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**English summary**

**Background**

Children with severe acute malnutrition (SAM) without medical complications are treated at home with ready-to-use therapeutic foods (RUTF). The current RUTF dose prescribed is designed to fulfil 100% of the nutritional needs of recovering children and aims for quick regain of lost body tissues while providing sufficient micronutrients to restore diminished body stores. However, there is doubt concerning the dose as it seems to be shared with other family members resulting in sub-optimal cost-efficiency of SAM treatment. Furthermore, little evidence exists on the success of the treatment to establish normal body composition and micronutrient status by recovery.

This thesis is part of the MANGO study that aimed to investigate the response to treatment of children with SAM given a reduced RUTF dose compared to children given the standard RUTF dose. The results presented in this thesis cover the main outcomes of the trial namely the anthropometric and programmatic outcomes and the secondary outcomes related to body composition and vitamin A and iron status. Additionally, changes occurring in the body composition and vitamin A and iron status of children during treatment were studied.

**Methods**

The MANGO study was an individually randomised controlled trial testing the efficacy of a) standard RUTF dose for two weeks followed by a reduced dose thereafter (reduced) compared to b) standard RUTF dose throughout the treatment (standard) of SAM in a non-inferiority design. The main outcome investigated (Paper 1) was weight gain velocity where a mean difference of 0.0 g/kg/d was expected with a non-inferiority margin fixed at -0.5 g/kg/d. Other outcomes included mid-upper-arm circumference (MUAC) and height gain, length of stay, recovery rate and other programmatic outcomes (Paper 1), changes in body composition (Paper 2) and vitamin A and iron status (Paper 3).

Children who were included in the trial returned to the health centre for weekly monitoring of anthropometry (weight, length or height and MUAC) and clinical status. Body composition was measured via bio-electrical impedance analysis and a sample of non-malnourished children of same age measured to represent community controls. Blood samples were collected from trial children and analysed for haemoglobin (Hb) and serum concentrations of retinol binding protein, ferritin, soluble transferrin receptor, C-reactive protein and α1-acid glycoprotein. Linear and logistic mixed regression analyses were performed with study site and team as random effects and adjusting for potential confounders.

**Results**

A total of 801 children with uncomplicated SAM aged 6-59 months were enrolled in the trial. At admission the mean age (±SD) was 13.4 months (±8.7), 49% were male and the mean weight was 6.2 kg (±1.3). The mean weight gain velocity from admission to discharge was 3.4 g/kg/d and did not differ between study arms (p>0.9) confirming non-inferiority. Programmatic outcomes including recovery rate, length of stay, defaulter rate and relapse rate did not differ between study arms (p>0.05). Height gain was 0.2 mm/w (p=0.015) slower in the reduced arm compared to standard arm. No differences were observed in fat-free mass (FFM), fat mass (FM) or fat mass index (FMI) between the study arms at recovery. However, FFMI was 0.35 kg/m² (p=0.007) higher at recovery with the reduced compared to standard dose. Vitamin A and iron status markers did not differ between trial arms with the exception of Hb that was 1.7 g/l (p=0.088) lower in the reduced dose arm compared to the standard dose, at recovery.
During SAM treatment, 45% of weight gain was FFM. At recovery, FFMI of treated children was not different from community controls contrary to FMI that remained deficient. Mean concentrations of all vitamin A and iron status biomarkers improved from admission to discharge. However, at discharge, deficiencies were still common as 55% had anaemia, 21% had iron deficiency anaemia and 9% had vitamin A deficiency.

Conclusions

Reducing the RUTF dose provided to children with SAM after two weeks of treatment resulted in similar response to treatment in most studied outcomes including the main outcome of weight gain velocity. Approximately half of the weight gain during SAM treatment was FFM and by recovery, a similar FFM had been attained compared to community controls when adjusting for height. The vitamin A and iron status of children improved during treatment but remained sub-optimal at discharge.

