e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2023; 15(10); 355-360
Original Research Article

A Randomized Placebo-Controlled Trial Assessing the Effect of Glutamine Supplementation on Infection and Clinical Outcomes among Burn Patients

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Received: 11-04-2023 / Revised: 23-05-2023 / Accepted: 20-06-2023

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Conflict of interest: Nil

Abstract:

Aim: The aim of the present study was to evaluate the effect of glutamine supplementation on infection and clinical outcomes among burn patients.

Methods: 100 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: 100 patients were enrolled in the study and allocated into two groups of 30 patients in each group, as shown in the study flow chart. Patients' demographic data and burn were comparable between the groups with insignificant differences. 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 8 patients in group I (2 Gram –ve and 4 Gram +ve organism) and 20 patients in group II with +ve wound culture (14 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. There was a significant decrease in WBC count in group I than in group II on day five and day 10 ($p = 0.003$ and 0.002).

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

Keywords: Glutamine; Infection; Burn; ICU; Mortality.

Introduction

Burns are devastating injuries affecting the human body. Burn victims face massive stress and tend to develop complications due to the significant impact on their body's physiologic and immunologic function, fluid, and nutrition. [1-4] Glutamine (GLN) is known to be the most abundant and versatile (nonessential) amino acid under normal healthy status. It contributes as a substrate to the production and synthesis of glutathione and ammonia, which are essential for all cellular replication. [5] Nonetheless, GLN is known to be dramatically deficient in critically ill individuals, including burn victims. This deficiency is explained by increased body requirements exceeding production in response to the stressful status and catabolic events. These findings indicate that GLN has a significant role in such severely ill patients. [6-9] GLN supplements in critical illness have gained extreme popularity among researchers over the years, and their safety and efficacy are still under question. Many systematic reviews showed that GLN supplements effectively reduced mortality and complications such as gram- negative bacterial infection. [10-12]

Furthermore, a meta-analysis conducted in 2015 found that enteral GLN supplementation is more effective among burn patients than trauma and nonburn intensive care unit (ICU) patients in reducing mortality and length of hospitalization (LOH), with no difference in infectious mortality. 12 However, over the past six years, new multicenter clinical trials have revealed that GLN supplementation, either parenteral, enteral, or in combination, is essential in early postburn management as it protects vital organs like the

heart, preserves the intestinal mucosal thickness, and alleviates the hyper-metabolic status, which prevents further loss of the muscular bulk. [13,14] Glutamine is the most abundant plasma and intracellular amino acid. It is known as an essential nutrient for the gastrointestinal tract during critical illness. The efflux of glutamine from the skeletal muscles serves as a carrier of nitrogen to the small intestine. [15] Increased glutamine use occurs during critical illness, which causes a significant glutamine deficiency and oftentimes results in an impaired immune response to infections. [16] Lower plasma and skeletal muscle glutamine levels have been associated with immune dysfunction [17] and a higher mortality rate in critically ill patients. [18]

The aim of the present study was to evaluate the effect of glutamine supplementation on infection and clinical outcomes among burn patients.

Material & Methods

The study was carried out during the duration of 2 years in the ICU of Darbhanga medical College and Hospital, Darbhanga, Bihar, India. 100 burn patients were enrolled, 18-50 yrs. 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.

Exclusion Criteria

- Patients who 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.

Patients were randomly categorized by opaque sealed envelopes after enrolment into two equal groups (thirty each). Computer-generated randomization generated 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. [13] 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.

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.

Results

Table 1: Comparative demographic data and burn

Variable	Group I(n = 50)	Group II(n =50)	p
Gender			
Male	22 (44)	24 (48)	0.610
Female	28 (56)	26 (52)	
Age (years)	29.31 ± 9.03	30.41 ± 8.42	0.912
Weight (kg)	73.47 ± 7.03	72.68 ± 9.51	0.830
Height (cm)	165.5 ± 6.46	165.5 ± 4.71	0.724
BMI (kg/m2)	25.55 ± 3.14	26.25 ± 3.35	0.625
Burn %	32.38 ± 6.24	31.29 ± 6.44	0.414

100 patients were enrolled in the study and allocated into two groups of 30 patients in each group, as shown in the study flow chart. Patient's demographic data and burn were comparable between the groups with insignificant differences.

