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Evaluating the Effect of Nutritional Supplementation Combined with Counseling on Nutritional Recovery in Immune - Compromised Indian Children

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Abstract

Background: Malnutrition in an HIV-infected child leads to muscle wasting, micronutrient deficiency, impaired immune system and reduced ability to fight infections. It also increases the susceptibility to infections due to an increased oxidative stress. Chronic oxidative state can weaken immune system's fight against HIV.
Aim: The present study was undertaken to assess the impact of nutritional supplementation on the HIV progression.
Methods: This open, prospective, interventional, case control pilot study was conducted in 100 HIV infected children, aged between 6 months to 15 years, fulfilling criteria of Moderate Acute Malnutrition (MAM) and criteria of thinness based on Body Mass Index (BMI) as per WHO definition, either not on ART and/or on ART, but failing to gain weight as observed in 2 consecutive visits one month apart. Study and control group had 50 subjects each. Intervention comprised of multigrain-micronutrient-rich *laddus* along with counseling for a period of 6 months for cases. Controls received nutritional counseling along with standard care.
Results: The male to female ratio was 2:1, median age being 132 months in cases and 120 months in controls. The mean weight was 24.53 kg in cases and 21.46 kg in controls after 6 months (p=0.03). Cummulative mean weight gain in cases over 6 months was 10.78 gms/day, while that in controls was 3.85 gms/day, with the maximum weight gain of 14.38 gms/ day noted in cases in the first month of intervention. There was higher weight gain in subjects receiving laddus as compared to subjects receiving only nutritional counseling. The mean gain in height after 6 months of intervention was 2.96 cm in cases and 2.19 cm in controls (p=0.007). The CD4 counts and antioxidant levels were statistically non-significant but showed improving trends.
Conclusions: Energy dense micronutrient rich supplementation will delay the HIV progression.
Keywords: Human Immunodeficiency Virus (HIV), Anti-Retroviral Therapy (ART), Moderate Acute Malnutrition (MAM), Nutritional supplementation.
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1. Introduction

Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) is a significant cause of global mortality and morbidity. Prevalence of HIV, according to UNAIDS fact sheet 2016, continues to be high with new infections in the age of 0–14 years being 1.5 lakhs in 2016. India has the third largest number of HIV cases in the world [1]. The state of Maharashtra has a high burden of HIV, with 1, 38,456 Children Living with HIV (CLHA) and 74,220 children on Antiretroviral Therapy (ART) [2].

HIV virus attacks the immune system especially the CD4 cells that help our body fight infections. If left untreated, CD4 cells are destroyed in large numbers by the HIV virus thereby leading to immunosuppression making the patients prone to opportunistic infections [3]. Perinatally infected babies have very high viral load. Furthermore, the body's response against the HIV virus is inadequate because of immature and developing immune system. Thus, these babies progress rapidly towards AIDS.

HIV with malnutrition is a complex medical condition that carries significant morbidity and mortality which often overlap and interact. Importantly, mortality from Severe Acute Malnutrition (SAM) is more than three times higher in HIV-positive children than their HIV-negative peers [4]. There exists a vicious cycle between HIV/AIDS and malnutrition. The need of energy and nutrients is increased to cope with HIV and other infections. If these increased needs are not met, malnutrition sets in; malnutrition contributes to a weakened immune system, which worsens the effect of HIV.

The impaired immune function resulting from lack of essential micronutrients has been called *Nutritionally Acquired Immune Deficiency Syndrome* (NAIDS). NAIDS may contribute to further depletion and dysfunction of CD4 cells and also makes a person susceptible to other infections which may in turn increase viral replication and quicken HIV progression [5].

In early stage of infection there is redox imbalance which results in increased damage to cells by free radicals, thus depleting antioxidants [6]. The antioxidants Vitamin A, C, E were found to be low in HIV infected children than normal [7].

HIV infected children are often deficient in one or more micronutrients because of inadequate intake, impaired absorption or utilization as well as increased nutrient needs from secondary infection [8]. Micronutrients are important for maintaining optimal functioning of the individual's immune response. A combination of vitamin/ mineral supplement offering a complete array of nutrients provides benefit to the immune system [9]. Children with HIV in general require high energy, high protein, and nutrient rich diets. Depending on the clinical status energy requirement may vary from 75 to 150% of recommended daily allowance along with, protein 100 to 150% of recommended daily allowance, to support the immune system and avoid muscle wasting [10].

