ARTICLES—FOCUS ON MALNUTRITION

Comparison of Milk and Maize Based Diets in Kwashiorkor

D R Brewster, M J Manary
Department of Paediatrics, College of Medicine, Malawi

Author for Correspondence: A/Professor D R Brewster
Royal Darwin Hospital
P 0 Box 41326
Casuarina NT 0811
AUSTRALIA

ABSTRACT

The dual sugar test of intestinal permeability is a reliable non-invasive way of assessing the response of the small intestinal mucosa to nutritional rehabilitation. Our aim was to compare a local mix of maize soya-egg to the standard milk diet in the treatment of kwashiorkor.

The diets were alternated three monthly in the sequence milk-maize-milk. There were a total of 533 kwashiorkor admissions of at least five days during the study who received either milk or maize. Intestinal permeability was assessed at weekly intervals by the lactulose-rhamnose test in 100 kwashiorkor cases, including 55 on milk and 45 on the maize diet.

Permeability ratios (95% confidence interval) on the milk diet improved by a mean of 6.4 (1.7 to 11.1) compared with - 6.8 (-16.8 to 5.0) in the maize group. The improved permeability on milk occurred despite more diarrhoea, which constituted 34.8% of hospital days compared to 24.3% in the maize group. Case fatality rates for all 533 kwashiorkor admissions were 13.6% v 20.9%, respectively, giving a relative risk of death in the maize group of 1.54 (1.04 to 2.28). The maize group also had more clinical sepsis (60% v 31%) and less weight gain (2.9 v 4.4 g/kg/day) than the milk group.

Milk is superior to a local maize based diet in the treatment of kwashiorkor in terms of mortality, weight gain, clinical sepsis, and improvement in intestinal permeability.

Introduction

Childhood malnutrition is a major health problem in Malawi. In a study of children aged 24-59 months, 69.3% of poor urban children and 83.2% of low income rural children were stunted (height for age <2 z scores) (1). A review of hospital admissions over 12 months in Blantyre in 1992-3 revealed that severe malnutrition was the principal diagnosis in 11% of all paediatric admissions, and had a 36.4% case fatality rate (378/1039) (2). Although this indicates a severe spectrum of disease, it also suggests a need for improved case management. This study focuses on the diet in nutritional rehabilitation of kwashiorkor. Milk has been accepted as appropriate treatment of kwashiorkor at least since a 1956 South African study showed improvement on skim milk without supplemental vitamins, and a milk based diet is still the recommended treatment (3,4). Nevertheless, there are many reports of satisfactory result with the use of local cereal mixes in the treatment of persistent diarrhoea and/or malnutrition. (5-7). The supply of milk powder to Malawi has been cut back by the World Food Program, so it was important for us to study an alternative diet based on maize, which is the staple diet in Malawi.

The aim of this study was to evaluate the recovery of intestinal function as measured by the lactulose-rhamnose (L-R) test in children with kwashiorkor on two different diets of similar energy and protein content (table 1). One diet was the standard milk based diet; the other a cereal based

TABLE 1 THE ENERGY AND PROTEIN CONTENT OF MILK AND MAIZE BASED DIETS

	Ingredients (g)		Energy (kJ)		*Protein (g)*	
Milk preparations	*Milk*	*Maize*	*Milk*	*Maize*	*Milk*	*Maize*
Premix (per 100 g)	–	–	2108	1646	18.0	11.4
Skim milk	50	–	163	–	3.96	–
Sugar	23	19	79	79	–	–
Oil	27	4	223	37	–	–
Maize mix*	–	77	–	312	–	2.96
Phase I (per 1)	–	–	2780	3049	10.2	14.2
Premix†	56.5	71.5	1193	1176	10.2	8.2
Sugar	101	101	1588	1588	–	–
Egg	–	50	–	286	–	6
Phase 2 (per 1)	–	–	4763	5279	40.7	44.6
Premix†	226	286	4763	4708	40.7	32.6
Egg	–	100	–	571	–	12

*Maize 80%, soya 20% as *likuni phala.*
†Measured by volume as 100 ml (phase 1) or 400 ml (phase 2).

diet of maize soya blend (likuni phala) to which egg was added to increase protein content and quality.

Patients and methods

Out of 149 children with kwashiorkor in whom permeability testing was done, 76 were treated with a milk based diet, 64 with an exclusively maize based (milk free) diet, and nine with both diets over a change over period. Repeat testing was not done in 21 children in the milk group and 19 in the maize group due to early death or being taken from hospital before discharge, leaving 100 subjects for comparison. The method of evaluating intestinal permeability by the L-R test is well described involving overnight testing for a mean of 7.6 hours.) L-R ratios were done at weekly intervals in hospital, with a total of 144 tests in the milk group and 117 in the maize group.

The milk and maize diets were similar in energy and protein densities, and were formulated into two separate phases of treatment; phase 1 for initiation of cure and phase 2 for rapid growth, which was generally started during the second week with clinical improvement (table 1). The energy dense maize porridge was thinned with germinated millet flour after cooking to improve palatability and intake. As part of standard treatment, all children received cotrimoxazole, albendazole, supplements of potassium, magnesium, zinc, and other micronutrients.

