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ORIGINAL RESEARCH INTENSIVE CARE

A randomized, controlled study to evaluate the effect of parenteral glutamine on the reduction of infection related morbidity in burn patients in ICU

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Abstract

Background: Burn patients are characterized by alterations within the immune system, increased exposure to infectious complications, sepsis, and potentially organ failure and death. Glutamine supplementation to parenteral nutrition has been proven to be related to improved clinical outcomes in trauma patients. We studied the effect of glutamine supplementation on infection and clinical outcomes among burn patients.

Methodology: Sixty burn patients were randomly divided into two equal groups. Group I received 0.5 gm/kg/day glutamine infusion as a part of parenteral nutrition for seven days after ICU admission. Group II received an intravenous placebo by continuous infusion (24 h/day). The primary outcome was the presence of infection assessed by the wound culture over a 15-days period. The secondary outcomes were: blood culture, WBCs count, serum C-reactive protein (CRP) and procalcitonin, sequential organ failure assessment (SOFA) score, and length of stay within the intensive care unit.

Results: The results showed that the incidence of positive wound culture was considerably reduced within the glutamine group, e.g., 6 (10%) patients) vs. control 19 (33%) patients; $P < 0.001$). The incidence of positive blood culture was significantly reduced within the study group (1 case) vs. control (9 cases; $P = 0.006$). In addition, the WBC, serum CRP and procalcitonin were better; and the SOFA score and the ICU-stay were reduced within the glutamine group vs. the control group.

Conclusion: The present results prove that IV glutamine supplementation in adult burn patients can reduce the impact of infectious morbidity and improve the clinical outcome.

Ethical committee approval: 19/5/2019 ANETS 4

Trial registration: www.clinicaltrials.gov No. NCT05140772

Abbreviations: ICU - intensive care unit; SOFA - Sequential Organ Failure Assessment; CRP - C-reactive protein; GFR-glomerular filtration rate; TBSA - total body surface area; BMI – Body mass index

Key words: Glutamine; Infection; Burn; ICU; Mortality

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1. Introduction

Glutamine is the most abundant non-essential amino acid in the blood and, therefore, the free amino acid pool within the body. [1] It is utilized by immune-competent cells, enteric cells, and hepatic cells. [2] Burn injury is related to major endocrine, inflammatory, metabolic, and immune alterations requiring specific nutritional interventions. [3] In the presence of critical illness and catabolic stress, the body's glutamine consumption exceeds the traditional supply. The gut mucosal cells, bereft of glutamine, cease to perform their barrier function and permit entry of luminal toxins and bacteria directly into the portal bloodstream. [4]

Despite improvements in prevention and management, burn injury continues to represent a serious risk to the health and wellbeing of individuals in all age groups. Even with early surgical intervention and aggressive antibiotic therapy, infectious complications cause death in severe burn injury, accounting for 75% of deaths after initial resuscitation. [5] Supplementation with glutamine or glutamine-containing dipeptides improve nitrogen balance and maintains the intracellular glutamine level. [6] The present study aimed to investigate the effect of glutamine supplementation on infection among burn patients by using various infection related parameters.

2. Methodology

After the approval of the local ethical committee and registration of the study at clinical trial.gov (NCT05140772), informed written consent from every patient was obtained. The study was carried out from June 2019 to December 2021 in the ICU of Menoufia University Hospital. We enrolled 60 burn patients, 18-50 y of age, of both sexes, total burn surface area of 20% - 60%, expected length of stay in ICU > 48 h, admission within 72 h of burn injury and with any sort of thermal injury like flame burns, scald burn and contact burns. Patients were excluded from the study if they had a hepatic failure, severe renal failure (glomerular filtration rate (GFR < 50 ml/min), coexisting severe cardiac or pulmonary disease, diabetes mellitus, or cancer. Patients with inborn errors of amino-acid metabolism (e.g., phenylketonuria), patients with metabolic acidosis (pH < 7.35), and electric burns were also excluded.

