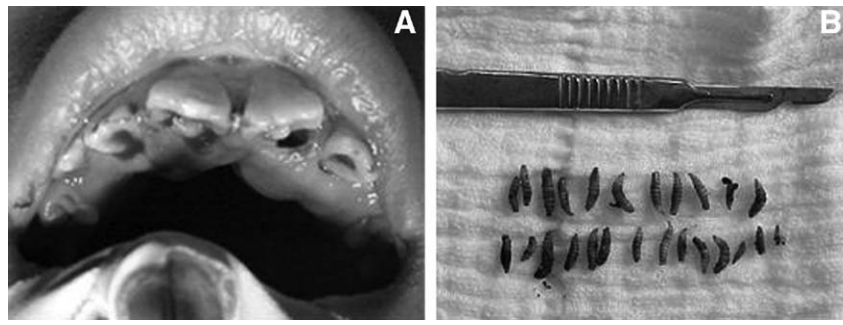

FIGURE 2. The patient of the Case 2 also exhibited mucosa swelling and gingival pockets around the maxillary teeth (A). Larvae were removed without the need for extraction of the teeth (B).

larvae that can cause the infestation (ie, *Dermatobia hominis*, *Cochliomyia hominivorax* and *Cordylobia anthropohaga*)[2], and the prevalence of each *Dipteran* spp depends on it geographical distribution.[2,3]

The diagnose of myiasis is clinical and usually easy by the appearance of the maggots except in some cases when the larvae are located below the skin.[3] Myiasis can be clinically classified according to the anatomic site of infestation (aural, ocular, nasal, oral, vaginal, anal, cutaneous, etc.) or on the basis of host relationships as 1) *obligatory myiasis*, when the flies require a living host (humans, domestic or wild animals) for the development of their larvae; 2) *facultative myiasis*, caused by flies that normally lay eggs in decaying tissues (animal or plants), but occasionally lay eggs on open wounds or orifices; and 3) *accidental myiasis* in which the flies do not need a host to develop, therefore, the infection is considered accidental.[6]

Most myiasis-causing flies are attracted to deposit their eggs or larvae in response to the odors of necrotic organic matter. Patients with draining or chronic wounds are at particular risk for myiasis.[7]

In humans myiasis is often subcutaneous producing a furunculoid or boil-like lesion. The mouth is rarely affected and when it occurs it is usually as an accidental or facultative case, by ingestion of infected material or direct inoculation by the fly.[3] In our cases the location of the lesions in the anterior part of the oral cavity suggests a direct inoculation of the tissues.

Conventional treatment for myiasis is careful surgical removal of the larvae and adequate debridement of necrotic tissue.[8,9] Recently, systemic treatment with ivermectin has been reported to be effective.[4]

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NO BENEFIT OF GLUTAMINE SUPPLEMENTATION ON PERSISTENT DIARRHEA IN UGANDAN CHILDREN

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Abstract: We evaluated the efficacy of oral glutamine supplementation in children 2 to 60 months of age with persistent diarrhea by 1:1 randomization to standard treatment alone or together with twice daily glutamine. The failure rate was similar in both arms (relative risk: 1.8 [95% confidence interval: 0.8–3.7], $P = 0.12$). Glutamine supplementation showed no benefit on the outcome of persistent diarrhea.

Key Words: efficacy, glutamine, outcome, persistent, diarrhea

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J.M.K. and E.W. conceived the idea. All the investigators were involved in designing the study. S.K. and J.M.K. had equal contribution to this work. J.M.K. directly implemented the study. All the investigators were involved in the interpretation of the study results. J.M.K. wrote the initial article. E.W., S.K. and R.B. reviewed, revised and approved the final article.

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Globally, diarrheal diseases are one of the leading causes of morbidity and mortality in children causing 1 billion episodes of illness and 1.6–2.5 million deaths annually.[1]

Approximately 3–20% of the acute diarrheal episodes become persistent and contribute to more than half of the total diarrhea-related deaths.[2,3] The commonest underlying causes of death in persistent diarrhea include severe malnutrition, septicemia, pneumonia and hypocalcemia.[4]

The basic pathology in persistent diarrhea is prolonged injury to the small intestinal mucosa,[5] leading to delayed epithelial regeneration and complete destruction of the villi.[6]

Glutamine administration has been shown to protect the intestinal mucosa in some conditions.[7] In animals, glutamine improves intestinal absorption of the jejunal mucosa, and decreases intestinal permeability.[8,9] In humans, glutamine improves diarrhea secondary to use of nelfinavir in HIV-infected adults[10,11] and ameliorates gastrointestinal effects of anticancer drugs.[12] When used within oral rehydration solution, glutamine reduces the duration of acute diarrhea among children.[13] This study evaluated the efficacy of glutamine supplementation on the outcome of children with persistent diarrhea in Uganda.