Due to constraints of nursing care and logistics in this setting, we could neither randomise patients into milk and maize diets, nor blind health workers about the diets. Consequently, the two diets were given alternately, using only one at a time. The timing of the maize based diet was determined by the shortage of milk supply. As skim milk powder from the World Food Program was unavailable in April, we gave the maize based diet from April to June which just overlapped the main seasonal change in malnutrition prevalence. The milk diet, as the standard treatment, was given January to March and July to September. The level of nursing care was not improved for the study, so mothers continued to feed and care for their children in the usual manner for this nutrition centre. Nasogastric tube feeding was not used due to systematic refusal by mothers at this centre. Clinical sepsis was defined as fever, respiratory distress, a change is mental status, shock, or any abrupt deterioration in condition, but was not confirmed due to the limited microbiology resources.

The study was approved by the Health Sciences Research Committee of Malawi. Informed verbal consent was obtained in the local language from a parent or guardian before permeability testing, and it was made clear that non-participation would not affect the child's treatment.

Results

Table 2 compares the two dietary groups on admission, showing that the parents of the maize group were better educated and of higher socioeconomic status than the milk group. There were no other significant baseline differences detected between the groups.

It was evident clinically during the study that the maize based diet was not as successful treatment for kwashiorkor as milk. For all 533 kwashiorkor admissions of at least five days during the study, the milk group had a lower mortality, less sepsis, and better weight gain than the maize group. Thus, the maize group had a 58.1% prevalence (100/172) of clinical sepsis compared with 45.7% (165/361) for milk, giving a relative risk of sepsis for maize of 1.30 (95%) confidence interval (CI 1.06 to 1.58). The mean weight gain in z scores after resolution of oedema for the milk group was 0.40 (CI 0.34 to 0.46) compared with 0.25 (CI 0.15

TABLE 2 BASELINE COMPARISON OF MALNUTRITION CASES: MILK V MAIZE BASED DIETS

*Feature**	*Milk diet (n=55)*	*Maize diet (n=45)*	*p Value*
Age (months)*	29.8 (25.1 to 34.6)	27.0 (19.5 to 30.8)	0.78
Travel time (min) to hospital*	59.2 (39.7 to 78.7)	65.8 (49.9 to 81.7)	0.80
Socioeconomic status score	13.6 (12.4 to 14.8)	15.4 (14.1 to 16.7)	0.04
Family size (members)	4.6 (4.2 to 5. 1)	4.5 (3.8 to 5. 1)	0.98
Still breast fed (%)	1 (1.8)	5 (11.1)	0.09
Previous malnutrition admission	10 (18.2)	9 (20.0)	0.98
Previous child deaths (%)	25 (45.5)	14 (31.1)	0.18
Days of diarrhoea before admission	12.0 (8.2 to 15.7)	12.1 (7.5 to 16.7)	0.96
Days oedema before admission	14.2 (11.7 to 16.8)	15.0 (10.6 to 19.4)	0.75
No kwashiorkor rash (%)	24 (43.6)	22 (48.9)	0.75
AIDS (%)	11 (20.0)	11 (24.4)	0.77
Mother's schooling (mean years)	3.1 (2.2 to 3.9)	5.3 (4.3 to 6.3)	0.001
Father has skilled job (%)	20 (37.0)	25 (55.6)	0.10
Wasting (WHZ) mean z score	-1.9 (-2.2 to -1.6)	-2.1 (-2.4 to - 1.8)	0.36
No wasted (< -2 SD) (%)	27 (49.1)	23 (51.1)	0.91
Stunting (HAZ) mean z score	-3.6 (-4.0 to -3.2)	-3.4 (-3.8 to -3.1)	0.53
No stunted (< -2 SD) (%)	48 (87.3)	41 (91.1)	0.75

*Geometric mean (95% confidence interval).
HAZ height for age z score; SD standard deviation (z score); WHZ weight for height z score.

to 0.35) for maize (p=0.00008). The case fatality rate was 20.9% (36/172) for maize and 13.6% (49/361) for milk, for a relative risk of death for the maize diet of 1.54 (CI 1.04 to 2.27).

For the 100 kwashiorkor cases with repeat permeability tests, there was also a higher mortality rate in the maize than the milk group (10/45 v 2/55), for a relative risk of death for maize of 6.3 (1.4 to 25.0). This increased risk of late death on a maize diet remained significant on logistic regression when controlled for diarrhoea and intestinal permeability.

