THE EFFECTS OF INTRAVENOUS GLUTAMINE SUPPLEMENTATION IN SEVERELY BURNED, MULTIPLE TRAUMATIZED PATIENTS

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Abstract

The severely burned patient is the most demanding patient from the metabolic point of view. The catabolic response is impressive - the most dramatic from all pathologies - and the body reacts by breaking down the skeletal muscle. Glutamine is the most abundant aminoacid with numerous functions in the body and even if it is not recognized as an essential amino acid in severely burned patients it becomes conditionally essential. Glutamine has many important functions in metabolism, in immune function, in wound healing and gut integrity. It is the preferred fuel for cells with high rate mitosis like immune cells, pulmonary alveolar cells and enterocytes. A number of studies attempted to analyze the efficacy of glutamine supplementation in severely burned patients. This study is a prospective, randomized one, performed on 47 patients with severe burns admitted in the Emergency Clinical Hospital of Bucharest, Romania, from 2005 to 2011, trying to assess the effects of intravenous glutamine supplementation.

Rezumat

Pacientul cu arsuri severe este cel mai consumptiv activ pacient din punct de vedere metabolic. Răspunsul catabolic este impresionant – cel mai important din toate patologiile existente – iar organismul recţionează prin proteoliza musculaturii scheletice. Glutamina este aminoacidul cel mai bogat reprezentat, având numeroase funcţii în organism şi în cazul pacienţilor cu arsuri severe el nu mai poate fi sintetizat paralel cu necesarul, devenind astfel "condiţionat esenţial". Glutamina are numeroase funcţii în metabolism, în imunitate, în vindecarea plăgilor şi în menţinerea integrităţii mucoasei intestinale. Ea este "combustibilul" preferat al celulelor cu o rată înaltă a mitozei – precum celulele sistemului imunitar, celulele alveolare pulmonare şi enterocitele. Mai multe studii au încercat să analizeze eficacitatea suplimentării cu glutamină la pacienţii cu arsuri severe. Acest studiu este un studiu randomizat, realizat asupra a 47 de pacienţi cu arsuri severe internaţi în Spitalul Clinic de Urgenţă Bucureşti în perioada 2005-2011, ce îşi propune să analizeze efectele suplimentării intravenoase cu glutamină la aceşti pacienţi.

Keywords: severe burns, glutamine, nutritional therapy

Introduction

The patient with severe burns – more than 25% of the total body surface affected – is a totally peculiar patient from the nutritional point of

view. If the great necessities of calories and proteins seems to be well understood in the last years the attention was focused on some dietary supplements that can improve the immune function, the wound healing and can reduce the ICU (Intensive Care Unit) and hospital stay and generally the morbidity and mortality. This was the beginning of "pharmacological nutrition". For some of these nutritional supplements debates still exist and further studies are needed to prove the efficiency or advantages of their use. The most promising from all these supplements seems to be the glutamine. Glutamine is the most abundant amino acid in the human body, more than 60% in skeletal muscle and 25% of the free amino acids pool in the extracellular fluid, with many important functions: precursor for protein synthesis, role in acid-base homeostasis, fuel for the cells with high rate mitosis like enterocytes, alveolar cells, lymphocytes, macrophages.[2,9] In extremely catabolic states the production of glutamine in the body doesn't meet the huge necessities for acute phase protein synthesis, wound healing and immune system function so the body reacts by breaking down the structural proteins.[8,9] Severely injured patients usually need parenteral nutrition. Standard amino acid solutions are poor in glutamine content due to the instability of the glutamine. This problem was overcome by the use of synthetic dipepetides alanyl-glutamine available in Romania under the name Dipeptiven® (Fresenius-Kabi). After infusion the dipeptide is hydrolyzed and glutamine is released.

Material and Methods

This randomized, double-blind, placebo-controlled study was conducted at the Emergency Clinical Hospital "Floreasca", Bucharest, Romania. This study was approved by the hospital ethical committee and after obtaining the written informed consent from patients families 59 severely burned patients admitted in the Emergency Clinical Hospital "Floreasca" from 2005 till 2011 were included in this study. Inclusion criteria were: age over 14 and under 75, burned surface more than 25% of total body surface and admission in ICU within the first 72 hours after the burn injury. Exclusion criteria were previous chronic illness like cardiovascular serious diseases, renal or hepatic diseases, patient's or patient's family refusal to participate at the study and death in the first 7 days from admittance. We enrolled 59 patients, 6 patients died in the first 7 days from admittance, 2 patients have been transferred towards another medical center and 4 patients decided to withdraw from the study. The 47 remaining patients were participants at the study being randomized in 2 groups: the control group composed of 23 patients and the study group composed of 24 patients. The care-givers were the same during this period,

