Metabolic and Immune Effects of Dietary Arginine, Glutamine and Omega-3 Fatty Acids Supplementation in Immunocompromised Patients

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Abstract

To evaluate the nutritional, metabolic and immune effects of dietary arginine, glutamine and omega-3 fatty acids (fish oil) supplementation in immunocompromised patients, we performed a prospective study on the effect of immune formula administered to 11 severe trauma patients (average ISS = 24), 10 burn patients (average % TBSA = 48) and 5 cancer patients. Daily calorie and protein administration were based on the patient's severity (Stress factor with the range of 35-50 kcal/kg/day and 1.5-2.5 g/kg/day, respectively) Starting with half concentration liquid immune formula through nasogastric tube by continuous drip at 30 ml/h and increasing to maximum level within 4 days. The additional energy and protein requirement will be given either by parenteral or oral nutritional support. Various nutritional, metabolic, immunologic and clinical parameters were observed on day 0 (baseline), day 3, 7, and 14. Analysis was performed by paired student-*t* test. Initial mean serum albumin and transferrin showed mild (trauma) to moderate (burn and cancer) degree of malnutrition. Significant improvement of nutritional parameters was seen at day 7 and 14 in trauma and burn patients. Significant increase of total lymphocyte count (day 7, $P<0.01$), CD4 + count (day 7, $p<0.01$), CD8 + count (day 7, $p<0.0005$ & day 14, $p<0.05$), complement C3 (day 7, $p<0.005$ day 14, $p<0.01$), IgG (day 7, and 14, $p<0.0005$), IgA (day 7, $p<0.0005$ & day 14, $p<0.05$), in all patients. C-reactive protein decreased significantly on day 7 ($p<0.0005$) and day 14 ($p<0.005$). 3 cases of burn wound infection, one case of UTI and one case of sepsis were observed. Two cases of hyperglycemia in burn, 3 cases of hyperbilirubinemia in trauma, 10 cases of elevated LFT (5 trauma/5 burn), and one case of hyponatremia in cancer patients were observed. Two cases of nausea, 4 cases of vomiting, 5 cases of diarrhea (< 3 times/day), 2 cases of abdominal cramp, 1 case of distension were observed. The feeding of IMMUNE FORMULA was well tolerated and significant improvement was observed in nutritional and immunologic parameters as in other immunoenhancing diets. Further clinical trials of prospective double-blind randomized design are necessary to address the so that the necessity of using immunonutrition in critically ill patients will be clarified.

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The immunocompromised patient may be defined as that individual who is at increased risk for infection, often a life threatening nature. Patients with host immune defense dysfunction most commonly observed in clinical practice include those with protein calorie malnutrition, cancer, organ transplantation, diabetes, surgery, anesthesia, injury, burns, infection, acquired immune deficiency syndrome (AIDS) or those undergoing immunosuppressive drug therapy or irradiation[1]. Failure to provide nutritional support to the critically ill patient may lead to an unopposed loss of lean tissue and vital organ structure (with subsequent dysfunction) and immunosuppression[2]. More recently, individual nutrient substrates have been shown to improve immunologic function in laboratory and animal studies. Certain nutrients may affect organ function, independent of their nutritional effects. Three of these nutrients are arginine[3], glutamine[4], and the ω-3 polyunsaturated fatty acids eicosapentanoic acid and docosahexaenoic acid[5]. The target cells for the action of these nutrients appear to be T lymphocytes and macrophages[6-8].

Previous enteral nutrition studies in animals and human beings have focused on individual nutrient components. Arginine, glutamine, and a balance of ω-6 and ω-3 fatty acids have been added as supplements to standard enteral feeding components in an attempt to normalize immune function in patients. This open study was performed in severe trauma, burn and cancer patients to evaluate the metabolic and immune effects of this supplemental dietary arginine, glutamine and ω-3 fatty acids.

MATERIAL AND METHOD

A prospective open protocol was designed. Eligible patients included men and women > 18 years of age who had experienced a defined event (severe trauma, burns, and cancer). To qualify, patients needed to achieve the following criteria: normal renal and hepatic function (serum creatinine <1.5 mg/dl; total serum bilirubin <1.5 mg/dl), no history of benign intestinal disease, no previous pelvic or abdominal radiotherapy, no preoperative evidence of infection (temperature >37.6°C, WBC >10,000 cells/mm^3, or bacteremia), no administration of steroids or other immunosuppressive medications. Patients were ineligible if they had severely debilitated conditions, serum albumin < 2 g/dl, history of IDDM, body weight greater than 130 per cent of ideal body weight. All patients gave informed consent to this study which was approved by the Institutional Review Board of the hospital.