Overall on permeability testing, there was a significant (p=0.001) mean improvement in L-R ratios in the milk group compared with the maize group (table 3). After one week of nutritional rehabilitation, the geometric mean (95% CI) L-R ratio (X100) improved in the milk group from 15.6 (12.4 to 19.6) to 10.2 (7.8 to 13.3), whereas it worsened in the maize group from 17.8 (14.6 to 21.7) to 19.2 (14.8 to 25.0). The improvement in permeability in the milk group occurred despite a significantly (p=0.01) higher mean percentage of hospital days with diarrhoea (34.8%, CI 29.8 to 39.8) compared with the maize group (24.3%, CI 17.8 to 30.8). Yet for the milk group as a whole, diarrhoea was still associated with a higher mean L-R ratio (18.9, CI 15.3 to 23.5) than for those without diarrhoea(9.9, CI 8.1 to 11.9, p=0.00007). During the initial low density phase 1 diet, the diarrhoea prevalence was 60% on the milk diet compared with 27% for maize, whereas for both high energy phase 2 diets (milk and maize) it was only 24-25% (odds ratio 0.40, CI 0.23-0.65). A milk diet remained a significant contributor to diarrhoea on logistic regression when controlled for intestinal permeability.

Discussion

In this study, we compared a cows' milk diet to a 4:1 maize-soya blend with egg at a nutrition rehabilitation centre, focusing on clinical improvement. Maize, the Malawian staple, has a moderately low protein content with relative deficiency of lysine and tryptophan. We improved the protein quality of the maize diet in this study by adding soya and egg.

Plant based diets are a cheaper source of protein than milk, so have been used to treat severe malnutrition. A study at a metabolic unit in Jamaica compared cows' milk with a soya formula (Sobee) in terms of resolution of wasting (8). Despite little difference in energy intake, weight gain was much greater in the cows' milk group, which was attributed to zinc deficiency limiting lean tissue synthesis on the soya formula.

Zinc deficiency is a particular concern for cereal-legume diets due to the high phytate content. Dietary studies of Malawian children have documented the high phytate content of the maize diet leading to zinc deficiency (9). Intestinal permeability is known to be increased with zinc deficiency, mainly due to increased lactulose permeation (10). In the present study, however, zinc was unlikely to be limiting since our subjects were supplemented with 40 mg/day and the maize was germinated.

The present study is further evidence against a local staple diet, but in this study the focus was on the treatment of kwashiorkor where the main aim was clinical improvement (resolution of oedema, infection, and anorexia) rather than catch-up growth. Our median hospital stay for kwashiorkor survivors was only 15 days, so children were not kept in hospital until wasting had resolved.

The activity of brush border disaccharidases is generally depressed in malnutrition, particularly lactase levels in kwashiorkor (11). From a clinical perspective, disaccharidase activity may not correlate with clinical intolerance of milk, although low levels usually cause increased stool weight. Many studies have concluded that milk is not contraindicated in severe malnutrition despite higher stool volumes, because it does not hamper clinical recovery (12-14). The main finding of this study is that children with kwashiorkor have improved intestinal permeability on a milk diet compared with a maize based diet. This is true in spite of the milk diet causing more diarrhoea, which is a risk factor for abnormal permeability. The late and presumably preventable deaths were also significantly lower in the milk group, both in the 100 cases with repeat permeability testing and also in the 533 kwashiorkor admissions of five or more days on an exclusive milk or maize diet. The poor results with the maize porridge are in spite of germination of the cereal, zinc supplementation, and the addition of soya and egg to the diet. The cause of continuing diarrhoea in kwashiorkor during the early phase of treatment with a milk diet is more likely to be from lactose intolerance than cows' milk allergy. We conclude that milk is superior to a local maize based diet of similar protein and energy density in the treatment of kwashiorkor. Our results warrant exerting pressure on health departments and donor agencies to continue to supply milk powder for the treatment of kwashiorkor.

Reference

1. Quinn VJ, Chiligo-Mpoma NO, Simler K, Milner J. The growth of Malawian preschool children from different socioeconomic groups. Eur J Clin Nutr 1995; 49:66-72.

2. Mbewe AL. Protein energy malnutrition in Malawian children (Treatise). Liverpool: University of Liverpool, 1993.

3. Pretorius PJ, Hansen JD, Davel JGA, Brock JF. Skimmed milk and kwashiorkor. S. Afr Med J 1956;49:447-50.

4. Waterlow JC. Protein-energy malnutrition. London: Edward Arnold, 19921:1-393.

5. Baker RD, Baker SS, Margo GM, Reuter HH. Successful use of a soya-maize mixture in the treatment of kwashiorkor. S. Afr Med F 1978;53:674-9.

6. Brown KH. Appropriate diets for the rehabilitation of malnourished children in the community setting. Acta Paediatr Scand Suppl 1991;374:151-9.

