Role of Early Enteral Glutamine Supplementation in Reducing Infectious Morbidity in Burn Patients: A Case-Control Study

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ABSTRACT
Severe burn injury is more challenging to sustain life than a preburn status. The situation changes drastically in terms of energy demands/ expenditure and the great degree of susceptibility to infections due to the loss of amino acids. Glutamine stimulates the immune system and prevents catabolism. The bacterial translocation from the gut can be decreased by glutamine supplementation, thereby suppressing the inflammatory response. In acute burn injury, plasma and muscle glutamine depletion is observed to contribute to muscle wasting, weight loss, and infection. Patients with 20%–50% TBSA burns presenting within 24 hours of injury to the emergency department or outpatient department were included in the study. The patients were divided into two groups randomly. In group 1 (Cases), all patients were given enteral glutamine supplementation at the dose of 0.5 mg/kg/day either orally or through a nasogastric tube started within 24 hours of injury. Group 2 (Control) had all the patients in whom enteral glutamine supplementation was not given. In both groups, blood analysis for total leucocyte count (TLC) and total serum proteins (TSP) was done upon admission. On Day 4, followed by analysis every fourth day, after that, till healing occurred or the patient was taken up for grafting. Blood and wound swab cultures were done on the third day of admission, then the first week, followed by weekly cultures for 4 weeks or till healing occurred or the patient was taken up for grafting. A total of 123 patients were studied. There was a decreasing trend in the mean values of the TLC and an increasing trend in TSP in both groups. The difference became statistically significant from Day 20 onwards. The pattern of wound cultures was found to be statistically significant in Week 3 and Week 4, whereas the difference in blood culture positivity among the groups was statistically significant in Week 3. We noted, in our study, that the glutamine supplementation to the early enteral nutrition increased the TSP levels and decreased the TLC, wound, and blood culture positivity rates in the study group. Glutamine supplementation can contribute to improved immunity and reduce burn wound sepsis and bacteremia. All these combined can lead to decreased morbidity, improved wound healing, and better outcomes with lesser costs.

KEYWORDS: Glutamine Supplementation, Infectious Morbidity, Burn Patients.

1. INTRODUCTION

Severe burn injury is significantly more difficult for sustaining life than the preburn status. The situation changes drastically in terms of energy demands/expenditure and the great degree of susceptibility to infections. Complications associated with infections are a significant cause of death in severe burns, even when treated aggressively right from the start of the injury [1].

Various metabolic and nutritional consequences result from significant burns, with the patient's metabolic rate often doubling. To meet the raised nutritional demands, mobilization of skeletal and visceral proteins occurs. The combination of changes in an affected body results in a severely catabolic state with negative nitrogen balance, decreased immunologic function, and protein and calorie malnutrition associated with wound-healing problems [2]. Gram-negative bacteremia can occur due to bacteria's translocation from the gut source [3,4]. The concentration of free glutamine decreases characteristically after surgical trauma. Though glutamine is a nonessential amino acid, it may become conditionally essential in various stressed states of the body like burns and trauma [5,6]. In acute burn injury, plasma and muscle glutamine depletion is observed to contribute to muscle wasting, weight loss, and infection [7]. The bacterial translocation from the gut can be decreased by glutamine supplementation, thereby leading to a better outcome, as has been demonstrated in animal studies [5,8] but needs further validation in the case of humans. The objective of this study was to compare the morbidity rates of bacteremia, septicemia, wound infection, total leucocyte count (TLC), total serum proteins (TSP), and duration of hospital stay between the two groups (Case and Control) receiving early enteral supplementation with or without glutamine.

2. METHOD(S)

This prospective case-control study was conducted in the department of plastic surgery from January 2017 to December 2020 with the following inclusion criteria for the patients' enrollment: Age (15–60 years), sex (both male and female), and percentage of burns (20%–50% TBSA according to Lund and Browder chart); whereas exclusion criteria include mortality within 72 hours, patients with co-morbid conditions, pregnant females, electrical burns, and nonconsenting patients.