Formula Administration. Patients complying with the study protocol received enteral formula by nasogastric tube within 24 hours. The day of entrance into the study was defined as day 0. No nutrition other than clear liquids taken orally was given during the first 7 days. Progression from clear liquids to regular diet was introduced and study formula diet was allowed to be taken orally from day 8 to day 13. All patients received 5 per cent dextrose and 0.45 per cent saline solution or 0.9 per cent saline solution as clinically indicated and the amount and the type of solutions were recorded. Burn patients were given intravenous parenteral nutrition as clinically indicated and the administered energy amount was recorded. Formula administration was given on day 0, 1, 2 with the concentration of 0.5 kcal/ml at the rate of 30, 50 and 60 ml/h progressively. On day 3, 0.75 kcal/ml concentration was given at 60 ml/h. From day 4 to 13, the concentration of 1 kcal/ml was given to achieve the optimal goal (80 ml/h) of the targeted energy requirement of 25-35 kcal/kg/day.

Formula Composition. The protein component of the study formula was composed of casein (70%), arginine (20%) and glutamine (10%). The lipid component was composed of corn oil (30%), fish oil (20%) and MCT (50%). The carbohydrate component was composed of dextrins (90%) and fructose (10%). Caloric density of 1 kcal/ml and osmolarity approximately 330 mOsm/L.

Metabolic Monitoring. Blood samples were drawn for laboratory measurements on day 0, 3, 7, and 14. Tests included complete blood count, platelet count, PT, PTT, plasma electrolytes, glucose, total protein, albumin, transferrin, and indices of renal (urea, creatinine) and hepatic (GOT, GPT, alkaline phosphatase). Urine was collected for 24-h periods for measurement of nitrogen balance. Serum amino acids were measured by high-performance liquid chromatography. Serum C-reactive protein was measured to evaluate the changes in the hepatic acute phase protein during the formula administration. Nitrogen balance is a monitored variable and was not a treatment parameter.

Immunologic studies. All cell samples were analyzed on a fluorescence-activated cell scan flow cytometer (Becton Dickinson) for lymphocyte phenotyping. Expressions of CD4 and CD8 were tested. All antibodies were purchased from Becton Dickinson. Serum complement C3, IgG, M, A were also measured by the same method.

Clinical monitoring. Clinical assessment was performed and recorded daily and body weight was assessed on day 0, 3, 7, and 14. Adverse GI symptoms were recorded daily (i.e., nausea or vomiting requiring antiemetics, diarrhea of three loose bowel movements per 24 hours, abdominal distension and cramping. If moderate to severe GI symptoms such as diarrhea, nausea, vomiting, or abdominal cramping occurred, infusion was discontinued for 6 to 12 hours and started again at the next lower infusion rate. The following clinical assessment of complications was done: cardiopulmonary, infection, wound, and urinary tract system. When complications occurred, they were treated adequately either with antibiotics or surgical revision.

Statistical analysis. Variable analysis was performed in separate groups (trauma, burn and cancer) by paired Student-*t* test. The analysis was performed on SYSTAT 5.0A, p value <0.05 was required for statistical significance.

Table 1. Patient characteristics (mean).

	Trauma	Burn	Cancer
No. of patients	11	10	5
Average age (yr.)	37	27	68
Male	9	8	4
Female	2	2	1
Per cent of ideal body weight	94	99	78

Table 2. Nutritional comparisons (Mean ± SD)