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

Wound culture	Group I	p0	Group II	p
Day 1	**(n = 50)**		**(n = 50)**	
Negative	30 (100)		30 (100)	
Positive	0 (0.0)		0 (0.0)	–
Day 5	**(n = 50)**		**(n = 50)**	
Negative	40 (80)	0.036	18 (36)	
Positive	10 (20)		32 (64)	0.001*
Day 10	**(n = 7)**		**(n = 20)**	
Negative	5 (71.43)	0.500	16 (80)	FEp = 0.606
Positive	2 (28.57)		4 (20)	
Day 15	**(n = 0)**		**(n = 14)**	
Negative	0		12 (85.7)	
Positive	0	–	2 (14.3)	–
Wound culture organism Day 5	**(n = 8)**		**(n = 20)**	
Gram -ve	3 (37.5)		14 (70)	0.001
Gram +ve	5 (62.5)	–	6 (30)	0.467

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 8 patients in group I (2 Gram –ve and 4 Gram +ve organism) and 20 patients in group II with +ve wound culture (14 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.

Table 3: Comparison between the two studied groups according to WBC

WBC	Group I	p0	Group II	p
Day 1	(n = 50)		(n = 50)	
Mean ± SD.	13.27 ± 2.58		14.36 ± 2.48	0.912
Day 5	(n = 50)		(n = 50)	
Mean ± SD.	11.77 ± 4.86	< 0.001	14.86 ± 5.86	0.003
Day 10	(n = 7)		(n = 20)	
Mean ± SD.	11.09 ± 1.42	< 0.001	13.27 ± 3.07	0.002
Day 15	(n = 0)		(n = 14)	
Mean ± SD.	–	–	8.52 ± 1.68	–

There was a significant decrease in WBC count in group I than in group II on day five and day 10 ($p = 0.003$ and 0.002).

Table 4: Comparison between the two studied groups according to blood culture

Blood culture	Group I		Group II		FEp
	n	p0	n	%	
Day 1	(n = 50)		(n = 50)		
Negative	50		30		–
Positive	0		0		
Day 5	(n = 50)		(n = 50)		
Negative	48		40		
Positive	2	1.000	10		0.005
Day 10	(n = 7)		(n = 20)		
Negative	7		16		
Positive	0	–	4		0.524
Day 15	(n = 0)		(n = 14)		
Negative	–		14		
Positive	–	–	0		-
Blood culture organism	(n = 1)		(n = 10)		
Gram -ve	1		8		0.022
Gram +ve	0	–	2		0.440

According to blood cultures, there was significantly increased bacteremia in group II than group I at day 5 ($p < 0.005$), 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, $p < 0.440$).

Table 5: Comparison between the two studied groups according to SOFA score and ICU stay

SOFA score	Group I(n = 50)	Group II(n = 50)	p
SOFA score			
Day 0 (Mean ± SD)	0.24 ± 0.56	0.28 ± 0.52	0.810
Day 5 (Mean ± SD)	0.88 ± 1.42	3.0 ± 2.68	0.001
p0	0.004	< 0.001	
ICU Stay (Mean ± SD)	7.53 ± 2.48	12.68 ± 4.56	< 0.001

There was a significant decrease in the SOFA score in the glutamine group than the control group on day 5 ($p < 0.001$). The mean ICU stay was statistically significant shorter in group I than group II.

Discussion

In animal studies [19], glutamine decreased gut mucosal atrophy when supplemented in the parenteral nutrition that was administered to the animals. In addition, glutamine also reduced bacterial translocation in additional animal models. [20] Some animal studies [21,22] also demonstrated that glutamine supplementation improved survival in experimental models of sepsis. In a human study [23] supplementation of enteral and parental nutrition with glutamine was observed to improve immunologic function and preserve intestinal morphology and function. In addition, glutamine supplementation may also reduce bacterial translocation. [24] Similar to previous meta-analyses, glutamine supplementation reduced nosocomial infections among critically ill patients. However, unlike previous meta-analyses [25], we found that glutamine supplementation conferred no overall mortality benefit in critically ill patients. Furthermore, our subgroup analyses suggested that high-dosage glutamine supplementation (above 0.5 g/kg/day) significantly increased mortality in the observed critically ill patients. In addition, we did not observe a shortening of the length of hospital stay due to glutamine supplementation.

100 patients were enrolled in the study and allocated into two groups of 30 patients in each group, as shown in the study flow chart. Patients' demographic data and burn were comparable between the groups with insignificant differences. 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 8 patients in group I (2 Gram –ve and 4 Gram +ve organism) and 20 patients in group II with +ve wound culture (14 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. There was a significant decrease in WBC count in group I than in group II on day five and day 10 ($p = 0.003$ and 0.002). 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. [26] 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. [27] Another explanation can be obtained from a study conducted by Garrel et al [28] 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. Together with the weakening of the gut immune system, related at least in part to glutamine deficiency, these phenomena may explain P. aeruginosa translocation. [29]

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). [30] 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. [31] 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. [32] According to blood cultures, there was significantly increased bacteremia in group II than group I at day 5 ($p < 0.005$), 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, $p < 0.440$). There was a significant decrease in the SOFA score in the glutamine group than the control group on day 5 ($p < 0.001$). The mean ICU stay was statistically significant shorter in group I than group II.

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.

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