All patients were divided into two groups randomly. In both groups, blood analysis for TLC and TSP was done upon admission. On Day 4, followed by analysis every fourth day, after that, till healing occurred or the patient was taken up for grafting. Blood and wound swab cultures were done on the third day of admission, the first week, followed by weekly culture for 4 weeks or till healing occurred or the patient was taken up for grafting. Group 1 (Cases): in this group, all patients were given enteral glutamine supplementation in the dose of 0.5 mg/kg/day either orally or through a nasogastric tube started within 24 hours of injury. Group 2 (Control): this group had all the patients in whom enteral glutamine supplementation was not given.

Written informed consent was taken from all patients or relatives, regarding their participation in the study, after disclosing the risks, benefits, and study design to them. Then the patient, with their consent, was assigned to one of the two groups according to the simple envelope method (one envelope used for each patient, taken out from a stack of 200 envelopes, randomly arranged at the start of the study). Regular I/V fluid management, Tetanus toxoid/vaccination, Antacid prophylaxis, Antiemetics, Analgesics, and other medication (if any) were provided to all patients. Regular oral/enteral nutrition was started in all patients (both groups) as early as possible (within 24 hours of burns). Energy requirements were calculated using the modified Curreri formula: [25 × weight (kg) + 20 × % of burns]. Group 1 patients were given enteral glutamine supplementation of 0.5 g/ kg/day (in powder form, which was mixed in water or milk) and continued till the end of the study, i.e., 4 weeks. The glutamine used for the supplement was available in powder form, in sachets containing 10 g of L-glutamine. Blood counts and TSP were done on Day 1, Day 4, and then every fourth day till Day 28. Blood culture and wound culture were done on Day 3 and then weekly till the fourth week. The mortality of patients in the study was also noted, excluding the one which occurred within 72 hours of admission.

The data of each patient were collected, and analysis was done as per the appropriate statistical tool with the help of SPSS software version 23. Unpaired Student "t" test was used to analyze the quantitative data: TLC, TSP, and duration of hospital stay in days. A chi-square test was used to measure the qualitative data: The number of wound culture positivity and blood culture positivity. Repeated measure analysis was used to analyze the data over a 4-week follow-up.

3. RESULTS

A total of 123 patients with 20%–50% TBSA burns presenting within 24 hours of injury to the emergency department or outpatient department were included in the study. The two groups had similar demographics, including age, gender distribution, and percentage of total body surface area burns, as shown in the following observation. There were 32 (46.4%) and 25 (46.3%) male patients in Group 1 and Group 2, respectively (Table 1). The number of female patients in Group 1 and Group 2 was 37 (53.6%) and 29 (53.7%), respectively. The p-value was >0.05, indicating that the difference in gender distribution among the two groups was statistically insignificant.

We noted that 115 patients had deep thermal burns (flame), and eight had scald burns, constituting 93.5% and 6.5%, respectively.

The highest number of patients was noted in the age group of 21–30 years, constituting 43.90% of the total number of patients (Table 2). The maximum numbers of patients were those who had sustained 50% TBSA burns and were 38, constituting 30.9% of the total patients under study (Figure 1). After placing the patients in various age range groups in a similar fashion in the two groups, the p-value was found to be >0.05, showing that the difference between the two groups was statistically insignificant.

There was a decreasing trend in the mean values of the TLC in both the groups (except for a slight increase on Day 8 in Group 1), and the difference became statistically significant from Day 20 onwards (Table 3).

It was noticed that the mean TSP decreased in both groups on Day 4 and increased slightly on Day 8. On Day 12, the mean values of TSP again decreased slightly in both the groups and continued till Day 16 in Group 1, after which it increased steadily till Day 28, whereas Group 2 showed a steady decrease in the levels after Day 8 till Day 28. However, the difference became statistically significant from Day 20 onwards (Table 4).

The mean duration of hospital stay was 18.52 days in Group 1 and 19.11 days in Group 2. The difference between the two groups was found to be statistically insignificant. In our study, the mortality was 10 out of 69 patients in Group 1 and 11 out of 54 patients. Although the mortality was less in Group 1 (14.4%) compared to Group 2 (20.3%), the difference was statistically insignificant.