Malondialdehyde (MDA), the product of lipid peroxidation is an enzyme that serves as a marker of oxidative stress in the body [8]. HIV infected patients commonly excrete higher than average quantities of MDA into their serum and urine, reflecting increased levels of lipid peroxidation [11-12]. Vitamin C is an antioxidant nutrient that protects tissues against damage by reactive oxygen and nitrogen species. Low plasma concentrations of vitamin C have been associated with a greater risk of progression to AIDS [13]. It must be emphasized that good nutrition cannot cure AIDS or prevent HIV infection, but it can help to maintain and improve the nutritional status of a person with HIV/AIDS and delays the progression from HIV to AIDS-related diseases [14]. Keeping this in mind, we planned the present study with an aim to determine the effectiveness of nutritional supplementation on nutritional and biochemical parameters such as antioxidant levels and CD4 counts in immuno-compromised children.

2. Methods

This was an open, prospective, interventional pilot study conducted in the Pediatric Centre of Excellence for HIV Care, at the Department of Pediatrics in a tertiary care medical college and hospital, from October 2013 to August 2015. Permission of Institutional Ethics Committee was taken and written informed consent was obtained from the parents before starting the study.

The inclusion criteria were HIV-infected children between 6 months to 15 years, fulfilling the criteria of Moderate Acute Malnutrition (MAM) and criteria of thinness based on Body Mass Index as per WHO definition, either not on ART and/ or on ART, but failing to gain weight as observed in 2 consecutive visits. The patients already on vitamin/ mineral or any other nutritional supplementation were excluded. For children above 8 years of age assent was also taken. History and examination findings were documented in a pre-designed case-record form. Being a pilot study, patients were randomized into study and control group with 50 patients in each using a computer generated random number table. The study group was started on nutritional supplements in the form of *laddus* which were multigrain, energy-dense, micronutrient enriched (composition in Table.1.0 A and 1.0 B.) along with counseling to receive 33% calories and 50% proteins of recommended dietary allowance (RDA) through the *laddus*, for a period of 6 months as per their body mass index (BMI).

Table 1 (A): Composition of Micronutrient Laddu Mix

Micronutrients in premix given	Amount / 0.9 g powdered mix FT092676: 0.18 g, FT092677: 0.72 g
Vitamin A	2500 IU= 1,375 mcg.
Vitamin C	30 mg.
Vitamin D3	200 IU =5 mcg.
Vitamin E	15 IU =11 mg.
Vitamin B1	0.75 mg
Vitamin B2	0.55 mg
Vitamin B6	1 mg
Vitamin B12	3 mcg.
Folic acid	0.2 mg = 200 mcg.
Niacin	10 mg.
Pantothenic acid	5 mg.
Biotin	0.15 mg
Iron	7.2 mg.
Zinc	3 mg.
Copper	0.4 mg.
Iodine	75 mcg.
Magnesium	80 mg.
Manganese	0.5 mg.
Phosphorus	100 mg.
Calcium	129 mg.
Maltodextrin	Base

Table 1 (B): Composition of Laddu Mix

Composition	Weight	Protein	Calories
Wheat Flour	3.0 gms	0.3	11
Bengal Gram	5 gms	1.2	17
Soya Flour	3 gms	1.4	14
Skimmed Milk Powder	7.5 gms	2.5	18
Powdered Sugar	6 gms	1.7	20
Refined Sunflower Oil	6 cc	0	54
Micronutrient Mix	0.45 gms	-	-
Total	**30.5 gms**	**5**	**146**

The control group received nutritional counseling along with standard care. A detailed anthropometry weight (Wt), height (Ht) and BMI of both the groups was recorded on enrolment and at each monthly visit. All patients were investigated for baseline CD4 count at enrollment and after 6 months. CD4 count was done using flow-cytometry. Oxidative stress was assessed by monitoring vitamin C and MDA levels in a randomly selected subgroup of 20 children (10 from each group) at enrollment and after 6 months. MDA was measured by thiobarbituric acid reactive substances assay (TBRAS) method and ascorbic acid (Vitamin C) measured by dinitrophenyl hydrazine (DNPH) method. The optical densities of MDA and ascorbic acid were measured at 532 nm and 520nm, respectively, using spectrophotometer.

Statistical analysis using Chi square test was performed on *GraphPad Prism QuickCalcs*. Their mean and rate of change in weight, height, CD4 count, Vitamin C and MDA levels were calculated and analyzed using Student's-T test.