TRAUMA	Day 0	Day 3	Day 7	Day 14
Caloric intake (kcal/d)	610±330	1378±688	1225±298	1794±667
Nitrogen balance (g/day)	-15±5.0	-6±0.8	-14±3.5	-6±0.8
Weight (kg)	54±6	na	52±6	49±7
Serum protein (g/dL)	5.45±0.8	6.11±0.5	6.62±0.3[a]	7.55±0.7[a]
Serum albumin (g/dL)	3.25±0.6	3.52±0.6	4.15±1.5[a]	3.9±0.5[a]
Serum transferrin (g/L)	1.92±0.4	1.77±0.4	1.96±0.4	2.13±0.6
BURN	**Day 0**	**Day 3**	**Day 7**	**Day 14**
Caloric intake (kcal/day)	1919±663	2450±632	2128±244	2260±737
Nitrogen balance (g/day)	-6±4	-22±4	-5±7	-5±9
Weight (kg)	54±11	na	50±9	50±9
Serum protein (g/dL)	4.7±0.7	5.5±0.5[b]	6.0±0.7[b]	6.6±1.1[a]
Serum albumin (g/dL)	2.5±0.6	2.9±0.5[a]	2.9±0.5	3.4±0.7[a]
Serum transferrin (g/L)	1.1±0.3	1.5±0.4	1.7±0.4[b]	2.9±1.2[a]
CANCER	**Day 0**	**Day 3**	**Day 7**	**Day 14**
Caloric intake (kcal/day)	520±315	1044±80[b]	2208±262[a]	na
Nitrogen balance (g/day)	-4.5±1.9	-1.7±0.6	2.9±3.2[b]	19.2±4.7
Weight (kg)	44±6	na	43±6	42±6
Serum protein (g/dL)	6.6±0.4	7.0±0.5	7.4±0.5	7.7±0.3
Serum albumin (g/dL)	3.45±0.5	3.82±0.8	4.0±0.8	3.8±0.5
Serum transferrin (g/L)	1.75±0.6	1.67±0.4	2.21±0.5	2.15±1.0

[a] $p < 0.01$; [b] $p < 0.05$; na = not available

RESULTS

Patient characteristics are shown in Table 1.

Nutritional results. Results of plasma protein, albumin, and transferrin are presented in Table 2 together with caloric intake, nitrogen intake, nitrogen output, nitrogen balance, and weight. There was a significant increase of those parameters in trauma and burn patients at day 7 and 14. There was no significant change in cancer patients.

Metabolic results. Mean plasma amino acid concentrations were significantly changed before and after feeding. However, mean plasma arginine levels increased from 86 μmol/L (day 0) to 218 μmol/L and 198 μmol/L, respectively on day 7 and day 14. Mean plasma ornithine levels also increased from 122 μmol/L (day 0) to 546 μmol/L and 456 μmol/L respectively on day 7 and day 14. Mean plasma glutamine level was maintained from 146 μmol/L (day 0) to 152 μmol/L and 187 μmol/L respectively on day 7 and day 14. Mean plasma alanine level increased from 374 μmol/L (day 0) to 592 μmol/L and 655 μmol/L respectively on day 7 and day 14. Mean plasma citrulline level increased from 28 μmol/L (day 0) to 38 μmol/L (day 7) and 56 μmol/L (day 14). Mean plasma branched-chain amino acids (BCAA) was maintained at 651 μmol/L (day 0), 700 μmol/L (day 7) and 805 μmol/L (day 14).

Serum C-reactive protein. In the trauma patients, plasma levels decreased significantly from baseline at day 7 ($p<0.005$) and day 14 ($p<0.01$). In the burn patients, plasma levels decreased significantly from baseline at day 7 ($p<0.05$) and day 14 ($p<0.05$). In the cancer patients, no significant change was noticed although decreasing trend existed.

Liver function tests. 2 trauma and 1 burn patients experienced hyperbilirubinemia (>1.8 mg/dl). Liver enzyme (SGOT >185 U/l) increased in 1 trauma and 1 burn patients; (SGPT >200 U/l) increased in 2 burn patients; (SGGT >250 U/l) increased in 1 trauma, 1 cancer and 4 burn patients; (alkaline phosphatase >585 U/l) increased in 1 trauma patient.

Plasma glucose. 2 burn patients experienced hyperglycemia (>250 mg/dl).

Immunological data as Figure 2

Absolute lymphocyte count. In the trauma patients, mean increase was 1268 and 307 cells/mm^3 on day 7 and day 14. In the burn

