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ORIGINAL CONTRIBUTION

Acceptability and efficacy of ready-to-use therapeutic food using soy protein isolate in under-5 children suffering from severe acute malnutrition in Bangladesh: a double-blind randomized non-inferiority trial

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Abstract

Background and objective Globally, around 20 million children suffer from severe acute malnutrition (SAM). Identifying a more economical treatment for those affected has the potential to make treatment more available and improve prognosis for recovery and future health.

Design/methods The double-blind randomized study compared taste acceptability (measured by the eagerness to eat) and efficacy of soy-based RUTF (S-RUTF) with milk-based RUTF (M-RUTF) in 6- to 59-month-old children suffering from SAM (WHZ < −3) at icddr,b, in Bangladesh. These SAM children were enrolled in the study after completion of their stabilization phase of treatment. Tolerance of test-RUTF was also tested during the efficacy trial.

Results The cross-over taste acceptability study, conducted in 36 children, revealed similar results between products and an absence of side effects. The efficacy trial enrolled 260 children (130, each group) with similar baseline characteristics, including mean ± SD age 15.0 ± 8.0 months, WHZ − 3.41 ± 0.40 and mid-upper arm circumference (MUAC) 11.1 ± 0.7 cm. The features at the end of study by RUTF group were (in S-RUTF vs. M-RUTF, respectively): total days from enrollment: 44 ± 34 versus 39 ± 30; weight gain (kg): 0.698 ± 0.438 versus 0.741 ± 0.381 and rate of weight gain (g/kg/d): 3.9 ± 3.2 versus 5.2 ± 4.6; MUAC gain (cm): 0.9 ± 0.7 versus 0.9 ± 0.6; and improvement of WHZ: 1.12 ± 0.82 versus 1.22 ± 0.68 (all data were man ± SD and none were significantly different between the groups). At enrollment and the end of intervention, the body composition [total body water (TBW): 70.3 ± 3.2 vs. 69.9 ± 3.5%, and fat: 11.0 ± 4.0 vs.11.5 ± 4.3% at baseline; and TBW: 65.5 ± 4.1 vs. 65.9 ± 4.6%; and fat: 16.8 ± 5.2 vs. 16.2 ± 5.8% in S-RUTF and M-RUTF group, respectively] was found similar. Moreover, the increment of total TBW, FM, and FFM was also observed similar between the groups.

Conclusions This is the first randomized trial comparing S-RUTF using soy protein isolate with milk-based RUTF including comparison of body composition. S-RUTF was found equally acceptable as of milk-based RUTF without any adverse event. Children receiving S-RUTF showed similar pattern of changes in anthropometric indices, and body composition as of milk-based RUTF. Greater number of SAM children can be managed in the community with comparatively low-cost soy-based RUTF.

Trial registration NCT01634009.

Keywords Soy-based RUTF · Milk-based RUTF · Severe acute malnutrition · Under-5 children · Body composition

Abbreviations

WHZ	Weight-for-length or -height *z*-score
MUAC	Mid-upper arm circumference
NNP	National Nutrition Programme
SAM	Severe acute malnutrition
HAZ	Height-for-age *z*-score
CTC	Community-based therapeutic care
CMAM	Community-based management of acute malnutrition

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RUTF	Ready-to-use therapeutic food
M-RUTF	Milk-based RUTF
Soy-RUTF	Soy-based RUTF

Introduction

Severe acute malnutrition (SAM) defined by weight-for-length or -height *z*-score (WHZ) < −3 or bi-pedal nutritional edema [1] is an important cause of death in children globally. Worldwide, approximately 20 million children suffer from SAM and its prevalence is most common in Asia (https://data.unicef.org/wp-content/uploads/2017/06/JME-2017_brochure_June-25.pdf). In Bangladesh, an estimated 500,000 children (~ 3% of all under-five children) are suffering from SAM [2]. Once properly treated, children suffering from SAM have the potential to grow up to lead a normal life. Even with limited resources, it has been shown to be feasible and sustainable to treat children with SAM by implementing the World Health Organization (WHO) guidelines or with minor modifications. This has been observed through the substantial reductions in case fatality rates have been achieved [3–6].

Since the Community-Based Therapeutic Care (CTC) approach and subsequent community-based management of acute malnutrition (CMAM) were developed [7], the use of ready-to-use therapeutic food (RUTF) for the treatment of children with SAM has gained ground [8–12]. Consequently, huge amounts of RUTF were used particularly in African countries [13]. Studies in Ethiopia [9], Malawi [10] and Senegal [14] show that RUTF given to children with SAM promotes weight gain in classical nutritional rehabilitation center, in home-based treatment and refugee conditions, respectively. RUTFs are energy-dense lipid pastes enriched with vitamins and minerals administered at 175–200 kcal/kg/day for children with SAM, and are equivalent in formulation to Formula 100 (F-100), which is a WHO-recommended product to treat children suffering from SAM [15–17]. However, recent studies have shown that out-patient treatment with RUTF promotes faster recovery than in-patient treatment with F-100 [18]. In addition, RUTF has very low water activity and, as such, can be stored and administered at home with little risk of microbial contamination. It does not require any mixing, diluting or cooking, however, can be eaten directly from the sachet/small packet, and has 18- to 24-month shelf life. The typical composition (ingredient % of weight) of milk-based RUTF (M-RUTF) is whole milk powder 30%; sugar 28%; vegetable oil 15.4%; peanut paste 25%; and mineral vitamin mix 1.6%. The innovation of RUTF has made easier and cheaper the management of SAM children by moving treatment from the hospital to the community. Monetary savings are due to a reduction in the resources associated with hospitalization, a freeing of parents and guardians from the burdensome travel and loss of economic productivity associated with caring for a hospitalized child, and a reduction in the need for more costly therapeutic formula (F-100). Although the CMAM model promises treatment of SAM at a considerably lower cost than inpatient model, the cost of RUTF is still considered as a significant barrier to universal roll-out of SAM treatment and has made CMAM implementation too expensive in many high-need countries.