TABLE 3 RESULTS OF KWASHIORKOR CASES: MILK V MAIZE DIET

Outcomes	*Milk diet (n=55)*	*Maize diet (n=45)*	*p Value*
Clinical			
Mortality (%)	2 (3.6)	10 (22.2)	0.01
Clinical sepsis (%)	17 (30.9)	27 (60.0)	0.01
Diarrhoea during initial week (%)	35 (63.6)	14 (31.1)	0.002
% Days with diarrhoea in hospital	34.8 (29.8 to 39.8)	24.3 (17.8 to 30.8)	0.01
Weight gain:			
Mean No of days	5.3 (3.9 to 6.7)	2.7 (1.7 to 3.7)	0.01
In g/kg/day*	4.4 (3.4 to 5.5)	2.9 (2.1 to 3.7)	0.03
Days in hospital	15.5 (13.9 to 17. 1)	15.8 (13.9 to 17.7)	0.81
Oedema resolved (days)	9.3 (7.7 to 10.9)	8.8 (6.6 to I 1.0)	0.71
Permeability			
Mean urine output (ml/kg/hour testing)*	1.29 (1.13 to 1.45)	1.21 (1.05 to 1.37)	0.51
Mean % lactulose recovery*	0.145 (0.12 to 0.17)	0.192 (0.16 to 0.23)	0.03
Mean % rhamnose recovery*	1.08 (0.90 to 1.29)	0.99 (0.83 to 1.19)	0.51
Differences in L-R permeability*†			
Improved ratio (%)	44 (57.9)	25 (41.7)	0.09
Worsened ratio (%)	19 (25.0)	28 (46.7)	0.01
Mean differences in L-R ratio	6.4 (1.7 to 1 1. 1)	-6.8 (-16.8 to 5.0)	0.001

* Geometric mean (95% confidence interval), L-R ratios x 100.
† Differences between weekly tests 1-2 and 1-3.

7. John C, Gopaldas T. Evaluation of the impact on growth of a controlled 6-month feeding trial on children (6–24 months) fed a complementary feed of a high energy-low bulk gruel versus a high energy-high bulk gruel in addition to their habitual home diet. J. Trop Pediatr 1993; 39:16–22.

8. Golden BE, Golden MH. Plasma zinc, rate of weight gain and the energy cost of tissue deposition on children recovering from severe malnutrition on a cow's milk or soya protein based diet. Am J Clin Nutr 1981;34:892-9.

9. Ferguson EL, Gibson RS, Opare-Obisaw C, Ounpuu S, Thompson LU, Lehrfeld J. Zinc nutriture of preschool children living in African countries. J. Nutr 1993;123:1487-96.

10. Roy SK, Behrens RH, Haider R, et al. Impact of zinc supplementation on intestinal permeability in Bangladeshi children with acute diarrhoea and persistent diarrhoea syndrome. J Pediatr Gastroeterol Nutr 1992; 15: 289–96

11. James WP. Tejunal disaccharidase activities in children with marasmus and with kwashiorkor. Response to treatment. Arch Dis Child 1971;46:218-20.

12. Brand JC, Dornton Hill I, Gracey MS, Spargo RM. Lactose malabsorption in Australian Aboriginal children. Am J Clin Nutr 1985;41:620-2.

13. Solomons NW, Torun B, Caballero B, Flores-Huerta S, Orozco G. The effect of dietary lactose on the early recovery from protein-energy malnutrition. I. Clinical and anthropometric indices. Am J Clin Nutr 1984;40:591-600.

14. Rothman D, Habte D, Latham M. The effect of lactose on diarrhoea in the treatment of kwashiorkor. J. Trop Pediatr 1980;26:193-7.

Potassium Supplementation in Kwashiorkor

M.J. Manary, MD

D.R. Brewster, MD, MPH, FRACP

Department of Paediatrics, College of Medicine, Malawi

Author for correspondence: Dr M J Manary
Washington University
School of Medicine
1 Children's Place
St Louis,
MO.63110,
USA

ABSTRACT:

Potassium depletion is common in kwashiorkor and contributes to the high case fatality rate. The aim of this study was to determine if high potassium supplementation improves the outcome of treatment. We performed a randomized, doubled-blind, placebocontrolled, clinical trial of high potassium supplementation in 99 children with kwashiorkor. Controls (n=51) received a standard potassium intake of 4.7 mmol/kg/day. The experimental group (n=48) received 7.7 mmol/kg/day. Both groups were treated in the hospital-based nutrition unit with a standard regime of milk feeds, mineral and vitamin supplements, and antibiotics. There were no significant differences between the experimental and control groups in early deaths (0–5 days), length of hospitalization, or time for resolution of edema. The overall hospital case-fatality rate was reduced from 39.2% in the control group (20/51) to 29.2% in the experimental group (14/48), which was not statistically significant (p=0.40). There was a significant reduction in late deaths after 5 days, including those who left hospital in a moribund state, (13 in controls vs 3 in the experimental group; odds ratio 5.3, 95% confidence interval 1.2 – 31.0, p=0.02). The experimental group also had significantly fewer presumed septic episodes (3 vs 18, odds ratio 8.9, confidence interval 2.2-50.9), respiratory symptoms, and new skin ulcerations than controls. We conclude that the high potassium supplementation reduced late deaths and morbidity in kwashiorkor. This may be due to improved myocardial and immune function from earlier repletion of intracellular potassium. We suggest that the recommended potassium intake for the initial phase of treatment of kwashiorkor should be increased from 4 to 8 mmol/kg/day.

Potassium depletion in kwashiorkor is severe and worsened by diarrhoea and the low mineral content of a maize weaning diet

INTRODUCTION

Potassium (K^+) deficiency is a well-recognised feature of kwashiorkor, and K^+ supplementation is part of the routine treatment. The usual recommended supplement is 4 mmol/kg/day for 2–3 weeks.[1,2] K^+ deficiency in kwashiorkor is exacerbated by stool losses in diarrhoea, and the low K^+ content of weaning foods[3]. Intracellular K^+ depletion promotes sodium (Na^+) and water retention, reduces myocardial contractility and affects transport across cell membranes. Severe hypokalemia may cause apathy, weakness, hypotonia, paralytic ileus, ECG abnormalities and sudden death[4].

