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The impact of glutamine supplementation on the short-term mortality of COVID-19 diseased patients admitted to the ICU: A single-blind randomized clinical trial

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ABSTRACT

Background: Intravenous glutamine supplementation of nutrition in ICU patients is based on substantial clinical evidence that it boosts the immune system, particularly by inhibiting inflammatory reactions. This study aimed to see how glutamine affected COVID-19 short-term ICU mortality (7 days) and its clinical course.

Methods: Sixty patients were randomized in this single-blind clinical study and were divided into equal groups. Group EN, was delivered with standard enteral nutrition. Group GN was delivered intravenous glutamine supplementation to enteral nutrition. Both groups were monitored and assessed for 7 days. Short-term ICU mortality, monitoring of the inflammatory response and oxygenation, were compared between the two groups.

Results: During the 7-day follow-up period, ten patients (33.3%) died in the GN group, compared to 11 patients (37.6%) in the EN group, with no statistically significant difference between the two groups. On the 7th day, both NLR and PLR showed considerably higher values in the EN group than in the GN group, and on the 4th day, the PLR ratio showed significantly higher values in the EN group than in the GN group. In terms of unsuccessful enteral nutrition and transition to total parenteral nutrition, group GN had a considerably lower rate than group EN (ten patients (33.3%) against 22 patients (73.3%), respectively, *P*-value = 0.002).

Conclusions: Although there is little indication that glutamine supplementation could prevent short-term mortality in COVID-19 ICU admitted patients, the GN group had a lower inflammatory response and fewer patients switched to total parenteral nutrition.

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus discovered in December 2019 in Wuhan, China [1]. The World Health Organization declared Covid-19 a pandemic on 11 March 2020. The Covid-19 quickly spread throughout China, and eventually to the rest of the world. The fight against the outbreak has devolved into a battle between people and viruses [2].

There is currently no specific treatment available. The main focus is on improving respiratory functioning, especially in patients with lower respiratory tract involvement. In the early stages of the condition, supportive care appears to be the most successful therapeutic method. The condition has a greater morbidity and mortality rate, particularly in elderly patients with weakened immune systems, those with dietary deficits, and those with chronic illnesses. [3,4] Normal protein intake is insufficient to sustain recovery in COVID-19, as it is in other acute disorders, because the catabolic process is still going on. Increasing the amounts of particular amino acids that reduce acute stress, such as cysteine, arginine, and glutamine, enhances immunity in such patients [5]. These highlighted amino acids are known to influence various functions in the cell and aid recovery by acting as signal molecules and mediators on a cellular level [6]. Glutamine is a non-essential amino acid found in large quantities in the human body. It is mostly produced by skeletal muscle and makes up 30% of plasma free amino acids [7]. In times of high stress, endogenous glutamine production may not be enough to meet patients' needs [8]. Exogenous glutamine supplementation is therefore essential in this situation to maintain normal plasma glutamine concentrations [7].

In this study, we hypothesized that parenteral L-Glutamine supplementation added to standard enteral nutrition could affect the short-term ICU mortality (7 days) in Covid-19 diseased patients.

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2. Materials and methods

2.1. Ethical considerations

This was a randomized, single-blind, controlled clinical trial, approved by the University's Institutional Review Board (IRB17300609), and registered before patient enrolment in the Clinical Trials.gov trial registry (NCT04909905). The methodology of this study follows the 1975 Helsinki Declaration (revised, 2013). A written informed consent was obtained from the patients or their 1st degree relatives.

2.2. Participants

The study involved adults (age ≥18 years) who were diagnosed with COVID-19 needing ICU admission (any cases with a respiratory rate (RR) > 30 breaths /min, a partial pressure of oxygen in arterial blood/fraction of inspired oxygen (P/F) ratio < 300 or > 50% infiltrates as in CT chest), and had positive real-time reverse-transcriptase-polymerase-chain reaction (RT-PCR) test in oro-nasopharyngeal swab with standard enteral nutrition were enrolled. Patients with renal failure (creatinine >180 mmol/l) or hepatic failure (bilirubin >40 mmol/l, alanine aminotransferase >100 U/l and aspartate aminotransferase >100 U/l) [9] were excluded. Patients with severe neutropenia (<500 cells/mm3), those receiving cytotoxic, radiation and/or steroid therapy, those with hemodynamic instability, pregnant women, those resistant to aggressive fluid resuscitation, and those allergic to the intervention drug were also excluded.

