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A NOVEL APPROACH TO EVALUATE THE HOLISTIC CLINICAL UTILITY OF ENTERAL GLUTAMINE SUPPLEMENTATION ON MORBIDITY AND MORTALITY IN MAJOR BURNS

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Abstract

Introduction- Glutamine plays a vital defensive role in the body during events of acute severe stress including burns, and affects the immune response, inflammatory pathway and catabolic responses.Thus, the effects of glutamine on body defenses is multifold, anddefiningthe criteria for a comprehensive look at the clinical benefit of glutamine supplementation in such cases can be troublesome.In this study, we compare serial sequential organ failure assessment (SOFA) scores, C-reactive protein (CRP) levels and mid-arm circumference (MAC) of burn patients in an attempt to assess the benefit of enteral glutamine supplementation in a holistic sense.

Materials And Methods- The studyincluded60 patients with more than 30% TBSA burns at admission and ages between 18 and 60 years. The subjectswere randomly allocated to two groups of 30 subjects each. The control group received standard nutritional supplementation, and the test group received an additional 0.3g/kg/day of enteral glutamine supplement. SOFA scores were assessed at admission and on day 4, and deltaSOFA (4-0) were calculated. CRP levels were assessed at day 4, 7 and 10 and MAC was measured at admission and at day 10. Results were tabulated and compared statistically.

Results-The average age among the test and control group were 33.50 +/- 12.01 years and 34.47 +/- 11.99 years respectively, with the average percentage of burns in the former and latter groups as 45.87 +/- 15.03 % TBSA and 45.73 +/- 12.99 % TBSA respectively. The deltaSOFA (4-0) among the two groups were 0.04 +/- 1.07 and 1.17 +/- 2.05, with a statistically significant reduction noted (p-value of 0.0444) in the glutamine group. There was a significant reduction (p 0.0173 = 0.0107)

in CRP levels at day 10 among the groups, whereas the differences in values at day 4 and 7 were found to be insignificant. The difference in MAC (10-0) was also found to be significant (p = 0.0173).

Conclusion- Prophylactic enteral glutamine supplementation appears to confer protection against immune dysregulation, multi-organ dysfunction and hypercatabolic response in major burns, thereby reducing the overall morbidity and mortality in adult burn population.

Keywords- glutamine, burns, burn mortality, enteral glutamine, antioxidants, burns nutrition, burn morbidity, SOFA score, delta sofa, severe burns

INTRODUCTION-

Glutamine is a crucial amino acid that plays multiple roles in the body. Although classified as a non-essential amino acid, it is thought to become 'conditionally essential' during events of severe catabolism [1,2] such as major burns, trauma, critical illnesses and major surgeries. The hypothesis is backed by the rapid depletion of plasma glutamine levels noted in such events [3]. It is unsurprising however, considering the role played by glutamine over critical defense functions such as immune regulation, cell turnover and nitrogen transport [4].

Prophylactic glutamine supplementation is shown to limit the inflammatory response, reduce apoptosis of immune cells and reduce morbidity and mortality in both animal models and human studies [5,6] and is generally thought of as beneficial in such cases. However, some studies show equivocal or even a negative impact of supplemental glutamine in critical illnesses [7,8]. The conflicts in opinion can perhaps be attributed to the different parameters measured, and different inclusion criteria in different studies. The difficulty in defining the parameters to assess is understandable given the rather diverse roles played by glutamine, and we make yet another attempt to assess its benefit to the patient, albeit in a broader, holistic sense.

In this study, we have used a comparison of Sequential organ failure assessment (SOFA) scores, serial serum C-reactive protein (CRP) levels and reduction in mid-arm circumference (MAC) as parameters to assess immune dysregulation, sepsis, risk of multi-organ dysfunction, inflammatory and hypercatabolic responses, and thereby derive an overall idea of the effect of glutamine on morbidity and mortality in adults with major burns.

MATERIALS AND METHODS-

The studywas prospective in design and was conducted from March 2021 to December 2022. Sixty adult burn patients meeting the inclusion and exclusion criteria were randomized to two groups of 30 subjects each. The control group received standard enteral nutritional supplementation, while the test group received 0.3g/kg/day of glutamine supplement additionally. The rest of treatment and management protocols were kept consistent among all subjects.

