DOI: 10.7860/JCDR/2021/49599.15605

Original Article

Nutrition Section

Impact of Oral Nutritional Supplement on Growth, Nutrient Intake and Frequency of Illness in Children aged 4-6 Years: A Randomised Controlled Study

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ABSTRACT

Introduction: Protein-Energy Malnutrition (PEM) and prevalence of under-weight children in India, is an important health concern.

Aim: To evaluate the effect of Oral Nutritional Supplement (ONS) on growth, overall nutrient intake and frequency of illness in nutritionally at-risk Indian children.

Materials and Methods: In this prospective, randomised, gender-stratified, controlled, parallel group, open label study, 216 children (aged 4-6 years with weight-for-age z-score between -2 and -1) were randomised (1:1) to receive either 45 g of ONS {Test product+Dietary advice (T+D)} or control group {Dietary advice only (D-only)} for three months. Primary endpoints included weight-for-age z-score and weight gain in terms of g/kg/day from baseline to three months. Secondary endpoints included change in height-for-age z-scores; frequency of illness, change in dietary nutrient intake and Protein/Energy (P/E) ratio from baseline through three months. Safety endpoint included Adverse Events (AEs). PROC MIXED was used to perform Repeated Measures Analysis Of Variance (RMANOVA) based on the changes in z-scores. The z-scores changes within the group from baseline to the end of three months End-of-Study (EOS) were compared using paired t-test.

Results: At baseline, the mean (SD) weight-for-age z-scores were similar in both the groups {1.50 (0.309) and -1.49 (0.312) in T+D and D-only groups, respectively}. At the EOS, only T+D group showed significant mean (SD) change from baseline in weight-for-age z-score compared to the D-only group {0.59 (0.296), $p<0.001$ vs. 0.04 (0.267), $p=0.0974$}. Mean rate of weight gain (g/kg/day) was significantly higher in T+D group vs. D-only group (1.12 vs. 0.26, $p<0.0001$). At baseline, height-for-age z-scores were similar in both the groups {-1.36 (0.668) vs -1.37 (0.638) in T+D and D-only groups, respectively}. At EOS, the mean (SD) change from baseline in height-for-age z-score was -0.02 (0.198), $p=0.2389$ in T+D group and -0.15 (0.171), $p<0.001$ in the D-only group. However, the change was not proportionate to weight-for-age z-score. Total absolute number of illness episodes was less in T+D group vs. D-only group (9 vs. 13). Improvement in dietary nutrient intake (carbohydrate, fat, protein and energy) and P/E ratio was significantly higher ($p<0.001$) in T+D group vs. D-only group. Overall, 8.3% children in T+D group experienced at least one treatment-emergent AE.

Conclusion: The ONS helps to improve growth, nutrient intake and reduces frequency of illness in nutritionally at-risk children.

Keywords: Childhood malnutrition, Dietary advice, Growth, Nutrient intake, Preschool children

INTRODUCTION

Protein-Energy Malnutrition (PEM) is a major health concern in India, particularly affecting the preschool children (<6 years of age), who are in the most crucial period of continuous cognitive, emotional and physical growth [1-3]. Globally, ~149 million children of age <5 years suffer from stunting and 49.5 million suffer from wasting [4]. National Family Health Survey-4 (NFHS-4) 2015-16, reported 38% of children <5 years of age in India were stunted, 21% were wasted and 36% were underweight. Undernutrition is substantially higher in rural areas than in urban areas of India. However, even in urban areas, 31% of children are stunted and 29.1% are underweight [5]. Altogether, over 2 million deaths in children of <5 years of age occurs due to nutritional stunting, severe wasting and intrauterine growth restriction [6,7]. Undernutrition accounts for 22% of disease burden in India affecting country's economic growth with an estimated adult productivity loss of 1.4% of gross domestic product [8].

Poor nutrition in early childhood is associated with long-term consequences, such as impaired intellectual and school performance, shorter adult height and, subsequently, reduced work capacity, obstetric complications and delayed maturation [2,9]. A pooled data analysis showed that even mild anthropometry deficits ($-2 \leq$ z-scores <-1) were associated with a significantly higher risk of mortality, particularly from an infectious diseases [10]. Mild and moderate under-weight population in children go unnoticed and this effect at an early age makes the process irreversible [10-13]. Therefore, identifying malnutrition (or children at nutritional risk) at an early stage and implementing timely nutritional interventions are important to achieve optimal growth potential.

