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Glutamine as a modulator of the immune system of critical care patients: Effect on Toll-like receptor expression. A preliminary study

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Abstract

Objective: We evaluated the expression of Toll-like receptors 2 and 4 (TLR-2 and TLR-4) in circulating monocytes from peripheral blood of critical care patients treated with and without glutamine. Because no research has been published to date on the effect of glutamine on TLR receptors in critical patients, it was determined in an initial sample of 30 patients.

Methods: This was a prospective, randomized, single-blind study with 15 patients assigned to receive parenteral nutrition with a daily glutamine supplement of 0.35 g/kg. The control group received isocaloric-isonitrogenous parenteral nutrition. Blood samples were extracted before beginning the treatment and at 5 and 14 d. Expressions of CD14, TLR-2, and TLR-4 were determined by flow cytometry. Levels of TLRs were expressed as mean fluorescence intensity (mfi).

Results: Basal characteristics were similar in both groups. The expressions of TLR-2 in the treatment group with glutamine were 4.67 ± 3.82 mfi before treatment, 3.91 ± 2.04 mfi at 5 d, and 4.28 ± 2.47 mfi at 14 d. The expressions of TLR-2 in the control group were 5.49 ± 3.20 mfi before treatment, 4.48 ± 2.15 mfi at 5 d, and 4.36 ± 2.36 mfi at 14 d. The expressions of TLR-4 in the treatment group were 1.65 ± 1.89 mfi before treatment, 1.23 ± 1.10 mfi at 5 d, and 1.77 ± 1.97 at 14 d. The expressions of TLR-4 in the control group were 1.51 ± 1.76 mfi before treatment, 1.36 ± 0.99 mfi at 5 d, and 1.26 ± 0.59 mfi at 14 d. Infections were detected in 11 patients who received glutamine and 13 control patients ($P = 0.51$).

Conclusion: In critical care patients, parenteral nutrition supplemented with glutamine does not increase the expression of TLR-2 or TLR-4 in peripheral blood monocytes.

Keywords: Glutamine; Immune system; Parenteral nutrition

Introduction

Various studies [1–6] have demonstrated that using glutamine as a dietary supplement for patients in critical condition decreases the incidence of infection, primarily pneumonia, bacteremia, and sepsis. According to recent reports, the most beneficial results have been obtained with parenteral administration of high doses of glutamine ($0.35\ g \cdot kg^{-1} \cdot d^{-1}$) [7,8]. However, the mechanisms underlying the benefit observed have not been identified in their entirety [9–11].

The beneficial effect could be due to the fact that glutamine is an essential amino acid for various cells in the immune system, such as monocytes/macrophages and lymphocytes. Monocytes consume large quantities of glutamine but are incapable of synthesizing it, so they depend entirely on what is available in plasma [12]. Therefore, in critical care patients, it is possible that glutamine may be a modulator for the innate immune system. This system represents the organism's first

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line of defense against infection. Activation of the innate immune system relies on the recognition of structural motifs expressed only by pathogens, the so-called pathogen-associated molecular patterns [13,14]. These motifs are recognized by pattern-recognition receptors, chiefly the Toll-like receptors (TLRs) [13,15,16]. TLRs constitute a family of transmembrane receptors whose activation is also implicated in shaping adaptive immune responses resulting in antigen-specific immunity [13,15,16]. To date, 10 TLRs have been identified in humans, of which TLR-2 and TLR-4 have been most studied [17]. TLR-2 responds to a wide variety of ligands, whereas TLR-4 is the essential receptor for recognition of lipopolysaccharide, a component that is present only in gram-negative bacteria. In addition to lipopolysaccharide, TLR-4 recognizes other ligands, such as shock proteins 60 and 70, extracellular A domain of fibronectin, low-molecular-weight oligosaccharides, and polysaccharide fragments [18]. All these ligands, whether infectious or not, are present in critical care patients admitted to an intensive care unit (ICU). Several studies using knockout mice for TLRs have clearly established that the absence of these receptors increases susceptibility to infections [19]. Mechanistically, the evidence shows that an absence of TLRs impairs the activation of host defense mechanisms such as secretion of inflammatory mediators, phagocytosis, and presentation of antigens [14,20,21].

