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Choice of design and outcomes in trials among children with moderate acute malnutrition

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Abstract

There is a need for trials on the effects of food aid products for children with moderate acute malnutrition, to identify how best to restore body tissues and function. The choice of control intervention is a major challenge, with both ethical and scientific implications. While randomized trials are needed, special designs, such as cluster-randomized, stepped-wedged or factorial designs may offer advantages. Anthropometry is widely used as the primary outcome in such trials, but anthropometric traits do not refer directly to specific organs, tissues, or functions. Thus, it is difficult to understand what components of health might be impacted by public health programs, or the underlying mechanisms whereby improved nutritional status might benefit short- and long-term health. Measurement of body composition, specific growth markers and functional outcomes may provide greater insight into the nature and implications of growth failure and recovery. There are now several methodologies suitable for application in infants and young children, e.g., measuring body composition with deuterium dilution, physical activity with accelerometers and linear growth with knemometers. To evaluate the generalizability of the findings from nutrition trials, it is important to collect data on baseline nutritional status.

Key words: food aid products, MAM, children, study design, outcomes

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Introduction

There is a need for acceptable and affordable food aid products for children with moderate acute malnutrition (MAM) that effectively restore body tissues and functions [1, 2]. If the supplement offered fails to meet the requirements for energy and specific nutrients, then the regain of body tissues and functions will be inadequate and the child may progress to severe acute malnutrition (SAM) and die, or may survive with short- or long-term risks of infectious and chronic diseases and impaired physical and intellectual potential [3].

Therefore, it is important that the effects of potential products for treatment of acute malnutrition are assessed through sufficiently large randomized, controlled trials to get accurate and precise effect estimates. This leads to two generic issues that are the focus of this paper. First, how should we design the trials in order to obtain the best-quality evidence regarding the efficacy of nutritional interventions? Second, what outcomes should we assess in order to demonstrate that the intervention improves health and reduces disease risk?

Study design issues

Nutritional randomized, controlled trials pose ethical and scientific challenges, and these challenges are different between MAM and SAM. For SAM, death is the outcome of greatest concern, but foods already exist that have proven to considerably reduce mortality. Hence, having an unsupplemented control group would be not only unethical but also scientifically irrelevant. For MAM, although progression to SAM and death may occur, these outcomes are uncommon. Hence, the design issues and choice of outcomes are different in MAM.

Control intervention

In trials among children with MAM, those in the control group are usually given "standard of care,"

even if no evidence for effect is available. Yet, recommendations for treatment of MAM do not exist in all settings or are not implemented, or supplements are not always available. But even in settings where treatment is nonexistent, not giving any foods to children with MAM is not without ethical concerns. However, from the public health and scientific perspectives, it is also problematic to compare the effect of an experimental supplement with the effect of supplements that are not recommended or the effect of which is unknown. First, it is of questionable value in a low-income country to conduct a trial to compare an experimental supplement with a supplement that is not already standard of care, and national ethics committees may not grant permission for such a trial. Second, it is difficult to interpret findings from a trial comparing an experimental supplement with one that has not been properly tested. Hence, where supplementation is not standard of care, it may be ethically justifiable to have an unsupplemented control group. In such cases, mothers should receive health education and the children should receive medical attention, be monitored closely, and be referred for further medical examination and treatment if they do not recover. Delayed supplementation may also be considered.

Study design

Food interventions are complex, since supplements with the same energy content may be based on different ingredients, different processing methods, and different forms and amounts of antinutrients and nutrients. Consequently, there is an infinite number of potential food supplements, yet only a few can be tested in trials, as such trials are costly. The traditional approach would be to decide on an experimental supplement and then test it against a control intervention in a randomized, controlled trial, with only two arms in order to maximize statistical power. However, there are a couple of alternative designs that may be used and that may address some of the difficulties experienced with the conventional randomized, controlled trial, i.e., risk of spillover between experimental and control interventions, having an unsupplemented control group, and deciding on a single experimental supplement to test.