The pattern of wound cultures, in terms of growth (culture positivity) being present or absent among the two groups in our study, was statistically insignificant on Day 3, Week 1, and Week 2 (15.3%, 52.5%, and 45.8% of patients in Group 1 and 16.3%, 53.3% and 51.2% of patients in Group 2, respectively). Nevertheless, the difference was statistically significant in Week 3 and Week 4 (16.9% and 3.4% of patients in Group 1 and 46.5% and 27.9% of patients in Group 2, respectively). We noticed no growth in blood cultures in both the groups on Day 3 and Week 4. The difference in blood culture positivity among the groups was statistically insignificant in Weeks 1 and 2 (23.7% and 11.9% of patients in Group 1 and 34.9% and 27.9% of patients in Group 2,

Figure 1: Distribution of patients as per TBSA Burn % in the study.

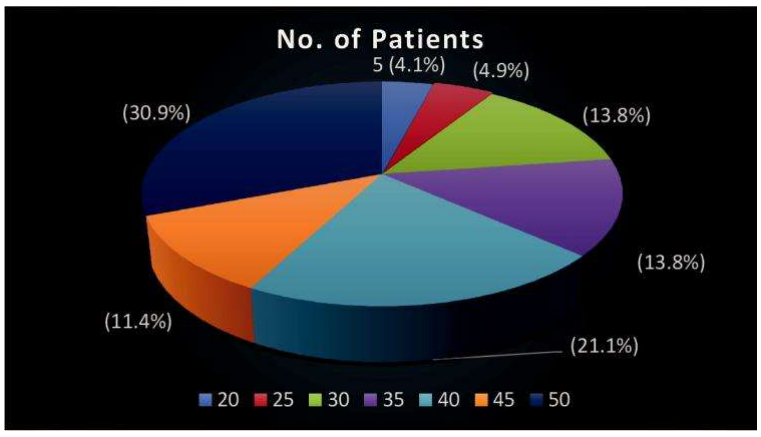

Table 1: Distribution of gender.

			Sex		Total
			Male	Female	
Group	Group 1	**Count**	32	37	69
		% within group	46.4%	53.6%	100.0%
	Group 2	Count	25	29	54
		% within group	46.3%	53.7%	100.0%
Total		Count	57	66	123

Table 2: Distribution of "age in years" in two groups.

			Age in Years					Total
			<20	21–30	31–40	41–50	51–60	
Group	Group 1	Count	10	33	16	6	4	69
		% within group	14.5%	47.8%	23.2%	8.7%	5.8%	100.0%
	Group 2	Count	6	21	18	7	2	54
		% within group	11.1%	38.9%	33.3%	13.0%	3.7%	100.0%
Total	Count	16	54	34	13	6	123	
	% of Total	13.0%	43.9%	27.6%	10.6%	4.9%	100.0%	

Table 3: Mean total leucocyte count (TLC) in the two groups.

	Total Leucocyte Count (Mean) per µl							
	Day 1	**Day 4**	**Day 8**	**Day 12**	**Day 16**	**Day 20**	**Day 24**	**Day 28**
Group 1	16920.3	13796.6	14640.6	13157.6	12732.2	10523.7	9596.6	8683.5
Group 2	16669.7	15041.8	14888.3	13395.3	12832.5	12088.3	11339.5	10306.9
p-value	>0.05	>0.05	>0.05	>0.05	>0.05	**<0.05**	**<0.05**	**<0.05**

Table 4: Mean total serum protein (TSP) in the two groups.

	Total Serum Protein (Mean) g/dl							
	Day 1	**Day 4**	**Day 8**	**Day 12**	**Day 16**	**Day 20**	**Day 24**	**Day 28**
Group 1	6.1458	4.7644	4.9407	4.8627	4.8068	4.8407	4.9186	5.0932
Group 2	6.1488	4.8651	4.9140	4.7581	4.6326	4.5762	4.5186	4.5047
p-value	>0.05	>0.05	>0.05	>0.05	>0.05	**<0.05**	**<0.05**	**<0.05**

respectively) but significant in Week 3 (no growth in blood culture of all the patients in Group 1, whereas 18.6% of patients in Group 2 showed growth). None of the patients among both groups showed any growth in their blood cultures on Week 4.