3. Results and Discussion

A total of 100 children were enrolled in the study and divided in two equal groups i.e. case and control group. Table 2 demonstrates demographic parameters, anthropometric measurements and subjects in respective WHO clinical staging of HIV. The mean age group of cases and controls were 125.24 months and 120.38 months respectively with 28 male (56%), female 22 (44%) in case group, while there were 32 male (64%) and 18 female (36%) in control group. Thus, we observed male predominance in both the cases and controls. The mean weight, height and BMI at enrollment were comparable in both the groups as depicted in Table 2. The mean BMI in case group was 13.89 and in control groups were 13.68. 80% of the children in both the groups belonged to WHO clinical stage I. Children receiving Antiretroviral therapy in cases and controls were 37 and 42 respectively. The calculated p value in demographic and anthropometric data was statistically comparable between the two groups.

Table 2: The Baseline Characteristics of Children

Characteristics	Case Group (n=50)	Control Group (n=50)	P value
Demographics			
Age (in months)	125.24 (38.65)	120.38 (34.16)	0.50
Male [n (%)]	28 (56.0%)	32(64.0%)	0.54
Female [n (%)]	22 (44.0%)	18 (36.0%)	
Anthropometric measures			
Weight (kgs)	22.58 (7.08)	20.71 (5.71)	0.50
Height (cms)	125.82 (17.47)	121.70 (16.93)	0.2
BMI	13.89 (1.33)	13.68 (1.00)	0.37
Clinical Staging			
1	40(80.0%)	40(80.0%)	0.34
2	6(12.0%)	5(10.0%)	
3	2(4.0%)	0(0.0%)	
4	2(4.0%)	5(10.0%)	
ART Status			
Pre ART	11(22.9%)	8(16.0%)	0.45
On ART	37(77.1%)	42(84.0%)	

Data: Mean (SD) or n (%), Level of Significance (α) P<0.05

The mean weight at the time of enrolment was 22.59 kg in cases versus 20.76 kg in controls (p=0.17) as depicted in table 3A. The mean weight was 24.53 kg in cases and 21.46 Kg in controls after 6 months (p=0.03). There was higher weight gain in cases as opposed to controls. There was statistically significant weight gain in cases between visit 3 - 4 (p=0.043), visit 4 - 5 (p=0.037), visit 5 - 6 (p=0.03) as shown in table 3A and 3B. Gain in weight is a more appropriate indicator than the actual weight.

Table 3: The Actual Weight during Intervention and Weight Gain between Two Visits (Visit was Made Monthly)

Visits	Case		Control		P value
A	**Weight (kgs) during Intervention**				
	n	**Mean (SD)**	**n**	**Mean (SD)**	
Visit 0	46	22.59 (7.18)	49	20.76 (5.83)	0.17
Visit 1	46	23.03 (7.28)	49	20.85 (5.87)	0.11
Visit 2	46	23.33 (7.36)	49	20.97 (5.82)	0.08
Visit 3	46	23.66 (7.48)	49	21.08 (5.81)	0.06
Visit 4	46	23.99 (7.54)	49	21.17 (5.85)	0.043
Visit 5	46	24.28 (7.65)	49	21.33 (5.85)	0.037
Visit 6	46	24.53 (7.78)	49	21.46 (5.83)	0.03
B	**Weight (kgs) gain between two visits**				**P value**
Visit 0 -1	46	0.43 (0.62)	49	0.09 (0.44)	0.003
Visit 1-2	46	0.30 (0.41)	49	0.10 (0.42)	0.022
Visit 2-3	46	0.33 (0.42)	49	0.12 (0.40)	0.018
Visit 3-4	46	0.34 (0.37)	49	0.09 (0.35)	0.001
Visit 4-5	46	0.29 (0.43)	49	0.16 (0.28)	0.10
Visit 5-6	46	0.25 (0.36)	49	0.12 (0.20)	0.03

The maximum rate of weight gain (grams/day) was 14.38 in cases and 3.05 in controls (p=0.003) in between visit 0 - 1 as revealed in table 4A. At the same time the rate of weight gain (grams/kg/day) was maximum during the same visit with 0.66±0.91 in cases versus 0.18 in controls respectively as shown in table 4B. There was statistically significant rate of weight gain (grams/kg/day) in further visits i.e. between visit 1-2 (0.022), visit 2-3 (0.018), visit 3-4 (0.001), visit 5-6 (0.03) shown in table 3B.

Cumulative mean weight gain in cases over 6 months was 10.78 gms/day while that in controls was 3.85 gms/day, with the maximum weight gain of 14.38 gms/ day noted in cases in the first month of intervention (p<0.005). Controls continued to gain weight steadily all through 6 months with the maximum weight gain of 5.41 gms/ day in the 5th month.