The single most expensive raw ingredient in RUTF is the source of high-quality protein, milk powder, contributing around 50% of raw ingredient cost or between 30 and 35% of the total cost of the final product. The high cost of milk-based RUTF (M-RUTF) may limit its use in many of the low- and middle-income high-need countries. Alternative RUTF recipe using comparatively lower-cost soy protein isolate (Soy-RUTF) other than whole or skimmed milk powder, if found statistically non-inferior or similar acceptable and effective in treating children with SAM, would have greater implications. Therefore, we conducted a pilot study to compare the taste acceptability (measured by the eagerness to eat by the children) and efficacy (in terms of children's weight gain) of a RUTF made from isolated soy protein (Soy-RUTF) and currently used milk-based (M-RUTF) in 6- to 59-month-old children suffering from SAM. Tolerance of test-RUTF was also tested during the efficacy trial.

Methods

Study design and site Children were recruited from the Dhaka Hospital of the International Centre for Diarrhoeal Diseases Research, Bangladesh (icddr,b) for participation in this randomized double-blind intervention trial. Children admitted in this hospital are from the urban and peri-urban area of Dhaka, mainly from impoverished areas. Subsequent study visits with the enrolled children were conducted at the nutrition follow-up unit (NFU) of this hospital. The code of the assigned RUTF was broken after the analyses were completed.

Eligibility criteria Children (both boys and girls) with SAM defined by WHZ < −3 of WHO—2006 standard, without other medical illness or clinically improved from medical illness, no edema, regaining appetite and aged 6–59 months were included. Additional enrollment criteria were: no signs of concurrent infection; mothers/caregivers agreed to stay in their current address for next four months (for tracking the children); and informed written consent given by the parent or guardian.

Exclusion criteria Children without any fixed address; tuberculosis (according to WHO criteria) or any congenital/

acquired disorder affecting growth, i.e., trisomy-21 or cerebral palsy; children on an exclusion diet for the treatment of persistent diarrhea, and having history of soy, peanut or milk protein allergy.

Treatment groups

1. Milk-based standard RUTF group (M-RUTF) (control)
2. Soy-based RUTF group (Soy-RUTF) (intervention). Soy-RUTF does not contain any milk powder.

The two formulations were adjusted and prepared (Table 1) in compliance with the WHO nutritional requirements for RUTFs. Additionally, the micro- and macronutrient content was equivalent to standard RUTF [9, 19–21]. Due to the micronutrient differences between skimmed milk powder (SMP) and soy protein isolate, adjustments were required in the mineral–vitamin premix used for Soy-RUTF compared to the ones used for SMP. Intervention products were developed by DuPont Nutrition and Health, St. Louis, USA and assigned blinded identification codes.

Pilot study for acceptability testing

The taste acceptability of the RUTFs was compared in SAM children. These SAM children were enrolled in the study after completion of their stabilization phase of treatment. The eagerness of taking/eating (eagerly, not eagerly) the assigned RUTF on the days of following procedures was observed. Mothers were asked about their perception of eagerness. Refusal/resistance by the child at the beginning or during RUTF feeding was used as a 'proxy" indicator of not

Table 1 Nutritional value of and ingredients used for the two types of ready-to-use therapeutic food groups (per 100 g)

	WHO recommendation	Soy-based RUTF (experimental)	Milk-based RUTF (control)
Energy (kcal)	520–550	548	545
Protein (g)	Not available	14.5	15.1
Protein/energy ratio (%)	10–12	11	11
Total fat (g)	Not available	34.1	33.4
Fat/Energy ratio (%)	40–60	56	55
Carbohydrate (g)	Not available	45.6	46.0
Moisture (%)	≤2.5	1.1	1.2
Ash (%)	–	4.5	4.3
Sodium (mg)	290 (max)	94	197
Potassium (mg)	1100–1400	1460	1440
Calcium (mg)	300–600	463	492
Phosphorus (mg)	300–600	463	492
Magnesium (mg)	80–140	124	133
Iron (mg)	10–14	11.4	11.9
Zinc (mg)	11–14	11.8	12.9
Copper (mg)	1.4–1.8	1.6	1.6
Selenium (µg)	20–40	21	32
Iodine (µg)	70–140	98	179
Vit A (mg)	0.8–1.1	1.0	1.0
Vit D (µg)	15–20	17.8	16.6
Vit E (mg)	20 (min)	26.7	26.6
Vit K (µg)	15–30	37.4	59.5
Vit C (mg)	50 (min)	55.4	51.4
Vit B1 (Thiamine) (mg)	0.5 (min)	0.6	0.7
Vit B2 (Riboflvin) (mg)	1.6 (min)	1.4	1.6
Vit B6 (mg)	0.6 (min)	0.8	1.2
Vit B12 (µg)	1.6 (min)	1.5	2.1
Folic acid (µg)	200 (min)	353	288
Niacin (mg)	5 (min)	4.6	6.7
Pantothenic acid (mg)	3 (min)	3.1	3/3
Biotin (µg)	60 (min)	66.6	65.5

eagerly eating. The pilot acceptability study of RUTFs was completed in a double-blind randomized cross-over manner in 36 children with SAM (defined by WHZ < −3), but without any other illness, or on improvement from acute illness in the Nutrition Rehabilitation Unit of the Dhaka Hospital of icddr,b. One type of RUTF was offered randomly as ad lib in a single meal time (total maximum time for eating was 30 min). On the next day at the same meal time, the other RUTF was offered. The children were not allowed to take any other food and breast milk during the previous 2 h of these 2 days' observed RUTF acceptability testing period. The amount of RUTF actually ingested was calculated by subtracting the leftover from the offered amount. A pre-weighed towel and bowl were used to collect vomiting, if any, which was subtracted from the calculated amount. Any possible side effects/adverse events (e.g., rash, urticaria from food allergy or any significant changes in clinical status) were looked for.