2.3. Randomization

Patients satisfying the enrolment criteria received an ascending serial number in the order of their enrolment. Based on this number, the patients were assigned to one of the study groups. The patient's number appeared on the patient's prescription and was used to prepare the all-in-one bag for the patient. Study masking was for patients who were blind to the randomization until the 7-day (during the ICU stay) follow-up had been completed for all subjects.

2.4. Study protocol

The patients admitted to the general ICU in our university hospital were included, who fulfilled the inclusion criteria and signed informed consent. Patients had central venous catheter placement at the time of admission (by the intensivist using sonar guided right or left internal jugular vein). Patients were randomly assigned to receive either standard enteral nutrition **(Group EN)** or intravenous glutamine supplementation to enteral nutrition **(Group GN)** with a dose of glutamine of 0.4 g/kg/day (Berg 2005) (Dipeptivens, Fresenius Kabi, Bad Homburg, Germany) during their ICU stay [9]. Haemoglobin, white blood cells (WBCs) count, platelets (recorded at days 0 and 7), neutrophil/lymphocyte ratio (NLR), platelets/lymphocyte ratio (PLR), serum C-reactive protein (CRP), lactate levels, D-dimer, and serum ferritin (recorded at days 0, 4, and 7), and IL-6 level at days 0 and 7. Sodium, potassium, chloride, AST, ALT, blood glucose, urea, creatinine, albumin, and total bilirubin (recorded at days 0 and 7). The number of patients who failed enteral nutrition and shifted to parenteral nutrition was also recorded. The primary outcome was short-term ICU mortality (7 days). Secondary outcomes were need for upgrading oxygenation and or ventilation, multi-organ affection, NLR, and any recorded complications, especially hyperglycaemia (≥180 mg/dl) and superadded bacterial infection. Adverse events or complications were treated and recorded.

3. Statistics

3.1. Calculation of sample size

According to data from a previous study [10], a sample size of 30 per group was required to provide 80% power to detect a difference in mean levels with a significance of 0.05 (2-sided). To overcome dropout, a total sample size of 78 patients was required.

3.2. Data analysis

A value of $P < 0.05$ was accepted as statistically significant. Comparison between means was assessed by using the unpaired Student's t-test. When data was not distributed normally, comparisons were made with the Mann–Whitney U-test (when appropriate) to determine the significance when comparing proportions. The cut-off points of NLR and PLR in its correlation to mortality was calculated in each group using the receiver operating characteristic (ROC) curve. A P-value <0.05 was accepted as statistically significant. The analysis was performed using SPSS version 22.

4. Results

Among the 78 patients admitted to COVID-19 ICU, 18 patients were not eligible for this study (10 patients did not fulfil the inclusion criteria and 8 patients did not sign consent). Finally, 60 patients were eligible for our study, as shown in flow chart Figure 1. No significant difference was noticed among the two groups regarding demographics, smoking history, and co-existing diseases (Table 1).

Ten patients (33.3%) died in the GN group in comparison to the EN group, where 11 patients (37.6%) died during the 7-day follow-up period, with an insignificant difference between the two groups (*P*-value = 0.78).

