Effect of Standardized Milk-Based Versus Standardized Non-Milk-Based Formulation on the Biochemical Parameters of Children Aged 6–59 Months with Moderate Acute Malnutrition

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ABSTRACT

Differences in composition of dietary formulations could affect the biochemical parameters of under-fives with moderate acute malnutrition (MAM). To determine the effect of standardized milk-based formulation (SMBF) versus standardized non-milk-based formulation (SNMBF) on the biochemical parameters of under-fives with MAM. Children aged 6-59 months with MAM were randomized to receive either SMBF or SNMBF. Blood samples were obtained at baseline and endline for packed cell volume (PCV), serum protein, serum electrolytes, urea and creatinine estimation. Changes in biochemical parameters were considered statistically significant at p value < 0.05. Seventeen (SMBF group) versus 16 (SNMBF group) children were recruited. Both formulations were associated with a significant increase in the mean serum bicarbonate (p = 0.003 and 0.0001) and PCV (p= 0.021 and 0.012), and a significant reduction in mean serum albumin (p = 0.003 and 0.006) respectively. The endline mean serum potassium and globulin were significantly higher in the SNMBF than the SMBF group (4.71 ± 0.69 vs 4.3 ± 0.20; p = 0.025) and (38.14 ± 9.23 vs 31.45 ± 6.21; p = 0.02) respectively. Serum globulin was significantly higher in the SMBF than the SNMBF group (37.32 ± 5.84 vs 20.1 ± 7.04; p = 0.0001). Both formulations were associated with a significant increase in the mean PCV and serum bicarbonate. The endline mean serum potassium and albumin were higher in the SNMBF than the SMBF group, while the serum globulin was higher in the SMBF group.

Keywords: Under-fives, Biochemical, Milk-based, Non-milk-based, Malnutrition

INTRODUCTION

Moderate acute malnutrition (MAM) is a nutritional deficiency characterized by significant wasting. It is defined as weight for height Z score of < -2 but ≥ -3 or a mid-upper arm circumference of ≥ 11.5 cm to 12.5 cm based on the World Health Organization (WHO) growth standards.1,2 The condition is associated with impaired cognitive, immunologic and metabolic functions.[3] There are also biochemical changes which are mediated by metabolic, hormonal and glucoregulatory mechanisms.[4]

WHO recommends supplementary feeding programme as a strategy for managing MAM. This entails provision of additional meal, usually on programmatic basis, to supplement the child's regular family dietary intake.[5,6] There is presently no consensus on the nutrient composition of formulations used for supplementary feeding of under-fives with MAM. However, energy dense formulations containing adequate amounts of calorie, protein and micronutrients to foster rapid recovery and catch-up growth are recommended.[7-9]

The formulation for managing MAM in childhood could be commercially or locally prepared. Animal-based proteins, plant-based proteins or a combination of both have been used in preparing formulations for supplementary feeding of under-fives with MAM. Animal and

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plant-based proteins can support growth and recovery of under-five children with MAM. However, the difference in their amino acid compositions could influence the anabolic effect of the proteins, their metabolism and biochemical changes.

Supplementary feeding programmes can modify the biochemical parameters of children with MAM, which in turn could impact on their homeostatic and immunologic mechanisms. Available studies on supplementary feeding programmes in under-fives with MAM have focused on the effect of the formulations on recovery from the disorder.[10,11] Studies assessing the effect of the formulations on biochemical changes in children with MAM are lacking. Understanding these changes and their possible effect on the children are crucial considering the high contribution of MAM to the global under-five morbidity and mortality.

There is presently no data on biochemical changes in under-fives with MAM managed with nutritional formulations containing plant-based or animal-based protein. Commercially prepared standardized milk-based formulation (SMBF) containing milk (animal protein source) and standardized non-milk-based formulation (SNMBF) containing soybeans (plant protein source) were evaluated in the management of under-fives with MAM. The objective of the study was to determine the effect of the formulations on the biochemical parameters of the children.

