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D.K. Kibor, MBChB, MMed, Chuka District, Hospital, P. O. Box 8, Chuka, O.E. Nyaim, MBChB, MMed, Senior Lecturer, K. Wanjeri, MBChB, MMed, Senior Lecturer, Department of Surgery, College of Health Sciences, University of Nairobi, P. O. Box 19676-00202, Nairobi, Kenya

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D.K. KIBOR, O.E. NYAIM and K. WANJERI

ABSTRACT

***Objective*: To determine the effect of enteral glutamine in reducing the incidence of post burn infections in patients with severe burns.**
***Design*: A double blind randomised clinical trial.**
***Setting*: Burns unit and ward 4D of Kenyatta National Hospital, Kenya**
***Subjects*: Sixty patients with severe burns who were randomised to two arms of treatment: (1) the glutamine group and (2) isonitrogenous arm acting as the control.**
***Results*: Patients' demographic and baseline clinical characteristics were similar in both arms of treatment. For the entire four-week treatment period, the odds ratio of a positive blood culture was almost three-fold higher among patients in the control group compared to those in the Glutamine group (p = 0.04). There was also a higher incidence of positive swab cultures from the non glutamine group.**
***Conclusion*: Enteral glutamine supplementation in severely burnt adult patients reduces blood infection by a factor of three. It also significantly reduces the incidence of burn wound infections.**

INTRODUCTION

Incidence of burns-related infection has remained high despite different preventive modalities currently in use. These modalities include among others; topical antibacterial agents, early excision of eschar, and timely closure of burn wounds. All these methods have been demonstrated to significantly reduce the occurrence of invasive burn wound infection and its related mortality (1). However, severe thermal burns have an intrinsic systemic immunosuppressive effect and this could possibly explain the high incidence of burns related infection and mortality despite the aforementioned preventive modalities in use (2). In this regard, the concept of immunomodulation (in the prevention and management of burns related infections) has been introduced. This is exemplified by glutamine supplementation.

The incidence of burns-related infections is similar to that of trauma patients, with 50% being due to primary endogenous infections. The isolated pathogens are predominantly gram positive cocci (3). In a retrospective study done elsewhere, 71 % of hospitalised burn patients' deaths were due to sepsis, septicaemia and complications of septicaemia (4). Incidence of burns-related infections and mortality rates among patients with moderate and severe burns in the local scene is 13.3% as reported by Nthumba & Oliech in a prospective analytical study of 2003 (5).

Enteral glutamine has been demonstrated to be effective in decreasing infections in several clinical settings. For instance, in a prospective Randomized Controlled Trial (RCT) done by Castel, *et al* (6), infection rate in bone-marrow transplant patients who received glutamine supplemented nutrition was 12% as compared to 43% in non-supplemented group.

Similarly, infection rate was found to be three times lower in the glutamine group as opposed to the control group in patients with multiple trauma (7). Many of the clinical trials on enteral glutamine supplementation have focused on critically ill patients (with mixed diagnoses) such as trauma patients, oncological and haematological patients demonstrating positive effects on reduction of infection rates. However, there is limited published data focused on effect of enteral glutamine on infection rate in patients with severe burns. Results from recently published RCT on effects of enteral glutamine, show a trend of an overall reduction in incidence of bacteraemia, lower antibiotic usage and lower mortality rates in patients with severe burns (8-10). These results are particularly from developed countries and based on these studies majority of burn centres in Europe and United States of America routinely put their patients with severe burns on

glutamine-rich diet. In our local setting, the supply of glutamine is erratic and is only given to critically ill patients but not to severely burned patients. There was therefore a need for a local study to illustrate the efficacy of enteral glutamine in reduction of infectious, morbidity and mortality in patients with severe burns to justify routine supplementation of the same to this subset of patient population.

MATERIALS AND METHODS

Study design and setting: Double blinded randomised clinical trial over a period of six months from September 2010 to February 2011 and carried out in the burns unit and plastic surgery ward 4D of Kenyatta National Hospital (KNH).

Study population: All patients with severe burns admitted in the burns unit and ward 4D.

Data collection and handling: All patients who satisfied the inclusion criteria and consented to the study were randomised into either the glutamine or the control group. The principal investigator collected the data using a predesigned questionnaire. Data were coded and entered into Microsoft excel spreadsheet and analysed using STATA version 9.2.

Ethical considerations: Necessary approvals were obtained from the Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee (KNH/UoN-ERC). All the information gathered was kept confidential and was utilised for the purposes of this study only.

RESULTS

A total of 240 wound surface cultures and 240 blood cultures were performed in the entire treatment period. All the sixty patients were included in the intention-to-treat analysis. The ages of the patients ranged from 17 to 74 years with a mean of 29.5 years (SD 10.7).

Various micro-organisms were isolated from the pus swab cultures with the frequency of isolation always remaining higher in the non-glutamine group Table 1.

Table 1
Frequency of microbes isolated in pus swabs per treatment group

Bacterium isolated	Glutamine (n=120 cultures)	Fresubin (n=120 cultures)	Odds Ratio (95% CI)	P
S Aureus	51/120(42.5%)	61/120(50.8%)	1.4(0.8-2.3)	0.2
Enterococcus	0/120(0)	2/120(1.7%)	-	0.16
MRSA	8/120(6.7%)	2/120(1.6%)	0.23(0.05-1.2)	0.05
Pseudomonas spp	3/120(2.5%)	10/120(8.3%)	4.5(1.0-20)	0.03
Klebsiella spp	1/120(0.8%)	4/120(3.3%)	0.2(0.03-2.2)	0.17
Acinetobacter spp	5/120(4.1%)	7/120(5.8%)	1.4(0.4-4.6)	0.55
Proteus spp	2/120(1.6 %)	14/120(11.7%)	7.8(1.7-36.3)	0.002

The most common organism in both arms of treatment was *Staphylococcus aureus*; 42.5% and 50.8% in glutamine and fresubin respectively. Other common pathogens isolated in patients receiving glutamine-free diet were *proteus spp* (11.7%) and *pseudomonas spp* (8.3%).