Efficacy trial

Sample size calculation For sample size calculation to observe the efficacy of RUTFs, we considered the findings of the study of Sandige et al. [22], where the authors reported a mean ± SD weight gain of 4.8 ± 4.0 g/kg/day with M-RUTF (Plumpy'nut®). We also considered the report of Collins et al. [9], where they found a median weight gain of 3.16 g/kg/day with M-RUTF in similar type of children as we were planning to enroll in this study. With that background, we considered a non-inferiority design and we further assumed that the lower value of the 95% confidence interval (95% CI) of the weight gain in Soy-RUTF group would not touch or be less than 3.16 g/kg/day. Thus, a sample size of 130 children in each of the RUTF group would detect a difference in weight gain, if the lower value of 95% CI is less than 3.16 g/kg/day. Sample size was calculated considering the only primary outcome (rate of weight gain), a 5% type 1 error (95% confidence interval), 80% power, which could accommodate up to 28% attrition.

Subject enrollment and intervention All hospitalized children with SAM received the standardized management [3, 15] during the acute/initial phase of treatment. After completion of the treatment of associated medical complications and fulfilling enrollment criteria, an appetite test with the standard RUTF was performed. According to the child's body weight, RUTF containing ~5 kcal/g was offered (30 g of RUTF for ≤7 kg body weight group, and 45 g of RUTF for ≥7 kg group) and observed if the child eat ≥23 g or ≥30 g, respectively, according to the above-mentioned body weight range within 30 min (reflecting the child passed the appetite test) (http://motherchildnutrition.org/malnutrition-management/info/appetite-test.html). If the child failed, the process was repeated on subsequent day(s). After passing the appetite test, the child was enrolled in the study and subsequent alternate feeds of the child were replaced with randomly assigned RUTF providing the equivalent calorie of that feed and further observed for one day to monitor any possible side effect, e.g., rash, urticaria from food allergy or any significant changes in clinical status. The child was then discharged from the hospital with respective RUTF ration for one week (the ration provided 175–200 kcal/kg/day) with proper instruction, i.e., "RUTF is both food and medicine; offer the daily ration of RUTF in 6–8 divided meals over the day and night; provide sufficient water as per child's need; and other family food may be given if the day's RUTF ration is completely ingested". Breastfeeding was always encouraged.

At the beginning of the study, the importance of bringing the child at the NFU on weekly basis for clinical/nutritional follow-up was explained to the mothers/caregivers. During each follow-up visit at the NFU growth monitoring, health education, clinical check-up and RUTF ration for next week were provided and the research assistant recorded child's morbidity since the previous visit on a pre-coded form. In addition, self-referral was encouraged and entertained at any hour and day for intercurrent illnesses. Inquiries were made to the mothers/caregivers regarding the eagerness of taking/eating of RUTF at each visit. At each visit, the mothers/caregivers were asked to return used RUTF sachets provided to the index child. At the beginning of the study, data were gathered on family socioeconomic status, including standard of housing, family structure and parental characteristics. At baseline and each follow-up visit, the research team recorded the children's nude weight, using a digital scale (Seca, model-345, Hamburg, Germany) with 10 g precision, length (in < 2 years old) or height (in ≥ 2 years old) using a calibrated length board and mid-upper arm circumference with a non-stretch insertion tape to the nearest mm, and triceps skin fold thickness by Harpenden calipers to nearest 0.2 mm. Anthropometrics were done according to the standard procedures [23, 24] and all measurements were taken twice. If variability was observed (> 20 g for weight, > 0.5 cm for length or height, > 2 mm for MUAC, and > 0.2 for SFT), a third measure was collected and the average of the nearest two measures was recorded. All eligible children received RUTF until they have an edema-free WHZ ≥ −2 or for 12 weeks from the time of enrollment, which was earlier. Children not fulfilling the graduation criteria by 12 weeks were medically re-evaluated and received standard treatment from the hospital.

Assessment of body composition For assessing the changes of body composition, guardians of the enrolled children were asked (on voluntary basis) for body composition analysis by a non-invasive standard procedure, i.e., deuterium

oxide (^2H_2O) technique. A subset of the subjects consented and participated in this procedure. Deuterium oxide (^2H_2O) was used for body composition assessment. After collection of baseline saliva sample, 5gm of deuterium-oxide-labeled water was given to the children. Two post-dose saliva samples were collected after 3 and 4 h. Children avoided drinking water during the equilibration period. From each child, 1 ml saliva was collected using a cotton wool swab (by wrapping an extra piece of cotton wool around the swab). The swab was moved gently around the child's mouth until the cotton wool was sodden (5–10 min), then it was squeezed in a syringe to extract saliva and the specimen was preserved in an Eppendorf tube. All specimens labeled with the participant's study number, and date and time of collection were stored at − 20 °C until analysis [25]. This procedure was repeated in same sequence in all study children approximately after 10 weeks of intervention when the children were supposed to be improved from their SAM status (in the nearest follow-up visit). The concentration of deuterium in saliva samples was measured with Fourier Transform Infrared Spectrometer (FTIR) following standard procedure for total body water (TBW) calculation in the St. Jone's Research Institute, India. From measured TBW, we have estimated the amount of fat-free mass (FFM) using following calculation/formula. Body fat mass (FM) is the difference between body weight and FFM [26].

Calculation of body composition

The dilution space of ^2H (VD) is 4.1% higher than TBW due to exchange of H with non-aqueous H in the body.

$$\text{TBW (kg)} = V_D/1.041$$

where V_D (kg)—dose ^2H_2O (mg)/enrichment ^2H in saliva (mg/kg); FFM (kg)—TBW (kg)/hydration coefficient; hydration factor—hydration of FFM (%FFM)/100; FM was calculated by difference between body weight and FFM; FM (kg)—body weight (kg)—FFM (kg); results were often expressed as % body weight; FM (%)—FM (kg)/body weight (kg) × 100.