A recent study has demonstrated that monocytes from trauma patients express less TLR-4 than those from healthy individuals, which in turn affects the recognition of pathogen-associated molecular patterns by monocytes from trauma patients [22]. Therefore, it is tempting to postulate that an increased TLR expression would have beneficial effects. Given the well-known effects of parenteral nutrition (PN) treatment supplemented with glutamine on the incidence of infections, we hypothesized that glutamine might increase the expression of TLRs, which in turn may have beneficial effects to clear infections. In this report, we present our initial efforts to investigate this hypothesis. We evaluated TLR-2 and TLR-4 expression patterns in circulating monocytes from peripheral blood of critical care patients treated with and without a glutamine nutritional supplement. Data indicate that PN treatment supplemented with glutamine did not affect expressions of TLR-2 and TLR-4.

Materials and methods

Study design

We designed a random, single-blind, prospective study, with comparative therapeutic intervention, using two groups: critical care patients treated with PN supplemented with glutamine and those receiving PN without glutamine.

This research was approved by the clinical research commission of Son Dureta University Hospital. As a randomized prospective study, informed consent was sought from a patient or closest family member if the patient was unconscious. Random selection was based on a computer-generated list that assigned patients to groups consecutively. Those who processed samples did not know whether or not the patient had received glutamine.

Patients and study protocol

All patients 18 to 75 y of age who were admitted to the ICU and received PN as part of their treatment were selected for inclusion in the study. Indications for PN treatment were based on guidelines of the American Society of Parenteral and Enteral Nutrition [23]. The indication for PN was a contraindication for enteral nutrition (mainly abdominal surgery or abdominal trauma) or failure to achieve nutritional goals with enteral nutrition. The study excluded patients whose life expectancy was <5 d, who were allergic to glutamine, whose basic pathology included any serious immune system condition (diabetes, human immunodeficiency virus, lupus, etc.), or who, in their long-term treatment before admission to the ICU, received corticoids or any other immunosuppressant medication. A negative pregnancy test result was required before women of child-bearing age could be included in the study.

Of 30 consecutive patients who met the inclusion criteria, 15 were randomly assigned to receive a daily glutamine supplement of 0.35 g/kg of body weight as N2-L-alanyl-L-glutamine (0.5 g $\cdot$ kg^{-1} $\cdot$ d^{-1}; Dipeptiven, Fresenius Kabi España, Barcelona, Spain) for 5 d. The treatment period of 5 d was chosen according to other clinical studies [24,25]. Basic PN support for both groups was identical: StructoKabiven (Fresenius Kabi España), with a caloric intake of 28 kcal $\cdot$ kg^{-1} $\cdot$ d^{-1} and the following distribution of macronutrients: 0.28 g $\cdot$ kg^{-1} $\cdot$ d^{-1} of nitrogen, 3.5 g $\cdot$ kg^{-1} $\cdot$ d^{-1} of glucose, and 1.08 g $\cdot$ kg^{-1} $\cdot$ d^{-1} of lipids, in addition to standard vitamins and trace elements. The control group (n = 15 patients) received a supplemental volume of the basic PN solution to achieve an isocaloric/isonitrogenous formula with the study group. The total duration of the PN, once the supplement with glutamine has been finished after the fifth day, was based on clinical data and was decided by the clinician responsible for the patient.

Screening the literature, we found no previous studies identifying a correlation between TLR and glutamine in humans. Therefore, it was determined that a sample of 30 patients would be sufficient for this pilot study.

