Enteral glutamine supplementation reducing infectious morbidity in burns patients: a randomised controlled trial

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Abstract

Purpose Enteral glutamine supplements have been shown to reduce infectious morbidity in trauma patients, but their effect on patients with burns is not completely studied. The objective of this study was to measure the impact of enteral glutamine supplementation on infectious morbidity and in turn, the hospital-stay in patients with burns.

Methods Thirty patients with burns were randomly divided into two groups with 15 patients in each, the study (glutamine supplemented) and control group. Patients were randomised to receive either isonitrogenous mixture without glutamine or isonitrogenous mixture with glutamine until complete healing of the burn wound occurred. Incidence of positive blood culture, wound culture, total leucocyte count, hospital-stay and mortality was recorded.

Results The results showed that the incidence of positive blood culture was considerably reduced in the study group (0.20 ± 0.41) vs. control (0.73 ± 0.96 ; $p = 0.065$). The incidence of positive wound culture was significantly reduced in the study group (1.00 ± 1.25) vs. control (3.53 ± 2.47 ; $p = 0.001$). In addition, the wound healing was better and hospital-stay days were reduced in the study group (22.73 ± 9.13 days) vs. (39.73 ± 18.27 days; $p = 0.003$).

Conclusions These results indicate that enteral glutamine supplementation in adult burn patients could abate the degree of infectious morbidity and reduce hospital-stay.

Keywords Glutamine · Intestine mucosal barrier · Burns · Bacterial translocation · Bacteraemia · Morbidity · Enteral nutrition · Length of care

Introduction

Despite improvements in prevention and management, burn injury continues to represent a major threat to health and welfare of people worldwide in all age groups. Even with early surgical intervention and aggressive antibiotic therapy, infectious complications are a major cause of death in severe burn injury, accounting for 75% all deaths occurring after initial resuscitation [1].

It is proposed that, one source of these infections is translocation of gram-negative bacteria from the gut [2, 3]. However this mechanism of bacterial translocation through the gut wall remains a controversial mechanism of infection in humans [4]. In animal studies it has been demonstrated that, glutamine supplementation can decrease gut derived bacterial translocation and improve outcome from burn injury [5, 6]. Whether this holds true in humans has to be evaluated by additional studies. A recent study concluded that glutamine supplementation reduces gram-negative bacteraemia in burned patients but viewed itself as preliminary and suggested that more clinical trials are warranted to corroborate the study outcome [7].

Glutamine is a non-essential amino acid, which in stressed state such as trauma and burns it may become conditionally essential. This subject has been the focus of

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recent international research [8]. Very few comprehensive clinical randomised controlled trials have been done worldwide, especially in burn patients. All these points warranted the proposed study, to evaluate whether glutamine has any role in the management of burns patients.

Patients and methods

The study population consisted of all patients with burns, who are admitted in Plastic Surgery-Burns Center, KLES Dr Prabhakar Kore Hospital & MRC, Belgaum, Karnataka, India, consecutively during the period of 1 year (January 2005 to December 2005), with certain inclusion and exclusion criteria (Tables 1 and 2). The study design being randomised controlled trial. The sample size in this study was of 30 patients with burns, with 15 patients in each study and control group, which was quite similar to other similar studies.

special investigation reports collected on the day of admission and then once a week. The data of each patient was collected as per the proforma. The data of each patient was pooled and analysis is done using Chi-square test, Student 't' test and Fisher exact test.

The enteral nutrition in all patients was started within 24 hours of admission, through a nasoenteral tube. Upon insertion of the feeding tube (Fig. 3 *Nasoenteral feeding in a burns patient*), the patients either received glutamine (*glutamine – Claris Lifesciences Ltd.*) 0.5 gm/kg/day mixed with isonitrogenous mixture or an isonitrogenous mixture only, as per the assignment of study groups. The glutamine supplementation or the isonitrogenous mixture was given until the end of the study, which was determined as the time taken for complete wound healing or split thickness skin grafting. The routine investigations such as complete blood count, urine routine and microscopy, liver function test; blood glucose and mini renal were done on the day of admission. The special investigations such as blood culture, wound culture and blood cell counts were done once in

Figs. 1 and 2 Glutamine (GLUTAMUNE *Claris Lifesciences Ltd.*) being mixed with isonitrogenous mixture