Inclusion Criteria-

I. Partial thickness thermal burnsof >/=30% TBSA
II. Full thickness thermal burns of >/= 20% TBSA
III. Inhalational burns
IV. Age >/= 18y and <60y

Exclusion Criteria-

I. Known renal or hepatic dysfunction (contraindication for additional glutamine supplementation)
II. Presenting more than 48 hours of burn injury
III. Electrical burns and chemical burns

The demographic data and history of each patient was recorded before randomization. SOFA score was assessed in all patients at admission (SOFA 0), and again on day 4 (SOFA 4), and deltaSOFA(4-0) [difference in SOFA 4 from SOFA 0] was calculated. Serum C-reactive protein levels were measured at day 4, 7 and 10. The mid-arm circumference was measured in millimeters at admission, and again at day 10, and the difference calculated. The values obtained from subjects that did not survive up to day 10 were excluded from assessment of deltaSOFA(4-0) and difference in MAC.

Additionally, bacterial cultures from burn wounds were sent on the 4th post burn day, and if positive, repeated weekly until negative culture was obtained. Blood cultures were also sent in the second post-burn week among patients that still required inpatient care.

The results were tabulated and analyzed using appropriate tests for statistical significance (student's t test, Mann Whitney U test, Chi-square test and Fisher's exact test), with the assumption of p-value of less than 0.05 to be statistically significant.

RESULTS-

Parameter	Glutamine	Control	p-value
Mean age (years)	33.50 +/- 12.01	34.47 +/- 11.99	0.7562
Sex ratio (M:F)	19:11	17:13	0.598
Mean %TBSA burns	45.87 +/- 15.03	45.73 +/- 12.99	0.9708
Etiology- a) Thermal burns b) Scald burns c) Others	 16 (53.3%) 12 (40%) 2 (6.6%)	 17 (56.6%) 11 (36.6%) 2 (6.6%)	 0.964
Inhalational injury	11	13	0.598

Table 1: Demographicdata, extent and etiology of burns

As described in **Table 1**, the average age of subjects in the intervention and control groups were 33.50 +/- 12.01 years and 34.47 +/- 11.99 years respectively with a male predominance in both groups. The average percentage of burns were 45.87 +/- 15.03 % TBSA and 45.73 +/- 12.99 % TBSA in the two groups. The most common cause of burn was thermal injury in both groups, followed by scalds and other causes. There were 11 and 13 patients in the two groups with inhalational injury. The two groups show no significant variation in the demographic data, extent or etiology of burns, and can be considered comparable to measure outcomes.

Parameter	Glutamine group (mean +/- SD)	Control group (mean +/- SD)	p-value
SOFA score • **SOFA 0** • **SOFA 4** • **DeltaSOFA (4-0)**	 1.47 +/- 1.28 1.25 +/- 1.43 0.04 +/- 1.07	 1.20 +/- 0.81 2.45 +/- 2.54 1.17 +/- 2.05	 0.5287 0.1738 0.0444
Serum CRP levels (mg/L) • **Day 4** • **Day 7** • **Day 10**	 169.97 +/- 59.21 85.4 +/- 45.2 37.08 +/- 25.0	 178.0 +/- 83.36 120.6 +/- 82.97 64.17 +/- 51.97	 0.7489 0.1527 0.0107
Mid-arm circumference (mm) • **Day 0** • **Day 10** • **Reduction in MAC**	 223.87 +/- 34.26 225.32 +/- 31.28 6.36 +/- 7.76	 233.53 +/- 32.94 215.2 +/- 27.3 20.65 +/- 22.43	 0.2699 0.0173
Wound culture	1.11 +/- 0.33	1.50 +/- 0.67	0.129
Blood culture	2	7	0.145

Table 2: Comparison of outcome parameters in the intervention and control groups.*SOFA 0- SOFA score calculated at admission, SOFA 4- SOFA score at day 4, deltaSOFA (4-0) = SOFA 4 – SOFA 0.*

Table 2 elaborates the measurements of the outcome parameters and their comparative analysis. The average SOFA scores recorded at admission were 1.47 +/- 1.28 and 1.20 +/- 0.81 (SOFA 0), and those recorded on the fourth day were 1.25 +/- 1.43 and 2.45 +/- 2.54 in the glutamine and control groups respectively. The deltaSOFA (4-0) values averaged 0.04 +/- 1.07 and 1.17 +/- 2.05 in the two groups. The SOFA scores themselves did not show any significant difference. However, there was a significant reduction noted in the deltaSOFA values of the glutamine group ($p = 0.0444$) as compared to the control group, indicating lesser risk ofprogressive organ dysfunction in patients after glutamine administration.

