Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 09, 2023

Original research article

A clinical study evaluating the effect of glutamine supplementation on infection and clinical outcomes among burn patients: A randomized controlled study

[1]Dr. Sameera, [2]Dr. Pradeep, [3]Dr. Pruthvi Raj V

[1]Assistant Professor, Department of Anaesthesiology, ESIC PGIMSR, Kalaburagi, Karnataka, India

[2]Senior resident, Department of Anaesthesiology, ESIC PGIMSR, Kalaburagi, Karnataka, India

[3]DNB consultant, General Hospital, Jayanagar, Bengaluru, Karnataka, India

Corresponding Author:

Dr. Pruthvi Raj V

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: This randomized controlled study was carried out for the duration of 2 years. Total 200 burn patients were enrolled in two groups of 100 each, group I patients received glutamine whereas group II was a control group. Patients of 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: A total of 200 patients were recruited for the research and divided into two groups, with 100 patients in each group, as shown in the study flow chart. The demographic data and burn severity of the patients were similar throughout the groups, with no significant changes seen. Regarding wound culture, there was a noteworthy decrease in the number of positive wound cultures in the group receiving glutamine on day 5 ($p< 0.001$). In group I, there were 15 patients with positive wound cultures, consisting of 5 Gram-negative organisms and 10 Gram-positive organisms. In group II, there were 40 patients with positive wound cultures, consisting of 28 Gram-negative bacteria and 12 Gram-positive bacteria. There was a noteworthy decrease in Gram-negative bacteremia in group I compared to group II, with a statistically significant difference ($p< 0.001$). However, there was no statistically significant distinction between the two groups for Gram-positive bacteremia. Group I exhibited a substantial reduction in white blood cell (WBC) count compared to group II on both day 5 and day 10 (p = 0.005 and 0.007). Based on blood cultures, group II had a significantly higher level of bacteremia compared to group I on day 5($p< 0.005$).

Conclusion: Our research findings endorse the use of glutamine in patients with severe burns due to its ability to decrease the occurrence of wound infection and sepsis. It is instrumental in decreasing the length of hospitalisation and improves the SOFA scores in patients with burns.

.

Keywords: Glutamine, infection, burn, ICU, mortality

Introduction

Globally, burn injuries are the primary cause of disability-adjusted life-years lost in low- and middle-income nations and are among the costliest to treat among traumatic injuries [1, 3]. Severe burns lead to increased susceptibility to bacterial infections, as well as short- and long-term organ failure and mortality, due to the acute inflammation and catabolism they cause [4]. Multiple studies have assessed the impact of various dietary interventions in individuals suffering from severe burns [5, 6]. Glutamine, with a molecular formula of $C_5H_{10}N_2O_3$, is of significant importance due to its essential role in many critical stress-response pathways associated with severe medical conditions [7]. Glutamine levels have been seen to decline fast after burn damage, as demonstrated by many investigations [8, 10]. During critical illness, there is a notable increase in the utilization of glutamine, leading to a considerable shortage in glutamine levels. This shortfall generally leads to a compromised immunological response to infections [11]. Decreased levels of glutamine in the bloodstream and muscles have been linked to impaired immunological function and an increased risk of death in critically sick individuals [12].

In addition, a 2015 meta-analysis revealed that enteral Glutamine (GLN) supplementation is more efficacious in lowering mortality and length of hospitalization (LOH) among burn patients compared to trauma and nonburn intensive care unit (ICU) patients. Notably, there was no disparity seen in terms of infection mortality [13]. Recent multicenter clinical trials conducted over the past six years have demonstrated the crucial role of GLN supplementation in the early management of burn injuries. GLN supplementation, whether administered through injections, feeding tubes, or a combination of both, is

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 09, 2023

found to be essential in protecting vital organs such as the heart, maintaining the thickness of the intestinal lining, and reducing the excessive metabolic activity that can lead to further muscle loss [14, 15]. Glutamine is the amino acid that is found in the highest concentration in both the plasma and intracellular compartments. It is recognized as a vital amino acid for the digestive system during periods of severe illness. Glutamine is released from the skeletal muscles to transport nitrogen to the small intestine [16]. During critical illness, there is an elevated utilization of glutamine, leading to a notable shortage in glutamine levels. This shortfall generally leads to a compromised immunological response to infections [17].