Cluster-randomized design

In a cluster-randomized trial, groups of individuals or treatment centers rather than individuals are the units of randomization. The advantage of this design is that it is operationally more feasible and the risk of spillover of the experimental intervention to the control group is lower. In contrast, it may be more difficult to blind the investigators as to which intervention the participants receive. Since the number of randomized units is lower, randomization will be less effective, and special statistical methods are needed to account for the fact that observations within a cluster are not independent. A cluster-randomized trial was recently conducted among children with MAM in Burkina Faso [4].

Stepped-wedge design

If a MAM intervention is to be implemented based on prior belief rather than evidence of benefit, then this design may be an option, provided it is not possible to implement the intervention simultaneously at all treatment sites. The rollout of the new intervention in geographic areas or treatment centers will then be sequential, based on randomization, and it will be possible to compare the effect of the new supplement with that of the existing supplement [5]. Thus, the design is basically cluster randomized, and individuals at all treatment sites, but not all individuals, will be given the new supplement. The randomization is considered to be without ethical concerns, since the intervention is withheld not for the purpose of research but as a logistical necessity. The limitations are similar to those of the cluster-randomized trial. A study on the effect of home-based therapy conducted in Malawi used a stepped-wedge design [6].

Factorial design

Some processing methods or components may be potentially important, but costly. If a combination of several factors is of interest, then a randomized trial using a factorial design may be needed. An example is the TreatFOOD trial in Burkina Faso among children with MAM (http://www.thelancet.com/protocol-reviews/13PRT-4687). It is an individually randomized trial using a 2-by-2-by-3 factorial design among 1,600 children to assess the effects of the food matrix (lipid-based nutrient supplement [LNS] vs. corn-soy blend [CSB]), soy protein quality (dehulled vs. isolate), and milk protein content (0%, 8%, and 20 w/w %). Thus, the children are randomly assigned to 12 different foods. The design allows assessing for interactions among the three factors, i.e., if the effect of one factor depends on the presence of another factor. This could be the case if milk proves to have a greater effect if given in CBS than in LNS. If so, then it will be necessary to make comparisons among the 12 individual interventions. If there are no interactions, then the full power will be available to assess, say, the effect of milk, without taking food matrix and soy quality into consideration.

Generalizability

Assessing the effect of a nutritional intervention may be more complex than assessing the effect of, say, a drug against a specific disease. The effect of a given nutritional intervention depends on the initial nutritional status and the background diet. Children with similar weight-for-height z-scores or mid-upper-arm circumference (MUAC) values may have different growth

patterns, body composition, and micronutrient status and intake. Hence, the effect of the same intervention may be different between children and populations. Therefore, it is important to collect data on baseline nutritional status to assess for effect modification and evaluate the generalizability of the findings.

Choice of outcomes

Our understanding of the effects of MAM in early life is primarily based on anthropometric measures—mostly weight and height, which are often converted to age- and sex-specific z-scores, but which may also be expressed as weight-for-height or body mass index, also in z-score format [7]. Another widely used outcome is MUAC, which in studies of children with SAM is a better predictor of mortality than weight-for-height [8]. One possibility is that MUAC acts as a better indicator of muscle mass than does weight-for-height [9], but this requires confirmation, since in older children MUAC indexes adiposity much better than lean mass [10]. These data provide indices of stunting (short stature) and wasting (low weight-for-age, low MUAC), categorized using cutoffs [11, 12]. Much information can be gained from such measurements, and data can readily be compared across populations because of the standardized format. However, the abstract nature of anthropometry also means that much is also concealed by these outcomes. None of these anthropometric outcomes refers directly to specific organs, tissues, or functions, making it difficult to understand what components of health might be impacted by public health programs or the underlying mechanisms whereby improved nutritional status might benefit short- and long-term health.

