MULTIPLE MICRONUTRIENT (ZINC, MAGNESIUM) THERAPY TO SEVERE MALNOURISHED CHILDREN: EFFECT ON GROWTH CATCH UP AND CLINICAL RECOVERY

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Abstract

Objective: to supplement zinc and magnesium to severe malnourished children aiming to improve catch up growth and clinical recovery. *Design:* It was a case control study conducted among one hundred severely malnourished children who were purposively enrolled from the nutritional unit of Dhaka Shishu Hospital, Dhaka, Bangladesh. The children were distributed in four groups each comprising twenty-five children having uniform morbidity. Along with the recovering diet and nutrient supplements, the interventional three groups received single zinc, single magnesium and combination of zinc and magnesium therapy. The control group received only the recovery diet and supplement. Increment of growth catch up and hospital stay time was measured and recoded. *Setting:* Nutritional unit of Dhaka Shishu Hospital, Dhaka, Bangladesh. *Subjects:* one hundred severe malnourished children. *Results:* It was resulted in that single zinc or magnesium and combination of zinc-magnesium therapy significantly

($p<0.05$) improved the growth catch-up and clinical recovery of the malnourished children. *Conclusions:* Multiple Zn and Mg therapy was found to be more effective than the single Zn or Mg therapy in improving the growth catch-up and clinical recovery of the malnourished children.

Keywords: Multiple micronutrient therapy, Zinc, Magnesium, Growth catch-up, Clinical recovery rate

Introduction

Malnutrition continues to be a major public health problem throughout the developing world, particularly in southern Asia and sub-Saharan Africa. The high prevalence of bacterial and parasitic diseases in developing countries contributes greatly to the malnutrition there. Likewise malnutrition increases susceptibility to and severity of infections and is thus a major cause of illness and death from disease. Malnutrition is consequently the most vital risk factor for the disease burden in developing countries. Poverty is the main underlying cause of malnutrition and its determinants (Müller & Krawinkel, 2005). Worldwide, an estimated 925 million people are undernourished, most of whom are living in developing countries (World Hunger and Poverty Facts and Statistics, 2012). Pregnant women, lactating mothers and children are particularly vulnerable to the consequence of malnutrition. Its devastating impact starts in the mother's womb – where the fetus cannot develop properly complicating its physical and mental development. Children under 5 years of age are at the highest risk of malnutrition because of their fast growth and hard time fighting off disease. It is documented that more than 70 percent of malnourished children live in Asia, 26 percent in Africa and 4 percent in Latin America and the Caribbean, half of whom live in India, China and Bangladesh (Unicef statistics, 2005). Malnutrition is by far the largest contributor to child mortality globally, currently present in half of all deaths- 5.5 million of the 11 million child deaths every year (World Hunger and Poverty Facts and Statistics, 2012). These young children are prematurely and needlessly lost. Overcoming malnutrition is a precondition for ensuring rapid and appropriate development.

Malnutrition is referred to as an "invisible" emergency because it is much like an iceberg and its deadly menace lies mostly hidden from view. It is documented that malnutrition is not the outcome of a single nutrient deficiency but a consequence of multiple nutrient deficiencies (Winichagoon, 2008). Protein-energy malnutrition, also referred to as malignant malnutrition (Wapnir, 2000; World Hunger Facts, 2009; El Hassan, 2004) is associated with multiple micronutrient deficiencies (Winichagoon, 2008; World Hunger Facts, 2009; Squali et al, 19978;

Romeyn, 1998). Micronutrients play a vital role in the development of physiological growth, cognitive function and immunity and in the reduction of morbidity and mortality in malnourished children (Doherty et al, 1998; Black & Sazawal, 2001; Black et al, 2004). Deficiency of micronutrients contributes to the etiology of impairment of physiological functions and development including impairment of immunity consequently increasing susceptibility to infections (Elizabeth, 2000).