MATERIALS AND METHODS

Study Area

The study was conducted in Uruan and Ibiono Ibom Local Government Areas (LGAs) of Akwa Ibom State. The state is located in the costal part of southern Nigeria. The inhabitants of this rich coastal region are predominantly Christians with farming, fishing, trading and public service as their main pre-occupation. *Ibibio* is the language commonly spoken in the study area.

Study setting

The study settings were Primary Health Centre (PHC), Adadiah in Uruan LGA and PHC, Okopedi Use in Ibiono Ibom LGA. The facilities had adequate complementary staff. About 20 to 30 children are seen in the facility monthly. Children with MAM and mild childhood illnesses are cared for on outpatient basis while those with severe acute malnutrition or comorbidities are referred to the University of Uyo Teaching Hospital (UUTH).

Study design

This was a comparative analysis of biochemical parameters in under-fives with MAM on SMBF and SNMBF. Participants were primarily enrolled in a clinical trial that evaluated the effectiveness and tolerability of both interventions.[12]

Sample Size Calculation

The sample size required to evaluate the effectiveness of the formulations was calculated based on non-inferiority of the SMBF versus SNMBF. Using 80% certainty that the lower limit of a 95% two-sided confidence interval will be above the non-inferiority limit of -0.3 assuming a standard deviation of 0.55 units gave a sample size of 48 children per group.[13] The minimum sample size was increased to 53 children per group to allow for 10% attrition of the participants. The biochemical parameters could not be evaluated in all the children enrolled in the study due to financial constraint. Thus, the evaluation of biochemical parameters was confined to 25% of children in each group resulting in 14 children per group.

Study Population

Children aged 6 to 59 months with MAM residing in the selected LGAs were screened for eligibility into the study. The case definition of MAM was based on weight-for-height/length of between -2 and -3 Z scores or mid upper arm circumference of 11.5 cm to 12.5 cm in the absence of oedema.[1,2]

ELIGIBILITY CRITERIA

Inclusion Criteria

1. Children aged 6 – 59 months with MAM.
2. Children whose parents/guardian consented to their participation.

Exclusion Criteria

1. Children with chronic illnesses that may affect growth (cardiac disease, chronic renal disease, tuberculosis, chronic liver disease, HIV/AIDS)
2. Children with feeding difficulties like gastroesophageal reflux disease, cleft palate and cerebral palsy.
3. Children below 6 month or greater than 59 months of age

Randomization Process

Each selected LGA was taken as a unit of randomization. The randomization was done by balloting technique and the process was implemented by a member of the research team. This was followed by consecutive enrollment of eligible children in the selected LGAs. Children enrolled in Uruan LGA received SMBF while those enrolled in Ibiono Ibom LGA received SNMBF.

Assessment of Participants

The basic demographic and clinical information of the children were obtained from their caregivers using a structured questionnaire. Information obtained included age, sex, socio-economic status of caregivers and nutritional history.

Anthropometric measurements were taken by trained research assistants using standard techniques. The weight of children aged 24-59 months was measured directly using the digital Seca bathroom weighing scale. The weight of children aged 6 – 24 months was determined indirectly by first getting the combined weight of the child and caregiver after which the weight of the caregiver was subtracted from the combined weight.

The height of children aged 25-59 months was measured with a stadiometer while the length of those aged 6 – 24 months was measured using an infantometer. The MUAC was measured at the mid-point of the left arm between the acromion and olecranion process using the Shakir's strip.

Laboratory Evaluation

HIV test was done using rapid diagnostic technique (RDT). Blood samples were obtained at baseline line for Packed Cell Volume (PCV), plasma protein, serum, electrolytes, urea, and creatinine (E, U & Cr) estimation. Venous blood was used for all the laboratory evaluations. Blood samples were obtained by aseptic procedure using standard techniques. A total of 3.5 mls of blood was collected in the lithium heparinized bottle for Serum E, U & Cr, albumin and globulin analysis. The processing and analysis of blood samples for haematocrit estimation was performed at the Paediatric side laboratory while the others were done at the Chemical Pathology Laboratory of the UUTH.

