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Efficacy of a low-dose ferric-EDTA in reducing iron deficiency anaemia among underfive children living in malaria-holoendemic district of Mvomero, Tanzania

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Abstract: Iron deficiency anaemia is a public health problem in Tanzania especially among children under the age of five years. In malaria holoendemic areas, control of anaemia by supplementation with iron has been reported to increase serious adverse events. The World Health Organization recommends that, programs to control anaemia in such areas should go concurrently with malaria control programmes. The objectives of the study were to: (i) to determine if a supplement providing 2.5 mg of iron as ferric EDTA and 2.5 mg of iron as ferrous lactate (low dose) is as effective in correcting anaemia as a supplement providing the standard 10 mg of iron as ferrous lactate (high dose); and ii) determine if iron supplementation increased the risk of malaria. This study was carried out in Mvomero District of east-central Tanzania. Two groups (69 and 70 subjects per treatment) of moderately anaemic children (7.0–9.1 g of Hb/dl), received one of the two micronutrient supplements differing only in iron content for a period of 60 days. Results showed that, the average haemoglobin (Hb) concentration improved from 8.30±0.60 g/dl to 11.08±1.25 g/dl. The average weight-for-age for all children increased from 16.0 to 20.6% while their weight-for-height increased from 4.0 to 13.3%. The incidence of asymptomatic and symptomatic malaria ranged from 10.0 to 10.4% at all time points with no apparent increase in malaria severity due to iron supplementation. Overall, there was a significant reduction in anaemia during the 60 day supplementation period. This study demonstrated that, micronutrient supplements containing low-dose ferric-EDTA is just as effective as the high dose iron in reducing anaemia and can be safely utilized in malaria holoendemic areas to control iron deficiency anaemia. It is recommended that, a large study should be conducted to affirm the effectiveness of the low-dose ferric-EDTA in controlling iron deficiency anaemia among underfive children.

Keywords: anaemia, ferrous lactate, ferric-ethyl diaminetetraacetic acid, EDTA, supplement, Tanzania

Introduction

Anaemia is a major global health problem and whenever the prevalence rate is greater than 40% it is considered as a public health problem (WHO, 2008). Prevalence of anaemia among children aged 6-59 months in Tanzania is 59%; with the highest incidence (81%) occurring during the 9 – 11 month age period (TDHS, 2011). Correction and prevention of anaemia requires a multi-faceted public health approach because anaemia is caused by several factors namely inadequate intake of micronutrients (WHO/UNICEF, 2004), malaria and parasite infestation (Crawley, 2004). During the 2005–2010 time period, prevalence of anaemia in Tanzania decreased from 72% to 59% primarily due to reductions in severe and moderate anaemia cases (TDHS, 2011). Anaemia is compounded by high childhood malnutrition which is still high (DPG, 2010) and the rate of clearing out under-nutrition among underfive children is still very slow (Twaweza, 2010).

Insufficient intake of absorbable iron, vitamin B_{12}, and folic acid are the major causes of dietary induced anaemia (WHO/UNICEF, 2004). Insufficient intakes of bio-available iron and vitamin B_{12} are particularly a problem in societies that consume plant based diets. Ninety two percent of Tanzanian mothers utilize a thin gruel prepared from cereal (maize, rice, millet or sorghum) as major supplementary foods for babies (TDHS, 2011). Such foods contain very little bio-available iron and no vitamin B_{12}. Lack of affordable fortified complementary foods in Tanzania is a major cause of anaemia in children who are 6 – 23 months old (WHO, 2001). Home fortification of complementary foods through addition of micronutrient powder containing

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vitamins and minerals is an effective approach to preventing anaemia and other micronutrient deficiencies in children (De-Regil *et al.,* 2011; Rah *et al.,* 2012).