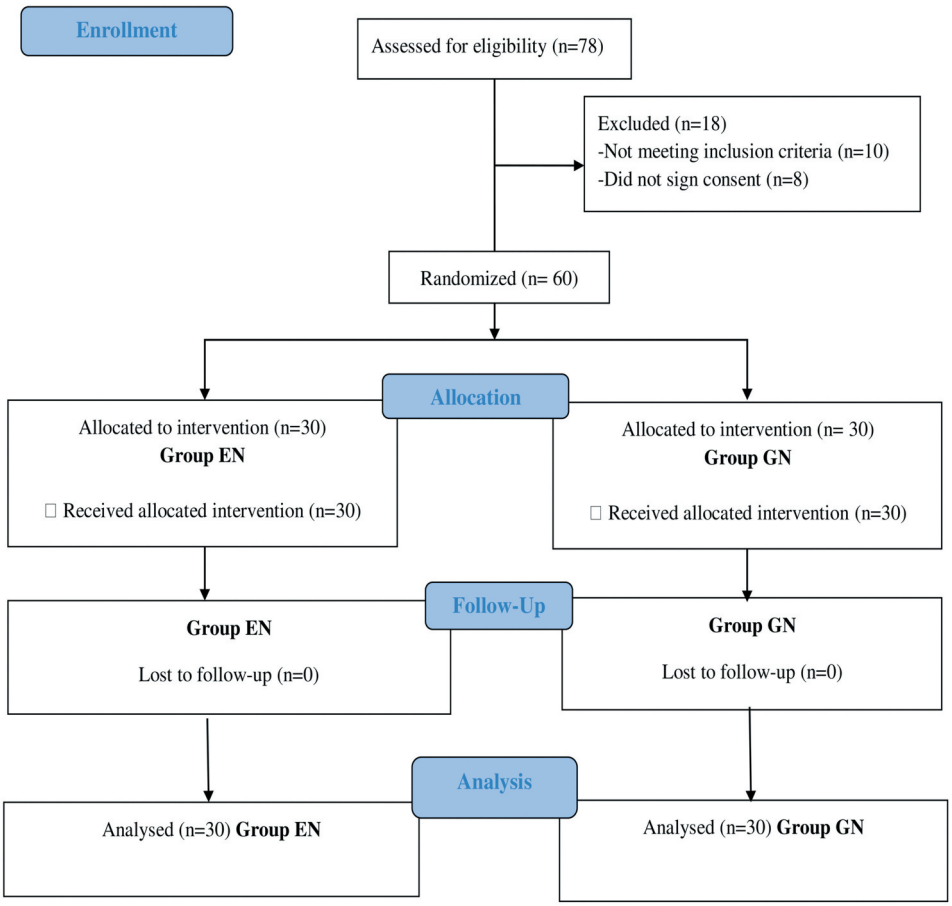


Figure 1. CONSORT Flow Chart between the study groups.

Regarding NLR and PLR; the two ratios showed significantly higher values in the EN group than the GN group on the 4th and 7th days for PLR and only in the 7th day in NLR. The follow-up values on the 4th and 7th days were significantly higher than the base-line values in the two group as regards to NLR and PLR as shown in (Table 2). The ROC curves for the 7th day NLR & PLR and their correlation in predicting short-term ICU mortality between the studied groups showed excellent diagnostic tests. ROC curves for 7th day NLR showed a higher area under the ROC curve in group GN in correlation to group EN (0.995 versus 0.909). The optimal cut-off points were 12.05 in group EN at SE = 72.7% and SP = 100% versus 7.4 in group GN at SE = 100% and SP = 95%. ROC curves for 7th day PLR showed a higher area under the ROC curve in group GN than in group EN (1 versus 0.909). The optimal cut-off points were 267

Table 1. Demographic and clinical data in the two study groups.

Variables	Group GN n = 30	Group EN n = 30	P-value
Age (years)	60.27 ± 8.4	55.9 ± 7.1	0.036
Gender (m/f)	19/11	22/8	0.4
Weight (cm)	92 ± 8.7	89.5 ± 8.2	0.24
Height (kg)	156.7 ± 4.3	166.4 ± 3.5	0.49
Body mass index (kg/m^2)	33.5 ± 2.5	32.35 ± 3.2	0.13
Smoking	14(47.6%)	16(53.3%)	0.61
Coexisting diseases			
Chronic obstructive lung disease	5(16.7%)	4 (13.3%)	0.71
Obstructive sleep apnoea syndrome	3 (10%)	2 (6.6%)	0.64
Hypertensive	11(36.7%)	9(30%)	0.58
Diabetes mellitus	12 (40%)	10 (33.3%)	0.59
Ischemic heart disease	2 (6.6%)	2 (6.6%)	1
Hepatic impairment	1 (3.3%)	1 (3.3%)	1
Chronic kidney disease	2 (6.6%)	2 (6.6%)	1
Previous cerebrovascular accident	-	1 (3.3%)	1
Oncology	-	1 (3.3%)	1