Patients were randomly categorized by opaque sealed envelopes after enrolment into two equal groups (thirty each). Computer-generated randomization generated

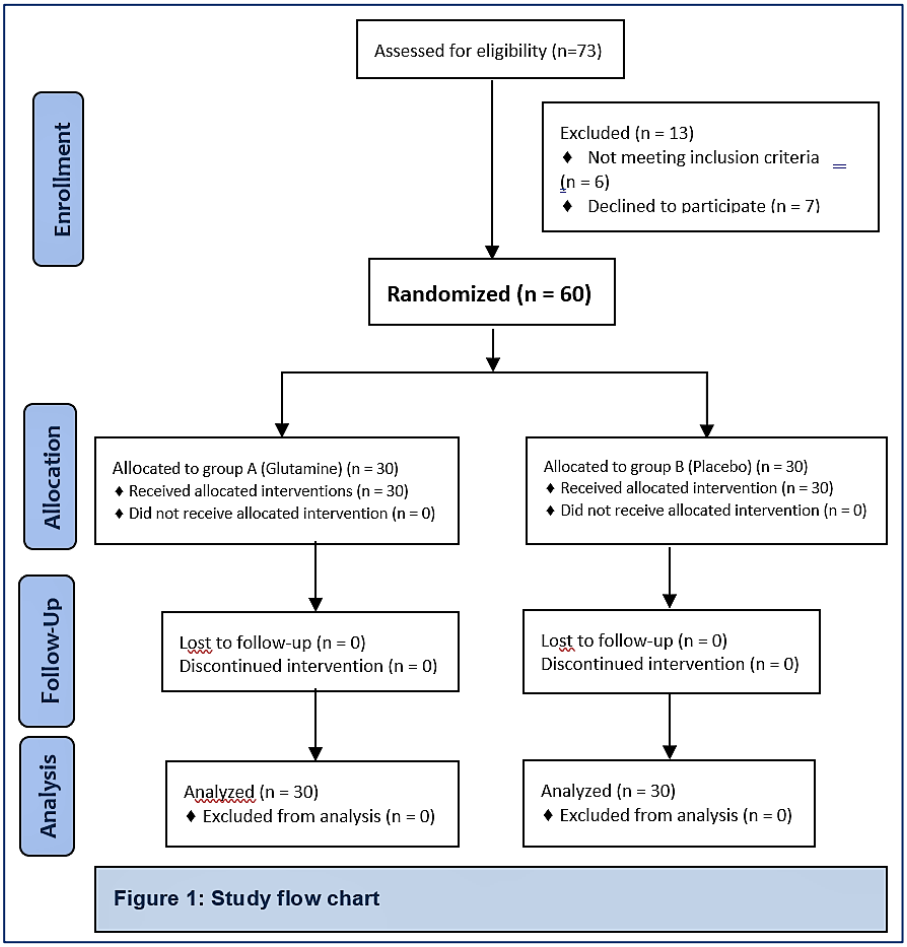

Figure 1: Study flow chart

Table 1: Comparative demographic data and burn %

Variable	Group I (n = 30)	Group II (n = 30)	Test of Sig.	p
Gender				
Male	13 (43.3)	15 (50.0)	$\chi 2 = 0.268$	0.605
Female	17 (56.7)	15 (50.0)		
Age (years)	30.33 ± 9.06	30.53 ± 7.50	t = 0.093	0.926
Weight (kg)	72.37 ± 7.05	71.97 ± 9.44	t = 0.186	0.853
Height (cm)	165.3 ± 6.44	165.8 ± 4.68	t = 0.321	0.749
BMI (kg/m2)	26.59 ± 3.29	26.20 ± 3.42	t = 0.449	0.655
Burn %	31.37 ± 6.29	30.23 ± 6.42	t = 0.691	0.493

Data presented as n (%) or mean ± SD. Group I: glutamine group, Group II: control group. $\chi 2$: Chi-square test, t: Student's t-test

Table 2: Comparison between the two studied groups according to wound culture

Wound culture	Group I	p0	Group II	p0	$\chi 2$	p
Day 1	**(n = 30)**		**(n = 30)**			
Negative	30 (100)		30 (100)		–	–
Positive	0 (0.0)		0 (0.0)			
Day 5	**(n = 30)**		**(n = 30)**			
Negative	24 (80.0)	0.031*	11 (36.7)	< 0.001*	11.589*	0.001*
Positive	6 (20.0)		19 (63.3)			
Day 10	**(n = 6)**		**(n = 19)**			
Negative	4 (66.7)	0.500	15 (78.9)	0.125	0.377	FEp = 0.606
Positive	2 (33.3)		4 (21.1)			
Day 15	**(n = 0)**		**(n = 14)**			
Negative	0	–	12 (85.7)	0.500	–	–
Positive	0		2 (14.3)			
Wound culture organism Day 5	**(n = 6)**		**(n = 19)**			
Gram -ve	2 (6.7)	–	13 (43.3)	–	10.756*	0.001*
Gram +ve	4 (13.3)		6 (20.0)		0.480	0.488

*Data presented as n (%). Group I: glutamine group, Group II: control group. $\chi 2$: Chi-square test, FE: Fisher Exact. p0: p-value for McNemar test for comparing between Day 1 and each other periods. *: Statistically significant at p ≤ 0.05*

numbers were marked on the envelopes. The unblinded pharmacist prepared the solutions by using the closed envelope technique.

