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Original Article

Effect of oral L-Glutamine supplementation on Covid-19 treatment

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SUMMARY

Objectives: The aim of this study is to investigate the effect of oral L-Glutamine supplementation on hospitalization time, need for intensive care unit and Coronavirus Disease-19 (Covid-19) mortality.

Methods: The study included 30 Covid-19 patients using L-Glutamine and 30 Covid-19 patients who did not use L-Glutamine with similar age, gender and clinical status. Diagnostic tests, laboratory examinations, clinical findings and computed thorax tomography imaging of the patients were evaluated.

Results: Hospitalization time was 10.4 ± 1.9 days in Covid-19 without L-Glutamine group and 8.9 ± 1.8 days in Covid-19 with L-Glutamine group ($p = 0.005$). In Covid-19 without the L-Glutamine group, four patients require the ICU though no one in the other group required that ($p = 0.038$). Only one mortality was observed in Covid-19 without the L-Glutamine group ($p = 0.999$).

Conclusions: Nutritional supplements such as L-Glutamine boost immune system especially by inhibition of inflammatory responses. Our results suggest adding enteral L-glutamine to the normal nutrition in the early period of Covid-19 infection may lead to a shortened hospital stay and lead to less need for ICU. Larger-scale studies are needed to evaluate the effect of adding enteral L-Glutamine to the currently used treatments in the infectious diseases especially like Covid-19.

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new coronavirus first discovered in December 2019 in Wuhan, province of China [1]. The disease was called Coronary Virus Disease-19 (Covid-19) on February 11, 2020. On March 11, 2020, the World Health Organization announced the Covid-19 as a pandemic [2]. As of the end of April, the disease affected more than 3 million people in the worldwide and caused more than 200 thousand of deaths.

In the treatment of Covid-19, antiviral agents such as lopinavir, ritonavir, remdesivir, antibacterial drugs such as macrolides and antimalarial drugs such as hydroxychloroquine are used. While international studies are going on to find to improve the course of the disease and reduce mortality, there is no precise treatment like vaccines found yet. Some approaches like Allopathic, Unani Homeopathic treatments except immune system booster treatment have been used but mostly did not get success [3]. The main approach, especially in those with lower respiratory tract involvement, is focused on optimizing respiratory functions. The most effective treatment approach in the course of the disease appears to be supportive therapy. The morbidity and mortality of the disease is higher, especially in the elderly patients with low immune function, in individuals with nutritional deficiencies and in people with chronic diseases [4,5]. As in other acute diseases, since the catabolic process continues in Covid-19, normal protein intake is not sufficient to support recovery. Promoting acute stress-decreasing levels of specific amino acids, such as cysteine, arginine and glutamine enhances immunity in such patients [6]. Acting as signal molecules and mediators at the cellular level, these featured amino acids are known to regulate many functions in the cell and help recovery [7].

Glutamine is the most abundant amino acid in the body, containing 60% of the total pool of free amino acids. The main synthesis sources of glutamine circulating in plasma are skeletal muscle, adipose tissue and lungs. Glutamine performs most of the transport of nitrogen from the skeletal muscle to the visceral tissues. Glutamine is used as a glucose-efficient primary fuel for many rapidly dividing cells, including enterocytes, colonocytes, lymphocytes, and fibroblasts [8]. It has been shown that glutamine, whose many functions are known, plays a role in acid-base balance through the production of ammonia in the kidney, its oxidized form provides the substrate for the synthesis of purines and pyrimidines necessary for DNA, RNA and mesenger RNA. Glutamine is also a precursor to glutathione, a powerful antioxidant produced endogenously. It is one of the most researched amino acids on multiple aspects of medical nutritional care, including conditions such as gastrointestinal diseases, oncology, burn injury, HIV/AIDS, and chronic wound management [9].

Giving all the nutrition to be provided with glutamine support, which is very important in immune nutrition, on time and as much as necessary, is very important for recovery. However, it should not be forgotten that in all diseases, timely recognition and correction of malnutrition has the potential to improve the outcome in a cost-effective way [5].

The aim of this study is to investigate the effect of oral L-Glutamine supplementation on hospitalization time, intensive care unit requirement and mortality in Covid-19 patients, over 50 years of age who are hospitalized with lower respiratory tract involvement.

2. Methods

2.1. Informed consent

The sample collection protocol was approved by the Ethics Committee of the Biruni University Faculty of Medicine (Authorization Number: 2020/39-39) and carried out in accordance with the requirements of the Second Declaration of Helsinki. Before the written consent, all patients were given complete information about the study procedures.