Data analyses

Between the two RUTF groups, parametric continuous variables were compared by Student's t test and nonparametric data by Mann–Whitney *U* test. Categorical variables were compared by Chi square test and the Fisher's exact test was applied when the expected number in any cell was 5 or less. For pilot acceptability study dataset, intake of RUTF (gm) and calorie, and eagerness to eat during each single meal time were analyzed by paired *t* test and Fisher's exact test as appropriate. A *p* value less than 0.05 was considered as statistically significant.

Role of the funding source

There was no role or influence of the donor in study design; collection, analysis, and interpretation of data; writing the report; and in the decision to submit the paper for publication.

Results

Results on acceptability of products

Total 36 children were participated in the pilot taste acceptability trial. Their mean ± SD age was 23.3 ± 13.0 months and WHZ was—4.96 ± 1.05. Analyses showed that the taste acceptability of both types of RUTF was similar without any side effect (Table 2).

Table 2 Children's description and comparison of the results of pilot acceptability test between the two types of ready-to-use therapeutic food

	Soy-based RUTF $n = 36$	Milk-based RUTF $n = 36$	*p* value*
Absolute amount (g) taken over 30 min (single meal time): mean ± SD	38.8 ± 16.1	40.7 ± 17.4	0.170 (paired *t* test)
Amount (g) taken per kg: mean ± SD	6.4 ± 2.8	6.8 ± 3.4	0.128 (paired *t* test)
Child refused (*n*)	2	1	
Mother disliked (*n*)	1	1	
Significant vomiting (*n*)	0	1	(Same child with mild diarrhea)
Diarrhea	0	1	(Same child with vomiting)
Rash	0	0	
Other side effect	0	0	

*All variables were comparable between the two RUTF groups

Results of efficacy trial

Baseline characteristics of the total 260 children enrolled (130 each in the two types of RUTF) in the study can be found in Table 3. Their mean age was 15.0 months and 37% were female child. The age and sex distribution, anthropometry (WHZ, WAZ, HAZ, BMI-for-age, MUAC, MUAC-for-age, TSF, and TSF-for-age), breastfeeding and complementary feeding status, vaccine status, socioeconomic status, and parental status were found similar between the two RUTF groups on enrollment (Table 3). Figure 1 describes the trial profile. Features by RUTF group at the time when the child achieved WHZ ≥ -2 or last visited before discontinued (those who at last attended two follow-up visits before discontinuation) are described in Table 4. It shows: the number of total follow-up attended, total days from enrollment, body weight, length or height WHZ, WAZ, HAZ, MUAC, gain in body weight, length or height gain, improvement in WHZ and WAZ, changes in HAZ, MUAC gain and rate of weight gain, and all variables were found comparable between the two RUTF groups. The absolute gain in body weight of the children was 0.698 ± 0.438 kg versus 0.741 ± 0.381 ($p = 0.553$); and rate of weight gain was 3.9 ± 3.2 (median: 3.63; 95% confidence interval: 3.29–4.51) versus 5.2 ± 4.6 (median: 4.29; 95% CI: 4.35–6.07) g/kg/d ($p = 0.078$) in Soy-RUTF group and M-RUTF group, respectively. Morbidities (mean days (per child) of diarrheal disease, vomiting or any rash during the prior period of follow-up 2, 4, 6, 8 and 10 were queried/asked for and found similar between the two RUTF groups (Fig. 2).

Table 3 Baseline characteristics of the enrolled children in the two ready-to-use therapeutic food groups

Variable	RUTF group		*p* value*
	Soy-based *n*-130	Milk-based *n* = 130	
Age in month	15.0 ± 7.7	15.0 ± 8.4	0.971†
Enrollment weight (kg)	6.015 ± 1.073	6.018 ± 1.207	0.985
Enrollment length or height (cm)	68.6 ± 6.3	68.5 ± 7.0	0.879
Enrollment weight-for-length or -height *z*-score	−3.42 ± 0.41	−3.39 ± 0.39	0.463
Enrollment weight-for-age *z*-score	−4.22 ± 0.73	−4.21 ± 0.79	0.926
Enrollment length-for-age *z*-score	−3.44 ± 1.36	−3.43 ± 1.36	0.956
Enrollment body-mass-index-for-age *z*-score	−3.24 ± 0.53	−3.26 ± 0.49	0.720
Enrollment mid-upper arm circumference (MUAC) (cm)	11.2 ± 0.7	11.1 ± 0.8	0.584
Enrollment MUAC-for-age *z*-score	−3.38 ± 0.7	−3.43 ± 0.74	0.584
Enrollment Triceps skin fold (cm)	3.53 ± 0.58	3.56 ± 0.62	0.688
Enrollment TSF-for-age *z*-score	−4.09 ± 0.66	−4.07 ± 0.70	0.852
Duration of exclusive breastfeeding (month)	0.8 ± 1.6	1.0 ± 1.9	0.344†
Age (month) when other types of milk was started	3.5 ± 2.0	3.4 ± 2.3	0.481†
Age (month) when other family foods started	6.5 ± 1.1	6.7 ± 1.3	0.179
Mother's/caregiver's age (year)	25.4 ± 7.4	25.4 ± 6.7	0.993
Mother's/caregiver's educational status (in school year)	3.9 ± 3.8	4.3 ± 3.9	0.301†
Mother was the caregiver, *n* (%)	126 (96.6)	122 (93.8)	0.672
Father's educational status (in school year)	5.1 ± 4.2	5.3 ± 4.4	0.785†
Father lives with the family, *n* (%)	119 (91.5)	122 (93.8)	0.733
Total family income/month (taka)	9500 ± 6100	10000 ± 8500	0.505†
Number of 6- to 59-month-old siblings (including he/she)	1.3 ± 0.4	1.3 ± 0.5	0.797
Duration of diarrhea prior to enrollment (day)	3.2 ± 2.3	3.2 ± 2.6	0.402†
If fever was present, days prior to enrollment	1.7 ± 1.5	1.5 ± 1.5	0.457†
Female child, *n* (%)	51 (39.2)	45 (34.6)	0.521
Breastfeeding continuing, *n* (%)	85 (65.4)	89 (69.0)	0.597
BCG given, *n* (%)	128 (98.5)	128 (98.5)	1.000
Age appropriate Polio/Penta vaccination given, *n* (%)	124 (95.4)	127 (97.7)	0.500
Measles vaccine given (if aged > 9 months), *n* (%)	61 (59.8)	71 (71.7)	0.102
Had measles within last 6 months of enrollment	21 (16.2)	21 (16.2)	1.000

