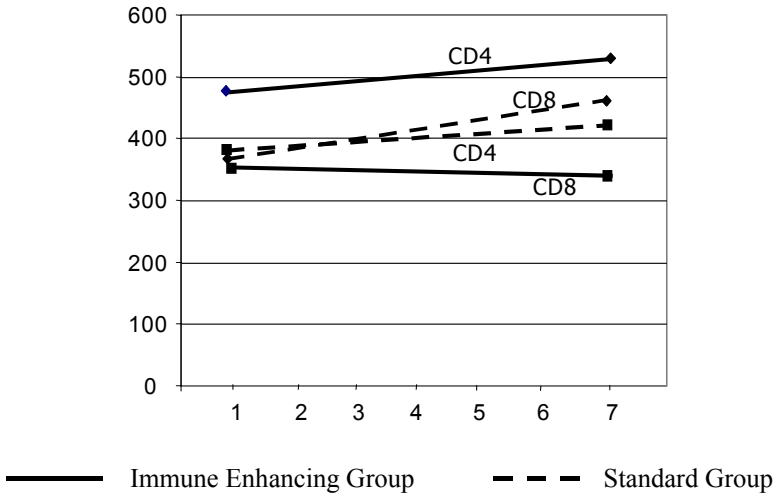

Figure 2. CD4-CD8 Level (Cell/ul)

Table 4. Immunological Parameter

	CD4/CD8 Ratio	
	< 1	≥ 1
Immunoenhancing formula	1	9
Standard formula	7	3

DISCUSSION

This study asked the question: Does this formula have a beneficial influence on nutritional, immune function and clinical outcome of critically ill, non-septic patients? Bartons and Atkinson (1998) mentioned that the immune nutrition should be administered only to the sickest patients, but Galban (2001) and Sacks (2003) had conflicting result, i.e., the beneficial effects on mortality rate seems more pronounced in less ill patient. This study was done for APACHE 10-15 patients and the result showed enhancement of some immunological parameters (CD4 cells count, CD4/CD8 ratio). Enhancement of the immune cell response will support the host immune defense function, as there was no mortality in subgroup with more than 1 week on ventilator.

Arginine is classified as semi essential amino acid. An increased need becomes apparent when tissue repair is needed, such as in subject suffering from disease or trauma. During the past 15 years it is clear from animal and human studies that arginine plays a pivotal roles in wound healing, modulation of leucocytes, platelet adhesion and leucocyte transmigration and blood flow as well (Hamendra, 2002). However, in patients with shock, sepsis or organ failure, arginine may not be beneficial (Heyland 2001, Schunier, Heyland, Peter K 2002). Glutamine represent one third of amino acid released by muscle during stress and used as fuel by rapidly proliferating cells, particularly of immune system. This substrate is an important nutrient for enterocytes that prevent intestinal barrier function as well.

There are substantial data to support glutamine supplementation in surgical and critically ill patients, to decrease infectious complication and length of hospital stay (Sacks, 2003). Unlike L arginine and glutamine, omega 3 fatty acid does not stimulate immune system. However, EPA and DHA help the system by competing with arachidonic acid for cyclooxygenase metabolism in cell membrane. Arachidonic fatty acid is an omega 6 fatty acid that in high level suppressed the immune function and promotes inflammation. The ratio of omega 3 and omega 6 in enteral formula is important for optimizing immune functions.

Research has shown that predictive Harris Benedict equations tend to overestimate the actual energy expenditure (Marino, 1997). For this reason, measurement of energy expenditure using indirect calorimetry is more accurate. But for practical reason we use simplified predictive equation and decided that the target calorie is: BEE (kcal/day) + 25 x BW(kg) and apply professional judgement in adding stress factors. Generally, a protein requirement for postoperative and critically ill patient is approximately 1-1.5 g/kg BW/day. Uehara et al (1999) calculated TEE in sepsis and trauma patients and the result were 25 +5 kcal/kg BW/day and 31 + 6kcal/kg BW/day during first week after admission.

Compared to immune enhancing group, the standard group received more calories (33,3 kcal/kg BW/day vs 24,9kcal/kg BW/day), but less protein (0.98 g/kg BW/day vs 1.51/ kg BW/day). The higher mortality in standard group may indicate that the nutritional need was not calorie loading but the quantity and quality of protein intake.

CONCLUSION

This preliminary study showed that in critically ill patient, scored APACHE II 10 -15, early enteral feeding using enteral formula enriched with Arginine,Glutamine and Omega 3 fatty acid, 25 kcal/kg BW /day and 1.5 g protein/kg BW /day enhanced quantity (prealbumin) and quality (inclination tendency of CD4) aspect that are necessary for metabolic and immune cell respond. There was lower mortality rate regarding subgroup using ventilator more than 7 days. Early feeding 24 hours after admission is safe and the formula is well tolerated.

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In theory, omega-3 fatty acids, pentoxifylline, growth hormone, testosterone, and beta blockade could also preserve muscle strength and dampen protein catabolism [2] and thereby help to prevent the long-term muscular consequences of the metabolic response to stress.Â Although the effects of energy and proteins are intertwined, we discuss caloric and protein requirements separately.Â Patients at risk should be fed slowly, and electrolyte and other micronutrient levels should be closely monitored and supplemented as required [74].Â In critically ill patients, enteral nutrition is frequently associated with underfeeding and intolerance, whereas parenteral nutrition has been associated with a greater risk of infectious complications and overfeeding [7,24,25,76]. Up until the early 1990s there were no investigations in critically ill patients available supporting these results from the clinical perspective although data from animal experiments already suggested that supplementing enteral formula with RNA, n-3 fatty acids, arginine and glutamine can improve outcome (Heyland et al.Â A third, more comprehensive and recent meta-analysis (Heyland et al. 2001) evaluated twenty-two studies of immunonutrition. The investigators found that immunonutrition may decrease infectious complication rates; however, the treatment effect varies depending on the intervention, the patient population and the methodological quality of the study. Do unresolved questions exist in immunonutrition? 3. Stimulation of the immune system. Contained in vegetables and fruits, phytoncides activate the defenses of the body and themselves effectively fight against viruses and bacteria. 4. Less salt. To give a taste to vegetable dishes, you need less salt than necessary for cooking meat. 5. Energy balance. The high content of easily digested glucose and fructose provides the body with energy and helps to lead an active lifestyle. 5 arguments against. 1. Lack of essential amino acids. Meat contains specific amino acids, which have no plant analogues. Their absence in the diet can lead to systemic d Early administration of enteral feeding, combined with immune-modulating nutrient supplementation, has been shown to promote both the structural integrity and immunological function of the gastrointestinal mucosa. Target caloric and protein intake goals should be calculated for each patient, accommodating fully for any baseline increases in nutritional needs due to the metabolic stress of injury.Â Specifically, we will discuss the use of omega-3 fatty acids, dietary nucleotides, arginine, glutamine, and various antioxidants in TBI.Â Omega-3 fatty acids (n-3FAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been shown to be of potential value in the management of patients with TBI.