Staphylococcus aureus remained the predominant organism isolated in both arms of treatment in the entire period of treatment. Gram negative bacteria such as *pseudomonas spp* started colonising the burn wound from day four onwards and its incidence rose sharply in the glutamine-free group in the last two weeks of treatment.

Overall, glutamine supplementation had a strong association with the reduction of the incidence of burn wound infection. Table 2 ($p = 0.014$).

There were no significant differences in the incidence of positive swabs during week one or week two in the two groups (Table 2). During the third and fourth weeks the odds of positive culture were significantly higher in the fresubin group, with OR = 4.0 (1.2-12.8) and OR = 3.3 (0.9-11.7), respectively. The effect of glutamine on the incidence of infection reached a significant level in week three and four with p-value less than 0.05.

Table 2
Positive swab cultures per week per treatment group

	All patients (n = 60)			
	Glutamine (n = 120 swab cultures)	Fresubin (n = 120 swab cultures)	Odds ratio (95% CI)	P
Positive swab				
Total (week 1-week 4)	56/120(46.6%)	75/120(62.5%)	1.9(1.1-3.2)	0.014
Week 1	21/120(17.5%)	19/120(15.8%)	0.7(0.2-2.2)	0.58
Week 2	21/120(17.5%)	25/120(20.8%)	2.1 (0.6-7.6)	0.23
Week 3	9/120(7.5%)	19/120(15.8%)	4.0(1.2-12.8)	0.01
Week 4	5/120(4.1%)	12/120(10%)	3.3(0.9-11.7)	0.04

Out of the 240 blood cultures conducted among the 60 patients over four weeks, a total of 54 bacterial pathogens were grown from 35 (58.3%) patients. The most common pathogen grown from blood cultures was *staphylococcus aureus*: 15.8% and 9.1% in the control and glutamine groups respectively. The least isolated microbe was proteus: 1.6% and 0% in the control and the glutamine group respectively. In respect to the other gram negative bacteria, it is evident from the Table 3 below that glutamine has a strong correlation with reduction in the incidence of infection caused by of *klebsiela spp* and *pseudomonas spp* at a p-value of 0.02 and 0.04 respectively.

Table 3
Frequency of microbes isolated in blood culture per treatment group

Bacterium isolated	Glutamine (n=120 cultures)	Fresubin (n=120 cultures)	Odds ratio (95% CI)	P
S Aureus	11/120(9.1%)	19/120(15.8%)	1.9(0.8-4.1)	0.12
Proteus spp	0/30(0)	2/120(1.6 %)	-	0.15
Enterococcus	3/120(2.5%)	8/120(6.7%)	2.8(0.7-10.8)	0.12
MRSA	3/120(2.5%)	2/120(1.6%)	0.6(0.1-4.0)	0.65
Klebsiella spp	0/120	5/120(4.1%)	-	0.02
Pseudomonas spp	5/120(4.1%)	12/120(10%)	3.3(0.9-11.7)	0.04

In the first two weeks the rate of positive blood cultures remained the same in both treatment arms, with the glutamine free arm showing a significantly sharp increase from the third week. Table 4.

Table 4
Frequeny of positive blood culture per treatment group at different time points

	All patients (n = 60)			
	Glutamine (n=120 blood cultures)	Fresubin (n=120 blood cultures)	Odds ratio (95% CI)	P
Positive blood culture				
Total (week 1-week 4)	13/120(10.8%)	30/120(25%)	2.7 (1.3-5.6)	0.004
Weekly positive blood cultures				
Week 1	1/120(0.83)	1/120(0.83%)	1.0(0.06-17.2)	0.99
Week 2	8/120(6.7%)	7/120(5.8%)	0.8(0.25-2.7)	0.76
Week 3	2/120(1.6 %)	14/120(11.7%)	7.8(1.7-36.3)	0.002
Week 4	3/120(2.5%)	10/120(8.3%)	4.5(1.0-20)	0.03

DISCUSSION

Infection in patients with severe burns remains a major challenge and a major cause of morbidity and mortality especially in the developing countries (1).

Gram negative bacteria such as *pseudomonas* and *proteus* were isolated from the swab cultures from day four onward with the incidence being higher in the last two weeks in the non glutamine group. This compares closely with a study done in Syria by Dayoub in 19954.

Glutamine does not seem to have a significant impact on the incidence of bacteraemia in the first two weeks. These results are similar to findings by Garrel in 2003 in a randomised controlled trial (9). The study also compares closely with the results of a study done in India in 2009 (11). This study also shows that glutamine reduced the incidence of gram negative bacteria such as *Pseudomonas spp* by 3.3 to 4.5 times. Overall, there was a lower incidence of infection in the glutamine group as opposed to the control group as evidenced by swab cultures and blood cultures.

It is recommended that criteria for the use of glutamine in patients with severe burns be developed as it is evident that it is beneficial in reducing the incidence of infection.

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