Childhood undernutrition can be prevented and treated by providing diets with adequate energy including essential macro and micronutrients, to promote adequate growth, strengthen resistance to infections, and support normal physical, mental, and metabolic development [7,14-17]. Dietary Counselling (DC) is the first step and integral part of treating malnutrition [14,15]. However, there are several challenges that limit the efficacy of a food-based approach, especially in developing countries [18]. Considering the intensity and the variety of physical activities that the children of age group 4-6 years undertake, they may require, on an average, ~1350 Kcal/day [19]. National Nutrition Monitoring Bureau (NNMB) surveys conducted in 2006 indicate that the daily intake of all foods except cereals and millets in Indian households is lower than the recommended dietary allowances. Indian diets are majorly vegetarian and derive about 60% of their protein from cereals (wheat, rice, jowar and bajra). However, proteins in cereals are not of superior quality and hence it is evident that the absolute protein intake is inadequate in Indian children [20].

In this environment, Oral Nutritional Supplement (ONS) have been known to be effective for linear growth, physical health and cognition of children in developing countries [3,21,22]. Several studies conducted in developing countries demonstrated positive effect of ONS along with DC in children who were nutritionally at-risk or in state of malnutrition [21-24]. Studies depicting effect of ONS in Indian nutritionally at risk children are limited. However, the available short-term and long-term data on the effect of ONS showed significant improvement in growth parameters and resistance to infection in Indian malnourished children or picky-eaters [13,25,26].

The objective of current study was to evaluate the impact of a protein rich ONS on weight, height, and episodes of illness in Indian children aged 4-6 years, with weight-for-age z-scores between -1 and -2, who are otherwise healthy but require special attention to their dietary needs. The ONS along with dietary advice was expected to bridge the daily nutritional requirements, improve weight gain, and help in building immunity or reduce number of illness episodes during the crucial growth stage.

MATERIALS AND METHODS

This was a prospective, randomised, gender-stratified, controlled, parallel group, open-label study conducted between December 2018 and June 2019 at Sant Dyaneshwar Medical Education and Research Centre and Jehangir Clinical Development Centre Pvt., Ltd., in India.

The study was approved by the Institutional Review Board or Independent Ethics Committee (ECR/127/Inst/MH/2013/RR-19.). The study was performed in accordance with the ethical principles that had their origin in the declaration of Helsinki. Written informed consent was obtained from each child's parents/Legally Acceptable Representatives (LARs).

Sample size calcuation: Considering expected mean difference 0.1 in the primary endpoint (weight-for-age z-score), variance 0.0625, based on previous study data [27], and a dropout of 10%, 216 children were enrolled to have 196 evaluable children in the study, which was required to have at least 80% power at 5% level of significance.

Inclusion criteria: Children 4-6 years of age (boys and girls) with weight-for-age z-scores between -1 and -2, with good general, mental health and whose parents agreed to remain in the same locality for the study duration were included in the study.

Exclusion criteria: Children who were severely malnourished, immunocompromised, had history of surgery (within 3 months prior to study), serious infections or injuries, had known congenital diseases or malformations, currently on medication (e.g., systemic corticosteroids) which could interfere with the study objectives, or had the following conditions: jaundice, asthma, diabetes, cancer, tuberculosis, diarrhoea, etc., were excluded from the study. Additionally, children who had intolerance or hypersensitivity to any of the ingredient of the study product, or lactose intolerance and/or aversion to drinking milk were also excluded from the study.

Study Procedure

All the eligible children were first provided dietary advice as per their age, physical status, and daily physical activities by the study centre nutritionist. Children were then randomised (1:1) to either the interventional {Test product+Dietary advice (T+D)} or control group {Dietary advice only (D-only)}. Randomisation was gender stratified to recruit at least 40% of either gender, to control for possible effects of gender.