Group I: (glutamine group) patients received 0.5 g/kg/day IV glutamine infusion (Dipeptiven® 100 ml contains 20 g N(2)-L-alanyl-L-glutamine in water for injections) as part of his nutrition for seven days after ICU admission.

Group II: (control group) patients received normal saline in equal volume as glutamine infusion.

Demographic data of all of the patients including age, sex, weight, BMI, and height, were recorded. Medical history and physical examination were completed. Routine laboratory investigation including CBC, liver and renal function, and random blood glucose level, were ordered.

Percentage of the body surface burnt was calculated by Wallace rule of nine. [7]

All patients received ceftriaxone 2 gm IV every 24 h as a prophylactic antibiotic which would be changed according to the wound and blood cultures. The nutrition was started within 24 h of admission. IV fluid supplementation was calculated according to the percent area of the burns.

Outcome measures were taken by a blinded investigator every 5 days for 15 days or until the discharge or death of the patient. The primary outcome measure was the presence of infection proved by a tissue culture test. The secondary outcomes were: serum C-Reactive Protein (CRP), serum procalcitonin (PCT), white blood cell (WBC) count, blood culture, and duration of ICU stay.

SOFA score was recorded at the time of admission to ICU, and after five days.

Table 3: Comparative values of CRP and procalcitonin in the two groups

	Group I	Group II	U	p
CRP				
Day 1	n = 30 3.37 ± 0.72	n = 30 3.77 ± 0.73	333.0	0.056
Day 5	n = 30 29.77 ± 20.09	n = 30 50.17 ± 32.68	266.50*	0.007*
Day 10	n = 6 28.42 ± 11.71	n = 19 34.74 ± 24.22	56.0	0.975
Day 15	n = 0 -	n = 14 24.43 ± 14.98	-	-
Procalcitonin				
Day 1	n = 30 0.14 ± 0.07	n = 30 0.13 ± 0.05	413.0	0.496
Day 5	n = 30 0.18 ± 0.2	n = 30 0.68 ± 0.8	322.5*	0.043*
Day 10	n = 6 0.18 ± 0.16	n = 19 0.37 ± 0.29	35.5	0.176
Day 15	n = 0 -	n = 14 0.20 ± 0.12	-	-

*Data presented as or mean ± SD, n = (number of patients). Group I: glutamine group, Group II: control group. U: Mann Whitney test. p: p-value for comparing between the two studied groups. p0: p-value for Wilcoxon signed ranks test for comparing between Day 1 and each other periods. *: Statistically significant at p ≤ 0.05*

2.1. Sample size calculation

The sample size was calculated using G Power version 3.1.9.7, 2020. Based on a previous clinical study, where an effect size of parenteral glutamine supplementation on reducing positive blood culture and positive wound culture among burn patients of 0.8, [9] alpha (α) error of 5%, power of 80%, and the ratio of sample sizes in group 1: group 2 of 1:1, the sample size was calculated to be 52 patients (26 patients per group). The sample size was rounded to 60 patients (30 patients in each group) to compensate for dropouts and protocol violations.

2.2. Statistical analysis

Data were statistically analyzed using IBM SPSS software package version 20.0**.** **(**Armonk, NY: IBM Corp**)**. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Numerical variables were presented as mean ± SD, whereas categorical variables were presented as a number of cases and percent. Between-group comparisons of numerical variables were made using the Independent Student's t-test or Mann–Whitney test, whereas those of categorical variables were made using $\chi 2$ -square test or Fisher's exact test (when more than 20% of the cells have expected count less than 5). The significance of the obtained results was judged at the 5% level.

3. Results

Seventy-three patients were evaluated for eligibility; six did not match the inclusion criteria, and seven refused to participate. Sixty patients were enrolled in the study and allocated into two groups of 30 patients in each group, as shown in the study flow chart (Figure 1). Patients' demographic data and burn % were comparable between the groups with insignificant differences (Table 1).

As regard wound culture, there was a significant reduction of positive wound cultures in the glutamine group on day 5 ($p < 0.001$), there were 6 patient in group I (2 Gram –ve and 4 Gram +ve organism) and 19 patients in group II with +ve wound culture (13 Gram –ve and 6 Gram +ve bacteria). However, there was a statistically significant drop in Gram -ve bacteremia in group I than in group II ($p < 0.001$), whereas there was no statistically significant difference between the two groups in respect to gram +ve bacteremia ($p < 0.488$) (Table 2).