Specific growth markers

Beyond whole-body anthropometry, more detailed measurements are increasingly recognized to provide greater insight into the nature of growth failure and recovery. The thrifty phenotype hypothesis proposed that the body responds to malnutrition by preserving some tissues and organs at the expense of others [13]. Studies have shown that the brain is generally spared, at the cost of reductions in growth of organs such as the pancreas, kidney, and liver [14]. This approach can also be extended to growth, with, for example, some body proportions being protected at the expense of others. **Figure 1** illustrates deficits in specific body components in high-altitude versus low-altitude Peruvian children, illustrating that some components of growth (e.g., trunk–head length, hand and foot lengths) are protected at the expense of others (e.g., tibia length) [15]. Thus, growth traits may potentially provide proxy information for constraints on organ development; however, this hypothesis requires confirmation.

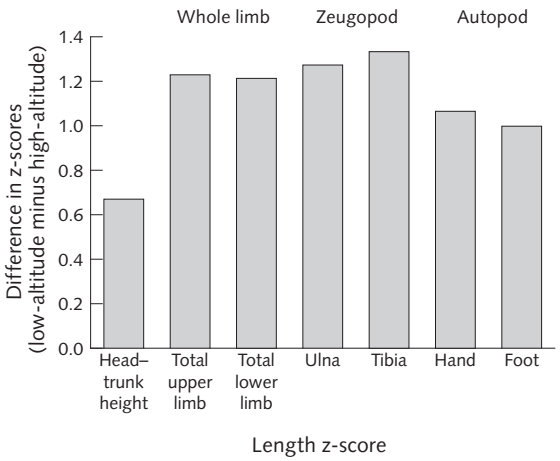

FIG. 1. Differences in growth z-scores between high-altitude and low-altitude children from Peru, demonstrating greater contrasts in total limb and lower limb lengths, intermediate differences in hand and foot lengths, and the smallest difference in head–trunk height [15].
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Measurements of specific body components can thus be made using customized equipment. Growth velocity of the legs is faster during early life than growth velocity of the rest of the body. Lower leg length contributes about 25% of total length at birth and about 29% at 5 years [16]. There are some indications that foods containing dairy products have a specific effect on leg growth [17]. By subtracting crown–rump length, which can be measured with standard equipment used for measuring length, it is possible to estimate growth of the legs and compare it with growth of the rest of the body. Leg growth can be estimated with a knemometer, a modified electronic caliper that measures linear growth velocity over short periods with high precision [18]. Head circumference can also be measured as a simple proxy for brain growth, which may be useful in studies on the potential effects of MAM on cognitive development.

Body composition

Measurement of body composition represents a novel approach to the assessment of nutritional status and may help to resolve some of this uncertainty. The simplest approach aims to differentiate fat from lean mass [19]. There is increasing recognition that these two traits have very different implications for short- and long-term outcomes [20]. Fat represents a store of energy that may fund immune function or future growth. Lean tissue represents functional organs and tissues, which may likewise contribute to immune function, but also in the longer term to diverse other

aspects of health and function. The relative proportion of fat to lean provides an indication of how the body is allocating energy between these competing ends [21]. Low levels of fat may indicate reduced resilience to ecological stresses in the short-term future, whereas low levels of lean mass indicate cumulative exposure to prior stresses. The relative "survival" value of fat versus lean tissue in early life remains uncertain; hence it is unclear what constitutes the optimum pattern of tissue accretion during recovery from MAM, and whether variation in fat and lean accretion across populations represents local adaptation or simply different stresses. Equally, it remains unclear whether public health interventions should promote lean mass, fat, or a particular ratio of the two. These are key questions for the next generation of trials to assess.