2.2. Study population

A total of 381 Covid-19 patients were screened and 60 patients who met the inclusion criteria were included in the study. Patients who applied to the Covid-19 outpatient clinics of Biruni University Hospital between March 31 and April 31, those who had lower respiratory tract involvement in computed thorax tomography (thorax CT) and positive real-time reverse-transcriptase-polymerase-chain reaction (RT-PCR) test in oro-nasopharyngeal swab were included in the study. Thirty Covid-19 patients (12 female, 58.2 ± 8.4) using L-Glutamine and 30 Covid-19 patients (14 female, 58.8 ± 7.4) with similar age, gender, and clinical status were included in the study.

Patients with kidney and liver dysfunction, alcoholism, malignancy, connective tissue diseases, cardiovascular diseases (hypertension, ischemic heart disease, arrhythmia, serious valvular disease), diabetes mellitus, neurological and psychiatric problems (Parkinson's disease, cerebrovascular disease, delirium, bipolar disorder, depression), or severe disease that can not be measured their weight or height were excluded from the study. The Sequential Organ Failure Assessment (SOFA) scoring was performed to all patients for evaluating the severity of disease before the beginning of the study. The patients had a point of quick SOFA (qSOFA) $\geq$2 were also not included in the study. When a patient was classified with or at risk of malnutrition at the beginning or in the following period of the hospital stay, we planned a nutritional care plan and excluded them from the study. The patients whose clinical courses and laboratory parameters worsened though all given treatments were evaluated as severe sepsis according to the criteria of SOFA. Firstly qSOFA was calculated with the blood pressure, respiratory rate and mental status, if the qSOFA is 2 and/or bigger than 2, the patient was taken to the ICU. SOFA measures individual or aggregate organ dysfunction in six organ systems (respiratory, coagulatory, liver, cardiovascular, renal, and neurologic) in the ICU and mostly predict the hospital mortality [10].

2.3. Diagnosis of Covid-19

Thorax CT screenings of all patients, included in the study, were taken at the time of hospital admission. As stated in the guidelines of Turkish Ministry of Health, an oropharyngeal sample was first taken with a swab, then a nasal sample was taken using the same swab, and placed in the same transport medium for diagnosis. Samples were tested by RT-PCR assay developed from the virus sequence.

2.4. Laboratory analysis

Fasting blood samples were taken at the time of admission. Serum C-reactive protein (CRP) levels were measured by a nephelometric method (Immage 800, Beckman Coulter, Istanbul, Turkey). The other biochemical parameters as complete blood count (CBC), creatinine, sodium, potassium, alanine aminotranferase (ALT), aspartate aminotransaminase (AST), lactate dehydrogenase (LDH), D-dimer, ferritin, troponin were measured by routine methods with commercial kits.

2.5. L-Glutamine supplementation and nutritional status screening

The nutritional status of all our patients were investigated with the Nutritional Risk Screening (NRS-2002) at the time of hospital admission. NRS-2002 consists of two levels such as impaired nutritional status and severity of disease (such as low, moderate or severe for both of them), with an adjustment for age $\geq$70 years. The status of nutrition as considering first level of this screening was evaluated by the variables; Body Mass Index (BMI), weight loss in the last 3 months and decreased of food intake in the last week. Degrees of severity of disease as considering second level of NRS-2002 were defined as absent, mild, moderate or severe that were converted to a numeric score between 1 and 3 according to recommendations. A total score under 3 suggested no nutritional risk. A data collection sheet was used to obtain all informations according to the ESPEN guidelines [11].

All given meals for the studied patients were prepared in accordance with the appropriate guidelines in COVID-19 and consisted with equal protein and calori contents [12].

To the group using L-Glutamine, 10 g L-Glutamine available in powder forms (Resource Glutamine, Nestle) were given 3 times a day with meals.

2.6. Data collection

Data on patients' gender, age, clinical symptoms, treatments used, swab sample and presence of thorax CT findings, laboratory results, vital signs, the results of nutritional status screenings and the results of Pneumonia Severity Index Grades on the day of diagnosis, the number of hospitalization days, need of ICU and mortality were recorded [12,13].