It is reported that micronutrient deficiencies are widespread among 2 billion people in the developing and developed countries (Wapnir, 2000; Jamil et al, 2008;Tulchinsky, 2010). It is the underlying cause of morbidity and mortality. Zinc is an essential trace element of 'exceptional biologic and public health importance'. It affects growth by stimulating DNA and RNA synthesis and cell division. It is a cofactor of many metalloenzymes that are involved in numerous biochemical processes like skin integrity, tissue growth, bone formation, cognitive development and immunity (Wapnir, 2000; Zemel et al, 2002; Siklar et al, 2003; Nriagu et al, 2007).

Zinc deficiency is a key micronutrient deficiency and is associated with many diseases. It is a likely marker for monitoring the severity of disease and the response to therapy (Karyadi, 2002). Zinc deficiency affects about 2 billion people in the developing world resulting in growth retardation, hypogonadism, immune dysfunction and cognitive impairment (Prasad, 2009). Magnesium is essential for maintaining normal muscle and nerve function, keeping a healthy immune system, maintaining heart rhythm and building strong bones. This element is involved in at least 300 biochemical reactions in the body. Magnesium deficiency is also prevalent in severely malnourished children (Bhan et al, 2003). In protein energy malnutrition, hypomagnesaemia may lead to develop the manifestation of neuromuscular hyperirritability and cardiac complications. As cofactor of many enzymatic reactions, magnesium is indispensable for a large number of metabolic steps including most of those concerned with transfer or utilization of energy, protein synthesis and normal activity of the nervous system (Bhan et al, 2003).

Micronutrient deficiencies remain as a major health concern for children in Bangladesh, where nearly half of the population is children (Jamil et al, 2008). This study has attempted to supplement zinc and magnesium to severe malnourished children aiming to improve catch up growth and clinical recovery.

Methods

It was a prospective case-control study. Single and combined zinc and magnesium therapies were given to severe malnourished children to improve their growth catch-up and clinical recovery.

Study Population: One hundred hospitalized malnourished children of 6-60 months age were enrolled from the nutritional unit of Dhaka Shishu Hospital, Dhaka, Bangladesh. On admission into the hospital, weight, height and mid arm circumference of the children were measured. Their nutritional status was assessed by height for age (s*tunting)*, weight for age *(underweight)*, weight for height (*wasting)* and the presence or absence of edema. The children were clinically classified into marasmic, marasmic-kwashiorkor and kwashiorkor

The degree of malnutrition was diagnosed by resident physician on the basis of clinical signs and anthropometric data. The children were enrolled purposively on the basis of certain defined exclusion criteria. Inclusion criteria were 6-60 months age of both sex, nutritional status comprising <70% weight for height of NCHS mean (Waterloo classification), <60% weight for age of NCHS mean (Gomez classification) and presence or absence of edema. Exclusion criteria were receipt of any micronutrient therapy before and after admission into the hospital, renal failure, edema due to other disease like congestive cardiac failure, nephrotic syndrome, liver cirrhosis and congenital anomalies, unconscious and meningitis. In order to conduct the study, ethical permission was obtained from the Ethical Board of Dhaka Shishu Hospital.

Interventional subject and control: One hundred severe malnourished children were distributed in four groups each comprising twenty-five children having uniform morbidity. All of the enrolled children were receiving recovery diet (according to nutritional dietary protocol followed in the nutritional rehabilitation unit of the hospital) and supplements of multivitamins, potassium chloride and high potency vitamin-A capsules (100000-200000 I.U) as recommended by World Health Organisation (Ashworth et al, 2003). The interventional groups received zinc or magnesium or combination of zinc and magnesium along with the recovery diet and supplement. The control group received only the recovery diet and supplement.

Interventional dose design, dose content and dose schedule

Study group	***Intervention given***
	Supplementation subject
Group I	*Zinc*+Multivitamins+vitamin A+KCl
Group II	*Magnesium*+Multivitamins+vitamin A+ KCl
Group III	*Zinc+Magnesium+(*Multi-vitamins+vitamin A+ KCl
	Control subject
Group-IV	Multi-vitamins+vitamin A+KCl

Dose design*		**Dose content**
Zinc	oral elemental zinc	2-3mg/kg/day for 30days
Magnesium	Injection $MgSO_4$	0.3mmolMg/kg/day for 7days
Multivitamin	>1year age	Iml twice daily for 30 days
	<1year age	0.5ml twice daily for 30days
Vitamin A	>1year age	200000 IU on day 1, 2 and 15
Potassium	syrup K-20	4mmol/kg thrice daily for 15days

*The dose was designed as recommended by WHO (Ashworth et al, 2003).