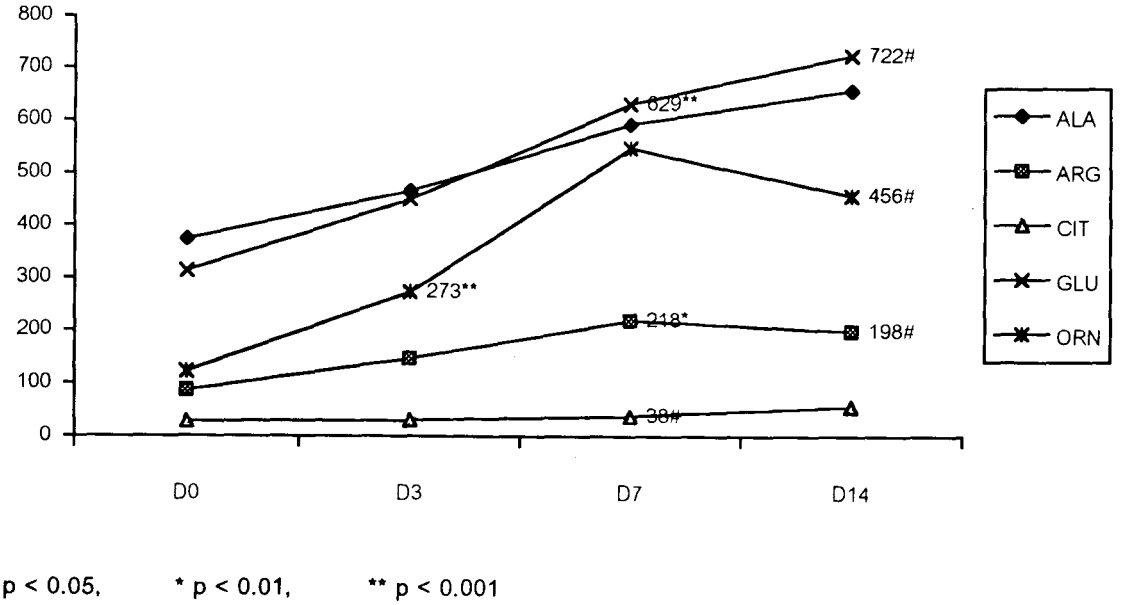

Fig. 1. Plasma Amino acids (Mean) in all patients.