Although measurements of skinfolds can be used to assess subcutaneous adiposity, they do not quantify whole-body fat content. Likewise, there is no reliable anthropometric marker of lean mass. Until recently, therefore, body composition was difficult to measure in young age groups with accuracy under field conditions; however, several techniques have now become available. Measurement of body water by isotope dilution is the only technique that can be used in all age groups [22], while air displacement plethysmography (ADP), a form of densitometry known as the Peapod, can be used from birth to 6 to 8 months, depending on the size of the infant [23]. Both of these techniques assume constant properties of lean tissue when raw data are converted into final body composition values; however, this assumption may be invalidated during chronic malnutrition. This issue can be solved in younger age groups by combining the two methods, thereby measuring the hydration and density of lean tissue [23]. Recent studies have successfully used isotopes and ADP in large samples of infants in developing countries* [23] demonstrating their suitability for future trials.

Bioelectrical impedance analysis (BIA) has conventionally been used to predict total body water and hence lean and fat masses, but it has low accuracy in individuals [19]. However, bioelectrical impedance vector analysis (BIVA) is a newer variant [24], which analyzes more detailed bioelectrical properties of lean tissue. Although the outcomes are expressed in abstract bioelectrical units, BIVA is showing promise for differentiating variability in lean tissue mass from variability in hydration in children with MAM and SAM** (and may prove particularly valuable for the assessment of body composition in populations where the severity of malnutrition extends to both categories.

Finally, ultrasound can be used to assess the size of organs such as the thymus, liver, and kidney [25]. For example, thymus size has been shown to mediate associations between nutritional status and infant mortality [26, 27]. Such data may be particularly valuable when acquired in combination with functional outcomes, as described below.

Whichever technique is selected, a key requirement is reference data, enabling data from individuals or trial groups to be assessed relative to normal ranges. Reference data have now been published for ADP in Ethiopian infants [23], and BIVA data are also being acquired. Other studies have collected isotope measurements of body water in large samples [28]. These emerging data are enabling the evaluation of the body composition characteristics underlying MAM and will help clarify its etiology and response to treatment.

Functional outcomes

While measurement of body composition can contribute novel information on the etiology of MAM and its response to treatment, it is also useful to have information on physiological function, in order to improve health assessment. The range of possible outcomes increases with age, as older children are able to comply with more complex protocols.

Blood pressure represents a valuable marker of homeostasis, and studies have already clarified that growth patterns in fetal life and infancy are associated with short- and long-term variability in this outcome [29, 30]. At older ages, outcomes such as grip strength, measured by dynamometry, can provide information on muscle function, while respirometry can be used to assess lung function [31, 32].

A variety of indices of cognitive or psychomotor ability can be assessed by developmental scales, which may need adapting to local cultural settings [33]. Physical activity can be assessed with questionnaires to quantify patterns of behavior, or accelerometers can be used to assess the intensity and duration of body movements [34].

Finally, blood samples clearly allow a wide range of markers of immune function to be assessed, as well as diverse parameters of metabolic health, such as glucose homeostasis and lipid profile. These outcomes are of especial importance, given growing evidence that growth patterns in early life may predict later risk of obesity and the metabolic syndrome [35].

A key point is that associations between early growth or nutritional status and later health outcomes in industrialized countries may not extend to populations in developing countries. Whereas rapid infant growth appears to exacerbate the risks of obesity and the metabolic syndrome in industrialized countries [36,

* Skau, J. Preventing undernutrition in Cambodia: Assessing the effect of improved local complementary food on growth. PhD thesis. University of Copenhagen, 2013. ISBN 978-87-7611-633-0. (unpublished)

** Girma, T. Bioimpedance in severely malnourished children: An emerging method for monitoring hydration of children with severe acute malnutrition. PhD thesis. University of Copenhagen, 2014. ISBN 978-87-7611-782-5 (unpublished)

37], the available evidence indicates that early rapid growth in developing countries boosts survival [38] and has beneficial effects on lean mass and homeostasis [37]. This difference may relate to variable durations between populations during which "critical windows" are sensitive to nutrition [39]; however, this hypothesis requires further testing.

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