The CRP levels at day 4 and 7 did not show any significant difference among the two groups (p values of 0.7489 and 0.1527 respectively), whereas the reduction in the levels at day 10 were noted to be of significance ($p=0.0107$). Although it does signify faster remission of inflammation in the glutamine group, it might not be of significance in patients that did not show clinical signs of systemic inflammatory response.

The baseline mid-arm circumferences were also noted to be comparable among the two groups. However, there was significant reduction in MAC in the control group after ten days when compared with the glutamine group ($p= 0.0173$), indicating lesser hypercatabolic response in the latter group. We also noted reduced number of positive wound and blood cultures, although the differences were not statistically significant.

DISCUSSION-

Glutamine participates in multiple vital pathways in the body. Not only is it crucial as a precursor of glutathione, the most important antioxidant in the system, but also helps maintain the immune system and cell turnover. Therefore, it is thought of to be beneficial in all conditions of severe stress, including major burns [5,6]. It is also protective towards damage due to inhalational injury and maintenance of gut mucosal barrier. **Figure 1** illustrates the many ways by which glutamine exerts a protective role during events of severe stress to the body.

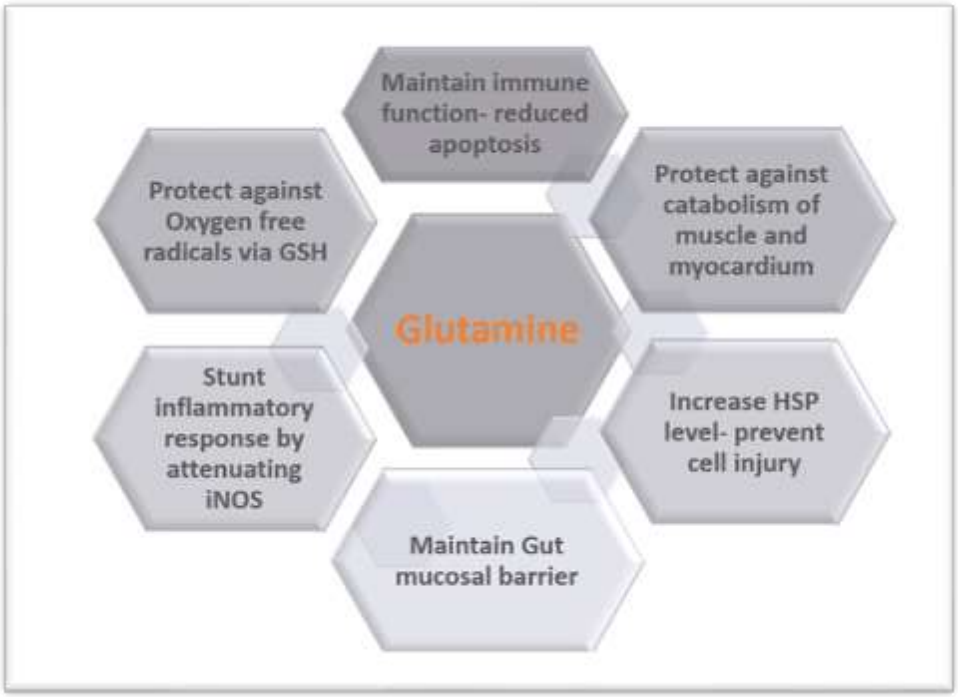

Figure 1. Vital pathways of glutamine action in major burns. *GSH- glutathione, iNOS- inducible NO synthase, HSP- heat shock protein.*

Glutamine can be supplemented by both enteral or parenteral routes, although the former is preferred. A major source for systemic sepsis in such conditions is the breakdown of the critical gut mucosal barrier, leading to bacterial translocation into the circulation [9], and enteral preparations both reduce the incidence of ileus, as well as maximize delivery of glutamine to the gut mucosal cells. It has therefore been largely accepted that enteral glutamine preparations are preferable in the management of burns.