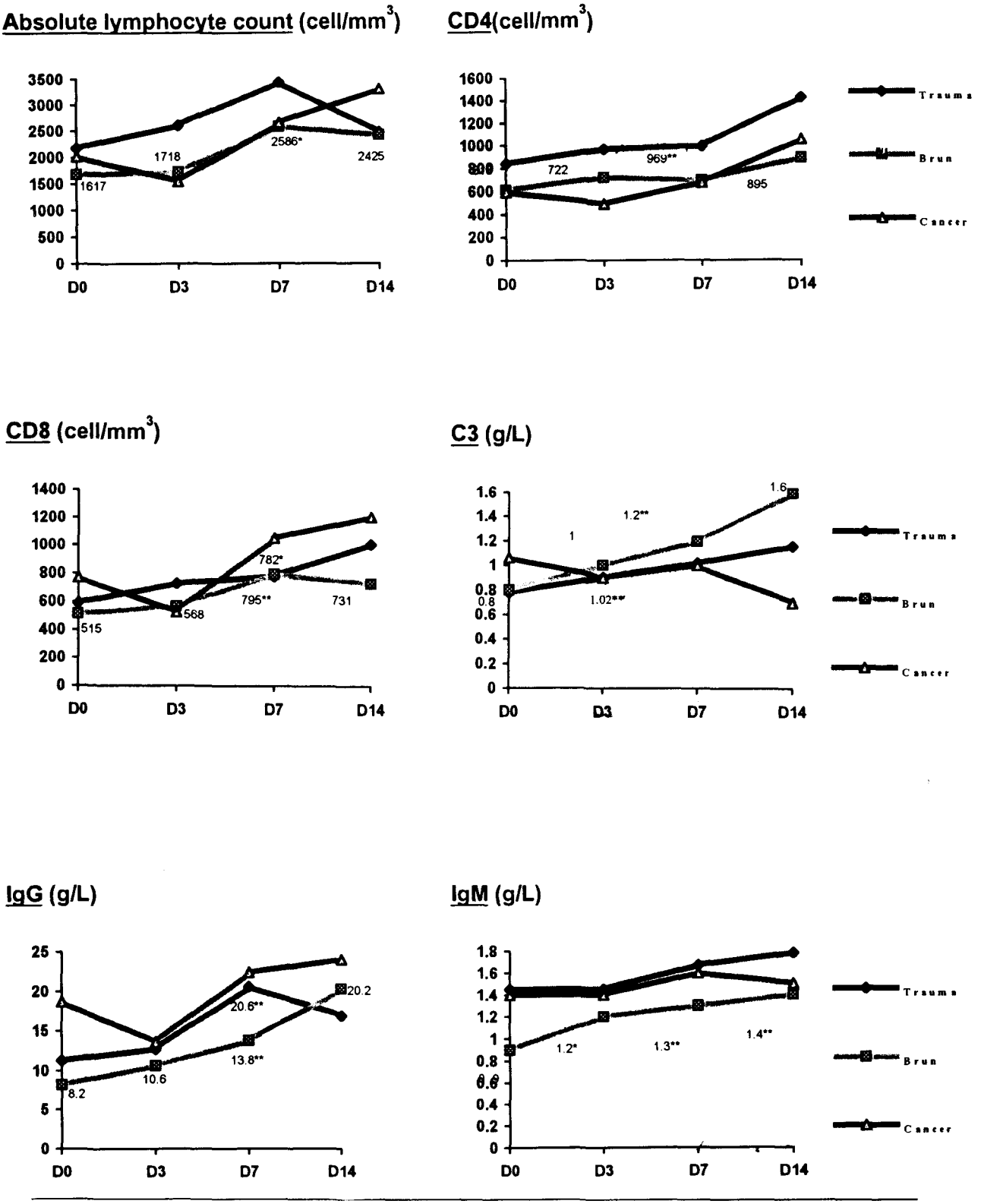

Fig. 2. Immunological results throughout the study (mean).

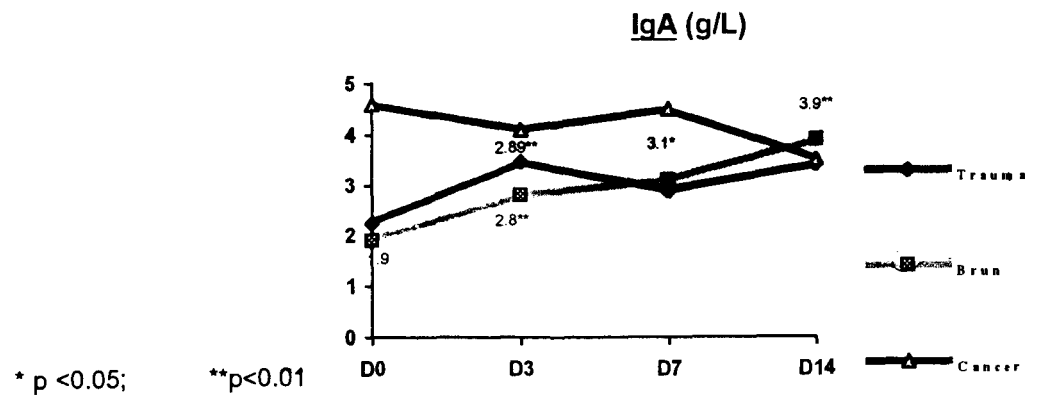

Fig. 2. Immunological results throughout the study (mean).

patients, mean increase was 910 (p=0.006) and 749 cells/mm^3 on day 7 and day 14. In the cancer patients, mean increase was 640 and 1301 cells/mm^3 on day 7 and day 14.

Lymphocyte phenotyping; CD4 cell count. In the trauma patients, mean increase was 156 and 588 cells/mm^3 on day 7 and day 14. In the burn patients, mean increase was 356 (p=0.007) and 282 cells/mm^3 on day 7 and day 14. In the cancer patients, mean increase was 79 and 460 cells/mm^3 on day 7 and day 14.

Lymphocyte phenotyping; CD8 cell count. In the trauma patients, mean increase was 191 and 417 cells/mm^3 on day 7 and day 14. In the burn patients, mean increase was 280 (p=0.004) and 216 cells/mm^3 on day 7 and day 14. In the cancer patients, mean increase was 284 and 439 cells/mm^3 on day 7 and day 14.

CD4 and CD8 ratio. There was no significant change of CD4:CD8 in all groups of patients.

Serum Complement C3. In the trauma patients, plasma levels increased significantly from baseline on day 7 ($p<0.0001$) and day 14 ($p<0.01$). In the burn patients, plasma levels increased significantly from baseline on day 7 ($p<0.01$) and day 14 ($p<0.001$). In the cancer patients, no significant change was noticed.