Iron status appears to be pivotal in regards to physiological requirements and human host well being against infections by pathogens (Prentice, 2008). Individuals without iron deficiency anaemia have a higher risk of asymptomatic and clinical malaria than individuals who have iron deficiency anaemia (Gwamaka *et al.,* 2012; Jonker *et al.,* 2012). This appears to be true regardless of whether the individual is iron replete due to a good diet and adequate control of infections or due to iron supplementation (Gwamaka *et al.,* 2012). A study in Tanzania has reported that iron deficiency decreased the odds of *Plasmodium falciparum* infection by 23%, severe malaria by 38%, all-cause mortality by 60% and reduction in malaria-associated mortality by 66% (Gwamaka *et al.* 2012).

Children with iron deficiency anaemia are recommended to receive iron supplement as a control intervention. Due to its chemical properties i.e. oxidative potential, iron functions in several biological systems that are crucial for human health. Negative effects of iron supplementation with normal recommended dose of iron (10 g iron salt per day) have, however, been reported in areas where malaria transmission is intense and infectious diseases are highly prevalent (Sazawal *et al*., 2006). Excessive iron absorption may be harmful by causing oxidative stress (that causes oxidative damage of DNA, proteins, lipids and other tissue injuries), interference with absorption or metabolism of other nutrients and suppression of other critical enzymatic activities (Iannotti *et al*., 2006). Recently, there has been growing concern about the effect of iron supplementation on increased susceptibility to infections for children living in malaria hyperendemic areas. A study of iron supplementation in Zanzibar (Sazawal *et al.*, 2006) showed a significant increase in serious adverse events among children under the age of five years. This led the World Health Organization to issue a cautious statement about iron supplementation in areas where malaria is holoendemic (WHO/UNICEF, 2006). The WHO recommends that, all iron supplementation initiatives in malaria endemic areas should have malaria control as a component of the programme (WHO, 2007).

In response to this problem, this study was designed to determine the effectiveness of using a low-dose iron supplement to control anaemia among underfive children. The aim of this study was to evaluate the efficacy, safety and acceptability of a low dose ferric-EDTA supplement for correcting iron deficiency anaemia among children under the age of five years. Specific objectives of the study were to: i) to determine if a supplement providing 2.5 mg of iron as ferric EDTA and 2.5 mg of iron as ferrous lactate (low dose) is as effective in correcting anaemia as a supplement providing the standard 10 mg of iron as ferrous lactate (high dose); and ii) determine if iron supplementation increased the risk of asymptomatic and symptomatic malaria.

Materials and Methods

Study area

The study was conducted in Kichangani, Lusanga, Manyinga, and Kilimanjaro villages in Turiani division of Mvomero district in east-central, Tanzania. The Mvomero district has a total population of 259,347, out of whom 130,552 are females and 128,795 are males (TDHS, 2012). The average household size is 5.0 ± 1.96 (range, 2 to12) with the mean number of children under the age of five years of 1.4 ± 0.5 (range, 1 to 3) per household. Most (82%) of the people are employed in the agricultural sector, with the majority of families practicing subsistence farming. Kichangani, Lusanga, and Kilimanjaro villages have dispensaries, while the Manyinga village receives health services from the Turiani Hospital. Malaria prevalence in Mvomero district ranges from 34.5-46.1% (Mboera *et al.*, 2006; 2011).

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Study design and sample size

The study was a community-based, randomized, double-blind longitudinal trial with the intent to treat anaemia. Two micronutrient supplements differing only in iron content and source were tested for efficacy to alleviate anaemia. Two groups of moderately anaemic children (6 to 36 months of age) received one of two micronutrient supplements. Incidences of malaria were recorded during the entire study period. Statistical power analysis suggested that 85 subjects per treatment would provide 95% power to detect a treatment difference using a two-side type error of 5% (Confidence interval 95%). A dropout rate of 25 children per treatment was projected and therefore a total of 110 subjects were enrolled to cover the attrition rate.