MATERIALS AND METHODS

Study Design

This was a randomized controlled clinical trial with an allocation ratio of 1:1 at a National referral hospital in Uganda from October 2011 to March 2012. The study was conducted at the pediatric emergency department and in patient wards of Mulago National Referral and teaching Hospital in Kampala, Uganda. Diarrheal diseases accounts for 6.3% of the annual admissions at the pediatric emergency department with persistent diarrhea accounting for 0.4%. Eligible patients were consecutively enrolled until the sample size was attained. Block randomization of ratio 1:1 was used. After the informed consent, children were randomized to either receive glutamine supplement mixed in a standard diet or the standard diet alone. The patients and study doctor who carried out the evaluations were blinded until the analysis of the data was complete.

Participants

We included children 2 to 60 months of age with persistent diarrhea and written informed consent from the caregivers/parents. We excluded children with documented antidiarrhea medications during the current illness and those with documented liver disease or renal disease due to safety uncertainty of glutamine in these conditions.

The data collected included: age, sex, feeding practices before admission, nutrition during illness, prior antibiotic use, diarrhea duration and nutrition status. Clinical data included: weight in kilograms, length/height in centimeters, edema, temperature and hydration status. Laboratory stool analysis was done for bacteriology, reducing sugars, pH and microscopy. The children's HIV status was obtained from the hospital routine counseling and testing registry.

The study was approved by the School of Medicine Research and Ethics Committee at Makerere University College of Health Sciences. The study was conducted according to the International Conference on Harmonisation Guidelines for Good Clinical Practice and registered with pactr.org (PACTR201207000371218).

Implementation of Intervention

The intervention was colorless and odorless glutamine powder that was tasteless when mixed with the diet. It was given under direct observation according to weight bands of 5–12.5 kg and 12.6–20 kg, the children in the weight bands receiving 1.5 g and 2 g 12 hourly, respectively, for the intervention group. The standardized diet for children over 6 months was rice based to provide 110 kcal/kg/24 hours while children <6 months of age who were not breastfeeding were given natural plain yoghurt to provide 143 kcal/kg/24 hours. No other feedings were encouraged during the study except breastfeeding.

All children received vitamin A at doses of 50,000 i.u, 100,000 i.u and 200,000 i.u for infants <6 months, infants 6–12 months and children >12 months, respectively, on days 1 and 2 of follow-up. Zinc supplementation was given at a dose of 10 mg/day for infants <6 months and 20 mg/day for participants >6 months for 10 days.

Safety

The study was monitored by an unblinded data and safety monitoring board constituting a pediatrician, a statistician and a pharmacist.

Outcome Measures

All study participants were followed up until discharge, death or a maximum of 12 days which ever occurred first. The primary outcome measure was proportions with cessation of diarrhea during the follow-up period. The diarrhea was deemed ceased if there were fewer than 3 watery or loose stools per 24 hours during a continuous 72 hour-period of follow-up. The secondary outcome measure was duration of diarrhea in hours during the follow-up period. The outcomes were determined when the criteria for cessation of diarrhea was met or at the end of the 12-day follow-up period for this study.

Statistical Analysis

Using the formula for sample size calculations comparing equal proportions,[14] a sample size of 69 per arm was adequate with power 80% testing a 2-sided hypothesis considering a reported[15] failure rate of 77% and assuming a clinically significant reduction of at least 30% by the intervention on the failure rate. Data were captured using Epi data from the participant case report forms. Data were exported to STATA 10 (Stata, College Station, TX) for analysis using intention-to-treat approach. The efficacy of glutamine was determined by comparing the proportions of treatment failures in the 2 arms using the chi-square test. The effect measure was relative risk. The median duration of diarrhea between the intervention and control arms during follow-up was compared using the Mann–Whitney U test. $P < 0.05$ was considered statistically significant.

RESULTS

We recruited 138 children into this study (see Figure 1). The baseline characteristics of the participants in the 2 arms were comparable (data not shown). Overall, 70% of the study participants were <12 months of age with 64% in the intervention and 67% in the placebo arm being <12 months of age.