Data are presented as mean ± standard deviation, ratio, number (percentage).*P* < 0.05 is considered statistically significant. Group GN (glutamine supplementation) and Group EN (Standard enteral nutrition).

Table 2. Inflammatory markers in the two study groups.

Variables	Group GN n = 30	Group EN n = 30	P-value
Neutrophil/lymphocyte ratio (NLR)			
Admission	5.3 ± 0.53	5.26 ± 0.42	0.69
4th day	7.8 ± 0.94*	8.12 ± 0.79*	0.28
7th day	8.7± 1.4*	10.56 ± 0.91*	0.008
Platelet/lymphocyte ratio (PLR)			
Admission	115.2 ± 11.56	115 ± 11.9	0.98
4th day	135.6± 17.2*	164.8 ± 18*	0.037
7th day	169 ± 25*	214 ± 26.9*	0.007
Interleukin-6 (IL-6) pg/ml			
Admission	8.7 ± 0.88	8.8 ± 0.9	0.89
7th day	16.12 ± 3.05	16.2 ± 3.08	0.28
C-reactive proteins (CRP) mg/dl			
Admission	30 ± 4.9	29.6 ± 4	0.77
4th day	45.9 ± 8.5*	48.5 ± 7.9*	0.72
7th day	58.3 ± 12.5*	68.7 ± 12.3*	0.19

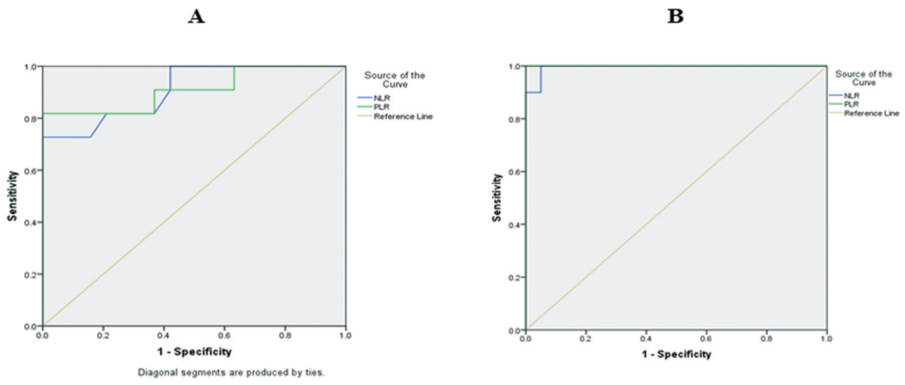
Data are presented as mean ± standard error. (*) significant change from the baseline value in the same group.$P < 0.05$ is considered statistically significant. Group GN (glutamine supplementation) and Group EN (Standard enteral nutrition).

in group EN at SE = 81.8% and SP = 100% versus 188 in group GN at SE = 100% and SP = 100% as shown in (Figure 2).

No significant variation was noticed between the two groups regarding IL-6 and CRP. However, the follow-up values of CRP showed a significant increase in comparison to the baseline value in both groups throughout the whole follow-up period (Table 2).

Other laboratory findings, including serum ferritin and lactate, and D-dimer, showed insignificant differences between the participants of the two groups. The 7th day serum ferritin mean value was significantly higher than its corresponding baseline value in the EN group. The 4th day D-dimer mean value was significantly higher than its corresponding baseline value in the EN group (Table 3).