2.7. Statistical analysis

This study is retrospective, non-controlled, non-blinded, cross-sectional study for evaluating the impact of glutamine effect on the clinical course of Covid-19 disease. A sample size of $n = 29$ per group is required to provide 80% power to detect a difference in the mean levels with a significance of 0.05 (2-sided α). The normal distribution of the data was tested using the one-sample Kolmogorov–Smirnov test. Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as counts. The statistical comparisons were performed using the two-sided Student's t-test. Categorical variables were compared using the Chi-square test or Fisher exact test for small samples. Values of $p \leq 0.05$ were considered to be statistically significant. The statistical analyses were performed using SPSS 20.0 software (SPSS, Chicago, IL, USA) for Windows.

3. Results

Demographic features and laboratory findings of the study groups are given in Table 1. Age, gender distribution, smoking and laboratory findings were similar between the groups. Symptoms, medications for Covid-19 and physical examination findings of the study groups are given in Table 2. All of the symptoms, medications and physical examination findings of the study groups were similar between the groups.

Duration of hospitalization, necessity of intensive care unit and number of mortality of the study groups are given in Table 3. Duration of hospitalization was found as 10.4 ± 1.9 days in Covid-19 without L-Glutamine group and 8.9 ± 1.8 days in Covid-19 with L-Glutamine group ($p = 0.005$). The

Table 1
Demographic characteristics and laboratory findings of the studied groups.

	Covid-19 (n = 30)	Covid-19 with Glutamine (n = 30)	P
Age (years)	58.8 ± 7.4	58.2 ± 8.4	0.782
Gender (female)	14 (46.7)	12 (40)	0.795
Body Mass Index (kg/m^2)	29.8 ± 3.2	30.1 ± 3.4	0.564
Smoking	9 (30)	8 (26.7)	0.835
Glucose (mg/dL)	91.1 ± 8.5	89.8 ± 7.7	0.806
Creatinine (mg/dL)	1.2 ± 0.9	1.1 ± 0.5	0.583
Leukocyte (10^3/mL)	6.9 ± 3.5	7.6 ± 4.6	0.535
Neutrophil (10^3/mL)	5.1 ± 3.3	5.8 ± 4.3	0.462
Lymphocyte (10^3/mL)	1.1 ± 0.4	1.3 ± 0.7	0.327
Haemoglobin (g/dL)	13.5 ± 1.9	13.4 ± 2.3	0.951
Platelet (10^3/mL)	192 ± 61	207 ± 69	0.382
CRP (mg/L)	48.3 ± 50.6	44.4 ± 81.3	0.823
ALT (U/L)	32 ± 16	35 ± 19	0.522
AST (U/L)	36 ± 21	29 ± 13	0.108
LDH (U/L)	267 ± 117	238 ± 103	0.323
Ferritin (ng/mL)	306 ± 256	227 ± 155	0.152
D-Dimer (ng/mL)	674 ± 467	533 ± 648	0.337
Troponin I (pg/mL)	14.2 ± 43.5	16.7 ± 48.1	0.314
Albumin (g/dL)	3.7 ± 1.1	3.5 ± 0.8	0.832

CRP; C-reactive protein, **ALT**; alanine aminotranferase, **AST**; aspartate aminotransferase, **LDH**; lactate dehydrogenase.

Table 2
Symptoms, medication for Covid-19 and physical examination findings of the study groups.

	Covid-19 (n = 30)	Covid-19 with Glutamine (n = 30)	p
Symptoms			
Fever	25 (83.3)	24 (80)	0.901
Cough	22 (73.3)	20 (66.6)	0.784
Dispne	8 (26.7)	9 (30)	0.835
Fatigue	23 (76.7)	21 (70)	0.771
Taste/smell abnormalities	6 (20)	3 (10)	0.225
Diarrhea	7 (23.3)	3 (10)	0.283
Medications			
Hydroxychloroquine	30 (100)	30 (100)	0.999
Oseltamivir	30 (100)	28 (93.3)	0.834
Azithromycin	15 (50)	13 (43.3)	0.796
Moxifloxacin	15 (50)	17 (56.7)	0.801
Lopinavir/Ritonavir	4 (13.3)	3 (10)	0.911
Favipiravir	2 (6.7)	2 (6.7)	0.999
Other antibiotics	2 (6.7)	3 (6.7)	0.913
Physical examination findings			
Fever (°C)	38.1 ± 0.7	37.9 ± 1.2	0.198
Systolic BP (mmHg)	116 ± 15	117 ± 15	0.763
Diastolic BP (mmHg)	74 ± 9	71 ± 8	0.101
Heart rate (/min.)	89.9 ± 10.8	88.1 ± 11.9	0.527
SO_2 (%)	93.1 ± 2.7	94.3 ± 4.3	0.225
Respiratory rate (/min.)	19.2 ± 3.3	17.8 ± 4.1	0.135
Pneumonia Severity Index	60.2 ± 15.9	56.2 ± 11.8	0.281
Pneumonia Severity Index Grade			
I	0	0	0.354
II	25 (83.3)	27 (90)	
III	3 (10)	3 (10)	
IV	2 (6.7)	0	
V	0	0	

