EFFECT OF IMMUNE-ENHANCING DIETS ON THE OUTCOMES OF PATIENTS AFTER MAJOR BURNS

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SUMMARY. The use of immune-enhancing diets (IEDs) has been shown to be beneficial in some categories of critically ill patients. This study aimed to evaluate the effect of early enteral feeding supplemented with glutamine and omega-3 fatty acids, as immune-enhancing diets, on the outcomes of patients after major burns. Forty thermally injured adult patients with 30-50% total body surface area (TBSA) burns, including deep areas ranging from 5-20%, were randomized into a prospective, double-blind, controlled clinical trial. They were placed into two equal groups: group A (IED group), in which patients received early enteral feeding supplemented with glutamine and omega-3 fatty acids as immune-enhancing diets; and group B (control group), in which patients received early enteral feeding not supplemented with immune-enhancing diets. Laboratory assessment of serum albumin, serum C-reactive protein, total lymphocytic count and serum immunoglobulins (IgA, IgG and IgM) was performed at admission, and on days 4, 7 and 14. Finally, outcomes were assessed by monitoring the survival rate, the length of hospital stay and the incidence of infection. There were no significant differences between the IED and control group regarding age (28.7±5.32 versus 29.85±5.94), sex, weight, %TBSA (37.75±4.4 versus 38.3±4.84) and %burn depth (11.7±2.36 versus 10.7±2.036). The incidence of infection (2 versus 8) and the length of hospital stay (16.3±0.92 days versus 17.95±2.96 days) were decreased significantly in the IED group versus the control group. There was no significant difference between the survival rates in both groups as there was only one death in the control group. Thanks to IEDs, patient outcome was improved and infectious morbidity and length of hospital stay were reduced, but there was no effect on the survival rates following major burns.

Keywords: immune-enhancing diets (IEDs), major burns, survival, glutamine, omega-3 fatty acids

Introduction

In major burns patients, severe traumatic stress, high inflammatory response and high catabolism lead to protein-energy malnutrition and further consumption of fat deposit and lean tissue.[1] This can cause a decrease in immune function, the structural and functional impairment of the intestinal barrier and the translocation of bacteria and endotoxin. The resultant systemic inflammatory response and the risk of infection thus affect the prognosis of patients.[2]

Despite improvements in prevention and management, burn injury continues to represent a major worldwide health threat to people of all ages. Even with early surgical intervention and early enteral feeding, infectious complications are a major cause of death in severe burn injury.[3] Increased understanding of the effects of different nutrients on disease processes has led to the development of specialized enteral nutrition formulas.[4]

Enteral immunonutrition (*also called immune enhancing diets = IED)* refers to the addition of some specific nutrients into enteral nutrition (EN), which help to increase the immune function, improve the gut mucosal barrier,[5] and reduce the inflammatory reaction and septic complications.[6] Nutrients of interest are glutamine, arginine, and omega-3 fatty acids (fish oil).[7]

Glutamine provides substrate for gut, immune cells, and kidneys.[8] Beneficial effects of glutamine include the following: anti-oxidant effects (as a precursor of glutathione), inducing production of heat shock proteins, maintaining gut barrier function by providing fuel for enterocytes, as an energy substrate for lymphocytes and neutrophils, and stimulation of nucleotide synthesis.[9,10]

Omega-3 fatty acids are incorporated into cell membranes and help reduce tissue inflammation and the general inflammatory response with subsequent immunosuppression that normally occurs after surgery.[11] They are unique in their ability to modulate the immune-response.[12]

This study was undertaken to evaluate the effect of early enteral feeding supplemented with glutamine and

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omega-3 fatty acids on the outcome of patients after major burns.

Patients and methods

This study included forty thermally injuried adult patients of both sexes, aged between 20-50 years, who were admitted for burn injuries affecting a total body surface area (TBSA) of 30-50%, including deep areas ranging from 5-20%. These patients were admitted to the Burn Unit of Tanta university Hospital between July 2009 and July 2012. Patients admitted more than 24 hours post injury, those with chronic diseases, inhalation injury and those who needed for life supporting measures were also excluded from the study.

All patients underwent detailed clinical evaluation, immediate resuscitation, and early enteral feeding with a high fiber diet from 12 hours post injury, with a caloric goal of 30 kcal/kg body weight, including 20% of calories given as protein. Early excision and auto-grafting using the tangential method was done for deep burns within 3-5 days post burn and selective gastrointestinal decontamination was also carried out.

All patients were randomized according to the sequence of their hospital admission into two equal groups:-

1) IED Group: these patients received early enteral feeding supplemented with 0.3g/kg/d glutamine and 3g/d omega-3 fatty acids (as L-glutamine and omega-3 plus capsules).
2) Control Group: these patients received early enteral feeding not supplemented with immune-enhancing diets.