Data collection

After admission to the burn unit, the patient was selected as per the inclusion and exclusion criteria. The calculation of total burn surface area (TBSA) was done as per Lund and Browder's burn estimate chart. Then from the patient or relatives, an informed consent was taken, regarding their participation in this study, with disclosing the risks, benefits and study design to them. Then with their consent, the patient was assigned to one of the two groups according to a randomisation table. Both control and glutamine groups received isonitrogenous mixture in addition to their regular nutrition. But the glutamine group patients received isonitrogenous mixture supplemented with glutamine (*Glutamine – Claris Lifesciences Ltd.*) (Figs. 1 and 2 *glutamine, being mixed with isonitrogenous mixture*). The routine and

Fig. 3 Nasoenteral feeding in a burns patient

every week till the complete wound healing occurred and also whenever the clinical condition is warranted as per the treating staff. Also the mortality of the patient of the either group was noted, excluding the mortality, which occurs within 72 hours of admission.

Results and discussion

The data of each patient was pooled and analysis was done using Chi-square test, Student 't' test and Fisher exact test. There were no obvious differences between groups for age, sex and TBSA ($p > 0.05$, Tables 3 and 4). The incidence of positive blood culture was considerably reduced in the glutamine-supplemented group vs. control group ($p = 0.065$). The incidence of positive wound culture was significantly reduced in the glutamine-supplemented group vs. control group ($p = 0.001$).

In addition, the wound healing was better and hospital stay days were reduced in the glutamine-supplemented group vs. control group ($p = 0.003$). There were 2 deaths in control group, which were not significant ($p < 0.241$). These two patients died due to multiorgan failure. There

was no statistically significant difference in the outcomes between genders (Table 5).

The significant mortality seen in burns patient stimulates every treating surgeon to explore, execute and develop methods to reduce it. This study was designed keeping in mind this objective. The use of enteral glutamine is already an established method in reducing infectious morbidity and mortality in trauma patients. Extending its use to patients with burns who are at the top most level of trauma severity was but a natural thought which needed to be substantiated.

The two groups of patients were similar with respect to age, gender distribution and severity of injury (TBSA). Patients were typically young adult subjects who were in good health before their injury. The quality of health care received by each patient was same.

The main observations in this study, which received supplemental glutamine, were: 1. Reduced incidence positive blood bacterial cultures. 2. Reduced incidence of positive wound culture. 3. Reduced need for hospital-stay. All these indicate that there was reduced infectious morbidity in these patients.

The reduction of bacteremia (positive blood culture) observed in our study group is in accord with the findings of Houdijk et al. [9] in trauma patients given enteral glutamine. In those patients who received placebo, blood infection was more frequent and more prolonged. The number of patients was not sufficient, however, for a meaningful comparison between survivors and nonsurvivors with regard to blood infections. Whether the effect of enteral glutamine administration on survival is specific to burn patients or could be observed in other ICU patients remains to be investigated.

Our results were also almost similar to a recently published study on burn patients who received glutamine parenterally [7]. The significantly reduced blood infection with mainly gram-negative bacteria in glutamine-supplemented patients suggests that glutamine may prevent the translocation of these particular bacteria across the gut mucosa. Whether the effect is related to the action of glutamine on the gut itself or on the behaviour of the bacteria remains to be determined. A hypothesis can be generated from the study conducted by Garrel D et al. [10] on *P. aeruginosa*: This bacterium may be sensitive to the amount of glutamine in its environment; a lack of glutamine may trigger both proliferation and crossing of the epithelial barrier. Together with weakening of the gut immune system, related at least in part to glutamine deficiency, these phenomena may explain *P. aeruginosa* translocation. Blood infection with

Table 1 Inclusion criteria

1.	Total burn surface area of 20–60%.
2.	Age between 15 years and 50 years.
3.	Admission within 72 hours of burn injury.
4.	Any type of thermal injury such as flame burns, scald burns and contact burns.

Table 2 Exclusion criteria

1.	Burn patients with pre-existing severe cardiac, hepatic, renal, pulmonary diseases or pregnancy or diabetes mellitus or cancer.
2.	Death within 72 hours of admission.
3.	Electrical burns.