Given the diverse actions of glutamine, it can become difficult to quantify the benefit of its supplementation in burn injury. Most existing studies use parameters pertaining to certain mechanisms of glutamine action to evaluate the utility. However, it is perhaps worthwhile to consider evaluating the utility in a broader sense rather than focusing on few areas. In our study, we attempt to provide a holistic view of the effects of glutamine in adult burn patients.

The action of glutamine can broadly be thought of as anti-inflammatory, immune regulatory and anticatabolic in nature. We have used three major parameters, SOFA scores, serum CRP levels and MAC measurement as determinants of the same. SOFA score is widely applied to predict prognosis in sepsis and critical illnesses, and is similarly considered to have good applicability in predicting mortality and outcomes in burns and burn-related sepsis [10,11]. It has also been regarded that deltaSOFA(4-0), i.e., the difference in SOFA score at day 4 from the score at day 0, offers a better predictive value of outcomes.

The choice of parameters was made so as to be easily measurable as well as have a good predictive value. C-reactive protein is widely accepted as an inflammatory marker, and is readily available for quantification in most clinical laboratories. Similarly, mid-upper arm circumference is considered reliable for assessing loss of lean body mass, often seen in cases of malnutrition, but also in cases of acute hypercatabolism such as burn injury. The utility is shown to be similar to measurement of BMI [12], and considerably simpler.

As derived from the results of our study, glutamine appears to confer significant protective effect against hemodynamic instability, vital organ dysfunction, immune dysregulation and catabolism, although the power of our study is limited by the relatively small sample size. We also noted significant reduction in serum CRP levels at day 10, although the values at day 4 and 7 seemed to have an insignificant difference. The inference of this finding is uncertain, as most survivors are clinically stable by day 10 regardless. However, the finding might be of value in the context of long-term inflammatory sequalae in survivors, and further follow-up and analysis is required to ascertain the same.

CONCLUSION-

Prophylactic enteral glutamine supplementation appears to confer protection against immune dysregulation, multi-organ dysfunction and hypercatabolic response in major burns, thereby reducing the overall morbidity and mortality in adult burn population.

REFERENCES-

1. Blomqvist BI, Hammarqvist F, von der Decken A, et al. Glutamine And alpha-ketoglutarate prevent the decrease in muscle free glutamine concentration and influence protein synthesis after total Hip replacement. Metabolism 1995; 44: 1215–1222.
2. Zhou YP, Jiang ZM, Sun YH, 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. JPEN J Parenter Enteral Nutr 2003; 27(4): 241–245
3. Planas M, Schwartz S, Arbos MA, et al. Plasma glutamine levels In septic patients. JPEN J Parenter Enteral Nutr 1993; 17: 299–300.
4. Kim M and Wischmeyer PE. Glutamine. World Rev Nutr Diet 2013; 105: 90–96.
5. Fan J, Wu J, Wu LD, et al. Effect of parenteral glutamine supplementation combined with enteral nutrition on Hsp90 Expression and lymphoid organ apoptosis in severely burned Rats. Burns 2016; 42: 1494–1506.

6. Garrel D, Patenaude J, Nedelec B, 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: 2444–2449.
7. Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized Trial of glutamine and antioxidants in critically ill patients. N Engl J Med 2013; 368(16): 1487–1495
8. Magnotti LJ, Deitch EA. Burns, bacterial translocation, gut Barrier function, and failure. J Burn Care Rehabil 2005;26:383–91.
9. Rose JK, Herndon DN (1997) Advances in the treatment of Burn patients. Burns 23:S19–S26
10. Lorente JA, Vallejo A, Galeiras R, Tómicic V, Zamora J, Cerdá E, de la Cal MA, Esteban A. Organ dysfunction as estimated by the sequential organ failure assessment score is related to outcome in critically ill burn patients. Shock 2009 Feb;31(2):125-31.
11. Calles J, Cohen B, Forme N, Guendil Z, Fermier B, Chassier C et al. Variation of the SOFA score and mortality in patients with severe burns: A cohort study. Burns 2023;49(1): 34-41.
12. Das A, Saimala G, Reddy N, Mishra P, Giri R, Kumar A et al. Mid-upper arm circumference as a substitute of the body mass index for assessment of nutritional status among adult and adolescent females: learning from an impoverished Indian state. Public health 2020 Feb; !&(: 68-75.