The Ion selective electrode (ISE) machine with serial number of SFRI 6000 FRANCE and manufactured by Bioevopeak Co. Ltd in China was used for analysis of plasma K, Na, $HC0_3$, and Cl. The modified Jaffe's kinetic and urease methodology using the UV-1200 UV-VIS Spectrophotometer Double Beam machine (made in China) was deployed for analysis of plasma creatinine and urea respectively. The Biuret methodology using the same spectrophotometer machine was used for estimation of plasma proteins including albumin and globulin.

The blood samples for PCV estimation were centrifuged at 5,000 rotation per minute for 5 minutes and read using haemocrit chamber reader. The biochemical parameters were obtained at the beginning of the study (baseline) and at the end (endline).

Study Procedure

The children were treated with anti-helminths following enrolment to prevent the negative impact of helminthiasis on nutrient absorption and growth. The parents/caregivers were required to bring their children/wards to the health facilities on biweekly basis for

evaluation and collection of rations of the feed. Nutrition counselling with food demonstration were carried out by the research team and the caregivers' given opportunity for hands-on exercise.

Interventional Products

The SMBF was provided in 50g sachet while the SNMBF was provided in 400g tin. The composition of the formulations was similar in carbohydrate, protein, and fat content but the SMBF contained a higher amount of sodium, calcium, and linoleic acid than the SNMBF (See appendix 1).

The batch number, manufacturing and expiry dates of the formulations were verified before being used. The formulations were stored in cupboards at a temperature range of 20^{o} C to 30^{o} C and a relative humidity of 40% to 60%.

Administration of Investigational Products

The children enrolled in Primary Health Centre (PHC) Adadiah in Uruan LGA received the SMBF while those enrolled in PHC Okopedi Use in Ibiono Ibom LGA received the SNMBF.

The children were brought to the health facilities on biweekly basis to receive their allocation of the formulation. Each child was given an allocation that provided 50% of his/her daily caloric requirement. This was calculated based on age range and weight band of the children. Children aged 6-24 months had 100kcal/kg/day while those aged 24-59 months received 90kcal/kg/day. Children aged 6-23 months were fed twice daily with the formulations in addition to being breast fed while those 24-59 months were fed thrice daily. The caregivers were encouraged to provide the additional 50% of the daily caloric requirements of the children using home diets. formulations were administered to the children daily for a period of four months.

Follow-up of Participants

The research team visited the selected health facilities on alternate week for follow-up of the participants. During the visits, a full clinical assessment of the children was performed and blood samples for haematocrit estimation, serum protein, serum E, U, Cr were taken at the last follow up visit for estimation of the endline biochemical parameters.

Ethical Issues

Ethical clearance was obtained from the University of Uyo Teaching Hospital, Uyo Institutional Health Research Ethics Committee. Parental consent was obtained either in writing or by thumb-printing. For caregivers that did not understand English Language, the nature of the study was explained to them in their local dialects before requesting for consent from them. The confidentiality of the participants was preserved by keeping the patients' case records under lock in a cupboard.

Data Management and Analysis

Data generated were entered into Microsoft Excel for analysis. Weight-for-height (WHZ) z-scores was calculated based on National Center for Disease Statistics, 2000 growth curves. The patient's characteristics were presented using descriptive statistics (mean). Normally distributed continuous variables were reported as means and standard deviations. Relationships of continuous variables were compared using the Independent Student's t-test. Statistical tests were deemed significant if p-value was < 0.05.

RESULTS

A total of 33 children were evaluated. Seventeen were enrolled in the standardized milk-based formulation (SMBF) group and 16 in the standardized non-milk-based formulation (SNMBF) group. Sixteen of them (48.5%) were males while 17 (51.5%) were females. The clinical characteristics of children in both groups were comparable at baseline as shown in Table 1.

The baseline values of the mean serum creatinine and total serum protein of the children in both groups were skewed and were excluded from subsequent analysis were comparable as

displayed in Table 2 below.