Serum Immunoglobulin G. In the trauma patients, plasma levels increased from baseline on day 7 ($p<0.005$) and day 14 ($p<0.01$). In the burn patients, plasma levels increased from baseline on day 7 ($p<0.005$) and day 14 ($p<0.0001$). In the cancer patients, no significant change was noticed although increasing trend existed.

Serum Immunoglobulin M. In the burn patients, plasma levels increased from baseline on day 7 ($p<0.0001$) and day 14 ($p<0.005$). In the trauma and burn patients, no significant change was noticed although increasing trend existed.

Serum Immunoglobulin A. In the trauma patients, plasma levels increased from baseline on day 7 ($p<0.01$). In the burn patients, plasma levels increased from baseline on day 7 ($p<0.05$) and day 14 ($p<0.0001$). In the cancer patients, no significant change was noticed.

Clinical complications. Complications were classified as cardiopulmonary, infectious (pneumonia, wound, abdominal, urinary and systemic) and wound healing (incision dehiscence, fistula, anastomosis). There were 3 wound infections, 1 urinary tract infection, and 1 septic complications. There was no case of organ failure, cardiopulmonary, bleeding, and wound dehiscence complications. One burn patient (80% BSA) accounted for one mortality case after 52 days of hospitalization.

Tolerance of Formula. There was 1 case of nausea (3.8%/burn), 1 case of vomiting (3.8%/burn), 5 cases of diarrhea (19.2%:1 trauma, 3 burn, 1 cancer), and 1 case of abdominal distension (3.8%/trauma). Three burn patients who experienced diarrhea had the serum albumin level of 1.6 to 2.7 g/dl (normal 3.5 - 5.5 g/dl). There was no case of treatment discontinuation due to intolerance. There was one trauma patient who refused to take oral study formula from day 8 to day 13.

DISCUSSION

Malnutrition, major operation, anesthesia, blood transfusion, and tumor burden all relate to generalized depression of both cellular and humoral immune function[10] in severe stress patients. Because of the multifactorial nature of immune suppression, the cause and extent are often unclear but appear to relate both to postoperative outcome and to disease-free survival. Recent studies suggest that the inflammatory response itself may contribute to immunosuppression through mediator inhibition of specific immunity at the level of macrophage function and lymphocyte proliferative responses.

Up to date the line of research has focused on the use of nutrients that have the potential of altering cellular responses to mediators, with a particular interest in the macrophage and in lymphoproliferative responses. In general, the doses of these nutrients necessary to produce these effects are higher than the doses necessary for general nutritional support. Hence, they have been referred to as pharmaconutrients, and their clinical use has been referred to as immunonutrition[16].

Individual nutrient substrates such as arginine, glutamine, and omega-3 fatty acids have been shown to improve host immune defenses through different mechanisms. Arginine appears to act as a promoter to T cells that are undergoing proliferation after stimulation by mitogens or cytokines. Reynolds et al[11] demonstrated increased IL-2 production and up-regulation of IL-2 receptor activity on T-cells. In patients undergoing operation dietary arginine supplementation improves mitogen-stimulated lymphocyte blastogenesis[12]. Dietary omega-3 fatty acids may affect monocyte function by means of changes in membrane phospholipid content and production of prostaglandin E2, which may be responsible for alterations in cell function such as macrophage phagocytosis, IL-1 production, and superoxide production. The purpose of this clinical study was to evaluate combinations of these supplements as part of an enteral feeding regimen in hypercatabolic patients with trauma, burn, and cancer. There were only 5 cancer patients recruited in this study so that the separate data analysis in cancer patients was not sufficient to observe the statistical differences. However, most of the clinical studies[9,13,14,15] suggested that postoperative enteral nutrition with supplementary arginine, RNA, and omega-3 fatty acids instead of standard enteral diet significantly improved immunologic, metabolic, and clinical outcomes by helping to overcome more rapidly the immunologic depression after surgical trauma. Moore F and Moore E confirmed that immune-enhancing diet enriched with arginine, glutamine, and omega-3 fatty acids is associated with improved lymphocyte proliferation, fewer abdominal abscesses, and less MOF than a standard enteral diet[17].