4. DISCUSSION

Burn injuries remain a significant challenge worldwide despite tremendous improvements in preventive measures. The burden of it falls predominantly on the world's developing nations. It not only threatens people's health but also affects the overall welfare of people across all age groups. The primary cause of death in severe burn injuries is infectious complications, regardless of early surgical intervention and aggressive antibiotic therapies. The incidence of immune dysfunction and gut atrophy may increase due to markedly reduced glutamine levels, known to occur in burn injuries. It can cause an increased incidence of Gram-negative bacteremia [6]. As glutamine consumption exceeds its synthesis in burn patients, its supplements are essential. We supplemented early enteral nutrition with glutamine (0.5 g/kg body weight) in our patients under study by oral route for the reason that in patients with severe burn injuries, the preferred method of feeding has become the enteral route, as there are comparatively fewer complications [9]. We noted, in our study, that the glutamine supplementation to the early enteral nutrition increased the TSP levels and decreased the TLC, wound, and blood culture positivity rates in the study group. In our study, we noted that the mean serum TLC showed a decreasing trend in both the groups (except for a slight increase on Day 8 in Group 1), with lower corresponding values in Group 1. The difference between the two groups became statistically significant (p-value <0.05) from Day 20 onwards (Table 3).

Sheridan *et al.* did a trial (stable isotope study) to evaluate the effect of 48 hours of enteral glutamine supplementation on protein accretion in children with burn injuries. Their study showed that short-term enteral glutamine supplementation does not cause rapid protein accretion. Glutamine supplementation for several days may be required to restore plasma glutamine levels and stimulate protein synthesis [10].

Pattanshetti *et al.*, in their randomized controlled trial to analyze the effect of enteral glutamine supplementation on infectious morbidity and hospital stay in patients with burn injuries, found a significant reduction in duration of hospital stay in the glutamine-supplemented group (p-value = 0.003) [1]. A double-blind, randomized controlled clinical trial conducted by Peng *et al.* to analyze the effects of enteral nutrition supplemented with glutamine granules on immunologic function in severely burned patients found that the hospital stay was significantly reduced in the glutamine granule supplemented group [11]. Khorasani and Mansouri in their clinical trial to study the effect of early enteral feeds in children suffering from burns by comparing early enteral nutrition (EEN) commencing between 3 and 6 hours post burns to those receiving late enteral nutrition (LEN), i.e., after 48 hours in 688 children across 2 years randomized into two groups. They found a significant decrease in the duration of hospitalization (12.6 ± 1.3 days in EEN vs 16.4 ± 3.7 days in LEN) [9]. Van Zanten *et al.,* in their systemic review to study the effects of enteral glutamine GLN supplementation in patients with critical illness, found that in the subset of studies of patients with burns, enteral GLN supplementation was associated with a significant reduction in hospital stay (p-value = 0.002), with no benefit in trauma patients [12]. In a retrospective case-control, descriptive study conducted by Juang *et al.* to evaluate the clinical application of enteral glutamine supplementation in critically ill patients and compare the frequency of nosocomial infections in these patients with a historical control group in a burn intensive care unit (BICU), and to assess lengths of stay in the hospital and BICU, mortality rates and safety profile of glutamine found that for the Glutamine group vs Control group, BICU length of stay, and hospital length of stay were statistically insignificant between groups [13]. Josef *et al.* conducted a blinded randomized study of enteral glutamine supplementation in 68 deficient birth weight neonates. In their study, they found no difference in mean hospital stay [14]. In our study, we found no statistically significant difference in the mean duration of hospital stay between the two groups (p-value >0.05). The mean hospital stay duration was 18.52 days and 19.11 days in Group 1 and Group 2, respectively. Moreover, in all the subgroups, the difference was statistically insignificant.