Children in the intervention group were administered 45 g of the test product (ONS) once daily (in 200 mL lukewarm commercially available carton milk) in addition to his/her regular diet, for which the individuals' parent/LARs received dietary advice for three months. The nutritional characteristics of ONS are shown in [Table/Fig-1].

Children in the control group did not receive any test product, the parent/LARs of these children were given dietary advice to bridge the nutritional gap and were instructed to follow a regular diet (without use of any supplements).

Nutrients	ONS per serving (45 g)
Energy (Kcal)	201
Protein (gm)	8
Carbohydrates (gm)	27
Total Fat (gm)	7

[Table/Fig-1]: Nutrient composition of the Oral Nutritional Supplement (ONS). Ingredient List: Partially skimmed milk, maltodextrin, skimmed milk powder, corn oil, lactose, whey protein concentrate, sucrose, soy protein isolate, cocoa powder, fructo-oligosaccharides, minerals, vitamins, algal oil (source of DHA), and taurine.

Children in both the groups were required to comply with the dietary advice imparted to them on day 1 throughout the study. The ONS was provided by the study personnel visiting each of the child's house daily. A 200 g tin of ONS, carton milk, and a graduated tumbler was provided to child's parents/LARs, to be used only in case the child was out-of-station or the study personnel failed to visit the child's home during the intervention period. The administration of ONS in absence of study personnel was restricted to ≤5 days per month and recorded in the subject diary. Additionally, parents/LARs was given weekly telephonic reminders to adhere to the dietary advice.

Study Assessments

The study assessment was done at four time points:

- Visit 1 screening (baseline visit/day 1),
- Visit 2 (at 15 days from baseline),
- Visit 3 (at 1 month from baseline),
- Visit 4 {End-Of-Study (EOS)/at three months from baseline}.

The maximum study duration was three months for each individual. Primary efficacy endpoint included change in weight-for-age z-score and weight gain in terms of g/kg/day from baseline through three months. Secondary endpoint included change in height-for-age z-scores, change in dietary nutrient intake, Protein/Energy (P/E) ratio and frequency of illness from baseline through three months. Safety endpoints included assessment of AEs, vital signs, and physical examinations.

Anthropometric assessments were performed at all four visits. Additionally, socio-economic status data was also collected at the first visit [Table/Fig-2] [28] . Parents/LARs of all enrolled children was provided a subject diary to record all the food and beverages consumed by the child, for 3 days per week (two weekdays + one weekend). The record was confirmed against the 3-day recall period at each scheduled visit. Any episode of illness and other AEs, between the study visits were also recorded. The severity of all AEs/severe AEs occurring during the course of the study were graded as per the clinical judgment of the investigator as follows, mild (the event was transient and easily tolerated by the child; does not generally warrant medical intervention), moderate (the event caused discomfort and interrupts the child's usual activities; may warrant medical intervention) and lastly, severe (the event caused considerable interference with the child's usual activities; generally warrants medical intervention).

Socio-economic status grade	Education of parent/ legally acceptable representative	Consumer durables own by children's family
A1	Graduate or post-graduate professional	Electricity Connection/Ceiling Fan/LPG Stove/Two Wheeler/Colour TV/Refrigerator/Washing Machine/Personal Computer/ Laptop/Car/Jeep/Van
A2	Graduate or post-graduate professional	Electricity Connection/Ceiling Fan/LPG Stove/Two Wheeler/Colour TV/Refrigerator/Washing Machine

A3	Graduate or post-graduate professional	Electricity Connection/Ceiling Fan/LPG Stove/Two Wheeler/Colour TV/Refrigerator
B1	SSC/HSC	Electricity Connection/Ceiling Fan/LPG Stove/Two Wheeler/Colour TV/Refrigerator
B2	School 5 to 9 years	Electricity Connection/Ceiling Fan/LPG Stove/Two Wheeler/Colour TV/Refrigerator
C1	School 5 to 9 years	Electricity Connection/Ceiling Fan/LPG Stove/Two Wheeler/Colour TV
C2	School 5 to 9 years	Electricity Connection/Ceiling Fan/LPG Stove/Colour TV
D1	SSC/HSC	Electricity Connection/Ceiling Fan/LPG Stove