In Malawi, kwashiorkor (including marasmic-kwashiorkor) accounts for 75% of malnutrition admissions to hospitals or Nutrition Rehabilitation Units (NRU) Nevertheless, K supplements are not available either from government medical stores or at NRU supplied by the World Food Program. In view of the beneficial effect of K on edema in kwashiorkor, we postulated that increasing the intake would hasten edema loss, clinical recovery and weight gain. This is an important objective, since prolonged hospitalization is not feasible. The geometric mean (95% CI) length of stay for survivors at this NRU is only 10.7 (10.1–113) days.

The purpose of this study was to determine whether children with kwashiorkor would benefit from an additional 3 mmol/kg/day of K^+ above the standard supplement.

Materials and Methods

All children admitted with kwashiorkor to the NRU at the Queen Elizabeth Central Hospital in Blantyre between February 10 and March 16, 1995 were enrolled in the study. Children with edema due to renal disease or malarial anaemia were excluded. On admission children were randomized into one of two groups: the experimental group was given an additional 3 mmol/kg/day of K^+ in corn syrup as a medication for the first seven days, while controls received a placebo of corn syrup alone. The initial routine medications were co-trimoxazole, albendazole, magnesium (2.8 mmol/kg/day), Zinc (40 mg daily as lactate) and multivitamins. Oral rehydration solution and intravenous fluid were used cautiously to avoid excess Na^+ and fluid loads.

The investigators, health workers and mothers were unaware of whether children were in the experimental or control group. Mothers were asked daily for 7 days whether their child was irritable, anorexic, or able to finish the feeds,' and whether they had diarrhoea, vomiting, cough or respiratory distress. Children were also weighed and examined daily for edema, fever, respiratory signs, oral ulcers, skin ulcers and irritability. Pedal edema was graded on a 0-3 scale where 1+ represented <0.5 cm of pitting edema of the dorsum of the foot and 3+ implied gross oedema of shins and eyelids.

The initial diet (phase 1) for all admissions consisted of dried skim milk, sugar, vegetable oil and water containing 278 KJ (66 kcal) and 1.0 g of protein per 100 ml. On recommended intakes,this meant a daily intake per kilogram of body weight of approximately 332 KJ (79 kcal), 1.2 g of protein and 1.5 mmol of K. This was supplemented with an additional 3.2 mmol/kg/day of K, for a total K^+ dose of 4.7 mmol/kg/day for controls whereas the experimental group received an additional supplement as a medication of 3 mmol/kg in corn syrup for a total of 7.7 mmol/kg/day. Once the edema, appetite and mental status were improving,

children were advanced to a phase 2 diet, generally in the second week of treatment after completion of the K' supplement or placebo. This comprised 4 feeds of high energy milk, containing 477 KJ (114 kcal) and 4.1 g of protein per 100 ml; and 2 feeds of a local weaning porridge of maize, soya, sugar and oil, containing 469 KJ (112 kcal) and 3.3 g of protein per 100 ml. On the recommended intake of 150 ml/kg/day, this diet provided 712 KJ (170 kcal), 5.8 g of protein and 7.6 mmol of K' per kg per day.

In addition to the data on table 1, the study patients had the following clinical signs and symptoms on admission: fever (39%), cough (53%) shortness of breath (12%) sore mouth (28%), oral thrush (24%), hair changes (58%), hepatomegaly of >2 cm below the costal margin (28%), and splenomegaly (10%). A clinical diagnosis of sepsis was based on fever, shock without dehydration, dyspnoea, or an abrupt change in mental status or general condition. This was not confirmed by microbiological investigations.

TABLE 1: COMPARISON OF EXPERIMENTAL AND CONTROL GROUPS ON ADMISSION

Clinical Parameters		Experimental Group (n=48)	Control Group (n=51)	p-value
Age (months)		29.3 (±14)	27.9 (±15)	0.62
Wasting	>-I	9 (1 9%)	8 (17%)	
Weight/Height	-2	15 (32)	6 (12)	0.91
(z-scores)	-3	12 (26)	20 (42)	
(edema free)	<-3	11 (23)	14 (29)	
	Mean	–2.04 (±1.20)	–2.40 (±1.13)	0.13
Stunting	>-2	11 (23%)	5 (10%)	
Height/Age	-3	10 (21)	13 (27)	0.92
(z-scores)	-4	11 (23)	15 (31)	
	<-4	15 (32)	15 (31)	
	Mean	–3.01 (1.73)	–3.44 (1.25)	0.16
Edema	1+	9 (1 9%)	9 (18%)	
on admission	2+	13 (27%)	16 (31%)	0.90
	3+	26 (54%)	26 (51%)	
	nil	16 (33%)	22 (43%)	
Rash	mild	16 (33%)	15 (29%)	0.90
	moderate	13 (27%)	9 (18%)	
	severe	3 (6%)	5 (10%)	
Cough		24 (50%)	34 (67%)	0.14
Clinical Sepsis		4 (8%)	7 (14%)	0.59
Fever >38.0'C		7 (15%)	11 (22%)	0.52
Hematocrit (mean)		31% (7)	30% (10)	0.49
Diarrhea (no of cases)		16 (33%)	19 (37%)	0.84
Mean days of diarrhea before admission		4.2 (3.1)	4.6 (4.0)	0.56
	Severe Anorexia		12 (25%)	14 (27%)
0.96				
	Irritability		40 (83%)	42 (82%)
0.89				
	Skin Ulcers		18 (37%)	19 (37%)
0.86				