Garrel *et al.*, in their double-blinded randomized clinical trial, analyzed the impact of enteral glutamine supplementation on infectious morbidity, length of care, and immune system of burn patients. They found that the mortality rate was significantly lower in the Glutamine group (p-value <0.05) [15]. Lin *et al.*, in their study, identified randomized controlled trials from the electronic databases and compared the supplementation with glutamine and nonsupplementation of glutamine in burn patients and found that glutamine-supplemented nutrition can be associated with a significant decrease in hospital mortality [16]. Van Zanten *et al.* undertook a systemic review to determine the effects of enteral GLN supplementation in patients with a critical illness. After identifying randomized controlled trials conducted from 1980 to 2014 involving 1079 patients, a total of 11 studies found that although, in the subset of studies of patients with burns, enteral GLN supplementation was associated with a significant reduction in hospital mortality (p-value = 0.010), but does not confer significant benefit in critically ill patients [12]. Also, Juang *et al.*, in their study on critically ill patients, found that the mortality rates were similar between glutamine-supplemented group and the historical control group [13]. In our study, the mortality in Group 1 and Group 2 was statistically insignificant. Josef *et al.,* in their study of enteral glutamine supplementation in deficient birth weight neonates, found that hospital-acquired sepsis was 11% in the Glutamine group as against 30% in the Control group. However, their study showed no difference in growth but points toward decreased morbidity in very low birth weight neonates who receive enteral glutamine supplementation Houdjik *et al.* conducted a randomized trial to study the effects of glutamine-enriched enteral diet on infectious morbidity in patients with multiple traumas. They found that the bacteremia rates were lower in the Glutamine group: 2 (7%) vs 13 (42%) (p <

0.005) [17]. Wischmeyer *et al.* conducted a prospective, double-blinded randomized trial to study the beneficial effect of intravenous glutamine supplementation on infectious morbidity in severely burned patients. In their trial, there was a significant reduction in Gram-negative bacteremia rates in the study group: 8% vs 43% ($p < 0.04$) [20] with no difference in Gram-positive bacteremia or fungemia. Although the number of positive blood cultures was reduced in their study, it was not statistically significant [14]. In a study conducted by Pattanshetti *et al.*, it was observed that enteral glutamine supplementation reduced the incidence of positive wound cultures (p-value 0.001) and also the incidence of positive blood cultures (p-value 0.065), thus reducing the infectious morbidity [1]. Garrel *et al.,* in their study, found that in adult burn patients, enteral glutamine supplementation reduces blood infection and prevents bacteremia with *Pseudomonas aeruginosa* [15]. Peng *et al.,* in their study, found that the wounds in severely burned patients in the Glutamine group healed faster than in the Control group [11,18]. In his umbrella review of published meta-analyses to study the effectiveness of glutamine as a therapeutic agent, McRae found that glutamine supplementation for critically ill or surgical patients through parenteral or enteral routes appears to reduce the rate of hospital-acquired infectious complications [19]. Lin *et al.,* in their study, found that glutamine supplementation was associated with a statistically significant decrease in the number of patients with Gram-negative bacteremia [16]. Our study showed no statistically significant difference in wound swab culture patterns between the two groups on Day 3 and Weeks 1 and 2. However, the difference was statistically significant in Weeks 3 and 4 (p-values being >0.05). This may be probably due to the better immunological status of the glutamine-supplemented group. In our study, the blood culture positivity rates between the two groups were comparable, with a statistically insignificant difference in Weeks 1 and 2. The difference was statistically significant in Week 3.

5. CONCLUSION

Enteral glutamine support is a practical and feasible supplementation method in severe burn patients. It lowered the wound and blood culture positivity from around three weeks postadministration. This implies that the effects are not immediate and can take time to manifest, as is also evident in view of the changes noted in the TLC and the TSP levels. Glutamine supplementation can contribute to improved immunity and reduce burn wound sepsis and bacteremia. All these combined can lead to decreased morbidity, improved wound healing, and better outcomes with lesser costs. More extensive standardized studies need to be carried out to prove the exact use of this important nutrient so that it can be used in the management of burn patients in order to reduce the costs of medication, hospital burden, and workforce.

ETHICAL APPROVAL AND PATIENT CONSENT

We declare that the study was assessed and approved by the institutional ethics committee / institutional review board. Prior to the commencement of the study, ethical approval was obtained from the following ethical review board: reference number: 2091A/FM; 22.01.2016; Institutional ethics committee of Faculty of Medicine, Aligarh Muslim University, India. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed written consent was obtained from all patients included in the study.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this work.

CONFLICT OF INTEREST

None.

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