Anaemia and malaria screening

The purpose of the study and the benefits of consuming the micronutrient supplements that contained iron were explained to the respondents. Eligibility criteria were: the family had to reside in one of the four pilot villages; the child must be 6–36 months of age, have moderate anaemia (haemoglobin) values from 7.0 – 9.9 g/dl), consume some solid food, and have a weight-for-height z-score (WHZ) ≥ -2.99. Exclusion criteria were Hb concentrations ≤ 6.99 g/dl or ≥ 10.0 g/dl), WHZ ≤ - 3.0), child who does not consume solid foods, age < 6 months or > 36 months of age, chronic conditions such as type 1 diabetes mellitus, some inborn errors of metabolism, HIV-infection or known hemoglobinopathies. The following demographic information was sought and recorded for each study subject: child's name, birth date, gender, father's name, mother's name and residence location. A physician examined the child for oedema, and the child's weight and height (length) were taken. Using safety lancet, a laboratory technician collected a drop of blood through finger prick. The drop of blood sample was used to determine haemoglobin (Hb) concentrations using a HemoCue® Hb 201^{+} photometer (HemoCue AB, Sweden).

A sub-sample of the blood was used to prepare a blood smear, stained with Giemsa and examined with a binocular microscope with an oil immersion lens to identify malaria asexual parasites. The number of asexual parasites was counted against 200 leukocytes using a hand tally counter. A slide was considered negative if no parasite was seen after scanning 200 fields. The blood films were examined by experienced microscopists at Turiani Hospital.

Table 1: Composition of supplements

Nutrients	Unit	Per 1g sachet
Vitamin A	IU	1250
Vitamin D	IU	200
Vitamin E	Mg	9
Thiamine	Mg	0.5
Riboflavin	Mg	0.5
Pyridoxine	Mg	0.5
Cobalamin	Mcg	0.9
Ascorbic acid	Mg	30
Nicotinamide	Mg	6
Folic acid	Mg	0.15
Iron	Mg	5 or 10*
Zinc	Mg	4.1

*The 5mg iron supplement contained 2.5mg of iron derived from ferric EDTA and 2.5mg of iron derived from ferrous lactate while the 10 mg iron supplement contained iron as ferrous lactate.

Selection of subjects for the Intervention

The data were ranked according to Hb concentration and all children with Hb concentrations of 7.0 – 9.1 g/dl were selected to participate in the study. The selected subjects were matched according to gender, Hb concentration, and age and then assigned to receive either treatment A or treatment B. The study was a randomized double-blind in design in which neither the

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researchers nor the subjects knew which group was receiving which treatment. The supplement codes A and B were broken after the data were analyzed. If a family had more than one child selected to be in the study, all children within a family received the same treatment. A total of 238 children qualified for enrolment into the study. However, parents of 20 children declined to have their children participate in the intervention part of the study.

The compositions of the micronutrient supplements are shown in Table 1. The subjects consumed one sachet per day by sprinkling the contents of the sachet on the subject's food. The sachets were labelled "A" or "B" and contained either 10 mg of iron as ferrous lactate or 5 mg of iron – 2.5 mg of iron from ferric EDTA and 2.5 mg of iron from ferrous lactate. The EDTA chelated iron is more bio-available than ferrous salts and the lower iron dose containing chelated iron was expected to provide the same physiological benefit as the higher dose of ferrous lactate because of its high bioavailability. Children 12–36 months of age were given two doses of 200 mg of albendazole to control for helminthes one week prior to supplement consumption. Six – 11 months old infants were not treated for helminthes.

Subject monitoring and compliance

A village health attendant recorded supplement usage and collected empty sachets on a daily basis to monitor compliance. Also, the village health attendant recorded information of all other foods that were taken for the past 24 hours. In addition to monitoring compliance, the village health attendant recorded information about supplement acceptance by the child, side effects, and health information including diarrhoea, fever, coughing, and other sicknesses and also behaviour changes such as increase in appetite and increase in the level of physical activity.