See methods section for a definition of "Clinical Sepsis"

Deaths were called *early* in the first five days, *late* if they occurred after at least five days of NRU treatment, and *unexpected* if there was no clinical indication of a lifethreatening complication. Since parents often take seriously ill children home against medical advice, we also reviewed blindly the charts of such children who had received at least seven days treatment to decide if they were likely to have died at home. These children were then added to the late deaths.

Of the 116 children enrolled in the trial, 17 (10 controls and 7 in the experimental group) were excluded because they absconded before completing the seven days of K' supplement or placebo, leaving a total of 99 children in the study. Table 1 shows that no significant differences between the randomized groups were detected on entry into the study.

TABLE 2: CLINICAL OUTCOMES OF EXPERIMENTAL AND CONTROL GROUPS

Clinical Parameter	Experimental[a] Group (n = 37)	Control[b] Group[b] (n = 41)	p-value
Late Deaths (after day 5)[b]	3 (8%)	13 (32%)	0.02*
Left Hospital before Discharge (after day 7)	3 (8%)	8 (19.5%)	0.15
Clinical Sepsis (days 2-7)	0	9 (22%)	0.01*
Clinical sepsis (days 8-24)	3 (9%)	9 (22%)	0.05*
New skin ulcers (no. cases)	4 (11%)	13 (33%)	0.05*
% Weight loss by day 7	5.6 (±8.0)%	4.0 (±7.2)%	0.36
% Weight loss by discharge	4.9 (±9.1)%	3.8 (±10.3)%	0.61
Cough (days)	2.3 (±2.6)	3.9 (±2.7)	0.01*
Dyspnea (no. of cases)	1 (3%)	10 (24.4%)	0.01*
Hospital stay (days)	11.6 (±0.9)	13.2 (±4.9)	0.21
Irritability (days)	3.4 (±1.7)	3.7 (±2.1)	0.47
Diarrhea (days)	0.9 (±2.5)	1.5 (±1.7)	0.14
Edema 2+ or 3+ (days)	2.7 (±2.2)	2.7 (±2.1)	0.99

*Statistically significant differences

[a]Excludes 21 early deaths (11 experimental group, 10 controls)

[b]Includes 3 controls who left hospital to die at home

Ethical Considerations

The K' treatment doses for both cases and controls were within the ranges of those recommended for severe malnutrition in the scientific literature (see discussion below). Informed verbal consent, appropriate to the literacy of mothers or guardians, was obtained on admission to the study, in particular it was made clear that their participation in the trial was optional. The study was approved by the Health Sciences Research Committee of Malawi.

Results

There were 34 known deaths in hospital during the study (34% case fatality), of which 21 were early and 13 were late deaths (after day 5). Death occurred in the first 48 hours in 12 children (6 in each group) and from days 3-5 in 9 children (5 experimental and 4 controls), whereas 10 of the 13 late deaths were in the control group. We assessed the causes (and number) of late deaths as: sepsis (3), anaemia (2), and unexpected (5) in the control group, and sepsis (3) for the experimental group. The unexpected deaths had persisting diarrhoea, and died between days 9-13. Thus, there were a total of 14 deaths (29.2%) in hospital in the experimental group and 20 deaths (39.2%) in controls (pvalue = 0.40), which is not a statistically significant difference.

In addition to deaths in hospital, 11 children (3 experimental and 8 controls) were taken from hospital before discharge after completing the seven day trial, but before reso-

lution of edema and clinical improvement. Three of these children (all controls) were assessed blindly to have been seriously ill and unlikely to have survived at home. Adding these to the late deaths gives 13/41 (31.7%) in controls compared to 3/37 (8.1%) in the experimental group (odds ratio=5.3, CI=1.2-31.0, p-value=0.02). Thus, only late deaths were significantly different between the experimental and control groups, if children taken home to die are counted as deaths. The validity of this late mortality result is of course weakened by it having been an unexpected finding, rather than a research hypothesis.

Sudden unexpected death is not uncommon in severe malnutrition and may be related either to a cardiac arrhythmia or unrecognised sepsis

Table II compares the clinical outcomes of the 37 children in the experimental group and 41 controls who completed the trial, excluding the 21 early deaths. Cases had significantly less coughing, dyspnea, suspected septic episodes, and new skin ulcerations than control children. Although we did not find significant differences for edema, diarrhoea, irritability, and anorexia, they were all less common in the experimental group.

