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Applied nutritional investigation

Development of a cross-over randomized trial method to determine the acceptability and safety of novel ready-to-use therapeutic foods

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ABSTRACT

Objective: To develop a method for determining the acceptability and safety of ready-to-use therapeutic foods (RUTF) before clinical trialing. Acceptability was defined using a combination of three consumption, nine safety, and six preference criteria. These were used to compare a soy/maize/sorghum RUTF (SMS-RUTFh), designed for the rehabilitation of human immunodeficiency virus/tuberculosis (HIV/TB) wasted adults, with a peanut-butter/milk-powder paste (P-RUTF; brand: Plumpy'nut) designed for pediatric treatment.

Methods: A cross-over, randomized, controlled trial was conducted in Kenya. Ten days of repeated measures of product intake by 41 HIV/TB patients, >18 y old, body mass index (BMI) 18-24 $kg \cdot m^{-2}$, 250 g were offered daily under direct observation as a replacement lunch meal. Consumption, comorbidity, and preferences were recorded.

Results: The study arms had similar age, sex, marital status, initial BMI, and middle upper-arm circumference. No carryover effect or serious adverse events were found. SMS-RUTFh energy intake was not statistically different from the control, when adjusted for BMI on day 1, and the presence of throat sores. General preference, taste, and sweetness scores were higher for SMS-RUTFh compared to the control ($P < 0.05$). Most consumption, safety, and preference criteria for SMS-RUTFh were satisfied except for the average number of days of nausea (0.16 versus 0.09 d) and vomiting (0.04 versus 0.02 d), which occurred with a higher frequency ($P < 0.05$).

Conclusion: SMS-RUTFh appears to be acceptable and can be safely clinically trialed, if close monitoring of vomiting and nausea is included. The method reported here is a useful and feasible approach for testing the acceptability of ready-to-use foods in low income countries.

Introduction

Ready-to-use therapeutic foods (RUTF) are high-energy, nutrient-dense products in which the powdered ingredients are usually suspended in fat. They do not require any preparation or the addition of water before ingestion [1] and can be stored for long periods without refrigeration. They can be individually packaged and can therefore be used effectively in situations with non-optimal hygiene conditions [1]. RUTFs are popular in feeding programs [2], including human immunodeficiency virus/tuberculosis (HIV/TB) interventions [1,3], because their use has been associated with an increase in successful treatment rates for severe acute malnutrition (SAM) when compared to other conventional treatments [4]. However, at present, the high price of RUTFs and their low regional availability hampers widespread use [5].

RUTF were initially developed for pediatric nutritional rehabilitation and the United Nations currently recommends [2,6] their use, at the community level, to help eradicate the one million child deaths that occur every year due to SAM [6]. In the next few years, $US2.6 billion will be spent on SAM treatment [4,7], and therefore, novel, cheaper, culturally acceptable, efficacious, and regionally manufactured products are already in

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demand for this patient group [2]. RUTF have also been used in feeding programs for HIV and TB patients and evidence from low-resource settings [8–14] shows that HIV/TB wasting in adults is still a public health issue in Sub-Saharan Africa, despite the increasing access to antiretroviral therapy.

In such countries, HIV programs aiming for nutritional rehabilitation and/or nutrition support tend to use a few specific types of food [10], usually either fortified blended foods [15] or RUTFs [16]. The most common commercial brand of RUTF is Plumpy'nut [17], which was designed for pediatric use and is the only one that has been clinically tested in several different studies [3,18–22]. In wasted adults, a number of factors have been shown to reduce compliance with Plumpy'nut including the taste of this pediatric formulation [23]. Moreover, the micronutrient densities in Plumpy'nut might not be appropriate for the needs of wasted adults with HIV/TB. For these reasons, there is demand for the development of a novel RUTF for this patient group.

Changes to the formulation of RUTF should be based on clinical evidence derived from randomized controlled trials (RCT) [24] but these are costly to implement. Therefore, robust data on product acceptability are required before implementation of a RCT, and determining adequate consumption, safety, and preference is a crucial early step in successful product development. However, at present there is no internationally endorsed protocol to assess the acceptability of products of this kind.

Here, we present a method for testing the acceptability of novel RUTF. To our knowledge, this is the first trial in a developing country that tests the acceptability of this type of product in wasted adults. The results of this randomized control study are presented according to recommended guidelines for cross-over trials [25].