[Table/Fig-2]: Grading of socio-economic status.
SSC: Secondary school certificate; HSC: Higher secondary certificate

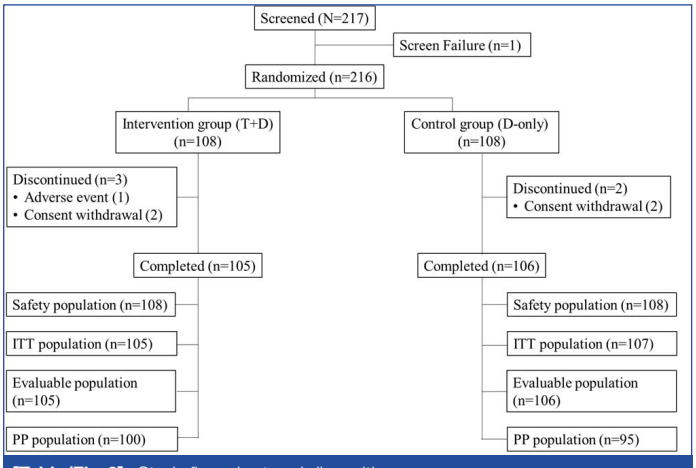
STATISTICAL ANALYSIS

A total of 216 children were planned to be randomised to either the T+D or D-only group. Efficacy analysis were performed in the Intent-To-Treat population (ITT; all children who received at least one dose of study product or followed at least one day of dietary advice), evaluable population (all children who completed at least 72 days of study product administration or dietary advice) and Per-Protocol (PP) (all children who completed the study visit as per protocol without any major protocol deviations). Safety analysis was conducted in safety population (all children who received at least one dose of study product or followed at least one day of dietary advice). The SAS® program (SAS® Institute Inc., USA, and Version 9.4) was used for statistical evaluation.

Weight-for-age, and height-for-age are expressed as gender-age-specific z-scores using the World Health Organization Multicentre Growth Reference Study (WHO MGRS) 2006 based AnthroPlus App in children 4-5 years of age and the Microsoft Excel Tool developed for children 5-6 years of age [29,30]. PROC MIXED was used to perform Repeated Measures Of Analysis Of Variance (RMANOVA) based on the changes in z-scores. The z-scores changes within the group from baseline to the EOS were compared using paired t-test. Mean frequency of illness was compared between treatment groups by using analysis of variance.

RESULTS

Disposition and baseline characteristics: Between December 2018 and June 2019, 216 of 217 screened children were enrolled and randomised to either the T+D group (n=108) or D-only group (n=108). Total 211/216 children completed the study and 5 (2.3%) children discontinued the study. Most common reason for study discontinuation was withdrawal of consent in 4 (1.85%) children, followed by an event of AE in 1 (0.46%) child. Of these, 212 children were included in the ITT population, 211 in evaluable population and 195 in PP population [Table/Fig-3].



[Table/Fig-3]: Study flow chart and disposition.
D-only: Dietary advice only; ITT: intent-to-treat; PP: per protocol; n: number of children; T+D: Test product+Dietary advice

The study included all Indian children, majority were girls and mean (SD) age of the children was similar in both study groups ~4.5 (0.60) years. Most of the children belonged to socio-economic grades B2, C1 and C2 [Table/Fig-4].

Characteristics	Intervention (T+D) group (n=108)	Control (D-only) group (n=108)
Age (years), mean (SD)	4.5 (0.60)	4.6 (0.63)
Gender, n (%)		
Boys	52 (48.1)	48 (44.4)
Girls	56 (51.9)	60 (55.6)
Race, n (%)		
Asian	108 (100.0)	108 (100.0)
Total of socio-economic status grade, n (%)		
A1	2 (1.9)	0
A2	6 (5.6)	9 (8.3)
A3	14 (13.0)	11 (10.2)
B1	9 (8.3)	6 (5.6)
B2	16 (14.8)	18 (16.7)
C1	32 (29.6)	38 (35.2)
C2	22 (20.4)	18 (16.7)
D1	7 (6.5)	8 (7.4)
Weight (kg), mean (SD)	14.2 (0.79)	14.3 (0.83)
Height (cm), mean (SD)	101.7 (3.96)	102.4 (3.91)
BMI (kg/m^2), mean (SD)	13.7 (0.89)	13.6 (0.78)