all the patients benefiting from the same protocols regarding surgical and intensive care protocols. The patients were in most of the cases politraumatized ones being the victims of car accidents, high voltage electrocution and fall from height, explosions. From this point of view each patient was unique and we used for severity trauma quantification the Injury Severity Score (ISS). ISS is an almost 40 years ago developed score for assessing the trauma severity. ISS correlates with mortality, morbidity and ICU and hospital length of stay for traumatized patients [1,3]. For reliable results we introduced this parameter in the statistical analysis. Other characteristics analyzed in the assessment of randomization were the age, the body burned surface, the sex, and the BMI (Body Mass Index) previous to the accident.

All patients included in this study received nutritional support based on individual calculation related to the magnitude of injury, the previous nutritional status and the individual characteristics of each patient [4]. We started nutrition as soon as possible trying to deliver as much as possible by enteral route and achieve the calculated goal by adding parenteral nutritional support. Patients included in the study were assigned in a double-blind manner to one of the two groups; patients from the study group received glutamine 0.5g/kgbw/day for at least 24 consecutive days. Glutamine was administred as Dipeptiven® – containing 20g/100mL L-alanyl-Lglutamyne, in continuous infusion from 6 p.m. to 6 a.m. The patients from the control group received an isonitrogenous standard amino acid solution in continuous infusion during the same period of the day (Aminomix®). We choose this kind of ”nocturnal” administration because during the day most of the severely burned patients are daily carried to the operatory room for wound dressing, wounds inspection, excision, grafting and all this takes a lot of time and impairs continuous infusion of the drugs. The team of surgeons (the same involved in all the study patients) assessed the wound healing. We monitorized during the first 30 days after the burn injury the number of positive blood cultures with Gram-negative germs, Gram-positive germs or fungi. Blood samples were collected when body temperature rised above 38.5 C degrees. We noted infectious complications (wound infections, pulmonary infections or central catheter type infection).

We analyzed the ventilation-dependent days, the ICU stay and hospital stay, morbidity and mortality.

We monitorized ammonia and liver enzymes every 3 days during the study. The antibiotic regimen was similar for all the patients; they received at admittance Imipenem® 1gx4/day and Linezolid® 600mgx2/day for at least

21 days. When antibiograms indicated the others antibiotics or antifungal were added.

Statistics used Student's *t*-test, chi-square test and Mann-Whitney U test. $p<0.05$ was considered statistically significant. Data are reported as mean ± SEM and were analyzed by the investigators. Programs used: Matlab version 7.10.0.499(R2010a) and MySQL version 5.5 (c) Oracle.

Results and Discussion

Baseline characteristics of the 47 subjects enrolled are summarized in table I. There were no significant differences in demographics, burned surface, BMI or ISS among the two treatment groups ($p > 0.05$).

Table 1

Characteristics of subjects at the entry in the study

	control group (n=23)	study group (n=24)	p
Gender (M/F)	21/2	22/2	
Age (yr)	30.5±11.9	34.2±10.2	0.26
BMI	24.35±2.98	25.66±3.8	0.21
ISS	41.95±15.52	45.72±20.28	0.53
Burned surface (%)	51.70±15.52	49.12±17.16	0.59

There were no statistical significant differences between length of stay in the ICU (Figure 1), mechanical ventilator dependent days (Figure 2), or the mortality rate (p=0,36). In the control group 4 patients died (17.4%) and in study group 3 patients died (12.5%).

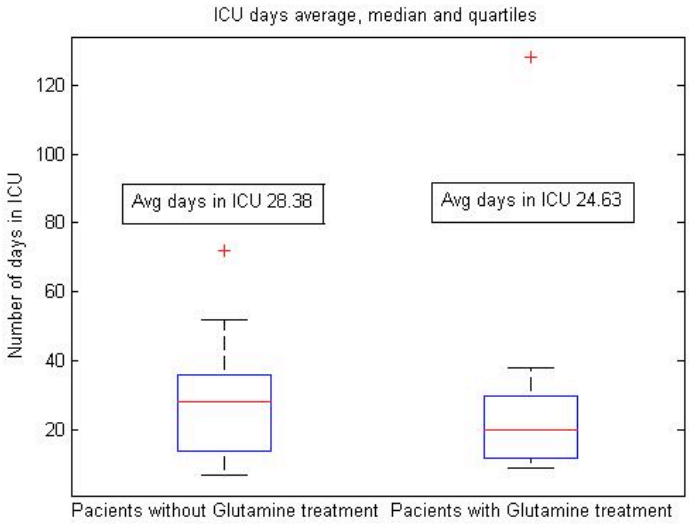

Figure 1

Patients from the study group spent less days in ICU (24.63±12.9) compared with those from the control group (28.38±16.71) but not statistically significant (p=0.48)