Based on the findings, the reduced dose could be recommended for scale-up if the effectiveness is also demonstrated in a routine program setting. More generally, there seems to be a need to reconsider RUTF fortification levels or test other potential strategies in order to fully restore a normal body composition and micronutrient status of children treated for SAM.
Danish summary
Baggrund

Børn med svær akut underernæring (severe acute malnutrition, SAM) uden komplikationer behandles i hjemmet med et klar-til-at-spise terapeutisk koststofskud (ready-to-use therapeutic foods, RUTF). Den normalt anvendte dosis RUTF er valgt så den forventes at dække de anslåede energi- og næringsstofbehov for børn under behandling for SAM, så de hurtigt kan genopbygge tabt kropsvæv og mikronæringsstofdepoter. Der er imidlertid tvivl om, hvorvidt dosis er for høj, da koststofskuddet bliver delt og behandlingen dermed ikke er kost-effektiv. Desuden er der ikke evidens for, at behandlingen fuldt ud genopbygger børnernes kropssammensætning og mikronæringsstofstatus.

Denne afhandling bygger på MANGO-studiet, som har undersøgt effekten af, at behandle børn for SAM med en aøvere dosis RUTF. I denne afhandling præsenteres effekten på antropometri og programindikatorer, samt kropssammensætning og A-vitamin og jernstatus.

Metoder

MANGO studiet var et lodtrækningsstudie hvori effekten af en standard dosis RUTF i de første to uger fulgt af en lavere dosis (herefter kaldt reduceret) sammenlignet med en standard RUTF dosis gennem hele behandlingen (standard) undersøgtes ved brug af et såkaldt non-inferiort studie design. Hovedeffektmålet præsenteret i Artikel 1 var vægtøgningshastigheden, hvor en gennemsnitlig forskel på 0.0 g/kg/d var forventet med en non-inferior grænse på -0.5 g/kg/dag. Andre effektmål var overarmsomkreds (MUAC) og længdevækst, helbredelse, behandlingsvarighed, og andre programindikatorer (Artikel 1), ændring i kropssammensætning (Artikel 2) og A-vitamin og jern-status (Artikel 3).

Børn, der deltog i studiet, blev fulgt ved ugentlige besøg på et sundhedscenter, hvor der blev målt antropometri (vægt, kropslængde eller højde og MUAC) samt vurderet klinisk status. Kropssammensætning blev målt via bioelektrisk impedansanalyse, og en stikprøve af ikke-underernærede børn af samme alder blev brugt som kontrolgruppe. Blodprøver blev taget på de børn der indgik i studiet og analyseret for hæmoglobin (Hb) and serum koncentrationer af retinol bindende protein, ferritin, opløselig transferrin receptor, C-reaktivt protein og α1-acid glykoprotein. Linear og logistik mixed effekt regressionsanalyser blev anvendt efter justering for potentielle konfoundere.

Resultater

I alt 801 børn mellem 6-59 måneder blev inkluderet i studiet. Den gennemsnitlige alder (±SD) var 13.4 måneder (±8.7), 49% var drenge og den gennemsnitlige vægt var 6.2 kg (±1.3). Den gennemsnitlige vægtøgningshastighed fra indskrivning til udskrivning var 3.4 g/kg/d og var ikke forskellig mellem interventionsgrupperne (p>0.9).

Der var ingen forskel i programindikatorerne mellem grupperne (p>0.05). Længdevækst var 0.2 mm/uge (p=0.015) mindre i den reducerede sammenlignet med standard gruppen. Der var ingen forskel i fedt-fri masse (FFM), fedtmasse (FM) eller fedtmasse index (FMI) mellem grupperne. Dog var fedt-fri masse index (FFMI) 0.35 kg/m2 (p=0.007) højere ved helbredelse i den reducerede sammenlignet med standard dosis. Vitamin A og jernstatus markørerne var ikke forskellige mellem grupperne, med undtagelse af Hb som var 1.7 g/l (p=0.088) lavere i den reducerede gruppe ved helbredelse.