BP; blood pressure, **SO_2**; oxygen saturation.

number of necessity of intensive care unit was significantly higher in Covid-19 without L-Glutamine group ($p = 0.038$). Although there was no difference in mortality rates between the groups, a death was observed in the Covid-19 group, which did not receive L-Glutamine. Demographic characteristics, laboratory and physical examination findings of before and after the treatment of glutamine groups are given in Table 4. The total qSOFA score and respiratory rate decreased after the glutamine treatment ($p = 0.015$ and $p = 0.024$, respectively).

4. Discussion

This study evaluates the effects of L-Glutamine supplementation on hospitalization time, intensive care requirement, and mortality in Covid-19 patients followed by lower respiratory tract involvement. The results of our study showed that in Covid-19 cases using L-Glutamine, the duration of hospitalization was shorter and the need for intensive care was less than those who did not use L-Glutamine. Our study deserves interest as it is the first study in the literature examining the effects of immune supplements such as L-glutamine added to standard current treatments on the progression of Covid -19.

Leukocytes fight endotoxin, cytokine and free oxygen radicals, which increase in serious inflammation situations such as sepsis, polytrauma and acute respiratory failure and also damage the functions of cell. In these acute stress situations, heat shock proteins 70 (Hsp 70) expressed from leukocytes only have a positive effect on complications and mortality in the presence of sufficient glutamine. Therefore, Hsp70 and leukocyte functions, which decrease with glutamine levels falling

Table 3
Duration of hospitalization, necessity of intensive care unit and mortality of the study groups.

	Covid-19 (n = 30)	Covid-19 with Glutamine (n = 30)	p
Duration of hospitalization	10.4 ± 1.9	8.9 ± 1.8	**0.005**
Necessity of intensive care unit	4 (13.3)	0	**0.038**
Mortality	1 (3.3)	0	0.999

$p \leq 0.05$ is statistically significant.

Table 4
Demographic characteristics, laboratory and physical examination findings of before and after the treatment of glutamine group.

	Before the Glutamine (n = 30)	After the Glutamine (n = 30)	P
Creatinine (mg/dL)	1.1 ± 0.5	1.2 ± 0.4	0.374
Total bilirubin (mg/dL)	0.9 ± 0.4	1.1 ± 0.5	0.312
Leukocyte (10^3/mL)	7.6 ± 4.6	6.9 ± 1.9	0.419
Neutrophil (10^3/mL)	5.8 ± 4.3	4.7 ± 1.6	0.186
Lymphocyte (10^3/mL)	1.3 ± 0.7	1.6 ± 0.6	0.068
Platelet (10^3/mL)	207 ± 69	199 ± 56	0.916
CRP (mg/L)	44.4 ± 81.3	14.2 ± 15.1	0.054
Physical examination findings			
Systolic BP(mmHg)	117 ± 15	122 ± 11	0.763
Diastolic BP(mmHg)	71 ± 8	78 ± 7	0.101
Heart rate (/min.)	88.1 ± 11.9	85 ± 6.9	0.527
SO_2 (%)	94.3 ± 4.3	94.7 ± 3.1	0.225
PaO_2 (mmHg)	71.6 ± 14.5	79.5 ± 13.3	0.089
Need for vasopressors	0	0	
Quick SOFA (qSOFA) Scoring System			
Altered mental status	1 (3.3)	0	0.513
Glasgow coma scale <15			
Respiratory rate ≥22 (/min.)	6 (20)	0	**0.024**
Systolic BP ≤ 100 mmHg	1 (3.3)	0	0.513
Total Quick SOFA Score (qSOFA)			
1	8 (26.7)	0	**0.015**
2	0	0	
3	0	0	

$p \leq 0.05$ is statistically significant.
CRP; C-reactive protein, **BP**; blood pressure, **SO_2**; oxygen saturation, **PaO_2**; partial pressure of arterial oxygen, **SOFA;** the Sequential Organ Failure Assessment.

below physiological doses in these patients, are considered as one of the causes of immune indulgence [14,15].