Ethical considerations

The study received ethical approval from the Medical Research Coordinating Committee of the National Institute for Medical Research. Written informed consent was obtained from the children's mothers/caregivers before inclusion into the study.

Data analysis

The quantitative data were tested for normality using the Kolmogorov-Smirnov test. Baseline Hb concentrations for the two groups were compared by t-test. Differences between Hb concentrations at baseline and 4 week and 8 week within a group were compared by paired t-test. Comparison of Hb differences (8 week Hb concentration – baseline Hb concentration) between the two supplement treated groups were done by the t-test. Comparison of the extent of recovery from anaemia (Hb ≥ 11.0 g/dl) between the two groups and malaria incidence among time periods was done with chi-squared test. An alpha value ≤ 0.05 was considered statistically significant.

Results

The total number of children involved and screened for anaemia was 1019 (females=525; males= 494). Of the screened children, 2.8% had severe anaemia (Hb < 7.0 g/dl), 44.8% had moderate anaemia (Hb 7.0 – 9.9 g/dl), 27.6% had mild anaemia (10.0 – 10.9 g/dl) and 24.8% had no anaemia based on WHO classification (WHO, 2011). The altitude of the study site was 400 to 500 m above sea level and therefore, no adjustments were made on the Hb values for altitude. Anthropometric measurements showed that 2.6% were severely underweight (WAZ ≤ -3.0); 14.9% were moderately underweight (WAZ -2.99 to -2); 6.7% were severely stunted (HAZ ≤ -3.0) while 22.6% were moderately stunted (HAZ -2.99 to -2). None of the children were severely wasted and only 2.8% of the children were moderately wasted (WHZ -2.99 to -2).

After the initial screening which involved 1019 children (females=525; males= 494), 192 children met the criteria for enrolment into the iron supplementation study. Out of 192 children

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who were enrolled into the study, 32 children (16.7%) dropped out of the study before the supplementation period of 60 days. Overall, 83.3% (n = 160) of the children who started the iron supplementation study completed it. The Hb data for each group and at each time point had normal distributions based on the Kolmogorov-Smirnov test for normality. There were no significant differences ($p > 0.05$) in Hb concentrations between the two treatments at baseline, at the 30 day period or at the 60 day period. The children enrolled in the study were moderately anaemic (average 8.3 g/dl, range 7.0 – 9.1 g/dl), but after consuming the supplements for 30 days, significant ($p \leq 0.01$) increases in Hb concentrations were noted. Consuming the supplements for an additional 30 days resulted in additional significant improvement in the Hb values (Table 2).

Table 2: Blood haemoglobin concentrations (mean ± SD)

Treatment	Baseline Haemoglobin, g/dl (N)	30 Day Haemoglobin, g/dl (N)	60 Day Haemoglobin, g/dl (N)
10 mg Fe			
Females	8.35 ± 0.62 (50)	9.88 ± 1.51 (41)	11.21 ± 1.39 (32)
Males	8.24 ± 0.57 (47)	9.61 ± 1.29 (39)	11.09 ± 1.06 (37)
All subjects in treatment	8.30 ± 0.58[a] (97)	9.75 ± 1.41[a,‡] (80)	11.18 ± 0.14[a,‡] (69)
5 mg Fe			
Females	8.32 ± 0.63 (40)	9.98 ± 1.38 (33)	11.42 ± 1.31 (29)
Males	8.32 ± 0.58 (55)	9.53 ± 1.45 (47)	10.73 ± 1.23 (41)
All subjects in treatment	8.32 ± 0.61[a] (95)	9.74 ± 1.42[a,‡] (80)	11.02 ± 1.30[a,‡] (70)

[a]Means in the same column with the same letter superscript are not significantly different ($p>0.05$)
[‡]Means in a row with the ‡ superscript are significantly greater than baseline

The average Hb concentration for the subjects that completed the study increased from 8.30 ± 0.60 g/dl at the beginning of the study to 11.08 ± 1.25 g/dl at the end of the study. Figure 1 shows the Hb concentrations before and after the supplements were consumed for 60 days. While the average Hb value indicated that overall the children were not anaemic, only 58.3% of the children actually achieved Hb values greater than 11 g/dl. About 23.7% of the children remained mildly anaemic (Hb concentrations ranged from 10 – 10.9 g/dl) while 18% of the children remained moderately anaemic.