In both groups, peripheral blood samples for the study of TLRs in monocytes were extracted before beginning treatment (basal sample), at the end of glutamine supplementation (day 5), and at 14 d $\pm$ 24 h after initiating treatment.

Flow cytometry

Expressions of CD14, TLR-2, and TLR-4 in peripheral blood monocytes were determined by flow cytometry as previously described [26]. Briefly, blood samples (one sam-

ple per patient) were collected and 100 μL was incubated with a combination of anti-CD14 fluorescein conjugate (clone My4, 10 μ/mL; Beckman Coulter, Fullerton, CA, USA) and anti–TLR-2 (clone TL2.1, 10 μ/mL; ebioscience, San Diego, CA, USA) or anti–TLR-4 (clone HTA125, 10 μ/mL; ebioscience) phycoerythrin conjugate in the presence of 25 μL of fetal calf serum for 30 min at 4°C. Two milliliters of FACS lysing solution (Becton Dickinson, Franklin Lakes, NJ, USA) was added to the samples, which were incubated for 10 min at room temperature. Samples were centrifuged in a clinical centrifuge (530 × *g*, 5 min, 25°C) and the cellular pellet was washed once with 1% bovine serum albumin/0.1% sodium azide in phosphate buffered saline. Cells were resuspended in 500 μL of IsoFlowTM Sheath Fluid (Beckman Coulter). The analyses were carried out in an Epics XL flow cytometer using Expo32 software. Monocytes were identified by gating on a side plot versus CD14 dot plot. Levels of CD14, TLR-2, and TLR-4 were expressed as mean fluorescence intensity measured in arbitrary units and non-specific binding was corrected by subtraction of mean fluorescence intensity values corresponding to isotype-matched antibodies. Five thousand monocytes were analyzed in every experiment.

Data collection

Epidemiologic data were collected, including date and time of sample extraction, description of the event that motivated hospital admission (diagnosis and scores of severity to compare the control and experimental groups), comorbidities of each patient (hypertension, cardiopathy, bronchopathy, hepatopathy, alcoholism, tobacco habits, and neurologic pathology), and the appearance of any complications during ICU stay (respiratory distress syndrome, reintubation, septic shock, infections, renal insufficiency, hepatic insufficiency, and hematologic insufficiency, and total days in the ICU and in the hospital).

With respect to infections, samples were analyzed for patients in the ICU whenever there was a clinical suspicion of possible infection [27]. The definition of nosocomial infection used in this study is that proposed by the Centers for Disease Control and Prevention [28]. Blood and other cultures were done at our institution according to standard microbiological procedures, including incubation in anaerobic atmosphere when applicable.

Among the data collected were all treatments patients received during their ICU stay, especially all pharmacologic treatments with known anti-inflammatory properties that could affect the study results. All members of the two patient groups were handled and treated equivalently.