[Table/Fig-4]: Baseline demographics, socio-economic status and anthropometry measurements (safety population).
Socio-economic status classify households in India and are recorded based on variables such as education of chief wage earner and number of "consumer durables" -owned by the family (listed as electricity connection, ceiling fan, LPG stove, two wheeler, colour television, refrigerator, washing machine, personal computer/laptop, car/jeep/van, air conditioner and agricultural land). BMI: Body mass index; D-only: Dietary advice only; SD: Standard deviation; T+D: Test product+Dietary advice

Treatment compliance: Overall, the compliance to ONS intake was >80% in most children in the intervention group.

Change in growth parameters: In ITT population, at baseline, the mean (SD) weight-for-age z-scores were similar in both the groups {-1.50 (0.309) and -1.49 (0.312) in T+D and D-only groups, respectively}. Over the three month study period, the weight-for-age z-scores increased in both study groups; however, the change was significant only in T+D group ($p<0.001$) at all visits compared to baseline. The mean (SD) change in weight-for-age z-score from baseline to visit 4 (EOS) in T+D group was 0.59 (0.296), $p<0.001$ and 0.04 (0.267), $p=0.0974$ in the D-only group [Table/Fig-5]. The T+D group showed significant increase in weight as early as at 15 days, where mean z-score increased by 0.20. Also, the T+D group demonstrated significantly higher mean rate of weight gain being maximum in the first 15 days of study treatment (2.11 g/kg/day, $p<0.0001$) compared to the D-only group (0.27 g/kg/day) at all post-baseline visits. Over three months, the mean rate of weight gain was 1.12 g/kg/day for T+D group and for the D-only group it was stable at 0.26 g/kg/day.

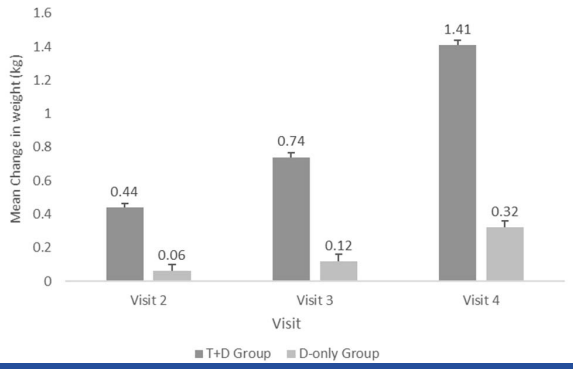
At baseline, the mean (SD) height {101.71 (3.961) cm vs 102.43 (3.928) cm in T+D and D groups, respectively} and height-for-age z-scores {-1.36 (0.668) vs -1.37 (0.638) in T+D and D-only groups, respectively} were similar in both the groups. At the EOS, the mean height increased significantly from baseline in both the study groups {1.07 (0.505) cm and 0.44 (0.349) cm in T+D and D-only groups, respectively} but more in T+D group ($p<0.0001$) as compared to D-only group. However, the height for-age z-scores, decreased in both the groups [Table/Fig-5].

Mean change in weight and height are represented in [Table/Fig-6a,b].

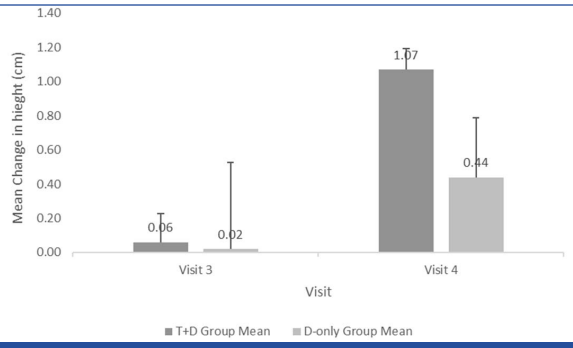
Dietary nutrient intake: Dietary intake results in ITT population are presented in [Table/Fig-7]. From baseline to EOS, mean (SD)