This study was performed in severe trauma patients with mean ISS of 24 and severe burn patients with mean %BSA of 47 and cancer patients. Enteral nutrition may prevent intestinal mucosal atrophy, enterocyte hypoplasia and decreased intestinal enzyme activity. High protein supplementation had a beneficial effect on the outcome as evidenced by improved survival; decreased incidence of infection; better opsonic index; higher levels of total serum protein, retinol binding protein, prealbumin, transferrin, C3 and IgG; and nitrogen balance[18]. Our preliminary study supported this evidence by showing significant increase in the total serum protein, transferrin, C3 and IgG. When deciding the protein supplements, not only the quantity but also the quality of amino acids necessary for the metabolic and immunologic response of the injured patients should be considered.

Glutamine is a non-essential amino acid that plays a major role in the maintenance of intestinal metabolism, structure and function. Glutamine concentration is 30 times higher in skeletal muscle than in the circulation[19]. Although glutamine release from skeletal muscle markedly increases during critical illness, circulating concentrations of this amino acid are decreased, indicating its increased uptake by other tissues such as intestinal tract in trauma patients. Oral glutamine may restore

depleted GSH (glutathione), a major antioxidant consisting of glutamate derived from glutamine, to normal levels in cancer patients, thereby, providing the intestinal tract and other organs a form of acquired resistance to oxygen free radicals generated by chemotherapy and radiation therapy. Thus, enteral glutamine supplementation may enhance the selectivity of antitumor drugs by protecting normal tissue and sensitizing tumor cells to chemotherapy related injury[19]. Administration of glutamine (0.1 to 0.57 g/kg/day) in enteral and parenteral nutrition for several weeks confirmed the clinical safety in a catabolic patient for 4 weeks[20] compared to our study in which glutamine was given 0.2 g/kg/day in average. In our study, the plasma glutamine did not increase significantly at day 7 and day 14. The possible explanation will be the selective uptake of glutamine in the gastrointestinal tract or whole blood glutamine is extracted by the splanchnic bed. An obligatory glutamine requirement by certain tissues (such as the enterocytes of the small bowel and stimulated macrophages) must first be satisfied before improvement in whole body nitrogen economy occurs[20]. If we could measure the intracellular muscle glutamine, the maintenance of intracellular muscle glutamine could be seen even if the plasma glutamine level did not increase significantly[21].

Accumulated scientific evidence showed that supplemental arginine decreased protein catabolism and enhanced nitrogen retention; accelerated wound healing; enhanced immune response; lessened the decrease in thymic weight and lymphocyte content that ordinarily follows injury; was necessary for maximal rate of recovery from malnutrition; corrected some cases of hyperammonemia; decreased the incidence of sepsis and reduced length of hospital stay[18].

Manipulation of macrophage eicosanoid production by use of omega-3 PUFA may reduce the cellular immune response (by competing with arachidonic acid, which produces inflammatory eicosanoids of the 2- and 4- series), whereas, inclusion of MCT may lower the arachidonic acid content of membrane phospholipids[22]. In our study, the inclusion of essential fatty acid, linoleic acid, omega-3 fatty acids, EPA & DHA, and MCT may have reduced inflammation and immune dysfunction observed in critically ill patients. Selection of optimal lipid sources in enteral nutrition should include medium-chain fatty acids, omega-3 fatty acids, and blended and structured lipids[23]. The optimal ratio for omega-6 to omega-3 fatty acid is unknown but a view is taken that this might be 5:1 but as yet this is not based on any firm evidence from controlled clinical trials[24]. The most prominent decrease in the rate of release of immunosuppressive eicosanoids from macrophages by dietary interventions has been reported with the use of a mixture of menhaden oil (fish oil) and medium-chain triglycerides[25,26]. The value of MCT and LCT compared to LCT alone in critically ill patients with impaired immune function was strongly supported by other studies[27,28].

The severity of injury or infection is also reflected in the nitrogen (N) balance. Isolated head injury induces marked N loss, and protein conservation has not been achieved even by increasing caloric intake up to and beyond twice the basal energy expenditure[29]. Nitrogen losses of patients with injury cannot be fully prevented by nutrition. In severe injury, the mandatory losses of N are much higher and may continue for weeks. During persistent catabolic stimuli, even high nutrient intakes will only reduce N losses, but N equilibrium or positive N balance will not be achieved before convalescence begins. Human growth hormone and IGF-1 have recently been studied to reduce net protein losses to some degree during TPN in severely catabolic injured patients. In our study, positive N balance was achieved in cancer patients as they were not as hypercatabolic as other trauma and burn patients. Less negative N balance was achieved on day 14 compared to day 0 or day 3 in severely injured and burn patients.