Clinical assessment included monitoring of changes in body weight, incidence of infection and nutritional complications. Laboratory assessment of serum albumin, serum C-reactive protein, total lymphocytic count and serum immunoglobulins (IgA, IgG and IgM) were performed on admission and on days 4, 7 and 14 post admission. Finally, outcomes were assessed through monitoring of the survival rate, the length of hospital stay and the incidence of infection.

The data derived from statistical analysis are presented as means and standard deviations. The incidence of infection and other qualitative parameters were compared by using the chi-square test. Laboratory data means between groups and other quantitative parameters were analyzed by unpaired Student's t-test. The level of significance was set at $p<0.05$.

Results

A total of 40 patients were included in the study between July 2009 and July 2012.

As shown in *Table I*, there were no significant differences between both groups regarding age, sex, weight, TBSA burned and burn depth. 82.5% of our patients underwent excision and grafting on day 4 post admission, while 17.5% of our patients underwent excision and grafting on day 5 post admission. There were no significant differences between both groups as regards the operative day, the excised deep burns and the amount of intra-operative blood loss. As regards clinical evaluation, there was no significant difference in the body weights showed between both groups at admission and on days 4 and 7, but on day 14 there was a significant increase in the body weights of the IED group compared to the control group (P=0.010).

Table I - Study population variables (means±SD)

Variable	*Group lED*	*Group Control*	*p Value*
Age (yrs)	28.7±5.3	29.9±5.9	NS
Body weight (kg)	73.8±5.8	72.4±6.6	NS
BSA %	37.8±4.4	38.3±4.8	NS
Deep burns %	11.7±2.4	10.7±2.04	NS (0.15)
Estimated blood loss (ml)	377.5±111.8	395.0±120.2	NS
Extent of excision (% BSA)	11.7±2.4	10.7±2.04	NS (0.15)
Body weight (kg) (admission)	73.8±5.8	72.4±6.6	NS
Day 4	77.4±5.8	76.4±6.9	NS
Day 7	74.2±5.6	72.7±7.2	NS
Day 14	65.9±5.8	60.5±6.5	0.010

There was no significant difference between both groups with regard to nutritional complications. However, the incidence of infection and the length of hospital stay were decreased significantly in the IED group compared to the control group. There was only one death in the control group and there was no significant difference between the survival rates in both groups, as shown in *Table II*.

Table II - Outcome data

Variable	*Group lED*	*Group Control*	*p Value*
No. of infections	2	8	0.028
Length of hospital stay (days)	16.3±0.92	17.95±2.96	0.023
No. of deaths	nil	1	NS

Table III shows that none of the laboratory variables differed at admissions. Serum albumin showed no significant difference between both groups at days 4, 7 and 14 post admission, and serum C-reactive protein showed no significant differences between both groups at day 4. However, a significant decrease in serum CRP was noted on days 7 and 14 in the IED group compared to the control

Table III: Laboratory data

Variable	*At admission*		*Day 4*		*Day 7*		*Day 14*	
	lED	Control	lED	Control	lED	Control	lED	Control
Alb(gm/dl)	3.72±0.21	3.69±0.23	3.28±0.15	3.27±0.20	2.89±0.15	2.83±0.13	3.84±0.17	3.70±0.25
CRP (mg/l)	25.30±3.7	25.75±2.7	54.75±3.7	56.75±4.4	26.0±2.90	31.55±6.6[a]	12.1±5.21	19.95±8.4[b]
TLC(cell/mm^3)	2029±306	2035±287	1965±311	1985±317	2394±293	2241±282	2728±297	2498±367[c]
IgA (mg/dl)	172.8±18.9	174.9±18.1	145.9±20.9	145.2±19.8	178.9±22.5	165.9±20.4	227.2±29.6	202.3±17.4[d]
IgG (mg/dl)	974.7±83.2	965.5±89.2	899.6±108.8	897±101.2	1019.9±124	959.9±98.4	1167.1±143.8	1080.3±93.5[e]
IgM (mg/dl)	91.9±17.2	93.1±19.2	73.7±22.3	72.2±20.9	100.5±24.0	97.7±24.0	150.9±30.0	133.7±20.5[f]

Alb=albumin CRP=C-reactive protein TLC=total lymphocytic count

[a]: p = 0.002 [b]: p = 0.001 [c]: p = 0.038 [d]: p = 0.003 [e]: p = 0.032 [f]: p = 0.044