The objective of this research was to assess the impact of glutamine supplementation on infection rates and clinical outcomes in burn patients.

Materials and Methods

This randomized controlled study was carried out for the duration of 2 years. Total 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 (100 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 OD 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: 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 =100)	Group II (n =100)	p
Gender			
Male	45 (45)	47 (47)	0.620
Female	55 (55)	53 (53)	
Age (years)	28.32±9.06	31.43±8.44	0.932
Weight (kg)	74.46±7.03	73.67±9.51	0.830
Height (cm)	165.5±6.46	165.5±4.71	0.724
BMI (kg/m2)	23.57±3.14	24.26±3.35	0.625

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 09, 2023

Burn %	32.38±6.24	31.29±6.44	0.414

200 patients were enrolled in the study and allocated into two groups of 100 patients in each group, as shown in the study flow chart. 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	100 (100)		100 (100)	–
Positive	0 (0.0)		0 (0.0)	
Day 5	(n = 100)		(n = 100)	
Negative	75(75)		60 (60)	0.001
Positive	15 (15)	0.036	40 (40)	
Day 10	(n = 15)		(n = 40)	
Negative	10 (66.66)		32 (80)	FEp = 0.606
Positive	5 (33.33)	0.500	8 (20)	
Day 15	(n = 0)		(n = 8)	
Negative	0		6 (75)	–
Positive	0	–	2 (25)	
Wound culture organism Day 5	(n = 15)		(n = 40)	
Gram positive	5 (37.5)		28 (70)	0.001
Gram negative	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 15 patients in group I (5 Gram negative and 10 Gram positive organism) and 40 patients in group II with positive wound culture (28 Gram negative and 12 Gram positive bacteria). There was a statistically significant drop in Gram negative 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 positive bacteremia.

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

WBC (thousands/µl)	Group I	p0	Group II	P
Day 1	(n = 100)		(n = 100)	
Mean ± SD.	13.27±2.58		14.36±2.48	0.922
Day 5	(n = 100)		(n = 100)	
Mean ± SD.	11.77±4.86	< 0.001	14.86±5.86	0.005
Day 10	(n = 7)		(n = 20)	
Mean ± SD.	11.09±1.42	< 0.001	13.27±3.07	0.007
Day 15	(n = 0)		(n = 28)	
Mean ± SD.	–	–	8.52±1.68	–

There was a significant decrease in WBC count in group I than in group II on day 5 and day 10 (p = 0.005 and 0.007).

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

Blood culture	Group I	p0	Group II	P
Day 1	(n = 100)		(n = 100)	
Negative	100		100	–
Positive	0		0	
Day 5	(n = 100)		(n = 100)	
Negative	96	1.000	80	0.005
Positive	4		20	
Day 10	(n = 15)		(n = 40)	
Negative	15	–	32	0.524
Positive	0		8	
Day 15	(n = 0)		(n = 28)	
Negative	–	–	8	-
Positive	–		0	
Blood culture organism	(n = 1)		(n = 20)	
Gram positive	1		16	0.022
Gram negative	0	–	4	0.448

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 negative bacteremia in the glutamine group than the control group whereas there was no statistically significant difference among the groups as regards gram positive bacteremia.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 09, 2023

Table 5: 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 ± 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

Glutamine supplementation in the parenteral feeding given to animals in animal studies was shown to reduce gut mucosal atrophy [18]. Furthermore, glutamine significantly decreased bacterial translocation in supplementary animal models [19]. Animal studies have also shown that glutamine administration enhances survival in experimental types of sepsis [20, 21]. In a clinical trial involving humans, it was shown that the addition of glutamine to enteral and parental nourishment improved immune function and maintained the structure and function of the intestines [22]. Furthermore, the addition of glutamine supplementation may help decrease the occurrence of bacterial translocation [23]. Consistent with other meta-analyses, the addition of glutamine supplements resulted in a decrease in nosocomial infections in critically sick patients. Similar to prior meta-analyses [24], our findings indicate that glutamine supplementation helps in reducing SOFA score and hospital length of stay in burns patients.