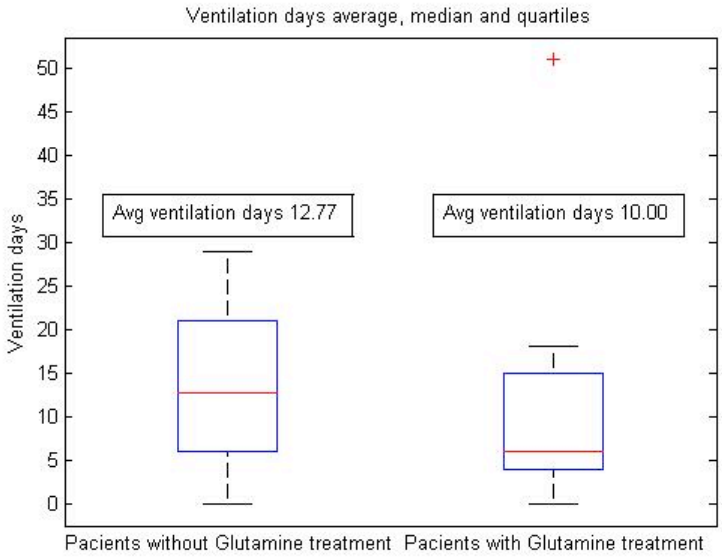

Figure 2
Patients from the study group had less ventilator dependent days (10.00±14.5) compared with those from the control group (12.77±16.5) but not statistically significant (p=0.24)

There were significant statistical differences regarding the general rate of complications (Figure 3), total hospital stay (Figure 4), the number of Gram-negative positive blood cultures (Figure 5), between the groups of patients.

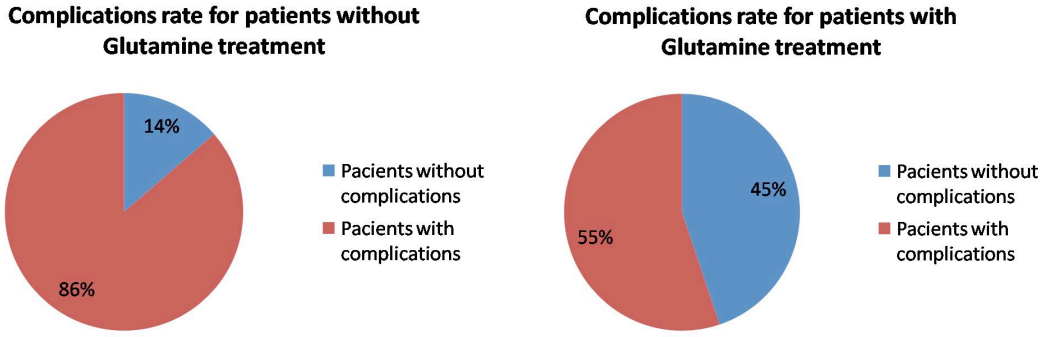

Figure 3
There were significantly statistic less complications in the study group (p=0.034)

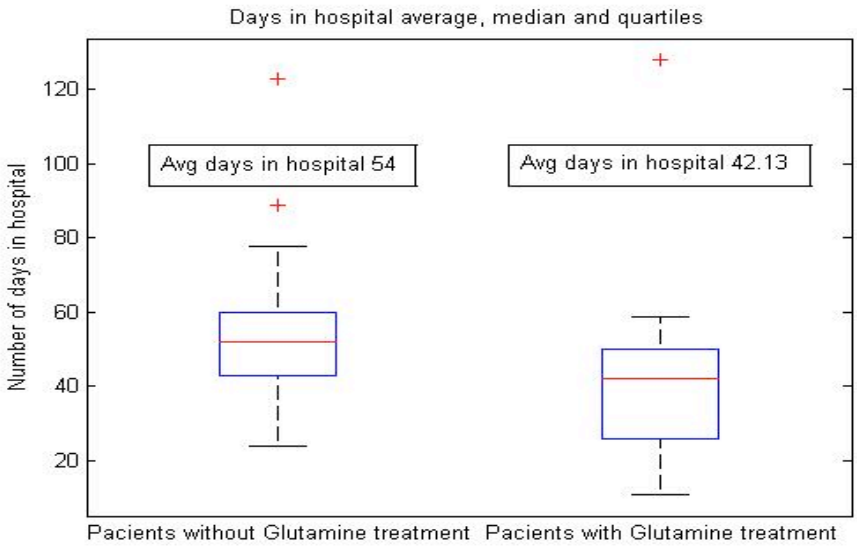

Figure 4
Patients from the study group spent less days in hospital (42.13±23.19) compared with those from the control group (54.02±24.36) p=0.027

