

A Clinical Study to Evaluate the Effect of Glutamine Supplementation on Infection and Clinical Outcomes among Burn PatientsUma Shankar Kumar¹, Anupama Priyadarshini², Parmod Kumar Sinha³¹Senior Resident, Department of Anaesthesia, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India²Consultant, Department of Biochemistry, Bodhi Hospital, Patna, Bihar, India³Associate Professor and HOD, Department of Anaesthesia, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India

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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:** The study was carried out during the duration of 2 years in the ICU. 200 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.**Results:** 200 patients were enrolled in the study and allocated into two groups of 50 patients in each group. 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 16 patients in group I and 40 patients in group II with +ve wound culture. 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). 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 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

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Introduction

Worldwide, burn injuries are the leading cause of disability-adjusted life-years lost in low- and middle-income countries and among the most expensive to treat of traumatic injuries. [1-3] The intense inflammation and catabolism associated with severe burns predispose patients to an increased risk of infectious complications, short- and long-term organ dysfunction, and death. [4] Numerous trials have evaluated the effect of different nutritional strategies in patients with severe burns. [5,6] Glutamine is of particular interest because it is vital for a number of key stress-response pathways in serious illness. [7] Observational studies have

shown that glutamine levels decrease rapidly after burn injury. [8-10]

Increased glutamine use occurs during critical illness, which causes a significant glutamine deficiency and oftentimes results in an impaired immune response to infections. [11] Lower plasma and skeletal muscle glutamine levels have been associated with immune dysfunction [9] and a higher mortality rate in critically ill patients. [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 Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India . 200 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 \pm 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 χ^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 = 100)	Group II(n =100)	p-value
Gender			
Male	45 (45)	49 (49)	0.713
Female	55 (55)	51 (51)	
Age (years)	28.33 \pm 8.02	31.42 \pm 8.46	0.842
Weight (kg)	74.46 \pm 7.04	73.67 \pm 9.61	0.852
Height (cm)	166.4 \pm 6.54	167.3 \pm 4.76	0.732
BMI (kg/m ²)	24.56 \pm 3.16	25.22 \pm 3.32	0.632
Burn %	33.37 \pm 6.24	32.28 \pm 6.44	0.416

200 patients were enrolled in the study and allocated into two groups of 50 patients in each group. Patients' 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 = 100)		(n = 100)	
Negative	1000 (100)		100 (100)	
Positive	0 (0.0)		0 (0.0)	–
Day 5	(n = 50)		(n = 50)	
Negative	80 (80)	0.034	35 (35)	0.001
Positive	20 (20)		65 (65)	
Day 10	(n = 14)		(n = 40)	
Negative	10 (71.43)	0.500	32 (80)	FEp =0.606
Positive	4 (28.57)		8 (20)	
Day 15	(n = 0)		(n = 28)	
Negative	0	–	24 (85.7)	–
Positive	0		4 (14.3)	
Wound culture organism Day 5	(n = 16)		(n = 40)	
Gram -ve	6 (37.5)	–	28 (70)	0.001
Gram +ve	10 (62.5)		12 (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 16 patients in group I and 40 patients in group II with +ve wound culture. 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 = 100)		(n = 100)	
Mean \pm SD.	13.27 \pm 2.58		14.36 \pm 2.48	0.912
Day 5	(n = 100)		(n = 100)	
Mean \pm SD.	11.77 \pm 4.86	< 0.001	14.86 \pm 5.86	0.003
Day 10	(n = 14)		(n = 40)	
Mean \pm SD.	11.09 \pm 1.42	< 0.001	13.27 \pm 3.07	0.002
Day 15	(n = 0)		(n = 28)	
Mean \pm SD.	–	–	8.52 \pm 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 SOFA score and ICU stay

SOFA score	Group I(n = 100)	Group II(n = 100)	p
SOFA score			
Day 0 (Mean \pm SD)	0.24 \pm 0.56	0.28 \pm 0.52	0.810
Day 5 (Mean \pm SD)	0.88 \pm 1.42	3.0 \pm 2.68	0.001
p-value	0.004	< 0.001	
ICU Stay (Mean \pm SD)	7.53 \pm 2.48	12.68 \pm 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 parenteral 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.

200 patients were enrolled in the study and allocated into two groups of 50 patients in each group. 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 16 patients in group I and 40 patients in group II with +ve wound culture. 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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