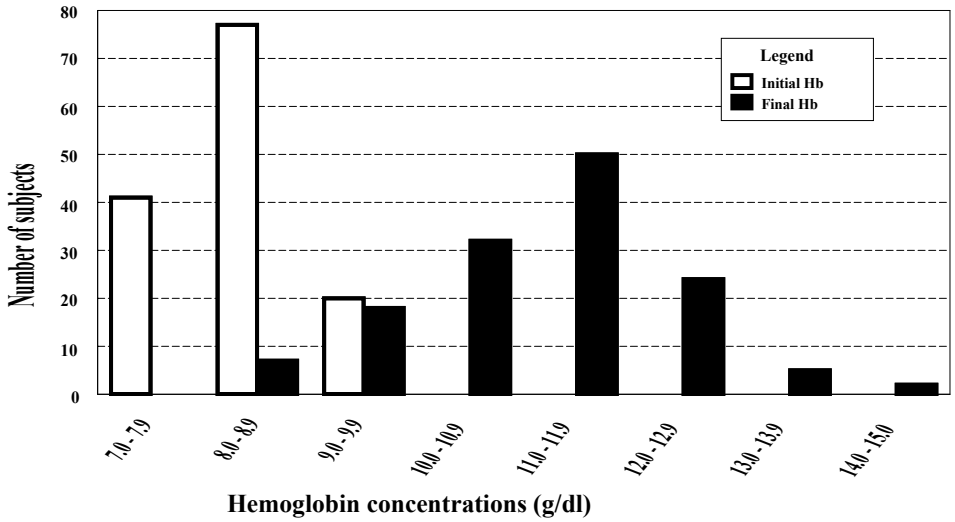

Figure 1: Blood haemoglobin concentrations before and after consuming supplements containing 5 or 10 mg Iron (Open bars illustrate the haemoglobin concentrations before supplement consumption and the solid bars illustrate haemoglobin concentrations after consuming the supplements for 60 days)

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Figure 2 shows individual responses to consumption of the micronutrient supplements. Most subjects (92.8%; n = 192) had an increase in Hb concentration of 1g/dl or more. Six percent of the subjects had only minimal gains in Hb concentrations (0–0.9 g/dl) while 3.5 % percent of the subjects had lower Hb concentrations at the end of the study than at baseline.