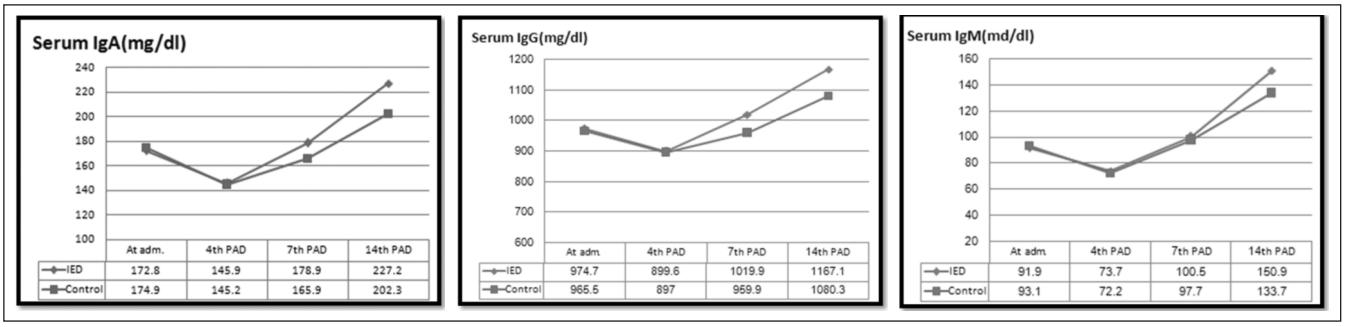

Fig. 1 - Serum immunoglobulins.

group (p=0.002 and p=0.001 respectively). As regards the total lymphocytic counts, there were no significant differences between both groups at days 4 and 7, while the total lymphocytic counts showed a significant increase on day 14 post admission in the IED group compared to the control group (p=0.038). The serum immunoglobulins (IgA, IgG and IgM) showed no significant differences between both groups on days 4 and 7, while they significantly increased at day 14 in the IED group compared to the control group, as shown in *Fig. 1*.

Discussion

Many studies evaluated the use of immunonutrients in patients with burn injury either alone or in combination, but still there is debate about their benefits in severely burned patients. In this study, we aimed to evaluate the effect of early enteral feeding supplemented with glutamine and omega-3 fatty acids on the survival rates of patients after major burns.

Forty adult acutely burned patients were enrolled in this study. The patients were randomly divided into even groups. There was no significant difference between both groups as regards the demographic data, but we observed a predominance of burn injuries in young adult males, which is consistent with other studies.[11,12]

The enteral feeding route is recommended in burn patients by Rousseau et al.[13] as it preserves gut barrier function, reduces infectious complications and prevents gut atrophy.

We noticed that there was a significant increase (P= 0.01) in the body weights of the IED group compared to the control group on day 14 post admission. Similar to our study and findings, Li et al.[14] studied the effect of total parenteral nutrition (TPN) with and without glutamine dipeptide supplementation on outcome in severe acute pancreatitis. They concluded that body weight increased significantly after 2 weeks of TPN supplemented by glutamine dipeptide when compared with standard TPN.

Our study demonstrated a significant decrease in the incidence of infection (p=0.028) and the length of hospital stay (p=0.023) in the IED group compared to the control group. These data are consistent with the results of Pattanshetti et al.,[15] who studied the impact of enteral glutamine supplementation on infectious morbidity and hospital-stay in burns patients. They are also consistent with the findings of Peterik et al.,[16] who performed a meta-analysis of published randomized controlled trials of IMD's in critically ill patients. These results could be explained by the hypothesis that glutamine may enhance gut barrier function and prevent bacterial translocation from the gut.

Contrary to our results, Jaung et al.,[17] in a retrospec-

tive case-control evaluation of the enteral glutamine supplementation in critically ill patients with burn injuries, found that enteral glutamine supplementation was not associated with a change in the infection rate compared to the control group. However, this was attributed to more cases of bloodstream infections and fewer cases of pneumonia and cellulitis in the glutamine group.

We observed a significant decrease in serum C-reactive protein on days 7 and 14 in the IED group compared to the control group (p=0.002 and p=0.001 respectively). This finding is consistent with the results of the study by Houdijk et al.,[18] in which trauma patients receiving glutamine showed decreases in serum concentrations of soluble tumor necrosis factor receptors. These results suggest that enteral immunonutrition decreases the overall systemic inflammatory response, which may be related to the relative decrease in bacteremia or affect the release of proinflammatory cytokines.