Regarding the failed enteral nutrition and shift to total parenteral nutrition, it was significantly lower in group GN in comparison to group EN (ten patients (33.3%) versus 22 patients (73.3%) respectively, *P*-value = 0.002) as shown in (Table 4). No significant difference was noted between groups regarding the need for oxygen therapy upgrade and/or ventilatory support. The same is true for other organ affections, as well as complications such as 2ry hyperglycaemia (≥180 mg/dl) and/or bacterial infection (Table 4).



A. Group EN (Standard Enteral Nutrition)

The 7th day NLR: AUC=0.909, the cutoff point=12.05 at sensitivity 72.7% and specificity 100%

The 7th day PLR: AUC=0.909, the cutoff point=267 at sensitivity 81.8% and specificity 100%

B. Group GN (Intravenous Glutamine Supplementation to Enteral Nutrition)

The 7th day NLR: AUC=0.995, the cutoff point=7.4 at sensitivity 100% and specificity 95%

The 7th day PLR: AUC=1, the cutoff point=188 at sensitivity 100% and specificity 100%

Figure 2. The 7th day NLR & PLR in relation to mortality.

Table 3. Serum ferritin, D-dimer, and lactate levels in the two study groups.

Variables	Group GN n = 30	Group EN n = 30	P-value
Serum ferritin ng/ml			
Admission	314 ± 16.6	315.8 ± 17	0.95
4th day	318.7 ± 12.9	335 ± 14.8	0.40
7th day	340.8 ± 17.8	362 ± 17*	0.39
D-dimer mcg/ml			
Admission	1.6 ± 0.13	1.63 ± 0.16	0.96
4th day	1.8 ± 0.18	2.3 ± 0.34*	0.60
7th day	2.2 ± 0.36	3.9 ± 0.79	0.23
Serum lactate mmol/L			
Admission	1.44 ± 0.12	1.5 ± 0.13	0.64
4th day	1.7 ± 0.13	1.8 ± 0.14	0.48
7th day	1.87 ± 0.188	1.9 ± 0.26	0.26

Data are presented as mean ± standard error. (*) significant change from the baseline value in the same group.$P < 0.05$ is considered statistically significant. Group GN (glutamine supplementation) and Group EN (Standard enteral nutrition).

5. Discussion

This study investigates the efficacy of adding parenteral L-Glutamine to enteral nutrition for COVID-19 admitted ICU patients. The results of this study have showed that there was no significant difference in the short-term mortality between the two groups, but there was a reduced inflammatory response in patients who received parenteral glutamine supplementation to enteral nutrition, especially at the 7th day NLR, 4th and 7th day PLR.

The increased and unregulated synthesis of soluble inflammatory markers known as "cytokine storm" is a common cause of acute respiratory distress syndrome (ARDS) in COVID-19 patients [11,12]. ARDS, which is defined by immune cell infiltration in both the lungs and hypoxemia, is the primary cause of death in COVID-19. Inflammation affects the alveolar-capillary membranes in ARDS, leading to increased lung permeability and the exudation of high-protein oedematous fluid into the air sacs [13]. It goes without saying that glutamine, as a crucial component of intermediate metabolism, plays a role in a variety of cellular processes. As a result, a glutamine deficiency isn't a well-defined clinical disease with distinct signs and symptoms. However, the free glutamine concentration in the blood may be easily determined specially in ICU patients. Low glutamine plasma concentrations on the day of admission have been linked to poor outcomes in such critically ill patients. In reality, this means that a low plasma glutamine concentration requires exogenous glutamine replenishment, whereas a normal plasma glutamine concentration does not rule out the possibility of intracellular glutamine depletion [14]. Furthermore, giving glutamine to patients by parenteral administration in the ICU ensures that they receive the correct dosage. The glutamine-containing dipeptide solutions can be given either centrally or peripherally [15].

It's vital to keep in mind that the endogenous de novo glutamine production rate is 60–70 g glutamine per 24 hours. Less than 20% of this comes through protein degradation, while the remainder is synthesized de novo, primarily from other amino acids contributing their carbon skeletons to the tricarboxylic acid (TCA) cycle, which produces glutamate and glutamine from alpha-ketoglutarate. When exogenous glutamine is administered, it is put on top of endogenous glutamine production, results in increased glutamine availability, at least in the near term [16]. Reduced proinflammatory cytokine production [17,18], better neutrophil bactericidal function [19], and higher glutathione and oxidative capability are only a few of glutamine's immune system impacts [20].