Under SAM-behandlingen var 45% af vægtstigningen FFM. FFMI blandt de behandlede børn var ved helbredelsen ikke forskellig fra kontrolerne, hvorimod FMI vedblev at være lavere. De gennemsnitlige koncentrationer af vitamin A jernstatus biomarkørerne forbedredes fra indskrivning til udskrivning.
Mangel var dog stadig udbredt, idet 55% havde blodmangel, 21% havde jernmangel-blodmangel og 9% havde vitamin A mangel.

**Konklusioner**

En reduktion af RUTF dosis efter de første to ugers behandling ændrede ikke vægtøgningshastigheden eller de fleste af de andre effektmål. Ca halvdelen af vægtøgningen under SAM behandling var FFM, og ved helbredelse var FFM ikke forskellig fra hvad man så hos kontrollerne. Vitamin A og jernstatus forbedredes under behandling, men forblev suboptimal ved udskrivning.

Den reducerede dosis RUTF kan anbefales, dersom man ser samme effekt under rutine programmer. Generelt synes der at være behov for at genoverveje niveauerne af berigelse for at sikre normalisering af kropssammensætning og mikronæringsstofstatus under behandling for SAM.
1 Introduction

Undernutrition is the world’s leading cause of death for children <5 years of age (1). It results from an insufficient nutrient intake to cover physiological needs, either due to limited food availability or due to illness affecting appetite, absorption and use of nutrients (2). The most fatal form with the highest risk of mortality is called severe acute malnutrition (SAM) and is characterised by severe emaciation and sometimes oedema. Children with SAM have a reduced immune function and as a result, a greater risk of dying from common infections (3,4). However, most SAM cases can be treated in outpatient care as long as they do not present with other severe illnesses such as severe pneumonia, high fever or severe anaemia (5).

The home-based management of SAM is done according to a standard protocol consisting of an antibiotic regimen for the first week and weekly distribution of ready-to use therapeutic foods (RUTF) until recovery (6). RUTF are energy dense highly fortified pastes prescribed according to the weight of the child and intended to fulfil all the nutritional needs of the recovering child (7). When used in tightly controlled settings, rapid weight gain has been observed (8) but in outpatient treatment the recovery is often much slower (9,10). It is suspected that this is due to incomplete consumption of RUTF by the treated child due to sharing of RUTF with other household members.

The cost of RUTFs and the large quantity administered per child have sparked attempts to reduce the RUTF dose prescribed (11,12). However, to date, no rigorous clinical trial has evaluated the effect of such reduction when compared to standard RUTF dose. The current study aimed to bridge this gap by testing the efficacy of a reduced RUTF dose in the treatment of uncomplicated SAM. The primary outcome of interest for the study was the weight gain of children during treatment which conditions their recovery.

The aim of SAM treatment is to enable a quick regain of lost body tissues while providing sufficient micronutrients to replenish diminished body stores. However, what type of weight is gained during SAM treatment remains largely unknown despite growing recognition of the importance of fat-free mass for healthy growth and development (13). Moreover, there is a lack of reference data to describe the normal variability in body composition of healthy children. Thus, in addition to looking into routine anthropometric outcomes, the study also sought to describe the body composition changes of children treated for SAM with different doses of RUTF and compare their body composition to that of non-malnourished children. Similarly, whether a normal micronutrient status is reached by the end of the treatment remains completely unknown even though it is well recognised that some deficiencies impair normal growth (14,15) particularly when severe. Therefore, the study also looked into the vitamin A and iron status of children treated with different RUTF doses.

The ultimate aim of this study was to build more evidence on the effectiveness of the current SAM treatment program in restoring a healthy physiologic state, and to contribute to the optimisation of SAM treatment by describing the impact of reducing the RUTF dose on physiological outcomes related to healthy growth. In combination, the aim was to improve the effectiveness and cost-effectiveness of SAM management and potentially enable the treatment of more children with the same resources.