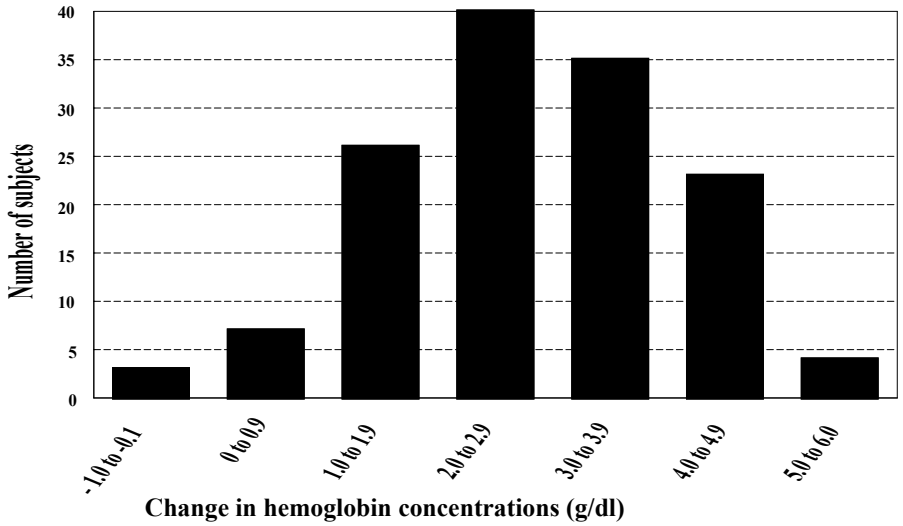

Figure 2: Changes in haemoglobin concentrations after consuming supplements for 60days

There were improvements in both weight for age and weight for height after consuming the micronutrients for 60 days. The average weight-for-age percentile for all children increased from 16.0 to 20.6% while their weight for height increased from 4.0 to 13.3%.

Malaria occurrence did not change ($p > 0.05$) when supplements containing iron were consumed. Since there were no differences in malaria occurrence between the two treatment groups at any time point, the data for the two treatments were combined (Table 3). At baseline screening, 10.3 % of the children had malaria parasitaemia. The incidence of malaria parasitaemia was 10.0% at the 30 day time point and 10.1% after consuming the supplement for 60 days.

Table 3: Malaria parasitaemia prevalence among children

Period	N	Children with malaria parasitaemia (%)
Baseline	192	20 (10.3)
30 days	160	16 (10.0)
60 days	139	14 (10.1)

Table 4 summarises the physical and behavioral changes that were reported by the parents/care givers after the iron supplementation period. The most common behaviour change was increase in appetite (80%, n = 128) followed by decreased mealtime problems (35%, n = 56), increased attention (22.5%, n = 36), increased interest in school (6.2%, n = 10) and decreased aggressive behaviour (5%, n = 8). Major physical changes were increase in monthly weight gain, child became more playful/active and decrease in the frequency of common illnesses.

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Table 4: Physical and behaviour changes observed after iron supplementation

Attribute	No. of respondents	Percent
Increased monthly weight gain	125	78.0
Increased appetite	128	80.0
Decreased frequency of illness	96	60.0
Child more playful or active	72	45.0
Increased interest in school	10	6.2
Decreased aggressive behaviour	8	5.0
Increased attention	36	22.5
Decreased meal time feeding problems	56	35.0

Discussion

A diversified diet and national food fortification of staple foods are considered the optimal long term approaches for minimizing under-nutrition. However, iron supplementation in the form of pills or micronutrient sprinkles is taken as a short term emergency approach to address the problem of iron deficiency anaemia. Tanzania, along with international development partners, is launching several food fortification initiatives to improve micronutrient intake especially for children under the age of five years (MoHSW, 2009). Achieving diet diversity and widespread utilization of fortified food is usually a very slow process. Moreover, even with diet diversity and use of fortified food staples, adequate intakes of iron and other micronutrients for children 6 – 24 months is very difficult due to the high nutrient demand for this age group which is also compounded by their limited capacity to ingest sufficient quantities of food. Use of fortified complementary foods for infants and young children especially in rural communities is still limited due to unavailability and high cost.

Deficiencies of iron, vitamin A, vitamin B_{12}, folate, riboflavin and copper are associated with anaemia, but iron deficiency is the cause of approximately 50% of global anaemia (WHO, 2001). There are also non-nutrient causes of anaemia. These include parasitic infection – hookworms, ascaris, and schistosomiasis that cause blood loss; malaria which causes red blood cell destruction and bacterial infections which cause acute or chronic inflammation (Crawley, 2004).