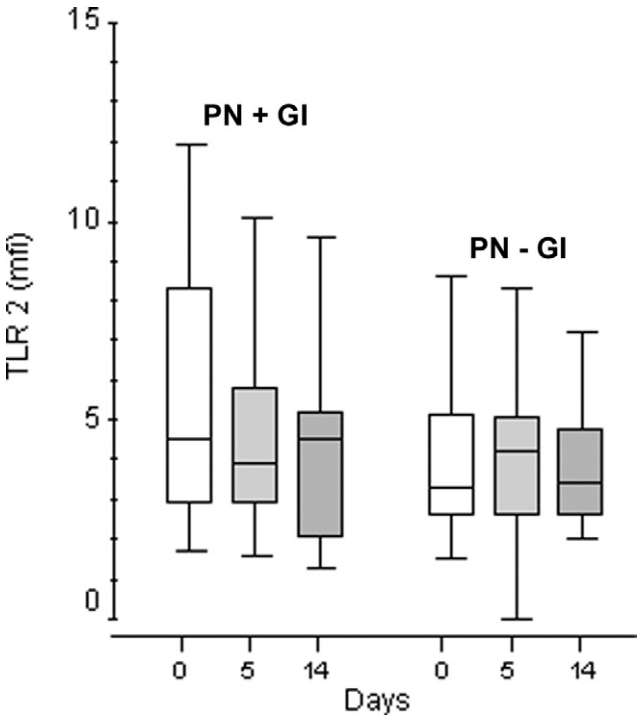

Fig. 1. TLR-2 expression (mean fluorescence intensity) changes in patients with and without glutamine in before treatment and at days 5 and 14 of treatment. Boxes represent the 25th–75th percentile data interval. Horizontal lines within boxes represent mean TLR-2 values. Error bars represent 95% confidence intervals. Pre, before treatment; TLR-2, Toll-like receptor-2.

Table 1
Basal characteristics of patients included in study*

	PN + Gl (n = 15)	PN − Gl (n = 15)	P
Age (y)	44 ± 18	52 ± 14	0.32
Male/female	12/3	10/5	0.68
Weight (kg)	80 ± 7	81 ± 11	0.9
Surgical patients	3	3	0.69
Trauma patients	9	7	0.69
Medical patients	3	5	0.69
SAPS II	32.7 ± 10.5	34.9 ± 12.0	0.65
APACHE II	16.6 ± 6.5	16.8 ± 8.9	0.95
APACHE III	42.0 ± 23.5	40.7 ± 16.1	0.72
SOFA pretreatment	8 ± 2	7 ± 3	0.3
PN beginning†	3 (1–6)	4 (3–7)	0.83
Total PN duration (d)	11 (7–19)	7.5 (6.75–17)	0.33
Norepinephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.26 ± 0.13	0.25 ± 0.27	0.8

APACHE, Acute Physiology and Chronic Health Evaluation; PN + Gl, parenteral nutrition treatment supplemented with glutamine; PN − Gl, isocaloric/isonitrogenous parenteral nutrition treatment (control); SAPS, Simplified Acute Physiology Score; SOFA, Sepsis-related Organ Failure Assessment

* Data are presented as mean ± SD, number of patients, or median (25th–75th percentile).

† Days of stay in the intensive care unit when patients were included in the study.

Statistical analysis

The quantitative variables are expressed as mean ± standard deviation from the mean. The qualitative variables are expressed as percentages, with 95% confidence intervals. Quantitative variables were compared using Student's *t* test

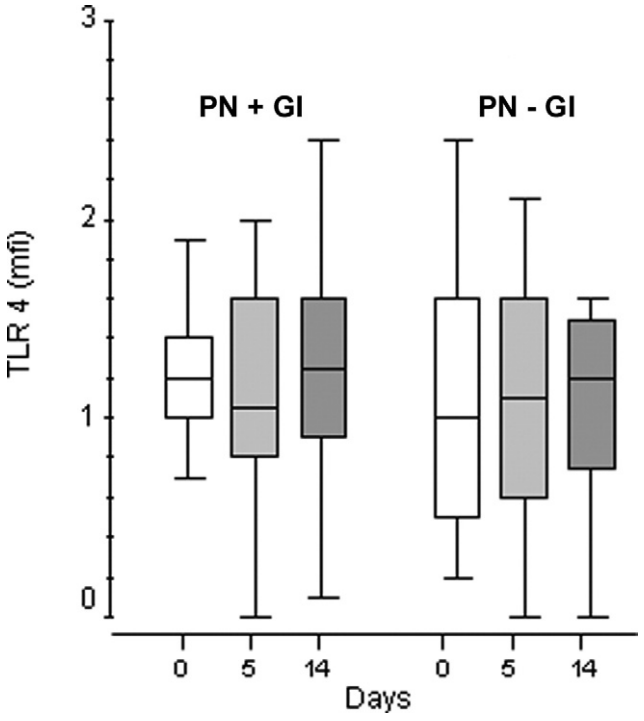

Fig. 2. TLR-4 expression (mean fluorescence intensity) changes in patients with and without glutamine before treatment and at days 5 and 14 of treatment. Boxes represent the 25th–75th percentile data interval. Horizontal lines within boxes represent mean TLR-4 values. Error bars represent 95% confidence intervals. Pre, before treatment; TLR-4, Toll-like receptor-4.