In our study, serum albumin showed no significant difference between both groups at all studied times. The above data were confirmed by Mauskopf et al.,[19] who studied the effect of immunonutrition on patients undergoing elective surgery for gastrointestinal cancer, and De-fang et al.,[20] who studied the effectiveness of enteral immunonutrition (EIN) in patients undergoing liver transplantation. De-fang et al. found that serum albumin showed no significant difference ($P > 0.05$) between both groups, while serum prealbumin and cholinesterase levels were significantly higher in the EIN group than the EN group ($P < 0.05$). This could be attributed to the long half-life of albumin (20 days) in comparison to the short half-life of pre-albumin (2 days), whose increase has been demonstrated to correlate with a positive nitrogen balance. They concluded that enteral immunonutrition can promote short half-life protein synthesis.

The total lymphocytic counts and the serum immunoglobulins (IgA, IgG and IgM), while not differing upon admission, significantly increased by day 14 post admission in the IED group compared to the control group. Our data confirmed Zheng et al.,[21] who evaluated the clinical and economic validity of perioperative immunonutrition and the effect on postoperative immunity in patients with gastrointestinal cancers. Our findings also agreed with those of Cetinbas et al.,[22] who administered intravenous glutamine-supplemented TPN to patients with systemic inflammatory response syndrome (SIRS) to investigate the effect of glutamine supplementation on immune states, and Li et al.,[2] who studied the effects of enteral immunonutrition on immune function in patients with multiple trauma.

These results indicate that enteral immunonutrition is more helpful for the recovery of both humoral and cellular immune function. This could be explained by the hypothesis that glutamine supplemented enteral nutrition preserves intestinal IgA concentrations, prevents atrophy by normalization of cellular population, maintains functional mucosal immunity and acts as a direct fuel for the lymphocytes.[23]

Despite the attenuation of infectious morbidity and systemic inflammation, there was no significant difference between the survival rates in both groups. These data are consistent with the findings of Wischmeyer et al.,[24] who studied the effect of intravenous glutamine supplementation vs. an isonitrogenous control on infectious morbidity in severely burned patients and found that there was no significant decrease in overall mortality. A larger trial would be necessary to examine the effect of enteral immunonutrition on mortality.

Conclusion

Enteral nutrition supplemented with glutamine and omega-3 fatty acids is a safe and effective tool in major burn patients. Although it has no effect on the survival rates after major burns, it is associated with improved patient outcome, as well as reduced infectious morbidity and length of hospital stay. This beneficial effect may be a result of improved gut integrity, enhanced immune function and modulation of inflammatory response.

RÉSUMÉ. L'utilisation de régimes qui stimulent le système immunitaire a été montrée à être bénéfique dans certaines catégories de patients gravement malades. Cette étude sur les patients atteints de grands brûlés visait à évaluer l'effet de l'alimentation entérale précoce complétée par la glutamine et les acides gras oméga-3 pour stimuler le système immunitaire. Quarante patients adultes thermiquement blessés avec 30-50% de la surface corporelle totale (SCT) brûlée, y compris les zones profondes allant de 5 à 20%, ont été randomisés dans une étude prospective et clinique contrôlée, en double aveugle. Ils ont été placés en deux groupes égaux: le groupe A, dans lequel les patients ont reçu une alimentation entérale précoce complété avec de la glutamine et acides gras oméga-3 pour stimuler le système immunitaire; et le groupe B (groupe de contrôle), dans lequel les patients ont reçu une alimentation entérale précoce sans la régime pour stimuler le système immunitaire. L'évaluation en laboratoire de la sérum-albumine, sérum protéine C-réactive, la numération lymphocytaire totale et les immunoglobulines sériques (IgA, IgG et IgM) a été réalisée à l'admission et aux jours 4, 7 et 14 après l'admission. Enfin, les résultats ont été évalués en surveillant le taux de survie, la durée du séjour à l'hôpital et l'incidence de l'infection. Il n'y avait pas de différence significative entre le groupe A et le groupe de contrôle relative à l'âge (28,7 ± 5,32 contre 29,85 ± 5,94), le sexe, le poids, le % de la SCT (37,75 ± 4,4 contre 38,3 ± 4,84) et la profondeur de la brûlure (11,7 ± 2,36 ± contre 10.7 2.036). L'incidence de l'infection (2 contre 8) et la durée du séjour à l'hôpital

(16,3 ± 0,92 jours contre 17,95 ± 2,96 jours) ont diminué significativement dans le groupe A par rapport au groupe de contrôle. Il n'y avait pas de différence significative entre les taux de survie des deux groupes car il y avait seulement une mort dans le groupe de contrôle. Il y avait une amélioration dans les résultats des patients, et une réduction de la morbidité infectieuse et la durée du séjour à l'hôpital, mais aucun effet sur les taux de survie après des brûlures importantes.

Mots-clés: régimes pour stimuler le système immunitaire, grands brûlés, survie, glutamine, acides gras oméga-3

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