Based on the results of this study, anaemia was corrected by the use of both low and high doses of iron with the average Hb concentration of 11.18 g/dl (high dose) and 11.02 g/dl (low dose). The findings of this study show significant improvements in Hb status at the end of the study. Similar increments in Hb concentrations were reported by Iannotti *et al*. (2006) among children 0–59 months who were receiving iron supplement. A study on growth performance of anaemic underfive children following iron supplementation also showed significant improvement in the Hb levels (Matla & Seshadri, 1993). About 18% of the children receiving the iron supplement remained moderately anaemic at the end of the study. This could be due to malaria episodes that were reported by some of the parents/care givers and also inadequate intake of nutrients from the normal diets and also presence of other hemoglobinopathies. Malaria infection has been reported to contribute to the development and severity of anaemia through the destruction of parasitized red blood cells, through immune mechanisms including the destruction of un-parasitized red blood cells and through dyserythropoiesis (Tortora & Grabowski, 2003).

During the second 30 day period, 15.1% of the children with Hb concentrations < 11 g/dl had a decline in their Hb concentrations. This could be due to presence of inflammation in response to infections by pathogens (bacteria, viruses and protozoa). Inflammation, is a strong deterrent to Hb synthesis (erythropoiesis) even if all nutrients required for Hb synthesis are present (Prentice, 2008; de Mast *et al.,* 2009a; de Mast *et al.,* 2009b; Prentice *et al.,* 2010; Wang *et al.,* 2011). Inflammatory cytokines in response to infection stimulate release of the peptide hormone hepcidin from the liver. Hepcidin reduces plasma iron concentrations by degrading the membrane-bound iron-transporting protein, ferroportin, (Nemeth *et al.,* 2004; Delaby *et al.,* 2005)

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and by inhibiting release of iron from iron stores in the liver, macrophages, reticulocytes, and intestines. Insufficient iron transport to the bone marrow impairs erythropoiesis leading to anaemia. Effective malarial treatment leads to reduced plasma hepcidin and normalization of erythropoiesis although impaired iron transport may linger for up to two weeks after malarial treatment (Doherty *et al.,* 2008; Cercamondi *et al.,* 2010). Since the study was conducted in a malaria holoendemic area where the children, the percentage of children that had an increase in Hb ≥ 2 g/dl in two months was quite remarkable.

Parents reported that their children had increased appetite and thus were eating more and were also engaged in more play activities as a result of consuming the micronutrient supplement (Table 4). This observation echoed findings from a study by Lawless *et al*. (1994) who reported a significant improvement in appetite, physical activities and growth among school age children who were receiving iron supplement in Kenya. The increase in weight for age and weight for height indicated "catch-up growth" was beginning and the parents' observation that there was greater voluntary food consumption was correct. Lawless *et al.* (1994) reported that, increase in weight for height and not weight for age was the typical marker of improvement in health associated with correction of anaemia. Increase in weight for height for children in this study ranged between 3–13%. Similar increase in weight for height among anaemic children receiving iron supplement has been reported in other studies elsewhere (Matla & Sheshadri, 1993; Lawless *et al*., 1994). In a separate study, Iannotti *et al.* (2006) noted that, good catch up growth was only observed among children who were moderately and severely anaemic and this growth declined as the iron status of the children improved to near-normal/normal.

The presence of malaria parasitaemia remained fairly constant with no increase of malaria prevalence during iron supplementation. Screening for malaria trophozoites and prompt treatment of malaria at early onset of fever appeared to be sufficient measures to prevent severe complications arising from malaria. Malaria was very common among residents of the study area and the risk of contracting more bouts of malaria was a major concern for the parents. The overall health of their children was therefore dependent on the combined efforts of controlling malaria and supplementing the children with micronutrients.

In conclusion, this study demonstrated that, micronutrient supplements containing low-dose ferric-EDTA can be safely utilized in malaria holoendemic areas to alleviate iron deficiency anaemia. This would in turn minimize the risk of serious adverse health events associated with the use of high dose iron supplement. It is recommended that, a larger study should be conducted to affirm the effectiveness of the low-dose ferric-EDTA in controlling iron deficiency anaemia among underfive children.

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