for normal distributions and Mann-Whitney U test for those distributions that were not compatible with normal distribution. Qualitative variables were compared using chi-square or Fisher's exact test. Statistical significance was a $\leq$5% probability of α error in the hypothesis testing.

Results

From October 2005 through October 2006, 30 patients were selected for inclusion in this pilot study: 22 men and 8 women with a median age of 48 ± 17 y. Of these patients, 16 were admitted for trauma, 6 after surgery, and 8 for a medical pathology. Of the 16 accident victims, 11 required some surgical intervention. All 30 patients received the 5-d supplement of glutamine or the isocaloric/isonitrogenous formula used as the control. There were no statistically significant differences with respect to comorbidity. Basal characteristics of both groups are summarized in Table 1.

Analysis of TLR expressions in peripheral blood monocytes revealed that TLR-2 and TLR-4 expressions in the experimental group were not significantly different from those found in the control group at the beginning or end treatment (Figs. 1 and 2). The exact values of TLR-2 and TLR-4 expressions are presented in Tables 2 and 3. Analysis by subgroups (trauma, surgery, and medical patients) also produced no statistically significant differences in TLR-2 or TLR-4 expression. Table 4 presents complications during patients' ICU stay.

Some type of infection was detected in 11 patients who received glutamine and 13 control patients ($P = 0.51$). Like some other investigators [7] we did not observe any adverse effect due to the use of these doses of glutamine.

Table 2
Toll-like receptor-2 expression in patients treated with and without glutamine

	PN + Gl	PN − Gl	*P*
Basal sample*	4.67 ± 3.82 mfi	5.49 ± 3.20 mfi	0.23
5-d sample†	3.91 ± 2.04 mfi	4.48 ± 2.15 mfi	0.24
14-d sample‡	4.28 ± 2.47 mfi	4.36 ± 2.36 mfi	0.46

mfi, mean fluorescence intensity; PN − Gl, isocaloric/isonitrogenous parenteral nutrition treatment (control); PN + Gl, parenteral nutrition treatment supplemented with glutamine

* Taken before beginning PN treatment.

† Taken at end of treatment (day 5 ± 24 h).

‡ Taken 14 d ± 24 h after beginning treatment.

Table 3
Toll-like receptor-4 expression in patients treated with and without glutamine

	PN + Gl	PN − Gl	*P*
Basal sample*	1.65 ± 1.89 mfi	1.51 ± 1.76 mfi	0.42
5-d sample†	1.23 ± 1.10 mfi	1.36 ± 0.99 mfi	0.24
14-d sample‡	1.77 ± 1.97 mfi	1.26 ± 0.59 mfi	0.18

mfi, mean fluorescence intensity; PN – Gl, isocaloric/isonitrogenous parenteral nutrition treatment (control); PN + Gl, parenteral nutrition treatment supplemented with glutamine

* Taken before beginning PN treatment.

† Taken at end of treatment (day 5 ± 24 h).

‡ Taken 14 d ± 24 h after beginning treatment.

Table 4
Complications during ICU hospitalization

	PN + Gl (n = 15)	PN − Gl (n = 15)	*P*
Septic shock*	1	1	1.0
Respiratory infection†	4	2	0.65
Urinary infection‡	1	0	1.0
Blood culture§	3	2	1.0
Catheter infection‖	2	5	0.39
Other infections¶	1	4	0.47
Total infections	11	13	0.51
Days on MV	14 ± 10	14 ± 10	0.94
ICU length of stay (d)	22.9 ± 20.6	20.5 ± 16.0	0.87
Hospital length of stay (d)	35.5 ± 33.6	42.9 ± 28.8	0.39
Hospital mortality (d)	3	0	0.22

ICU, intensive care unit; MV, mechanical ventilation; PN − Gl, isocaloric/isonitrogenous parenteral nutrition treatment (control); PN + Gl, parenteral nutrition treatment supplemented with glutamine

* Development of septic shock after beginning PN treatment.