A total of 200 patients were recruited for the research and divided into two groups, with 100 patients in each group, as shown in the study flow chart. The demographic data and burn severity of the patients were similar across the groups, with no significant changes seen. In relation to wound culture, there was a notable decrease in the number of positive wound cultures in the glutamine group on day 5 ($p < 0.001$). Group I consisted of 15 patients, with 5 having Gram-negative organisms and 10 having Gram-positive organisms. Group II consisted of 40 patients, all of whom had positive wound cultures, with 28 having Gram-negative bacteria and 12 having Gram-positive bacteria. Nevertheless, there was a notable decrease in Gram-negative bacteremia in group I compared to group II, with a statistically significant difference ($p < 0.001$). However, there was no statistically significant distinction between the two groups for Gram-positive bacteremia. Group I exhibited a substantial reduction in white blood cell (WBC) count compared to group II on both day five and day 10 ($p = 0.005$ and 0.007).

Glutamine is an essential nutrient for the growth and activity of immune cells in a controlled environment. It is possible to speculate that taking glutamine supplements orally might enhance immune activities in living organisms [25]. An alternative elucidation may be derived from research carried out by Garrel *et al*, which discovered that administering glutamine via the digestive system to adult burn patients decreases bloodstream infection and serves as a preventive measure against bacteremia caused by P. aeruginosa. It has been recorded that P. aeruginosa's sensitivity to the quantity of glutamine in its surroundings may lead to both increased growth and the ability to penetrate the epithelial barrier when there is a deficiency of glutamine. The weakening of the gut immune system, which is partially caused by glutamine deficiency, may contribute to the translocation of P. aeruginosa [26].

Based on blood cultures, there was a notable increase in bacteremia in group II compared to group I on day 5 ($p < 0.005$). Additionally, the glutamine group showed a significant decrease in gram-negative bacteremia compared to the control group. However, there was no significant difference observed among the groups in terms of gram-positive bacteremia. The glutamine group exhibited a substantial reduction in the SOFA score compared to the control group on day 5 ($p < 0.001$). The average duration of ICU hospitalization was significantly shorter in group I compared to group II.

Conclusion

Our research findings endorse the use of glutamine in patients with severe burns due to its ability to decrease the occurrence of wound infection and sepsis. It is instrumental in decreasing the length of hospitalization and improves the SOFA scores in patients with burns.

References

1. Peck MD. Epidemiology of burns throughout the World. Part II: intentional burns in adults. Burns. 2012 Aug 1;38(5):630-7.
2. Bessey PQ, Phillips BD, Lentz CW, Edelman LS, Faraklas I, Finocchiaro MA, *et al*. Synopsis of the 2013 annual report of the national burn repository. Journal of Burn Care & Research. 2014 May 1;35(2):S218-34.
3. Sánchez JL, Perepérez SB, Bastida JL, Martínez MM. Cost-utility analysis applied to the treatment of burn patients in a specialized center. Archives of Surgery. 2007 Jan 1;142(1):50-7.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 09, 2023