Data are mean ± SD if not mentioned otherwise

*All variables were comparable between the two RUTF groups

†Mann–Whitney *U* test

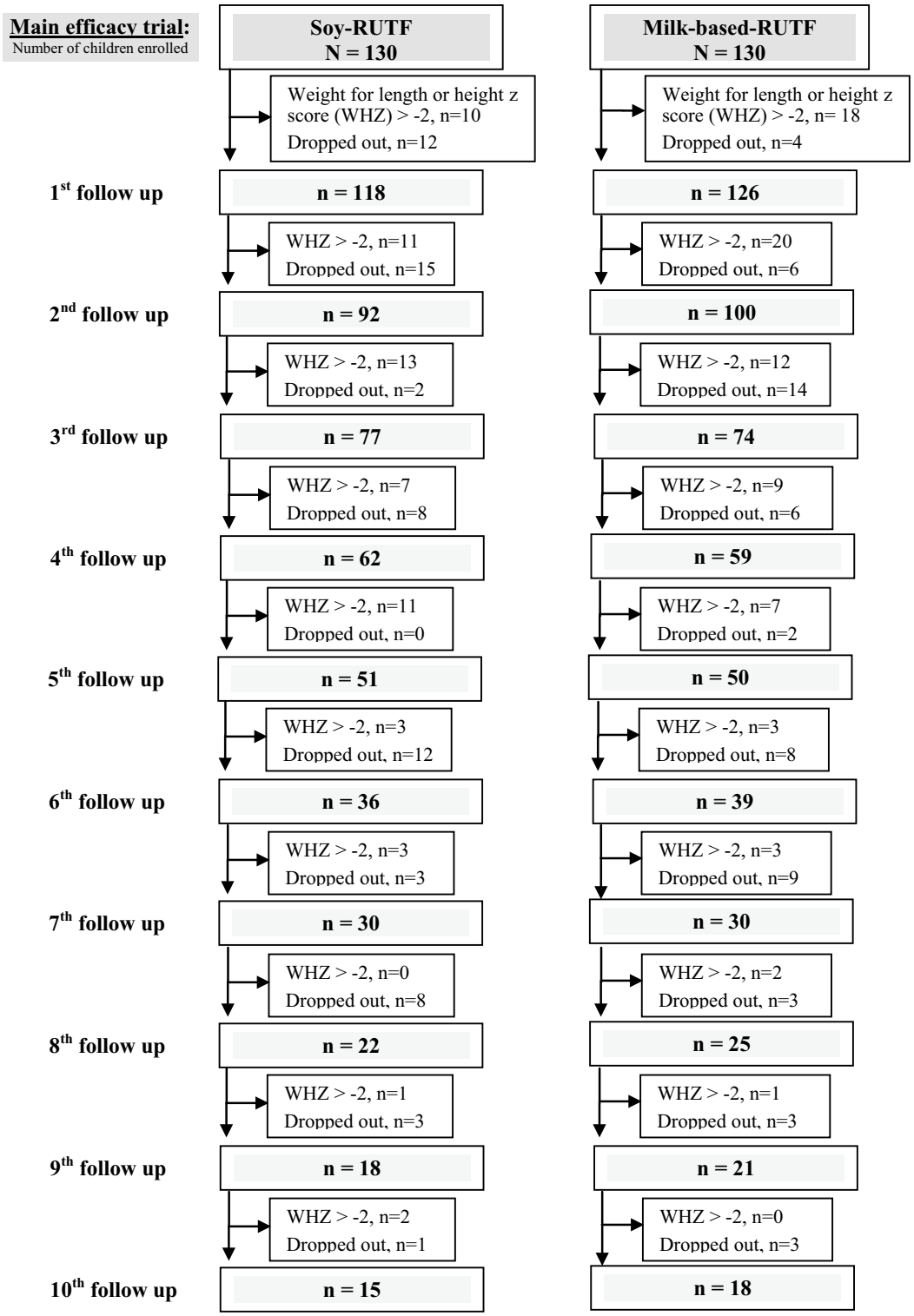


Fig. 1 Study profile

Results on body composition

Saliva sample could be collected from 72 children in Soy-RUTF group and 91 children in M-RUTF group both at enrollment (baseline) and after approximately 10 weeks of intervention. Among them, 54 in Soy-RUTF group and 66 children in M-RUTF group had sufficient saliva for analysis and interpretable results. Their age, sex, anthropometrics,

Table 4 Features and changes in anthropometry by ready-to-use therapeutic food group at the time when the child achieved weight-for-length or -height *z*-score ≥ −2 or until last attended follow-up before discontinuation