† Positive bronchial aspirate culture while in the ICU.

‡ Positive urine culture while in the ICU.

§ Positive blood culture while in the ICU.

‖ Positive catheter point culture while in the ICU.

¶ Positive culture from other locations while in the ICU.

Discussion

The results of this study show that in this heterogeneous population of 30 critically ill patients admitted to the ICU, supplementing PN with glutamine does not improve expression of TLR-2 and TLR-4 monocyte receptors in peripheral blood. As far as we know, no research has been published to date on the effect of glutamine on TLR receptors in critical care patients.

A recently published meta-analysis [29] reviewed seven studies with 326 cases that included a complication of infection and found a significant reduction in the number of infections in the group of patients treated with glutamine (relative risk 0.80, 95% confidence interval 0.64–1.00, $P = 0.03$). In this study, the treatment group also presented a reduced incidence of infection and a higher mortality, although neither finding achieved statistical significance. Moreover, given the small sample and the fact that this study was not designed to answer questions regarding mortality and efficacy, these data are not clinically relevant.

The mechanisms by which glutamine prevents the occurrence of infection are not totally clear. It is known that glutamine is converted to a conditionally indispensable amino acid in situations of metabolic stress, because it contributes to improving various functions as a source of cellular [30] and immunologic [31,32] energy, maintaining the integrity and function of various organs [33], tissue repair [34], homeostasis of the acid-base mean [29,30], and nitrogen transport [35].

Specifically, glutamine's effects on the immune system include decreased production of proinflammatory cytokines [36,37], improved bactericidal function of neutrophils [38], and increased levels of glutathione and oxidative capacity [39]. Nonetheless, the immune system is very broad and complex; therefore, we focused solely on the effect of glutamine on the innate part of this system. TLRs play a central role in the activation of the innate system due to the recognition of bacterial pathogen-associated molecular patterns, which triggers the activation of different intracellular signaling cascades involved in the activation of host defense mechanisms.

Not surprisingly, several studies have demonstrated that a decrease or even total lack of TLR expression is correlated with greater susceptibility to infection [14,19,20]. In addition, a recent study has demonstrated that monocytes from trauma patients express less TLR-4 than those from healthy individuals [22]. Therefore, it seems reasonable to believe that, if we could increase TLR expression by using a pharmaconutrient such as glutamine, the molecular mechanisms to detect micro-organisms might improve, resulting in a reduced incidence of complications involving infections.

There are various possible explanations for the lack of conclusiveness in our results. The study population was heterogeneous, although the basal characteristics between the experimental and control groups were similar and comparable to those of other published studies of glutamine. In light of the published results of various studies and meta-analyses, it is reasonable to begin to select from subgroups of patients where it appears that glutamine might be most effective, such as burn or trauma patients [40]. In these subgroups it is possible that a hyperinflammatory response coexists with a dysfunction in the immune system. As has been previously pointed out, TLR-4 expression is lower in trauma patients than in healthy volunteers [22,41], whereas in septic patients TLR expression is increased [42,43].

We also cannot rule out that the function but not the expression is positively affected by glutamine. It is tempting to speculate that glutamine may facilitate the activation of TLR-dependent signaling pathways, resulting in the activation of host defense responses. Studies are currently addressing these issues.

Conclusion

In this general population of critically ill patients, PN supplemented with glutamine does not increase the expression of TLR-2 or TLR-4 in peripheral blood monocytes.

Acknowledgments

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