4. Greenhalgh DG. Management of burns. New England journal of medicine. 2019 Jun 13;380(24):2349-59.
5. Heyland DK, Heyland J, Dhaliwal R, Madden S, Cook D. Randomized trials in critical care nutrition: look how far we've come! (and where do we go from here?). Journal of Parenteral and Enteral Nutrition. 2010 Nov;34(6):697-706.
6. Rousseau AF, Losser MR, Ichai C, Berger MM. ESPEN endorsed recommendations: nutritional therapy in major burns. Clinical nutrition. 2013 Aug 1;32(4):497-502.
7. Wischmeyer PE. Glutamine: mode of action in critical illness. Critical care medicine. 2007 Sep 1;35(9):S541-4.
8. Planas M, Schwartz S, Arbos MA, Farriol M. Plasma glutamine levels in septic patients. JPEN. Journal of parenteral and enteral nutrition. 1993;17(3):299-300.
9. Parry-Billings M, Calder PC, Newsholme EA, Evans J. Does glutamine contribute to immunosuppression after major burns? The Lancet. 1990 Sep 1;336(8714):523-5.
10. Zhou YP, Jiang ZM, Sun YH, Wang XR, Ma EL, Wilmore D, *et al*. The effect of supplemental enteral glutamine on plasma levels, gut function, and outcome in severe burns: a randomized, double- blind, controlled clinical trial. Journal of Parenteral and Enteral Nutrition. 2003 Jul;27(4):241-5.
11. Long CL, Borghesi L, Stahl R, Clark JA, Geiger JW, DiRienzo DB, *et al*. Impact of enteral feeding of a glutamine-supplemented formula on the hypoaminoacidemic response in trauma patients. Journal of Trauma and Acute Care Surgery. 1996 Jan 1;40(1):97-102.
12. Oudemans-van Straaten HM, Bosman RJ, Treskes M, Van der Spoel HJ, Zandstra DF. Plasma glutamine depletion and patient outcome in acute ICU admissions. Intensive care medicine. 2001 Jan;27:84-90.
13. van Zanten AR, Dhaliwal R, Garrel D, Heyland DK. Enteral glutamine supplementation in critically ill patients: a systematic review and meta-analysis. Critical care. 2015 Dec;19:1-6.
14. Wang ZE, Zheng JJ, Feng JB, Wu D, Su S, Yang YJ, *et al*. Glutamine relieves the hypermetabolic response and reduces organ damage in severe burn patients: A multicenter, randomized controlled clinical trial. Burns. 2022 Nov 1;48(7):1606-17.
15. Heyland DK, Wischmeyer P, Jeschke MG, Wibbenmeyer L, Turgeon AF, Stelfox HT, *et al*. A Randomiz Ed trial of ENtERal Glutamine to minim IZE thermal injury (The RE-ENERGIZE Trial): a clinical trial protocol. Scars, burns & healing. 2017 Dec 9;3:2059513117745241.
16. Lacey JM, Wilmore DW. Is glutamine a conditionally essential amino acid? Nutrition reviews. 1990 Aug 1;48(8):297-309.
17. Long CL, Borghesi L, Stahl R, Clark JA, Geiger JW, DiRienzo DB, *et al*. Impact of enteral feeding of a glutamine-supplemented formula on the hypoaminoacidemic response in trauma patients. Journal of Trauma and Acute Care Surgery. 1996 Jan 1;40(1):97-102.
18. Khan J, Iiboshi Y, Cui L, Wasa M, Sando K, Takagi Y, *et al*. Alanyl- glutamine- supplemented parenteral nutrition increases luminal mucus gel and decreases permeability in the rat small intestine. Journal of Parenteral and Enteral Nutrition. 1999 Jan;23(1):24-31.
19. Gianotti L, Alexander JW, Gennari R, Pyles T, Babcock GF. Oral glutamine decreases bacterial translocation and improves survival in experimental gut- origin sepsis. Journal of Parenteral and Enteral Nutrition. 1995 Jan;19(1):69-74.
20. Inoue Y, Grant JP, Snyder PJ. Effect of glutamine- supplemented intravenous nutrition on survival after Escherichia coli- induced peritonitis. Journal of Parenteral and Enteral Nutrition. 1993 Jan;17(1):41-6.
21. Ardawi MS. Effect of glutamine-enriched total parenteral nutrition on septic rats. Clinical Science (London, England: 1979). 1991 Aug 1;81(2):215-22.
22. Saito H, Furukawa S, Matsuda T. Glutamine as an immunoenhancing nutrient. Journal of Parenteral and Enteral Nutrition. 1999 Sep;23:S59-61.
23. Buchman AL. Glutamine: is it a conditionally required nutrient for the human gastrointestinal system?. Journal of the American College of Nutrition. 1996 Jun 1;15(3):199-205.
24. Bollhalder L, Pfeil AM, Tomonaga Y, Schwenkglenks M. A systematic literature review and meta-analysis of randomized clinical trials of parenteral glutamine supplementation. Clinical nutrition. 2013 Apr 1;32(2):213-23.
25. Guo GH, Deng ZY, Wang YX, Xing JJ, Peng Y, Li GH, *et al*. Effects of glutamine enriched enteral feeding on immunoregulation in burn patients. Zhonghua Shao Shang Za Zhi. 2007;23(6):406-8.
26. Garrel D, Patenaude J, Nedelec B, Samson L, Dorais J, Champoux J, *et al*. Decreased mortality and infectious morbidity in adult burn patients given enteral glutamine supplements: a prospective, controlled, randomized clinical trial. Crit. Care Med. 2003;31(10):2444-9.