Table 3 Demographic characteristics

	Glutamine group (n = 15)	Control group (n = 15)	p value
Age	33.86 ± 10.44	29.13 ± 9.18	0.198
Sex ratio (M:F)	6:9	3:12	0.426

Table 4 Study results

	Glutamine group (n = 15)	Control group (n = 15)	p value
Total burn surface area	40.30 ± 15.37	45.53 ± 12.89	0.321
Positive blood culture (no of times)	0.20 ± 0.41	0.73 ± 0.96	0.065
Positive wound culture (no of times)	1.00 ± 1.25	3.53 ± 2.47	0.001
Hospital-stay (days)	22.73 ± 9.13	39.73 ± 18.27	0.003

Table 5 Gender-wise analysis

	Male	Female	<i>p</i> value
Age	33.89 ± 5.62	30.47 ± 11.29	0.399
Total burn surface area	38.55 ± 14.83	44.78 ± 13.85	0.278
Positive blood culture (no of times)	0.53 ± 1.01	0.43 ± 0.67	0.689
Positive wound culture (no of times)	1.11 ± 1.45	2.76 ± 2.46	0.073
Hospital-stay (days)	24.67 ± 11.13	34.04 ± 17.98	0.160

P. aeruginosa may account for, at least in part, the results on mortality rate in their study, since four of eight patients in control group who died had septicemia with *P. aeruginosa*. In our study, the control group had two deaths, though this was found not to be statistically significant. Both patients died of septicemia with *P. aeruginosa*. This bacterium is a major cause of infectious morbidity and mortality in burn and ICU patients [11, 12].

Animal studies suggest that glutamine exerts a protective effect on gut mucosa and prevents bacterial and endotoxin translocation from the intestinal lumen to the bloodstream [13]. 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*. Our data could support the translocation theory but without definitive arguments. In an experimental study, the results indicated that enteral nutrition supplemented with glutamine is superior to conventional enteral nutrition with respect to improvement of intestinal immunity in burned mice [14]. In a recent study, it is suggested that glutamine enriched enteral feeding can improve nutritional status by promoting the synthesis of IgA, IgG, and increasing the prealbumin concentration, and corrected immunologic dysfunction in burn patients [15].

Another statistically significant finding of our study was considerable reduction in wound infection in glutamine-supplemented group. No other study has examined in detail this issue. The finding of increased incidence of positive wound culture raises certain issues, which though seem obvious, remain speculative at this juncture. The probable reason for the decreased incidence of wound infections in the glutamine-supplemented group could be their better immunological status as compared to the control group. The increased incidence of immunosuppression in the controls could be because of the increased incidence of bacterial translocation from the gut, leading to bacteraemia and/or endotoxemia and their effects on immune system of the body. In our study it has shown that, the most of the bacteria cultured from the wound were of gut origin. Thus, wound infection in patients with burns is not always due to contamination from hospital environment, it could be due to endogenous bacteria. This is how glutamine might have decreased wound infection in glutamine-supplemented group.

The other finding of our study was the effect of glutamine administration on mortality rate. No patient who received glutamine died. In control group, the observed mortality

rate was not statistically significant. The severity of injuries and the incidence of inhalation injury were identical in both groups, and the results cannot be explained by a reduced risk of dying at entry in the glutamine group. We may conclude that the decreased mortality in glutamine may or may not be related to its administration. This finding should be confirmed in a multicentre trial since our study was not powered to address the issue of mortality, and because such a study would take into account possible variations between burn centres. Such an effect of glutamine would establish it as the first intervention with a single nutrient that improves survival in burns patients.

In a retrospective case-control descriptive study, enteral glutamine supplementation was not associated with a change in the cumulative rate of infectious complications compared with the control group, but this was attributed to more cases of bloodstream infections and fewer cases of pneumonia and cellulitis in the glutamine group [16].

Drawback of our study being, that it was not a double-blinded study. However, measurers of study outcomes, such as blood culture and wound culture were, unaware of allocation of each patient to study or control group. That gave us fair unbiased results of the study. Another important issue to be mentioned is, the depth of burn wound which being difficult to assess clinically, might not have been same in all patients. However, the depth of burn wound has not got any role in the initial management of patients with burns. Larger studies need to be conducted on homogenous samples, like patients with burns in order to further establish the efficacy of glutamine supplementation in reducing the infectious morbidity. However, the results of this study support the use of glutamine in severely burned patients, and larger clinical trials that use glutamine as a pharmacologic intervention in this patient population clearly are warranted.

Conflict of interest The authors do not have any disclosable interest

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