There was a statistically significant reduction in the mean serum potassium and albumin at end line when compared to the baseline values among children enrolled in the SMBF group (p = 0.003; 0.003 respectively) on one hand and a significant increase in the mean serum bicarbonate, serum globulin and PCV (p = 0.003; 0.031; 0.021) on the other hand as represented in Table 3.

Appendix 1

Comparison of nutrient composition of the different formulations

	Cereal-based formulation (Standardized milk-based formulation)		Soya-Cereal based formulation (Standardized non-milk-based formulation)	
Average Nutrient Composition (unit)	Per meal (50g=200ml)	% RDA	Per meal (50g=200ml)	% RDA
Energy (Kcal)	205	29	199	29
Fat (gm)	5	17	4.5	15
Linoleic acid (gm)	0.75	16	1.7	37
Protein (gm)	7.5	68	7.5	68
Carbohydrate (gm)	32.5	34	32.1	34
Dietary fibre (mg)	2.15	43	3.5	70
Vit. A (IU)	650	130	750	150
Vit. D (IU)	100	50	100	50
Vit. E (IU)	3.4	68	3.4	68
Vit. C (mg)	25	50	25	50
Vit. B1 (mg)	0.3	100	0.4	133
Vit. B2 (mg)	0.37	94		
Niacin (mg)	1.5	38	2.0	50
Vit. B6 (mg)	0.5	50	0.15	50
Folic Acid (µg)	20	25	40.0	50
Vit. B12 (µg)	0.55	110	0.4	80
Calcium (mg)	300	111	195	72
Sodium (mg)	72.5	36	105	53
Iron (mg)	3.8	35	5.0	45
Zinc (mg)	3.0	100	3.0	100

Table 1: Baseline anthropometric characteristics of study participants

Characteristics of participants	SMBF	SNMBF	p-value
Mean age (months)	17.48 ±11.17	21.69±14.46	0.354
Mean weight (Kg)	7.82±2.08	8.15±1.99	0.645
Mean height/length (cm)	76.77 ± 10.0	76.78 ± 9.81	0.998
Weight for height/length (SD)	-1.9 ± 0.42	-1.78±0.46	0.439
Mean mid upper arm circumference (cm)	12.30±1.18	12.26±0.74	0.909

There was a statistically significant increase in the mean serum bicarbonate and PCV at endline when compared to baseline among children enrolled in the SNMBF group (p = 0.0001; 0.012) on one hand and a significant reduction in mean serum albumin

(p = 0.006) on the other hand as shown in Table 4.

The endline mean serum potassium and albumin were significantly higher in the SNMBF group than the SMBF group (p value = 0.025 and 0.02 respectively) while the endline mean serum globulin was significantly higher in the SMBF group than the SNMBF group (p value = 0.0001) as seen in Table 5.

Table 2: Baseline laboratory parameters of participants

Laboratory parameters of participants	SMBF	SNMBF	P – value
Mean PCV (%)	32.31 ± 5.96	29.57 ± 4.43	0.146
Mean serum Sodium	140.54 ± 3.69	140.57 ± 2.64	0.979
Mean serum Potassium	4.81 ± 0.35	4.59 ± 0.38	0.093
Mean serum bicarbonate	20.77 ± 2.42	19.71 ± 1.80	0.166
Mean serum Chloride	103.15 ± 3.60	101.14 ± 1.86	0.055
Mean serum Urea	2.32 ± 0.71	2.14 ± 0.59	0.436
Mean serum Creatinine	49.56 ± 10.42	40.43 ± 7.25	0.007*
Mean total serum protein	70.67 ± 9.90	79.29 ± 7.65	0.009*
Mean serum albumin	41.15 ± 10.53	47.86 ± 9.53	0.065
Mean serum globulin	29.62 ± 12.36	31.43 ± 9.33	0.640