Table 4. Respiratory and other organ affection variables in the two study groups.

Variables	Group GN n = 30	Group EN n = 30	P-value
Hyperglycaemia (≥180 mg/dl)	9 (30%)	6 (20%)	0.37
Bacterial infection	8 (26.7%)	6 (20%)	0.54
Shift to parenteral nutrition	10 (33.3%)	22 (73.3%)	0.002
Need for oxygenation	8 (26.7%)	6 (20%)	0.79
Need for ventilation	11 (36.7%)	13 (43.4%)	
Need for both	11 (36.7%)	11 (36.7%)	
Organ dysfunction	12 (40%)	8 (26.7%)	0.43
Single organ affection	13 (43.4%)	15 (50%)	
Two organs	4 (13.3%)	7 (23.3%)	
≥3 organs			

Data are presented as number (percentage)$P < 0.05$ is considered statistically significant. Group GN (glutamine supplementation) and Group EN (Standard enteral nutrition).

In line with our results, parenteral glutamine administered to rats with polymicrobial sepsis in vivo and glutamine given enterally and/or parenterally to humans diagnosed with sepsis in vitro trials have both been found to have favourable effects on the immune system [21,22]. According to Furst et al., 15–35 g of supplemented glutamine may be necessary during stressful periods to preserve muscle glutamine and intestinal integrity, to give fuel and enhance a positive nitrogen balance to the cells [23].

Glutamine supplementation as part of oncology treatment is a hot topic right now. The findings suggest that glutamine can help the host by increasing glutathione levels, preventing or repairing tissue damage, and alleviating some side effects [24]. Recently, there is evidence that restoring glutathione must be a part for lung protection in COVID-19 ARDS patients [25]. The time of hospitalization and the rate of developing infections have both lowered in patients receiving parenteral glutamine-supplemented nutrition during bone marrow transplantation. The cost reductions per patient were anticipated to be around $22,000 on average [26].

In the early stages of Covid-19 infection, Cengiz M et al. discovered that combining enteral L-glutamine with normal diet may result in a shorter hospital stay and less need for ICU. Larger research is needed to see how adding enteral L-Glutamine to currently utilised medications for infectious infections, like Covid-19, affects the outcome [10].

However, Avenell et al. [27] found that glutamine had no influence on the development of multiorgan and renal failure. Similarly, Tao et al. [28] found no significant change in biochemical indicators including serum creatinine (Cr), aspartate transaminase (AST), or alanine transaminase (ALT) that would indicate renal or hepatic injury. Furthermore, the risk of gastrointestinal problems remained unaffected.

6. Strengths and limitations

The study's strengths were that we introduced L-glutamine as a supplementary pharmaco-nutrient in COVID-19 ICU admitted patients, who already on enteral nutrition. Limitations: more patients should be included in the study to demonstrate the effect of L-Glutamine supplementation on mortality so, multicentre trials are needed. Second, when the participants were discharged from the ICU, they were not followed up, especially for pulmonary function tests and CT examinations. Our findings cannot be applied to all COVID-19 patients at all stages and degrees.

7. Clinical and future implications

Our findings suggest that adding parenteral glutamine to enteral nutrition could reduce the inflammation in cases of COVID-19 patients admitted to the ICU. The future research in the field of pharmaco-nutrition with glutamine in critical care needs large, well-designed RCTs that will focus on safety next to efficacy of the supplement administered, as well as the optimal dose and duration of administration.

8. In conclusion

According to the current trial, there is low evidence suggesting that glutamine supplementation could reduce the short-term mortality in COVID-19 ICU admitted patients, but the inflammatory response and the number of patients shifted to total parenteral nutrition were reduced in the GN group. Furthermore, the parenteral route of administration appears to be more beneficial, although so far, no definite conclusion has been reached on the proper dosage and duration of therapy.

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