Measurement of anthropometry and diagnosis of morbidity: Body weight of the children was taken to the nearest 100g on 25kg Salter spring scales (Salter Weigh-Tronis Model 235 PBW, UK). The child was held in a specially designed "bag" to measure the weight. Since the measurement of standing height for children under two years of age is not possible, a recumbent length (crown-heel length) was measured. The length of the child was read to the nearest 0.1cm. For children 2 years and above, a vertical height scale was used. The measuring scale was 175cm high and measured to an accuracy of 0.1cm. Mid arm circumference (MAC) was measured using a specialized tape designed for the purpose. Morbidity among the children was diagnosed by clinical signs and symptoms by a pediatric consultant (one of the author: ASM Mustafizur Rahman), and partly by laboratory investigation. The interventional therapy was carried out under direct care of the consultant.

Statistical analysis: The SPSS software package (12.5 version; SPSS, Inc., Chicago, USA) was used for statistical analysis. Data were presented as mean±SD. Comparison of growth catch up and clinical recover between and within groups were performed by student's *t* test and analysis of variance.

Results

The malnourished children were categorized into non-edematous (marasmas) and edematous (marasmic-kwashiorkor and kwashiorkor) (table 1). The majority of children were in age group of <12-24 months. By sex, children in both of non-edematous and edematous group were predominantly male.

The mean z-score for indices- height for age (s*tunting)*, weight for age *(underweight)*, and weight for height (*wasting)* of the non-edematous children (n=54) were -3.8±1.6, -4.7±0.7 and -3.1±1.1 respectively, while for the edematous (n=46) these scores were -3.4±1.4, -3.7±1.3 and -1.9±1.4 respectively (table 2). The z-scores for weight for age *(underweight)* and weight for height (*wasting)* were significantly (p=0.00) lower in edematous children than those in the non-edematous ones.

Table 1: Distribution of malnutrition by marasmas, marasmic-kwashiorkor and kwashiorkor by age and sex

Parameter	Marasmas(n=54) %(n)	Marasmic-kwashiorkor (n=28) %(n)	Kwashiorkor (n=18) %(n)
Age in months			
< 12	38.9 (21)	35.7 (10)	50.0 (9)
12 – 24	44.4 (24)	35.7 (10)	50.0 (9)
24 – 36	3.7 (2)	14.3 (4)	0.0 (0)
36 & above	13.0 (7)	14.3 (4)	0.0 (0)
Sex			
Male	51.9 (28)	53.6 (15)	61.1 (11)
Female	48.1 (26)	46.4 (13)	38.9 (7)

Table 2: Anthropometric indices of malnourished children expressed in mean±SD

Anthropometry	Non-edematous (n=54)	Edematous (n=46)	Significance
Z-scores			
Height for age	-3.8±1.6	-3.4±1.4	p= 0.19
Weight for age	-4.7±0.7	-3.7±1.3	p = 0.00
Weight for height	-3.1±1.1	-1.9±1.4	p= 0.00

Significance: $p<0.05$
Compare mean: Independent-t-test

In term of morbidity episodes, single morbidity was prevalent in the non-edematous children, while multiple sufferings were predominant in the edematous children (table 3). It was observed that 20.4%, 29.6% and 27.8% of non-edematous children were suffering from pneumonia, diarrhea, and pneumonia plus diarrhea respectively, while only 4.3% edematous children were suffering from diarrhea. It was seen that suffering from multiple morbidities were greatly high (23.9% to 43.5%) in edematous children than those in the non-edematous children (only 3.7% to 9.3 %).