Table 3: Change in the biochemical parameters in participants in the SMBF group

Milk based formulation (mean)	Baseline	Endpoint	Change	P value
Serum Sodium (µmol/l)	140.54 ± 3.69	141.85 ± 1.72	1.31	0.206
Serum Potassium (µmol/l)	4.81 ± (0.35	4.30 ± 0.20	0.51	0.003
Serum Bicarbonate (µmol/l)	20.77 ± 2.42	23.15 ± 1.82	2.38	0.003
Serum Urea (µmol/l)	2.32 ± 0.71	2.48 ± 1.23	0.15	0.648
Serum Chloride (µmol/l)	103.15 ± 3.60	103.54 ± 1.71	0.38	0.697
Serum Albumin	41.15 ± 10.53	31.45 ± 6.21	9.70	0.003
Serum Globulin	29.62 ± 12.36	37.32 ± 5.84	7.71	0.031
PCV	32.31 ± 5.96	34.92 ± 4.32	2.61	0.021

Table 4: Change in biochemical parameters of participants in the SNMBF group

Non Milk based formulation (mean)	Baseline	Endpoint	Change	P value
Serum Sodium (µmol/dl)	140.57 ± 2.64	144.29 ± 7.61	3.71	0.067
Serum Potassium (µmol/dl)	4.58 ± 0.38	4.71 ± 0.69	0.13	0.504
Serum Bicarbonate (µmol/dl)	19.71 ± 1.80	22.71 ± 0.95	3.0	0.0001
Serum Urea (µmol/dl)	2.14 ± 0.59	2.47 ± 1.22	0.33	0.326
Serum Chloride (µmol/dl)	101.14 ± 1.86	104.86 ± 7.71	3.71	0.063
Serum Albumin (mg/dl)	47.86 ± 9.53	38.14 ± 9.23	9.71	0.006
Serum Globulin (mg/dl)	31.42 ± 9.32	26.21 ± 9.63	10.43	0.124
P C V (%)	29.57 ± 4.43	33.14 ± 3.13	3.56	0.012

Table 5: Laboratory parameters of SMBF versus SNMBF

Biochemical parameters of participants (mean)	**SMBF**	**SNMBF**	**P value**
PCV (%)	34.92 ± 4.32	33.14 ± 3.13	0.187
Serum sodium (µmol/l)	141.85 ± 1.72	144.29 ± 7.61	0.207
Serum Potassium (µmol/l)	4.3 ± 0.20	4.71 ± 0.69	0.025
Serum bicarbonate (µmol/l)	23.15 ± 1.82	22.71 ± 0.95	0.395
Serum Chloride (µmol/l)	103.54 ± 1.71	104.86 ± 7.71	0.496
Serum Urea (µmol/l)	2.48 ± 1.23	2.47 ± 1.22	0.982
Serum albumin (g/dl)	31.45 ± 6.21	38.14 ± 9.23	0.02
Serum globulin (g/dl)	37.32 ± 5.84	± 7.04	0.0001

DISCUSSION

The use of standardized milk-based formulation (SMBF) for supplementary feeding of underfives with moderate acute malnutrition (MAM) was associated with a significant rise in the mean value of the packed cell volume (PCV), serum bicarbonate and serum globulin while those enrolled in the standardized non-milk-based formulations (SNMBF) group had a significant rise in mean PCV and serum bicarbonate as observed in the SMBF group.

The significant improvement in the mean PCV value of the children in both groups is quite important as anaemia is a recognized complication of childhood malnutrition and a risk factor for mortality in this category of children.[14,15] This improvement can be attributed to the mineral content of the formulations. The SMBF and SNMBF have similar amounts of protein, vitamin B and Vitamin C though the iron and folate contents were relatively lower in the SMBF compared to the SNMBF. These micronutrients which are important for haemapoiesis are likely to have contributed to the improved mean PCV observed in both groups. Thus, effective dietary therapy for managing under-fives with MAM should potentiate reticulocyte response and increase erythroid activities as observed with both formulations. However, the children should be regularly assessed for overt and covert bacterial infections which if present should be promptly treated with effective antibiotic as iron-containing formulations could worsen untreated bacterial infections in this category of children.[16]

Serum protein is an important biochemical parameter used in the assessment of nutritional status of children.[17] The estimate is generally low in children with malnutrition and increases with albumin regeneration during treatment.[15] The observed reduction in the mean serum albumin at endline when compared to

baseline values in both groups was unexpected. As expected, there was a significant improvement in the mean serum globulin among those treated with the SMBF. One of the indices for assessing effective rehabilitation of malnourished under-fives is improvement in their total serum protein, serum albumin and serum globulin. Increase in serum protein is associated with tissue accretion, body composition and overall growth and development of the child.[18] This paradoxical finding was not envisaged and the reasons for it could not be elucidated from the available data. Further studies are therefore needed to determine the reasons for the low post-intervention serum albumin observed in this study.