In general, most of the available critical care products are of a high fat, high linoleic acid, deficient in certain amino acids, and other substances, which may be necessary to mount an optimal response to major injury[18]. A modular tube feeding (MTF) formula, a high protein (20%), low fat (15%), linoleic acid-restricted, omega-3 fatty acids enriched, and arginine supplemented (2%) was designed to improve immune defense, optimize wound healing, and lower production of the proteolytic and immunosuppressive dienoic prostaglandins[18].

Infectious complications in our study were expected due to the nature and severity of the disease process in severe trauma and burns.

One case of sepsis was noted in our study which was not related to the severity of the I.S.S. (ISS= 14). 3 cases of wound infections were noted in burn patients which may be related to the severity of burns in our study (average %BSA=37.3). UTI was noted in one cancer patient which may be related to the secondary infection of the cancer chemotherapy. Further clinical trials of prospective randomized design are necessary to address the issue of reduction of infections, MOF score, and length of hospital stay to clarify the importance of immunonutrition in critically ill patients.

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การศึกษาผลของอาหารสูตรเพิ่มภูมิคุ้มกันในผู้ป่วยอุบัติเหตุ, ไฟลวก และโรคมะเร็ง

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ภาวะทุพโภชนาการมักเกิดร่วมกับภาวะภูมิคุ้นกันบกพร่องในผู้ป่วยหลังได้รับอุบัติเหตุรุนแรง เช่น ผู้ป่วยไฟลวก, หรือผู้ป่วยมะเร็ง ได้ทำการศึกษาผลของการให้โภชนบำบัดด้วยอาหารเหลวสูตรเพิ่มภูมิคุ้นกัน ซึ่งเป็นสูตรใหม่มีการเพิ่มความเข้มข้นของกลูตามีน, อาร์จีนิน และกรดไขมันประเภทโอเมก้าสาม ในผู้ป่วยอุบัติเหตุ 11 ราย ความรุนแรงของการบาดเจ็บ (ISS) อยู่ระหว่าง 15-35, ผู้ป่วยไฟลวก 10 ราย ขนาดของแผลอยู่ระหว่าง 30-60% ของพื้นที่ร่างกายและผู้ป่วยมะเร็ง 5 ราย โดยให้พลังงานต่อวันเท่ากับ 35-50 kcal/kg/day ให้โปรตีนประมาณ 1.5-2.5 g/kg/day เริ่มต้นให้อาหารเหลวสูตรอิมมูนด้วยความเข้มข้นเพียงครึ่งหนึ่งในวันแรกโดยผ่านทางสายยางเข้าจมูกในอัตรา 30 ลบ.ซม./ชั่วโมง จากนั้นจึงเพิ่มความเข้มข้นเป็นปกติและเพิ่มอัตรามากขึ้นใน 4 วันแรก และจะให้อาหารทางหลอดเลือดดำเสริมให้ได้เท่ากับพลังงานที่ผู้ป่วยต้องการในแต่ละวัน ผู้ศึกษาได้ทำการตรวจเลือดในวันแรก, วันที่ 3, 7, 14 ของการศึกษาเพื่อเปรียบเทียบในด้านระบบภูมิคุ้นกัน, การทำงานของตับ, และการเปลี่ยนแปลงของโปรตีน ผลการศึกษาพบว่า มีการเพิ่มขึ้นของลิมโฟซัยต์ในวันที่ 7 อย่างมีนัยสำคัญ, ผลของ CD4, CD8 คอมพลีเมนท์ C3 มีการเพิ่มขึ้น ในวันที่ 7 และ 14 ของการศึกษา รวมทั้ง IgG, IgA ด้วยส่วน C-reactive protein มีการลดลงในวันที่ 7 มีอาการแทรกซ้อนบางประการเกิดในระหว่างการศึกษา เช่น ผู้ป่วยไฟลวก 3 ราย เกิดแผลติดเชื้อ และการติดเชื้อในทางเดินปัสสาวะ มีอาการคลื่นไส้ อาเจียน และท้องเสีย เกิดขึ้นบ้าง กล่าวโดยสรุปแล้ว อาหารสูตรเพิ่มภูมิคุ้มกัน จะช่วยเพิ่มความแข็งแรงของภูมิคุ้นกันในผู้ป่วยอุบัติเหตุ, ผู้ป่วยไฟลวกและผู้ป่วยมะเร็งได้

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