Treatment failure in the intervention arm was 23% compared with 16% in the control arm (relative risk: 1.8 [0.8–3.7], $P = 0.12$). The median duration of diarrhea was similar in the 2 arms; intervention arm 5.0 days (interquartile range: 4–7) and control arm 5.0 days (interquartile range: 4–7) ($P = 0.9$).

Three participants in the intervention arm and 1 participant in the control arm died from causes deemed by the data and safety monitoring board to be unrelated to the study intervention.

DISCUSSION

We believe that this is the first randomized clinical trial to assess the efficacy of glutamine supplementation on the outcome of

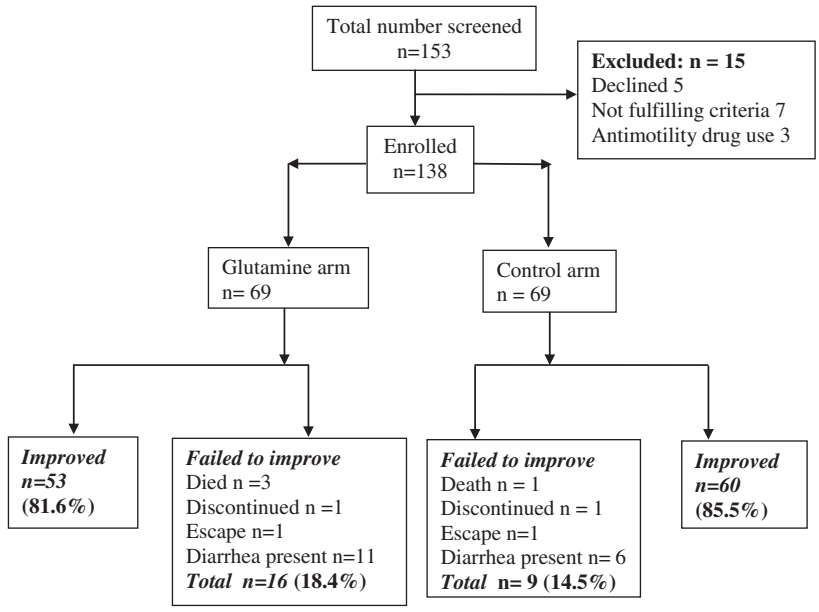

FIGURE 1. Trial profile.

persistent diarrhea in young children. In this study, glutamine supplementation did not improve the outcome of persistent diarrhea.

Our findings are consistent with results of Ribero et al[15] and Gutiérrez et al[16] in randomized controlled studies of infants with acute diarrhea. They found no benefit of glutamine supplementation on the diarrhea outcome. Similarly, among children with malnutrition, no difference in diarrhea duration was reported by Lima et al.[17] A study by Coghlin Dickson et al[18] in adults on the preventive effect of glutamine supplementation on chemotherapy induced diarrhea showed no benefit.

We cannot explain the inconsistency between our study results and those of Yalçin et al[13] where a reduction in duration of acute diarrhea was observed in healthy children with acute diarrhea or by Daniele et al[12] who found that glutamine reduced the duration and severity of diarrhea induced by anticancer drugs.

The strength of this trial lies with its design and its execution in a developing country where persistent diarrhea is a continuing problem. From previous studies on glutamine, we identified children with persistent diarrhea as a clinically relevant population who may benefit from supplemental glutamine.

Our trial has some limitations. About 50% of our participants were <12 months, an age group reported to show poor response to glutamine supplementation. Our study like many others had some inherent patient characteristics, a high prevalence of malnutrition and a high burden of infections. Malnutrition[4] and infections[19] have been reported as risk factors for poor outcomes in persistent diarrhea. We were not able to measure baseline serum glutamine levels and we are not sure to what extent breast milk glutamine in breastfeeding infants may have affected our results. Lastly, we adopted the intention-to-treat data analysis approach that included even participants who received <24-hour dose of glutamine. This created variability in the duration on glutamine supplementation that may have affected our results.

We recommend further research to examine the effect of a micronutrient mix on the outcome of persistent diarrhea while taking account of the age group, infections and malnutrition. Further research should also be done to identify children with persistent diarrhea who are at highest risk for failure with conventional therapy. Resources for novel interventions such as the role of micronutrients could then be directed at the most vulnerable group.

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