Table 4: Comparison between the two studied groups according to WBC

WBC	Group I	p0	Group II	p0	t	p
Day 1	(n = 30)		(n = 30)			
Mean ± SD.	14.22 ± 2.61		14.30 ± 2.49		0.126	0.900
Day 5	(n = 30)		(n = 30)			
Mean ± SD.	10.76 ± 4.95	< 0.001*	14.91 ± 5.86	0.411	2.969*	0.004*
Day 10	(n = 6)		(n = 19)			
Mean ± SD.	10.07 ± 1.46	< 0.001*	13.17 ± 3.09	0.003*	3.347*	0.003*
Day 15	(n = 0)		(n = 14)			
Mean ± SD.	–	–	8.60 ± 1.61	< 0.001*	–	–

*Data presented as mean ± SD, n = number of patients. Group I: glutamine group, Group II: control group. t: Student t-test. p0: p-value for Paired t-test for comparing between Day 1 and each other periods. * Statistically significant at p ≤ 0.05*

Table 5: Comparison between the two studied groups according to blood culture

Blood culture	Group I		p0	Group II		p0	χ2	FEp
	n	%		n	%			
Day 1	(n = 30)			(n = 30)				
Negative	30	100.0		30	100.0		–	–
Positive	0	0.0		0	0.0			
Day 5	(n = 30)			(n = 30)				
Negative	29	96.7	1.000	21	70.0	0.004*	7.680*	0.006*
Positive	1	3.3		9	30.0			
Day 10	(n = 6)			(n = 19)				
Negative	6	100.0	–	16	84.2	0.250	1.077	0.554
Positive	0	0.0		3	15.8			
Day 15	(n = 0)			(n = 14)				
Negative	–	–	–	14	100.0	–	–	-
Positive	–	–		0	0.0			
Blood culture organism	(n = 1)			(n = 10)				
Gram -ve	1	3.3	–	8	26.7	-	6.405*	0.026*
Gram +ve	0	0.0		2	6.7		2.069	0.492

*Data presented as n (%). Group I: glutamine group, Group II: control group. χ2: Chi-square test, FE: Fisher Exact, p0: p-value for McNemar test for comparing between Day 1 and each other periods. *Statistically significant at p ≤ 0.05*

CRP and PCT showed a significant decrease in group I than in group II on day5 (p = 0.007 and 0.043

respectively) with an insignificant decrease on day 10 (Table 3).

Table 4 showed a significant decrease in WBC count in group I than in group II on day five and day 10 (p = 0.004 and 0.003).

According to blood cultures, there was significantly increased bacteremia in group II than group I at day 5 (p < 0.006), with a statistically significant drop in gram -ve bacteremia in the glutamine group than the control group (1 vs. 8 patients, p < 0.026), whereas there was no statistically significant difference among the groups as regards gram +ve bacteremia (0 vs 2 patients, p < 0.492) (Table 5).

There was a significant decrease in the SOFA score in the glutamine group than the control group on day 5 ($p < 0.001$) (Table 6).

The mean ICU stay was statistically significant shorter in group I than group II (7.47 ± 2.46 vs. 12.63 ± 4.51 days respectively, $p < 0.001$) (Table 6).

4. Discussion

The burn-injured patient presents specific challenges regarding metabolic stress, complication pattern, and outcome determinants. [1] Nutritional support is a critical issue in the treatment of burn patients. The metabolic rate of burn patients can be greater than twice the normal rate, and this response can last for more than a year after the injury. [2]

Glutamine is one of the 20 common amino acids, and thus it is an essential organic compound. It is also the most abundant free amino acid in the human body. Although endogenous glutamine production is adequate in ordinary healthy people, glutamine depletion is associated with certain critical illnesses and poor clinical outcomes. [10]

Regarding wound culture and blood culture, our trial has shown a significant decrease of infection in the glutamine group, especially the gram –ve bacteremia. These findings are in agreement with other researchers' findings. [9, 11, 12, 131] Previous studies can explain this difference, which suggest that glutamine exerts a protective effect on gut mucosa and prevents bacterial and endotoxin translocation from the intestinal lumen to the bloodstream. [14] It is also a critical nutrient for the proliferation and function of immune cells *in vitro*, and enteral glutamine supplements could be hypothesized to improve immune functions *in vivo*. [15] Another explanation can be obtained from a study conducted by Garrel et al. [16] which found that enteral glutamine supplementation in adult burn patients reduces blood infection and prevents bacteremia with *P. aeruginosa*. They documented that *P. aeruginosa* may be sensitive to the amount of glutamine in its environment; a lack of glutamine may trigger both proliferation and crossing the epithelial barrier. [16] Together with the weakening of the gut immune system, related at least in part to glutamine deficiency, these phenomena may explain *P. aeruginosa* translocation. [17]