	RUTF group		Mean difference	% CI	*p* value*
	Soy-based *n* = 105	Milk-based *n* = 108			
Number of total follow-up (attended)	3.7 ± 2.4	3.4 ± 2.2	0.37	−0.26 to 13.67	0.322†
Total days from enrollment	44 ± 34	39 ± 30	5.05	−3.58 to 13.67	0.371†
Body weight (kg)	6.703 ± 1.260	6.740 ± 1.376	−0.03	−0.39 to 0.32	0.840
Length or height (cm)	69.4 ± 6.7	69.0 ± 7.3	0.35	−1.54 to 2.23	0.717
Weight-for-length or height *z*-score	−2.32 ± 0.84	−2.15 ± 0.78	−0.16	−0.38 to 0.06	0.145
Weight-for-age *z*-score	−3.59 ± 0.90	−3.46 ± 1.25	−0.13	−0.42 to 0.16	0.384
Length- or height-for-age *z*-score	−3.58 ± 1.36	−3.71 ± 1.40	0.13	−0.24 to 0.50	0.485
Mid-upper arm circumference (cm)	12.1 ± 0.9	12.0 ± 1.0	0.04	−0.22 to 0.30	0.744
Body weight gain (kg)	0.698 ± 0.438	0.741 ± 0.381	−0.04	−0.15 to 0.07	0.553†
Length or height gain (cm)	0.8 ± 0.9	0.7 ± 0.9	0.10	−0.15 to 0.34	0.476†
Improvement in weight-for-length or height *z*-score	1.12 ± 0.82	1.22 ± 0.68	−0.10	−0.31 to 0.10	0.333†
Improvement in weight-for-age *z*-score	0.65 ± 0.66	0.76 ± 1.13	−0.11	−0.36 to 0.14	0.404†
Changes in length or height-for-age *z*-score	−0.12 ± 0.63	−0.24 ± 0.82	0.12	−0.07 to 0.32	0.707†
Mid-upper arm circumference gain (cm)	0.9 ± 0.7	0.9 ± 0.6	−0.02	−0.20 to 0.16	0.614†
Weight gain (g/kg/d)	3.9 ± 3.2	5.2 ± 4.6	−1.29	−2.35 to 0.16	0.078†

Data are mean ± SD if not mentioned otherwise

*Over all, there was no significant difference between the RUTF groups

†Mann–Whitney *U* test

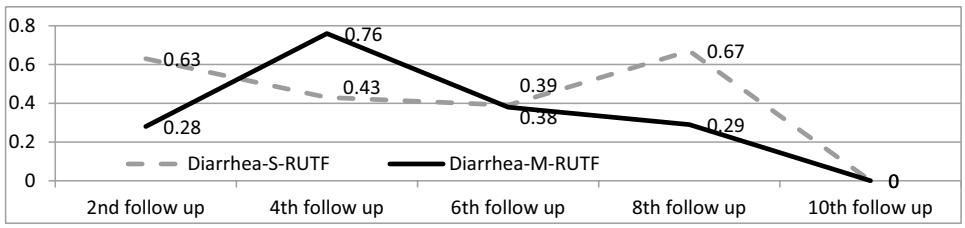
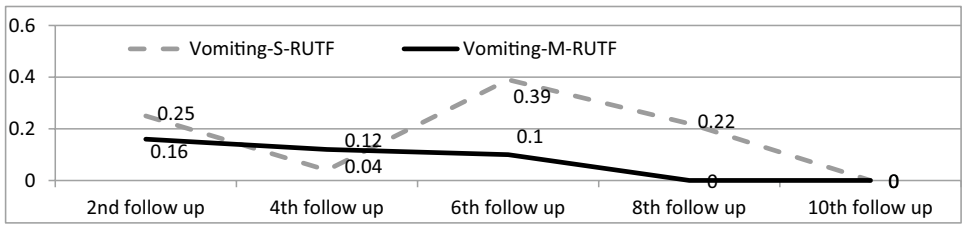
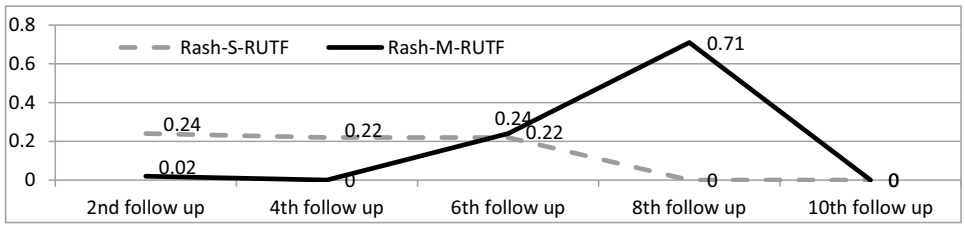


Fig. 2 Morbidities at different follow-up visit by RUTF group

a Mean day of diarrhea/child prior to respective follow up visit
(No significant differences between the groups in any follow up, analyzed by Mann-Whitney U test)



b Mean day of vomiting/child prior to respective follow up visit
(No significant differences between the groups in any follow up, analyzed by Mann-Whitney U test)



c Mean day of rash/child prior to respective follow up visit
(No significant differences between the groups in any follow up, analyzed by Mann-Whitney U test)

breastfeeding and complementary feeding status, and vaccine and socioeconomic status were found similar between the two RUTF groups on enrollment (Table 5). At enrollment and at the end of the study, the body composition was found similar between the groups (mean ± SD total body water at baseline was 70.3 ± 3.2 versus 69.9 ± 3.5% and fat was 11.0 ± 4.0 versus 11.5 ± 4.3%; and at the end of the study, total body water was 65.5 ± 4.1 versus 65.9 ± 4.6% and fat was 16.8 ± 5.2 versus 16.2 ± 5.8% in Soy-RUTF and M-RUTF groups respectively) (Table 6). Moreover, the increment of TBW, FM, and FFM was also observed similar between the groups (Table 6). The absolute increment of weight gain, rate of weight gain, increments in WHZ, MUAC and triceps' skin fold thickness, percentage of children improved from SAM and the morbidities (diarrhea and fever) were observed similar among these children between the groups (supplementary table).