Increased metabolic stress period, free glutamine release from skeletal muscle, resulting in intracellular glutamine concentration drops more than 50% [16,17[. In their study, Roth et al. found that survival in patients with intra-abdominal sepsis is associated with free intracellular glutamine concentration [18]. Glutamine is normally synthesized endogenously, however, it is considered as an essential amino acid in catabolic processes. Thus, the body's glutamine synthesis becomes unable to meet higher requirements during acute stress. Dietary protein, which is taken through oral nutrition and most enteral formulas, provides only maintenance levels of glutamine. There is no glutamine in parenteral amino acid solutions. Furst et al. suggest that during periods of stress, 15–35 g of supplemented glutamine may be required to maintain muscle glutamine and intestinal integrity, and to quickly provide fuel and positive nitrogen balance to the cells [19]. In our study, similar to the recommendations in the literatüre, we examined the effects of glutamine, on the course of the disease by adding ready 30 g/day ready glutamine preparations to patients treated with the Covid-19 pneumonia, by providing additional nutritional immune support.

Glutamine supplementation during oncology therapy is an exciting area of current research. The data show that glutamine can support the host by regenerating glutathione levels, preventing or repairing tissue damage, and improving some side effects [20]. With parenteral glutamine-supplemented nutrition given to patients undergoing bone marrow transplantation, the duration of hospitalization and the rate of developing infections have decreased. Estimated cost savings per patient was about $ 22,000 [21]. In our study, it was observed that the duration of hospitalization was shortened and the need for intensive care was reduced by giving L-Glutamine to patients with lower respiratory tract involvement due to Covid-19. Therefore, this decrease in morbidity also reduces health expenses.

In the literature, there are many randomized controlled studies and meta-analyzes investigating the effectiveness of glutamine in supplementary therapy in acute stressful diseases, and sometimes the results can be confusing. However, an umbrella study examining the results of meta-analyzes on this subject has recently been published. In many of the meta-analyzes, it was stated that glutamine, which became essential amino acid by decreasing its level in critical acute patients, had a positive effect on recovery time, development of secondary infection and mortality in parenteral or enteral ways [22]. Parenteral glutamine given in rats with in vivo polymicrobial sepsis, and glutamine given enterally and/or parenterally to patients diagnosed with sepsis in vitro studies have also been shown to have positive effects on the immune system [23,24].

In the light of these studies, in Covid-19 with lower respiratory tract involvement, which is the most important pandemic of the last century and has yet no curative treatment, we designed our study considering that glutamine supplementation, which can be given orally to the patients, will provide positive efficacy on immune modulation. The results of our study were also positive similarly to the literatüre. However, more comprehensive studies on this subject are needed to reconfirm the results from our study.

The current study has some limitations. First, the results cannot be generalized to the whole population because the study was conducted in a single center and included only patients over 50 years of age without comorbidity. Second, more patients should be included in the study to demonstrate the effect of L-Glutamine supplementation on mortality. Third, to demonstrate the improvement of pathophysiological changes in the lung, patients should undergo pulmonary function tests and CT examinations after 6–8 weeks. The last limitation is that the Covid-19 without L-Glutamine group's not using placebo creates a separate bias.

In conclusion, our results suggest adding enteral L-glutamine to the normal nutrition in the early period of Covid-19 infection can shorten the length of hospital stay and reduce the need for ICU. Larger studies are needed to demonstrate the effect of L-Glutamine supplementation on Covid-19-related mortality and also in other infectious diseases.

Author contributions

Mahir Cengiz, conceptualization; data curation; formal analysis; investigation; methodology; project administration; software; supervision; role/writing - original draft.

Betul Borku Uysal, data curation; investigation; visualization; roles/writing - review & editing.

Hande Ikitimur, data curation; investigation; supervision; visualization.

Erkan Ozcan, conceptualization; data curation; resources; software; supervision; validation.

Mehmet Sami Islamoğlu, conceptualization; data curation; investigation; resources; supervision; validation; visualization.

Emre Aktepe, data curation; formal analysis; resources.

Hakan Yavuzer, conceptualization; Formal analysis; investigation; methodology; software; Roles/Writing - original draft; Writing - review & editing.

Serap Yavuzer conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; supervision; visualization; roles/writing - original draft; writing - review & editing.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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