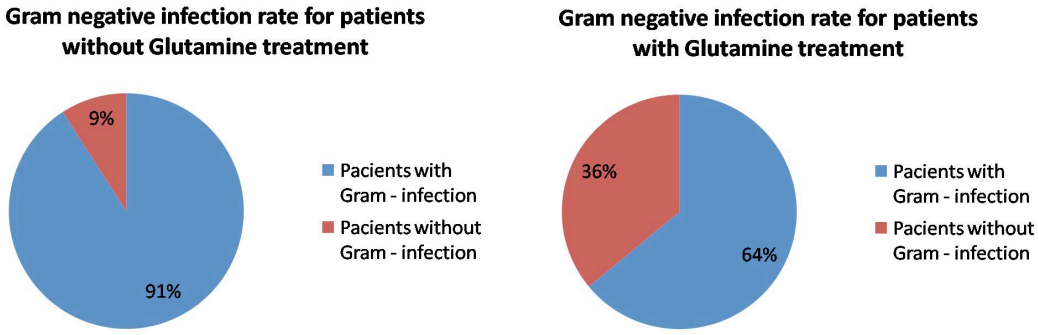

Figure 5
There were less Gram-negative infections in the study group (p=0.013), when compared with the control group

The most statistic significant result concerned the wound closure (p=0,003). Patients in the study group demonstreated evident improved healing characteristics compared with the control group (Figure 6).

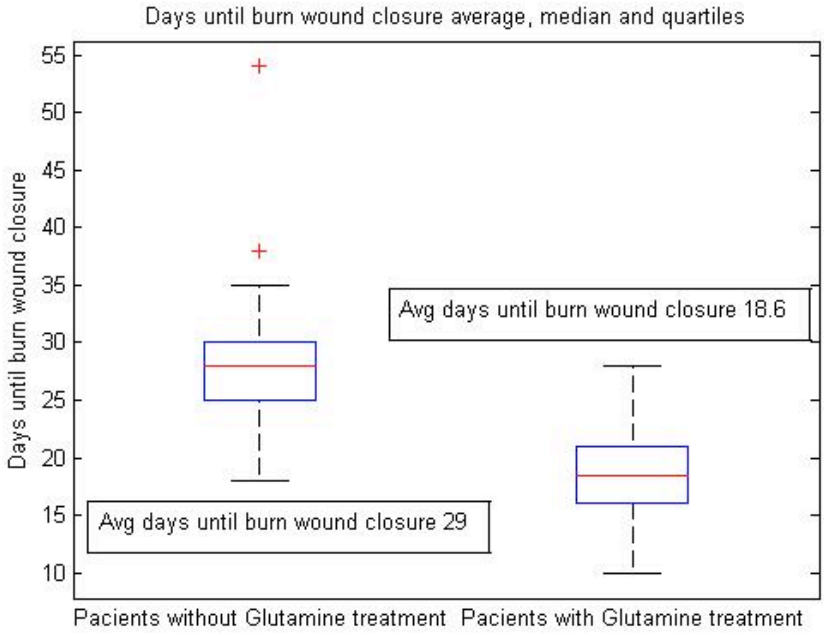

Figure 6
Patients from the study group demonstrated improved healing characteristics: average number of days until the wound healing for patients from study group was 18.63±3.88 compared with 29.04±7.97 for patients from the control group (p=0.003)

Conclusions

This study supports the results of other similar works concerning the benefits of glutamine supplementation in severely burned patients. These patients are in a complete different nutritional status being the most catabolic demanding patients from all the pathologies. In the same time the burned patient is a patient with a very high risk of infection, almost an usual and expected complication despite the effort made to avoid it. Glutamine becomes, for these patients, a conditionally essential amino acid and these patients experience a dramatic fall in glutamine body content. Glutamine deficiency is incriminated in favoring intestinal bacterial Gram-negative translocation due to gut atrophy [5,12], causing immune dysfunction [2,10] and impairing wound healing. Standard parenteral amino acid solutions do not contain glutamine due to its instability and glutamine supplementation seems to be very rational. This study confirms these suppositions and demonstrates that supplementary intravenous glutamine significantly

statistically decreased the incidence of Gram-negative bacteremia and the time of wound healing. This evidence supports the idea that glutamine must be a routine part of pharmacological treatment of severely burned patients.

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