Discussion

Children with SAM need safe, palatable foods with energy, protein, fat, minerals, and vitamins tailored to their needs to recover [27]. A number of studies have shown that milk-based M-RUTF successfully supports recovery in children suffering from SAM [12, 28]. Because M-RUTF is expensive, mainly owing to its milk component, we carried out this study with an alternative milk-free Soy-RUTF using soy protein isolate that has the potential to support local economy and reduce the cost of RUTF. This double-blind randomized trial was conducted in 6- to 59-month-old SAM children in Bangladesh to compare the acceptability and efficacy of a RUTF made from soy protein isolate (S-RUTF) and currently used M-RUTF. The taste acceptability of Soy-RUTF was found similar to M-RUTF without any side effect. The baseline characteristics of the enrolled children both in the acceptability and efficacy trials were similar between the RUTF groups, which were expected and that have strengthened this study. Features at the time when the children achieved WHZ ≥ −2 or discontinued (after attending at least two follow-up visits), the number of total visits, and days past from enrollment, all anthropometric indices, and the changes or improvement in anthropometric indices including the rate of weight gain were found similar between the two RUTF groups. At the beginning of the study, we assumed that we would consider Soy-RUTF as non-inferiority to M-RUTF if the lower value of the 95% confidence interval of the weight gain of the children in Soy-RUTF group would not be equal to or less than 3.16 g/kg/day. And we found that the 95% confidence interval was 3.23–4.5.

Table 5 Baseline characteristics of the children in the two ready-to-use therapeutic food groups, of whom the pre- and post-intervention body composition analysis from saliva sample could be done

Variable	RUTF group		*p* value
	Soy-based *n* = 54	Milk-based *n* = 66	
Enrollment (baseline) age (month)	15.9 ± 7.4	15.4 ± 8.8	0.727*
Female child, *n* (%)	18 (33.3)	23 (34.8)	0.985
Baseline weight (kg)	6.16 ± 1.09	6.16 ± 1.20	0.993
Female children; *n* (%)	18 (33.3)	23 (34.8)	0.985
Baseline length or height (cm)	69.5 ± 6.8	69.1 ± 7.3	0.707
Weight-for-length or height *z*-score at enrollment	−3.45 ± 0.42	−3.33 ± 0.27	0.071
Weight-for-age *z*-score at enrollment	−4.26 ± 0.76	−4.06 ± 0.74	0.163
Length- or height-for-age *z*-score at enrollment	−3.53 ± 1.36	−3.27 ± 1.33	0.298
Body-mass-index (BMI)-for-age *z*-score at enrollment	−3.26 ± 0.52	−3.14 ± 0.42	0.190
Mid-upper arm circumference (MUAC) (cm) at enrollment	11.3 ± 0.7	11.3 ± 0.7	0.684
MUAC-for-age *z*-score at enrollment	−3.35 ± 0.65	−3.22 ± 0.66	0.293
Triceps' skin fold thickness (mm)	34.7 ± 6.1	36.4 ± 6.3	0.130
Breastfeeding continuing; *n* (%)	36 (66.7)	43 (65.2)	0.984
Received BCG vaccine; *n* (%)	32 (59.3)	46 (69.7)	0.317
Received other vaccines (under the government program in Bangladesh); *n* (%)	52 (96.3)	65 (98.5)	0.860
Received measles vaccine (among > 9 months old children); *n* (%)	51 (94.4)	65 (98.5)	0.474
Mothers age (year)	25.6 ± 6.6	24.3 ± 4.1	0.862
Monthly family income (taka) (1US $ = 78 taka)	9000 ± 5800	9100 ± 3400	0.202

Data are mean ± standard deviation, if not mentioned otherwise; over all, there was no significant difference between the RUTF groups

*Mann–Whitney *U* test

Table 6 Body composition at baseline, end of intervention (approximately 10 weeks) and the difference of the children receiving the two types of ready-to-use therapeutic food

Variable	RUTF group		*p* value
	Soy-based *n* = 54	Milk-based *n* = 66	
Baseline total body water (kg)	4.32 ± 0.75	4.28 ± 0.74	0.764
Hydration factor (at enrollment)	0.791 ± 0.004	0.790 ± 0.005	0.484
Baseline fat-free mass (kg)	5.48 ± 0.96	5.42 ± 0.96	0.764
Baseline fat mass in (kg)	0.68 ± 0.29	0.74 ± 0.36	0.359*
Baseline total body water %	70.3 ± 3.2	69.9 ± 3.5	0.503
Baseline fat %	11.0 ± 4.0	11.5 ± 4.3	0.471
Duration in days from pre to post saliva sampling	69.5 ± 3.2	69.2 ± 3.4	0.570
Final total body water (kg)	4.77 ± 0.83	4.86 ± 0.72	0.542
Hydration factor (after intervention)	0.787 ± 0.004	0.787 ± 0.004	0.915
Final fat-free mass (kg)	6.07 ± 1.06	6.18 ± 0.93	0.547
Final fat mass in (kg)	1.24 ± 0.49	1.23 ± 0.57	0.932
Final total body water %	65.5 ± 4.1	65.9 ± 4.6	0.556
Final fat %	16.8 ± 5.2	16.2 ± 5.8	0.573
Increment of total body water (post–pre) (kg)	0.45 ± 0.40	0.58 ± 0.41	0.138*
Median (interquartile range)	0.46 (0.15, 0.74)	0.53 (0.31, 0.90)	
Increment of fat-free mass (post–pre) (kg)	0.59 ± 0.51	0.76 ± 0.52	0.110*
Median (interquartile range)	0.60 (0.20, 0.95)	0.70 (0.41, 1.14)	
Increment of fat mass (post–pre) (kg)	0.56 ± 0.43	0.50 ± 0.52	0.258*
Median (interquartile range)	0.57 (0.30, 0.82)	0.49 (0.07, 0.84)	

Data are mean ± standard deviation, if not mentioned otherwise

*Mann–Whitney *U* test

Moreover, at enrollment and at the end of intervention, the body composition, and the changes or improvement of total TBW, fat mass, and fat-free mass were also observed similar between the groups. The total body fat (TBF) % at the baseline was ranging from 11.0 to 11.5 in the children of both the groups and these values were extremely low. Garrow et al. [29] reported that the TBF % in 10- to 14-month-old male and female children ranged from 19.2 to 22.5%. Fomon et al. [30] reported in details the body composition of 1-month- to 10-year-old children. It shows that in 6- to 24-month-old group for male children, the range of TBF % is 22.5–25.4 and for female children the range is 20.4–26.4%. In our study, we found that the TBF % at the end of the intervention increased to 16.8% and 16.2% in Soy-RUTF and M-RUTF groups, respectively. The improvement of TBF % among our study children was observed in similar pattern in both the groups but still the values were far below the average 20% (approximately) in this age group.