Table 3: Morbidity pattern of severe malnourished children

Morbidity	Non-edematous (n=54) %(n)	Edematous (n=46) %(n)
Pneumonia	20.4 (11)	0.0 (0)
Diarrhea	29.6 (16)	4.3 (2)
Pneumonia + Diarrhea	27.8 (15)	0.0 (0)
Diarrhoea + others	7.4 (4)	28.3 (13)
Pneumonia + others	9.3 (5)	23.9 (11)
Pneumonia+Diarrhea+others	3.7 (2)	43.5 (20)
Others diseases	1.9(1)	0.0 (0)

Morbidity was uniformly distributed among the interventional and control groups (table 4).

Table 4: Morbidity pattern of severe malnourished children by interventional groups

Morbidity	Groups %(n)			
	Zn	Mg	Zn+Mg	No Zn+Mg
Pneumonia	0.0 (0)	12.0 (3)	12.0 (3)	20.0 (5)
Diarrhea	16.0 (4)	12.0 (3)	16.0 (4)	28.0 (7)
Pneumonia + Diarrhea	16.0 (4)	16.0 (4)	24.0 (6)	4.0 (1)
Diarrhoea + others	32.0 (8)	8.0 (2)	16.0 (4)	12.0 (3)
Pneumonia + others	20.0 (5)	16.0 (4)	16.0 (4)	12.0 (3)
Pneumonia+Diarrhea+other	16.0 (4)	36.0 (9)	16.0 (4)	20.0 (5)
Others	0.0 (0)	0.0 (0)	0.0 (0)	4.0 (1)

The effect of single and multiple micronutrient interventions on growth and clinical recovery are described in table 5 and 6. The growth catch-up was expressed in terms of increment of weight, height and mid arm circumference. The clinical recovery rate was expressed in term of hospital stay time. Significance of difference in growth catch-up between different interventional groups was tested by paired t-test, and that among edematous and non-edematous children was analyzed by one-way analysis of variance. Except for few cases, single zinc, single magnesium and combination of zinc-magnesium therapy improved growth catch-up significantly ($p<0.05$) in the malnourished children. The highest growth catch-up in term of increment of weight, height and MAC was obtained with zinc-magnesium therapy. The next increment was with zinc followed by magnesium therapy. It was further noted that the marasmic children had shown the highest growth increment, which was followed by marasmic-kwashiorkor and kwashiorkor children. Compared to the control group, zinc-magnesium therapy has had the highest ($p<0.001$) increment of weight, height and MAC value in the marasmic children followed by in the marasmic-kwashiorkor and the kwashiorkor children.

One-way analysis of variance showed that except the height gain by magnesium therapy ($F(2,21)=0.73$, $P=0.49$), there had a strong effect ($p=0.001$) of single and multiple micronutrient therapy on weight and height gain among interventional edematous and non-edematous children and between the interventional and control children ((table 5).

Table 5: Effect of micronutrient therapy on growth in term of gain in Weight (gm), Height (cm) and MAC (cm)*

Malnutrition	Zinc therapy[a]				Magnesium therapy[b]				Zn-Mg therapy[c]				No Zn-Mg (control)[d]			
	no	Weight[x]	Height[y]	MAC[z]	no	Weight[x]	Height[y]	MAC[z]	no	Weight[x]	Height[y]	MAC[z]	no	Weight[x]	Height[y]	MAC[z]
[1]Marasmas	13	130 5.0 ±3 11. 0	1.1 1 ±0. 10	1.0 6 ±0. 12	11	107 1.0 ±6 4.0	0.7 1 ±0. 05	0.6 3 ±0. 13	15	152 8.0 ±1 90. 0	1.3 1 ±0. 10	1.2 5 ±0. 12	14	891 .0 ±5 6.0	0.6 5 ±0. 10	0.5 4 ±0. 17
[2]Marasmic-Kwarshiorkor	7	584 .0 ±8 5.0	0.9 0 ±0. 13	0.7 3 ±0. 11	9	422 .0 ±1 30. 0	0.6 9 ±0. 12	0.6 2 ±0. 10	5	734 .0 ±3 19. 0	1.0 0 ±0. 10	0.9 6 ±0. 11	6	387 .00 ±5 8.0	0.5 7 ±0. 10	0.5 2 ±0. 07
[3]Kwarshiorkor	5	619 .00 ±6 7.0	0.9 4 ±0. 09	078 ±0. 16	4	489 .00 ±3 4.0	0.7 5 ±0. 06	0.5 5 ±0. 06	4	750 .00 ±9. 0	1.0 5 ±0. 10	0.8 3 ±0. 32	5	439 .00 ±1 3.0	0.6 0 ±0. 10	0.5 4 ±0. 07