Discussion

K^+ deficiency was first documented in kwashiorkor in 1956 by Hansen[8] in Cape Town as an increase in the ration of K^+ to nitrogen retention during the initial recovery phase. His group also confirmed the lower mean TBK[+] in kwashiorkor (31 mmol/kg) than marasmus (39 mmol/kg), with both rising to 45 mmol/kg on recovery[9]. Using a K body counter, Garrow[10] documented a mean 43% reduction in brain K content compared to the recovery level, which undoubtedly contributes to the pronounced apathy and misery in kwashiorkor.

From balance studies, Nicholas et al [11,12] determined a K^+ requirement (range) on admission of 7.0 (4-9) mmol/kg/day rising only slightly to 7.7 (5.7-9.7) with rapid growth. From muscle composition studies in kwashiorkor, they concluded that K^+ depletion was due to cell membrane leakiness, leading to a reduced capacity to retain K^+ and a rise in intracellular Na^+ and water content. Intracellular accumulation of Na^+ is a potent stimulus of the enzyme Na^+, K^+ATPase, which shows a two-fold increase in activity in kwashiorkor, returning to normal after 4-6 weeks of nutritional rehabilitation. The overactive Na^+ pump in kwashiorkor represents an attempt by cells to maintain normal cation gradients in the face of membrane damage. Although this overactive pump may be an immediate response to a threat to the cell's survival, it consumes a large fraction of the available energy supply.

With progression to death, there is an even greater shift of water and Na^+ into cells. Patrick[13] not only documented the increased Na^+ pump activity in kwashiorkor, but was able to predict which children were susceptible to sudden death from cardiac failure. This usually occurred about the time of introduction of high-energy feeds (6-15 days after admission) and responded to diuretics.

Although dose recommendations vary, the present consensus favours a K+ supplement of 4 mmol/kg/day[1,2] Any discussion of K^+ dose in the treatment of severe malnutrition needs to stipulate whether it is: (1) for the initial vs the rapid growth phase, (2) a supplement vs a total intake, and (3) for marasmus vs kwashiorkor. In view of the vastly different K^+ content of the diets used to treat different phases of severe malnutrition, it is crucial to distinguish between supplement and total intake of K^+.

There are regional differences in the prevalence of K^+ depletion in kwashiorkor, which may be related to the mineral content of weaning diets.[14,15] A staple diet of beans and bananas, for example, is richer in K^+ than a maize or sweet potato diet, whereas cassava and rice contain even less K+. Although maize contains 12.6 mmol/l in thick porridge, there is only about 4 mmol/l in thin porridge, which may mean as little as 0.6 mmol/kg/day of K^+ for weaned children on porridge only. Considerable additional losses of K^+ can occur in stool with diarrhoea which was present on admission at our NRU (n=745) in 52% of cases of kwashiorkor and occurred for a geometric mean of 41% of hospital days in the 89% of cases who had some diarrhoea in hospital.

In doing this study, we were seeking to reduce mortality by feasible changes in management. Our case-fatality is not that unusual for Africa, where recently published rates in hospitals vary from 13–49%, with the highest rates from regions where kwashiorkor predominates and child mortality rates are also high[16-20] Epidemiologists, of course, stress the limitations of hospital case-fatality rates because of biases of access, referral and publication as well as variations in severity of cases between sites (case-mix). From our paediatric experience in other African, Pacific and Caribbean countries, it is clear that the spectrum of malnutrition in Malawian children is severe.

Children with severe kwashiorkor are prone to cardiac failure and sepsis during recovery. Many studies have documented a reduction in cardiac output in kwashiorkor and inability to handle increased fluid loads during recovery.[21-24] Sudden unexpected death is not uncommon in severe malnutrition and may be related to either a cardiac arrhythmia[25] or unrecognized sepsis.

We conducted a clinical trial at a busy urban referral NRU with a high case-fatality rate. There are advantages to research

Our results suggest that the higher potassium dose in the initial week reduced case-fatality

of this kind being done in this setting, since so much nutritional research fails to reflect the realities of clinical care of malnourished children in developing countries. There are also drawbacks. Due to health manpower constraints, mothers provided most of the child-care and feeding. Although the feeds were prepared carefully and the mothers encouraged to follow prescribed regimes, dietary intakes were not monitored. Nasogastric tube-feeding was used infrequently due to resistance f rom mothers. Consequently, anorexic children (in both the experimental and control groups) may have received less than the prescribed baseline K+ supplement (4.7 mmol/kg/day) in phase 1 milk due to reduced intake, although the experimental group did receive the full

3 mmol/kg/day supplement as a medication. Furthermore, our diagnoses were largely clinical, since we could not rely on bacteriology and biochemistry analyses. This adds an element of uncertainty to the study from a scientific standpoint.