Largely plant-based diets without high-quality protein do not meet the requirements of protein, and need to be improved by processing, fortification, or adding animal source foods [31]. Soy is known to have a favorable amino acid profile and has successfully been substituted for animal products in a variety of other foods, including infant formula [32]. Partially or fully substituting soy in place of milk in RUTF might reduce its cost and/or increase its availability. This notion has led some food producers and nutritionists to advocate inclusion of soy in RUTF and offer alternative formulations of RUTF without or with less milk [33–36].

A previous study found that treating children with SAM with 10% milk added with whole soy flour-RUTF supported a lower rate of recovery compared with the standard M-RUTF containing 25% milk [34]. In that study, kwashiorkor was the predominant form of SAM and those who benefited were children with kwashiorkor, exhibiting an 88% recovery rate when receiving 25% milk RUTF compared with 85% when receiving 10% milk RUTF. However, the recovery rate in wasted/marasmic children did not differ. The results of that study may not be generalized to other populations (like the study population of our study) where severe wasting is the predominate form of malnutrition. Also, the soy used in that study was not dehulled. Soy that is less processed has lower digestibility, and the amino acids are less bio-available for use by the body to support recovery. The anti-nutrients present in less processed soy might have contributed to the lower recovery rate [37, 38]. Additionally, this was a quasi-effectiveness trial and not a strict efficacy trial.

A study [39] in Zambian children could not show any better effectiveness of the first-generation soy-, maize-, and sorghum-based RUTF (SMS-RUTF). A follow-up study conducted with a milk-free refined SMS-RUTF product in the Democratic Republic of Congo showed that SMS-RUTF's efficacy was as good as that of M-RUTF among children aged 24–59 months but not among younger children aged

6–23 months [40]. A very recent study subsequently done by the same group[39] demonstrated that SMS-RUTF formulation is not inferior to M-RUTF with respect to recovery rate in children aged 6–23 and 24–59 months and they suggested that it can be used as an alternative for the treatment of SAM. The result of our study demonstrating non-inferior efficacy of Soy-RUTF compared to M-RUTF is, thus, in the line of the results of the last two studies as mentioned before [40, 41]. One positive side of Soy-RUTF is that it does not contain some of the constituents in milk that are known to decrease iron bioavailability. It is well known that casein, whey protein, and calcium (all of which are abundant in cow milk) inhibit iron absorption [42, 43]. The study by Bahwere et al. [41] also demonstrated that the milk-free SMS-RUTF formulation was more efficacious in restoring hemoglobin and body iron stores than M-RUTF. This is imperative because the prevalence of low body iron stores and anemia is high in children with SAM [44, 45]. It is speculated that the relatively lower ratio of ascorbic acid to iron in the M-RUTF (1.4:1 in M-RUTF compared to 3:1 in the SMS-RUTF products) can aggravate the lower availability of iron in the M-RUTF, because ascorbic acid is known to reduce the effect of inhibitors such as calcium and casein on iron absorption [46].

Peanut is another main ingredient in conventional M-RUTF. The Soy-based RUTF used in this study contained no peanut. Removing peanuts from the RUTF recipe also would result in some advantages. Incidence of peanut allergy is not uncommon rather is increasing [47, 48]. The use of RUTF is greatly increasing in South East Asia, where the lower acceptability of peanuts has led many experts to advocate for non-peanut products on acceptability grounds [49–51]. Moreover, the frequent contamination of peanuts by aflatoxins increases the risks associated with the manufacture of peanut-containing RUTFs, and thus increases the costs of quality assurance [52, 53]. This may increase M-RUTF costs and decrease the ease with which M-RUTF can be made in the countries that require them.

Demand for RUTF has been extensively increased year by year. M-RUTF costs approximately 47 US dollar for each child treated and about 50% is still produced in developed countries and imported into the developing countries where it is needed [54, 55]. Because major cost of the M-RUTF is attributable to milk powder, which constitutes 25% by weight of the content of M-RUTF, removing milk from the RUTF and replacing it with soy protein isolate from soy grown in many of the countries usually affected by SAM has the potential to substantially trim down the cost of such products. Analysis in Malawi by Bahwere et al. [41] suggests that adopting the SMS-RUTF recipe used in their trial would lead to substantial cost savings of between 10 and 25% on the overall finished product cost. The savings for manufacturers in developing countries will be at the higher end of this range. Removing the requirement to import milk powder would decrease the high working capital costs faced by producers in developing countries. Evading the use of imported milk and the elimination of aflatoxin-contamination prone peanuts also decrease the working capital needed for at scale manufacture, and ease the manufacturing challenges of producing safe RUTF in the factories of developing countries. However, prediction of savings accurately before commercial scale trials is difficult and it also depends on global commodity prices (and exchange rates) at the particular time.

Although, it was a single-center study, a multi-center study would enhance its generalizability. But the strong points of the study were: it was a double-blind randomized trial, and at baseline all parameters were similar between the two RUTF groups. This is the first randomized trial in CMAM model comparing peanut-free soy-based RUTF using soy protein isolate with milk-based RUTF including comparison of body composition.

In conclusion, in this study, the peanut-free soy-based RUTF was found equally acceptable as of milk-based RUTF without any side effect or adverse event. Children receiving soy-based RUTF showed similar pattern of weight gain, rate of weight gain, changes in other anthropometric indices, and body composition as of milk-based RUTF. Greater number of SAM children can be managed in the community under CMAM programs with comparatively low-cost soy-based RUTF.

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Author contributions Conceived and designed the study: MIH, TA; data check and analysis: MIH, SH, MMI; manuscript writing and revision: all

Compliance with ethical standards

Conflict of interest None of the investigators has any affiliation with producer of neither product used in the study nor any financial interest that might be affected by the results of this study.

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