Materials and methods

Trial and control products

The control product (Plumpy'nut; Nutriset, Malaunay, France [17]) contains peanut butter, milk powder, and a premix of vitamins and minerals and is referred to here as P-RUTF. The trial RUTF (Valid Nutrition, Derry Duff, Ireland, at Insta Ltd., Nairobi, Kenya) contained soybeans, maize, and sorghum, no micronutrients premix, and is referred to here as SMS-RUTFh ("h" standing for adult HIV/TB). Both products contained sugar (28 and 15 100 g^{-1}, respectively, for P-RUTF and SMS-RUTFh) and their macronutrients (energy, protein, lipids) closely met the United Nations requirements for RUTF (Table 1). Both their consistencies were pastelike, but their tastes and colors were different. The detailed formulation and clinical efficacy of SMS-RUTFh will be reported in another article (in preparation).

Study population, recruitment, and setting

The study was carried out in two locations, 2 km from each other, in Homa Bay, Kenya. The participants, enrolled after written informed consent, were patients recruited from the District hospital, supported by the Ministry of Health (MoH) and Médecins Sans Frontières-France (MSF). The patients from the two study groups met each other only at enrollment (day 1), and/or incidentally in the routine medical hospital visits. The participants, HIV and/or TB infected, were considered eligible if receiving antiretroviral therapy and/or TB treatment; age $\geq$18 y; and BMI between 18 and 24 $kg \cdot m^{-2}$ (Table 2). The exclusion criteria consisted of previous enrollment in a nutritional therapeutic program; oral problems that prevented adequate swallowing (typical AIDS oral thrush was not an exclusion criteria); and any specific food intolerance (e.g., peanut allergy). Patients missing more than 3 d were considered defaulters.

Study design

The study design was a two-arm cross-over randomized control trial. At enrollment, the patients were given a number from 1 to 2, randomly generated using an Excel spreadsheet (RAND function), that corresponded to one of the trial groups. Each group received one of the two products during each phase (AB/BA sequence). Under direct observation, during 2 wk (10 working days), water ad libitum and 250 g of one of the two products were offered to the patients as a replacement of the midday meal, with the message "please, eat as much as you wish." An extra 50 g was available on request. A maximum of 2 h was allowed to consume the product, and no leftovers could be taken away. After 2 wk (phase 1), the study was interrupted for 7 d (washout period) and then resumed for two more weeks (phase 2).

The professional background of the research staff included nursing, nutrition, and counseling. No one worked for the MoH or MSF, and the staff worked in a different study group each day, interviewing randomly assigned patients (ratio of staff members and patients: 1:3). In-depth questionnaires and focus group guidelines were provided in both English and the local language (Dholuo), after being anonymously back-translated. The packaging concealed the product identification.

Study procedure and outcomes

To consider RUTFh acceptable and safe, it had to fulfill the following criteria and subcriteria for consumption, safety, and preference (Tables 3–5).

Criterion 1: Consumption

The consumption criterion consisted of three subcriteria. The subcriteria "average consumption" was satisfied if average SMS-RUTFh intake was more than 75% (187.5 g) of the offered amount within 1 h (criterion 1.1; Table 3), whereas SMS-RUTFh "daily consumption" was met if its intake was higher than 75% of the offered food for more than 75% of the days on the trial (criterion 1.2). Finally, the "comparative energy intake" criterion (1.3) was satisfied if the average energy intake per kilogram of body weight was significantly higher than 75% of the energy intake from the P-RUTF.

Table 1
Comparison of macronutrients in the two RUTFs

	SMS-RUTFh		P-RUTF	References
Ingredients:	Soy beans, maize, sorghum, sugar, and oil		Peanut butter, milk powder, sugar and oil, vitamin and mineral premix	n.a.
Source:	International food composition databases	Laboratory results	Diop et al.(2003)	UN reference for pediatric RUTF (2007)
Reference number	[36,37]		[19]	[6]
Energy, $kJ \cdot kg^{-1}$	20 900	22 350	22 810	21 740-22 990
Protein, $g \cdot kg^{-1}$	120	153	136	n.a.
Protein/energy ratio, %	10	11	n.a.	10-12
Lipid, $g \cdot kg^{-1}$	310	336	357	n.a.
Lipid/Energy ratio, %	56	56	n.a.	45-60
(ω-6) Fatty acids/energy ratio, %	9	n.a.	n.a.	3-10
(ω-3) Fatty acids/energy ratio, %	0.8	n.a.	n.a.	0.3-2.5
Protein digestibility-corrected amino-acid score, %	82	n.a.	n.a.	n.a.