A study conducted by De-Souza et al. on the effect of glutamine on intestinal permeability and systemic infection concluded that glutamine administration improves the prognosis of critically ill patients by maintaining the intestinal barrier. [18]

Regarding WBC counts, our results coincide with those of two of the earlier studies on the effect of parenteral and oral glutamine on biochemical parameters and found that total leukocyte count (TLC) increase was less evident in groups that received glutamine either parenterally or orally. [19, 20]

CRP, a biomarker of inflammation in acute-phase response, has been widely used in clinical settings. CRP may not be a specific sepsis biomarker, but its levels have important reference value in conjunction with other tools, such as PCT and some cytokines. [21,22] In our study, the mean change in the CRP levels, from day 1 to day 5, increased in both groups after the treatment. This increase was least evident in the glutamine group. The high CRP levels may be due to the presence of the factors that affect the CRP levels, such as fever, leukocytosis, surgical operation, and the presence of inflammation. These findings correlate with the results of studies by Gholamalizadeh et al. [23] and Singh et al. [19]

PCT showed a significant difference between group I and group II, and this difference is because of increased bacteremia in group II. PCT is mainly produced by neuroendocrine cells of the thyroid, and it is inhibited in non-endocrine tissues under normal conditions. Bacterial infection facilitates the transcription of the CALC-1 gene

Table 6: Comparison between the two studied groups according to SOFA score and ICU stay

SOFA score	Group I (n = 30)	Group II (n = 30)	U	p
SOFA score				
Day 0 (Mean ± SD)	0.27 ± 0.52	0.27 ± 0.58	439.0	0.821
Day 5 (Mean ± SD)	0.90 ± 1.45	3.0 ± 2.65	235.5*	0.001*
p0	0.004*	< 0.001*		
ICU Stay (Mean ± SD)	7.47 ± 2.46	12.63 ± 4.51	t 5.505*	< 0.001*

*Data were presented as mean ± SD, n = number of patients. Group I: glutamine group, Group II: control group. U: Mann Whitney test. p0: p-value for Wilcoxon signed ranks test for comparing between Day 0 and Day 5. *: Statistically significant at p ≤ 0.05*

in non-endocrine cells preventing its inhibition. PCT levels increase as early as 3 h after bacterial infection, reaching a peak around 20 h. After resolution of the infectious process, PCT levels decrease over days. [24, 25]

PCT in clinical practice can be used as a biomarker to distinguish bacterial from viral sepsis, as well as non-infectious systemic inflammatory response syndrome (SIRS). [26] In the present study, the PCT level was significantly higher in the control group due to bacteremia than in the glutamine group. The same was found in a study conducted by Ye and Song. [27] In contrast to our results, Ahler et al. found no beneficial effect of glutamine-enriched parenteral nutrition on PCT level in post-esophagectomy patients. This can be explained by the lower dose of glutamine used in Ahler study (0.15 g/kg/d) than used in our study (0.5 g/kg/d) and the type of patients. [28]

The ICU stay was significantly decreased in the glutamine group. This difference is because glutamine reduces infectious morbidity, so the length of ICU stay. [6] Some earlier studies showed similar results. [12, 19-20] Some authors reported that supplementation of enteral or parenteral glutamine showed improved immune function, reduced infections, and shortened the length of ICU stay. [29-31]

Day 1 SOFA score is an indicator of the severity of illness. The decrease in SOFA score was statistically significant in the two groups. However, the reduction in SOFA score from day 1 to day 5 was more marked in the glutamine group than the control group. This indicates an appreciable improvement in disease status in the glutamine group as shown by previous studies. [20, 32, 33]

5. Limitations

The study was performed at a single center. Larger studies need to be conducted in different cohorts of patients to further establish the efficacy of glutamine supplementation in reducing the infectious morbidity in burn patients.

6. Conclusion

The results of our study support the use of glutamine in severely burned patients, as it reduces the incidence of positive wound and blood bacterial cultures. It reduces the duration of hospital stay, and improves SOFA scores in the burned patients.

7. Data availability

The numerical data related to the study is available with the authors on request.

8. Conflict of interest

No conflict of interest was declared by the authors.

9. Funding

The study did not involve any internal or external funding. We used only the institutional resources.

10. Author contribution

AME: Study design, manuscript writing, analysis, review

HAA: Study design, manuscript editing, review

MEM: Manuscript writing, data collection

AAA: Study design, manuscript writing, data collection

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