Nevertheless, we found important clinical benefits of a higher K^+ intake in the early treatment of Malawian children with kwashiorkor in a region where kwashiorkor is common, where weaning foods have a low K^+ content and where intensive care of kwashiorkor is not feasible. Since most deaths in severe malnutrition are related to sepsis or cardiac failure, we need to try to explain how late deaths were prevented in this study by extra K^+. Perhaps the extra K^+ accelerated intracellular K^+ repletion in the lag phase, including in cardiac smooth muscle and immune cells. The earlier recovery in myocardial and immune function may have better enabled experimental group to cope with the physiological stresses to fluid shifts, anaemia, persisting diarrhoea and sepsis during recovery.

Our results suggest that the higher K^+ dose in the initial week of rehabilitation reduced the case-fatality from 39% to 29%, with the mortality impact delayed to the second week of treatment. We believe that our results as a whole justify putting pressure on donor agencies, nutrition programs and child health services to ensure adequate provision of K^+ supplements to provide a total K^+ intake of 8 mmol/kg/day in the early treatment of kwashiorkor.

References

1. Waterlow JC. Protein-Energy Malnutrition. London: Edward Arnold, 1992; 1-393.
2. Anonymous. The treatment and management of severe proteinenergy malnutrition. Geneva: WHOP 1981; 7-47.
3. Patrick J, Golden M. Leukocyte electrolytes and sodium transport in protein energy malnutrition. Am J. Clin Nutr 1977; 30: 1478-1481.
4. Walker A. A survey of diarrhoeal disease in malnourished aboriginal children. Med J Aust 1972; 1: 904-911.
5. Anonymous. Malawi Demographic and Health Survey, 1992. Zomba, Malawi: National Statistical Office, 1994.
6. Quinn VJ, Chiligo-Mpoma MO, Simler K, Milner J. The growth of Malawian preschool children from different socioeconomic groups. Eur J Clin Nutr 1995; 49: 66-72.
7. Courtwright P, Canner J. The distribution of kwashiorkor in the southern region of Malawi. Ann Trop Paediatr 1995; 15: 221-226.
8. Hansen JDL. Electrolyte and nitrogen metabolism in kwashiorkor. S Afr J Lab Clin Med 1956; 2: 206-231.
9. Mann MD, Bowie MD, Hansen JDL. The total body potassium, potassium retention and potassium intake in protein energy malnutrition. S Afr Med J 1975; 49: 613-615.
10. Garrow JS. Loss of brain potassium in kwashiorkor. Lancet 1967; ii: 643-645.
11. Nichols BL, Alvarado J, Rodriguez J. Therapeutic implications of electrolyte, water and nitrogen losses during recovery from protein-calorie malnutrition. J Pediatr 1974; 84: 759-768.
12. Nichols BL, Alvarado J, Hazlewood CF, Viteri F. Clinical significance of muscle potassium depletion in proteincalorie malnutrition. J Pediatr 1972; 80: 319-330.
13. Patrick J. Death during recovery from severe malnutrition and its possible relationship to sodium pump activity in the leucocyte. Br Med J 1977; 1: 1051-1054.
14. Kingston M. Electrolyte disturbances in Liberian children with kwashiorkor. J Pediatr 1973; 83: 859-866.
15. Vis H, Dubois R, Vanderborght H, De Mayer E. Etudes des troubles electolytiques accompagnant le kwashiorkor marastiques. Rev Franc Etudes Clin Biol 1965; 10: 729-741.
16. Caddell JL, Goddard DR. Studies in protein calorie malnutrition: I chemical evidence of magnesium deficiency, II A double blind clinical trial to assess magnesium therapy. N Engl J Med 1967; 276: 533-540.
17. Erinoso HO, Akinbami FO, Akinyinka 00. Prognostic factors in severely malnourished hospitalized Nigerian children. Anthropometric and biochemical factors. Trop Geogr Med 1993; 45: 290-293.
18. Brasseur D, Hennart P, Dramaix M, et al. Biological risk factors for fatal protein energy malnutrition in hospitalized children in Zaire. J Pediatr Gastroenterol Nutr 1994; 18: 220-224.
19. Gamatie Y, Prual A, Wollor J, Huguet D. Are pediatric wards in developing countries only places to die? A study of prior to hospitalization risk factors of death among 0-2 year old hospitalized children in Niamey, capital of Niger. J Trop Pediatr 1994; 40: 54-57.
20. Shimeles D, Lulseged S. Clinical profile of infection in Ethiopian children with severe protein-energy malnutrition. East Afr Med J 1994; 71: 264-267.
21. Piza J, Troper L, Cespedes R, Miller JH, Berensen GS. Myocardial lesions and heart failure in infantile malnutrition. Am J Trop Med Hyg 1971; 20: 343-355.
22. Smythe PM, Swanpoel A, Campbell JAH. The heart in kwashiorkor. Br Med J 1962; 1: 67-73.
23. Wharton BA, Howells GR, McCance RA. Cardiac failure in kwashiorkor. Lancet 1967; ii: 384-387.
24. Viart P. Hemodynamic findings during treatment of proteincalorie malnutritrion. Am J Clin Nutr 1978; 31: 911-926.
25. Talner NS. Cardiac changes in the malnourished child. In: Suskind RM, Lewinter-Suskind L, eds. The Malnourished Child, NY: Raven, 1990: 229-244.