Table 4: Rate of weight gain (gm/day) between 2 visits

Visits	Case		Control		P value
A	**Weight gain (gm/day)**				
	n	**Mean (SD)**	**n**	**Mean (SD)**	
Visit 0 -1	46	14.38 (20.54)	49	3.05 (14.69)	0.003
Visit 1-2	46	10.07 (13.75)	49	3.41 (14.08)	0.022
Visit 2-3	46	10.91 (14.16)	49	4.15 (13.25)	0.018
Visit 3-4	46	11.38 (12.21)	49	3.03 (11.67)	0.001
Visit 4-5	46	9.53 (14.24)	49	5.41 (9.29)	0.10
Visit 5-6	46	8.41 (12.09)	49	4.08 (6.69)	0.03
B	**Rate of weight gain (gm/kg/day) between 2 visits**				**P value**
Visit 0 -1	46	0.66 (0.91)	49	0.18 (0.75)	0.006
Visit 1-2	46	0.45 (0.63)	49	0.23 (0.70)	0.10
Visit 2-3	46	0.49 (0.60)	49	0.26 (0.83)	0.10
Visit 3-4	46	0.54 (0.63)	49	0.13 (0.64)	0.002
Visit 4-5	46	0.43 (0.72)	49	0.28 (0.49)	0.20
Visit 5-6	46	0.35 (0.55)	49	0.24 (0.38)	0.20

The mean height of cases increased from 125.55 cms at baseline to 128.51 cms as compared to 121.73 cms at baseline to 123.93 cms in controls. The mean BMI at enrolment was 13.94 in cases versus 13.70 (p=0.3) in controls respectively which improved to 14.44 in cases and 13.73 in controls after 6 months of enrolment (p = 0.004). The baseline CD4 count in intervention group was 961.22 cells/ mm^3 and 901.61 cells/ mm^3 in controls. The CD4 counts were 952.48 cells/ mm^3 in cases and 878.59 cells/ mm^3 in controls after 6 months. The basal MDA level was 11.06µmols/ L in cases versus 9.61µmols/ L in controls. At 6 months of enrolment MDA was 10.61µmols/ L & 10.01µmols/ L in cases and controls respectively. At enrolment Vitamin C levels were 0.79mg/ dl versus 0.75mg/ dl in cases and controls respectively. After 6 months intervention the Vitamin C levels were 1.01mg/dl in cases and 1.00 mg/ dl in controls, (Table 5).

Out of 50 children from the interventional group, 17 children were reported to have consumed only 20 – 40% of the laddus assigned to them per day, 18 children consumed 40-80% and 14 consumed 80-100% of the laddus assigned to them per day.

Table 5: Comparison of Various Parameters from Baseline to 6 months

Parameters	Case		Control		P value
Height (cms)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	
Baseline	46	125.55 (17.26)	49	121.73 (17.10)	0.3
6 months	46	128.51 (17.06)	49	123.93 (16.60)	0.2
BMI					
Baseline	46	13.94 (1.26)	49	13.70 (0.97)	0.3
6 months	46	14.44 (1.37)	49	13.73 (0.97)	0.004
Height gain (cms)					
Baseline to 6 months	46	2.96 (1.48)	49	2.19 (1.23)	0.007
BMI gain					
Baseline to 6 months	46	0.50 (0.60)	49	0.03 (0.51)	0.001
CD4 count (cells/mm^3)					
Baseline	46	961.22 (592.85)	49	901.61(757.13)	0.70
6 months	46	952.48 (584.75)	49	878.59 (536.48)	0.5
MDA (µmols/ L)					
Baseline	9	11.06 (3.40)	10	9.61 (2.36)	0.3
6 months	9	10.61 (4.90)	10	10.01 (5.24)	0.8
Vit. C(mg/ dl)					
Baseline	9	0.79 (0.36)	10	0.75 (0.20)	0.8
6 months	9	1.01 (0.40)	10	1.00 (0.29)	0.9

4. Conclusions

This project has led to the development of an indigenously prepared, micronutrient-fortified, nutrient dense supplement which has been useful in immunocompromised children with moderate malnutrition. The maximum weight gain was observed in the first 2 months, but cases continued gaining weight throughout the supplementation. The maximum rate of weight gain was 14.38 grams/ day which was observed in the first month of supplementation. The CD4 counts and antioxidant levels were statistically non-significant but showed improving trends. 44% of cases showed notable improvement in BMI that they no longer fitted into the MAM criteria after 6 months intervention.

This nutritional supplementation not only improved all the anthropometric parameters, but also showed improvement in biochemical parameters of HIV infected children and helped in preserving their immune function. To the best of our knowledge, this is the first study from India using an indigenously prepared WHO-recommended; micro-nutrient fortified, energy-dense nutritional supplementation in HIV infected children.

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Declarations

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