* expressed by mean±sd

[1abx]: t=-2.44, p=0.023; [1acx]: t=-2.35, p=0.028; [1adx]: t= -4.90, p=0.001; [1bcx]: t= -7.63, p=0.001; [1bdx]: t= -7.55, p=0.001; [1cdx]: t=-12.06, p=0.001
[1aby]: t=-12.27, p=0.001; [1acy]: t=-5.27, p=0.001; [1ady]: t= -8.96, p=0.001; [1bcy]: t= -7.63, p=0.001; [1bdy]: t= -1.74, p=0.096; [1cdy]: t=-17.22, p=0.001
[1abz]: t=-8.15, p=0.001; [1acz]: t=-4.0, p=0.001; [1adz]: t= -8.96, p=0.001; [1bcz]: t= -12.13,p=0.001; **[1bdz]: t= -1.35, p=0.191;** [1cdz]: t=-12.92, p=0.001

[2aby]: t=-2.8, p=0.013; [2acx]: t=-1.21, p=0.254; [2adx]: t= -4.76, p=0.001; [2bcx]: t= -2.63, p=0.022; **[2bdx]: t= -0.62, p=0.544;** [2cdx]: t=-2.64, p=0.027
[2aby]: t=-3.43, p=0.004; **[2acy]: t=-1.44, p=0.180;** [2ady]: t=-5.08, p=0.001; [2bcy]: t= -5.00, p=0.001; [2bdy]: t= -2.08, p=0.058; [2cdy]: t=-7.03, p=0.001
[2abz]: t=-2.04, p=0.061; [2acz]: t=-3.52, p=0.006; [2adz]: t=-3.94, p=0.002; [2bcz]: t= -5.87, p=0.001; [2bdz]: t= -2.24, p=0.043; [2cdz]: t=-7.75, p=0.001

[3aby]: t=-2.8, p=0.013; **[3acx]: t=-1.21, p=0.254;** [3adx]: t= -4.76, p=0.001; [3bcx]: t= -2.63, p=0.022; **[3bdx]: t= -0.62, p=0.544;** [3cdx]: t=-2.64, p=0.027
[3aby]: t=-3.48, p=0.010; [3acy]: t=-2.49, p=0.042; [3ady]: t=-5.67, p=0.001; [3bcy]: t= -5.2, p=0.002; [3bdy]: t= -2.65, p=0.033; [3cdy]: t=-5.67, p=0.001
[3abz]: t=-2.64, p=0.033; **[3acz]: t=-0.28, p=0.791;** [3adz]: t=-2.4, p=0.043; **[3bcz]: t= -1.69, p=0.142;** [3bdz]: t= -0.12, p=0.905; **[3cdz]: t=-1.78, p=0.119**

Significance: p< 0.05)

Legend: Paired t-test

[ax123]F(2,22)=28.04, P=0.00; [ay123]F(2,22)=10.60, P=0.00; [bx123]F(2,21)=138.29, P=0.00; [by123]F(2,21)=0.73, P=0.49
[cx123]F(2,21)=38.99, P=0.00; [cy123]F(2,21)=22.05, P=0.00; [dx123]F(2,22)=270.90, P=0.00; [dy123]F(2,22)=1.53, P=0.24

L*egend: Compara means: One-way ANOVA (Descriptive, ANOVA).*

Period of hospital stay was used as the indicator for clinical recovery rate by the micronutrient therapy. It was seen that except for magnesium therapy in marasmic children (p=0.282), there was a significant (p<0.05) clinical recovery within interventional groups and within interventional and control group in both edematous and non-edematous children (table 6).