The reduction in the mean serum albumin in the SMBF group was associated with an increase in the mean serum globulin giving rise to an inversion of the albumin/globulin ratio as against the SNMBF group wherein the serum albumin/globulin ratio was maintained. The inversion in the serum albumin/globulin ratio observed at the endline among those treated with the SMBF group was unexpected as most studies have reported superiority of the animal-based formulations over the plant-based diets for serum albumin generation in children with malnutrition.[19,20] Where an inversion of the albumin/globulin ratio existed at baseline, a milk-based formulation used over a period of four months as in this study, was expected to normalize the ratio. It is quite puzzling that the baseline albumin/globulin ratio was normal while the post-intervention ratio was not. This situation requires further investigations to determine the reasons for the relatively low synthesis of albumin compared to globulin in the children.

A great deal of caution is needed in the interpretation of the serum hypoalbuminaemia noted in this study. This is because the serum albumin level in malnourished children is not only determined by the dietary intake but also by the protein synthesis ability of the liver, the state of hydration of the child and the presence of concomitant infection.[21] Malnourished children usually have a number of co-infections which could be covert or overt. The co-infections are usually associated with serum hypoabuminaemia which is a negative acute phase reactant in this situation. [17] Thus, the low serum albumin noted at the end of the study among the participants could probably be indicative of subclinical infection in them.

Head-to-head comparison of the changes in biochemical parameters of the participants in both groups at end of the study showed a significantly high mean serum potassium and albumin in the SNMBF group when compared to the SMBF group. The observed level of serum potassium and albumin in the SNMBF group were within the acceptable normal limits and therefore, not likely to have significant clinical implications. The mean serum globulin was significantly higher in the SMBF group than the SNMBF group. The use of the formulations generally improved the electrolyte profile of the children but were associated with a reduction in the mean serum albumin.

Comparison of the findings of this study with others in relation to change in biochemical parameters of the participants could not be done as this is the first study to evaluate the changes in biochemical parameters of underfives with MAM following a supplementary feeding programme. Using a case control study, Gupta *et al*[22] in India and Adegbusi *et al*[23] in Katsina, Nigeria, reported significantly higher levels of total serum protein, albumin and globulin in well-nourished children than malnourished children. There is no randomized clinical trial that has evaluated changes in biochemical parameters in underfives with MAM to compare with our findings. This observation highlights the need for investigators to include changes in biochemical parameters in their outcome measures when evaluating the effect of nutritional interventions in underfives with MAM.

The limited number of participants (25%) evaluated for biochemical parameters, non-screening for new or occult infections

during the follow-up period and the exclusion of total serum protein and serum creatinine from the final analysis were obvious limitations that might have influenced some of the findings of the study.

CONCLUSION

Supplementary feeding of under-fives with MAM using SMBF and SNMBF was associated with a significant increase in the mean PCV and serum bicarbonate values, and a significant reduction in the mean serum albumin. The mean serum potassium and albumin levels of children in the SNMBF group were significantly higher than those in the SMBF group at endline as against the mean serum globulin level which was significantly higher in the SMBF group than the SNMBF group. Both formulations significantly improved the haematocrit and electrolyte profile of the children and so could be used in managing underfives with MAM.

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Conflict of interest

The standardized milk-based formulation and the standardized non-milk-based formulations evaluated in this study were provided by Nestle Nutrition Institute Africa (NNIA). However, NNIA did not influence the conception, design, conduct of the study or the interpretation of the results.

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