Table 6: Effect of micronutrient therapy on clinical recovery in term of hospital stay in day

Malnutrition	Zinc-therapy[a]	Ma- therapy[b]	Zn-Mg-therapy[c]	No Zn-Mg[d]
Non-edematous (Marasmas)[1]	12.00±2.25	16.00±3.10	9.00±1.64	17.00±2.25
Edematous (Kwarshiorkor& Marasmic-Kwarshiorkor)[2]	16.00±2.90	19.00±2.40	12.00±2.50	20.00±1.50

Significance: P<0.05

[1ab]: t=3.36, p=0.003 [1ac]:t=4.25, p=0.001 [1ad]: t=5.84, p=0.001
[1bc]: t=7.04, p=0.001 [1bd]: t=1.10, p=0.282 [1cd]: t=11.40, p=0.001
[2ab]: t=2.62, p=0.015 [2ac]: t=2.87, p=0.009 [2ad]: t=4.73, p=0.001
[2bc]: t=5.96, p=0.001 [2bd]: t=2.18, p=0.040 [2cd]: t=8.94, p=0.001

Legend: paired t-test

Discussion

Micronutrient malnutrition is a prevalent public health problem in the world. It is rapidly increasing among socio-economically deprived people of the developing countries like Bangladesh. Micronutrients stimulate growth, cognitive function and immunity, all of which impairs are impaired by micronutrient deficiency (Rodriguez-Soriano, 1990; Singla et al, 1998; Black et al, 2004)**.** Supplementation of micronutrients has been reported to pick up growth, improve cognitive function, develop immunity and consequently reduce morbidity in the malnourished children (Black et al, 2004; Doherty et al, 2002; 1998; Lira et al, 1998; Sazawal et al, 1998). Most of these findings have been reported for single micronutrient intervention. It is documented that malnutrition is the outcome of multiple nutrient deficiencies (Bachou, 2001; Bhan et al, 2003), therefore, malnutrition currently refers to multiple micronutrients malnutrition. Hence in order to overcome malnutrition, multiple micronutrients therapy should be initiated. Research on multiple micronutrient therapy, even it steps up growth or cognitive function or immunity, is still limited. Only few reports have recently been documented with multiple micronutrient supplementations (Black et al, 2004; Bachou, 2001; Hurrel, 2001). This study has attempted to supplement single zinc, single magnesium and combination of zinc and magnesium to the severe malnourished children aiming to improve their growth catch up and clinical recovery rate.

It was observed that the malnourished children were suffering from typical multiple morbidities, which were predominantly high in the edematous children. Micronutrient therapy either single or multiple significantly improved the catch-up growth amongst the interventional malnourished children. The growth increment was highest with the combination therapy of zinc and magnesium ant it was followed by single zinc and single magnesium. This outcome is consistent with other reports (Lira et al, 1998; Zemel et al, 2002) and it is because of potential role of Zn and Mg in growth regulation (Nriagu, 2007; Altura & Altura, 1996). Further it is documented that Zn and Mg deficiency are associated with infections including diarrhea, pneumonia and others (Nriagu, 2007; Sunguya et al, 2006; Sazawal et al, 1998; Caddell, 1969; Nichols et al, 1978). Present study showed that both the single and multiple zinc and magnesium therapy to the severe malnourished children significantly sped up clinical recovery in term of reducing the hospital stay. It was observed that like growth increment, zinc-magnesium multiple intervention also afforded the highest clinical recovery rate, which was followed by single Zn and then Mg therapy. Clinical recovery with zinc and magnesium supplementation has also been claimed by other investigators (Nriagu, 2007; Baqui et al, 2002; Sazawal et al, 1998; Altura & Altura, 1996).

Conclusion

Mutliple zinc and magnesium therapy to severe malnourished children manifested faster improvement of growth catch-up and clinical recovery. Therefore, along with recovery diets and supplements, multiple micronutrient therapy is to be given during rehabilitation of malnourished children.

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