Visits	n	Intervention (T+D) group Mean (SD)	n	Control (D-only) group Mean (SD)	Between group p-value*
Weight-for-age z-score					
Visit 1	105	-1.50 (0.309)	107	-1.49 (0.312)	
Visit 2	105	-1.29 (0.360)	107	-1.48 (0.341)	
Change from baseline to Visit 2	105	0.20 (0.210) p<0.001	107	0.01 (0.150) p=0.5152	<0.0001
Visit 3	105	-1.17 (0.362)	106	-1.47 (0.347)	
Change from baseline to Visit 3	105	0.33 (0.245) p<0.001	106	0.02 (0.208) p=0.2801	<0.0001
Visit 4	105	-0.91 (0.381)	106	-1.45 (0.337)	
Change from baseline to Visit 4	105	0.59 (0.296) p<0.001	106	0.04 (0.267) p=0.0974	<0.0001
Height-for-age z-score					
Visit 1	105	-1.36 (0.668)	107	-1.37 (0.638)	
Visit 3	105	-1.44 (0.650)	106	-1.44 (0.631)	
Change from baseline to Visit 3	105	-0.08 (0.093) p<0.001	106	-0.07 (0.108) <0.001	<0.0001
Visit 4	105	-1.38 (0.627)	106	-1.52 (0.632)	
Change from baseline to Visit 4	105	-0.02 (0.198) p=0.2389	106	-0.15 (0.171) p<0.001	<0.0001

[Table/Fig-5]: Change in weight-for-age, height-for-age and BMI-for-age z-scores by visit (ITT population).
Visit 1: baseline, visit 2: day 15, visit 3: day 30, visit 4: day 90. D-only: Dietary advice only; ITT: intent-to-treat; T+D: Test product+Dietary advice, p-value is obtained by performing paired t test within groups. p value* is obtained for change from baseline between two groups by performing repeated measures ANOVA; One patient in control (D-only) group discontinued after visit 2 due to withdrawal of consent



[Table/Fig-6a]: Mean change in weight from baseline (ITT population).
D: Dietary advice only; T+D: Test product+Dietary advice



[Table/Fig-6b]: Mean change in height from baseline (ITT population).
D: Dietary advice only; T+D: Test product+Dietary advice

Visits	n	Intervention (T+D) group Mean (SD)	n	Control (D-only) group Mean (SD)	Between group p-value*
Carbohydrates (gm)					
Visit 1	<0.0001	108.49 (25.154)	107	106.49 (23.889)	
Visit 3	105	135.77 (25.530)	106	112.76 (30.202)	
Change from baseline to Visit 3	105	27.28 (20.558) p<0.001	106	6.82 (18.615) p=0.0003	<0.0001
Visit 4	105	148.49 (20.362)	106	119.13 (31.294)	
Change from baseline to Visit 4	105	39.99 (19.396) p<0.001	106	13.19 (19.568) p<0.001	<0.0001
Protein (gm)					
Visit 1	105	23.39 (4.106)	107	22.57 (3.992)	
Visit 3	105	36.41 (3.737)	106	25.77 (4.568)	
Change from baseline to Visit 3	105	13.02 (5.943) p<0.001	106	3.25 (5.491) p<0.001	<0.0001
Visit 4	105	46.03 (5.765)	106	31.35 (3.399)	
Change from baseline to Visit 4	105	22.63 (8.340) p<0.001	106	8.82 (5.224) p<0.001	<0.0001
Fat (gm)					
Visit 1	105	15.70 (11.663)	107	14.37 (6.124)	
Visit 3	105	26.00 (5.247)	106	16.63 (7.948)	
Change from baseline to Visit 3	105	10.30 (11.039) p<0.001	106	2.30 (5.007) p<0.001	<0.0001
Visit 4	105	33.20 (7.152)	106	22.15 (6.153)	
Change from baseline to Visit 4	105	17.50 (13.214) p<0.001	106	7.83 (5.006) p<0.001	<0.0001
Energy (calories)					
Visit 1	105	698.02 (207.457)	107	690.69 (198.069)	
Visit 3	105	954.28 (177.876)	106	736.91 (241.529)	
Change from baseline to Visit 3	105	256.27 (104.482) p<0.001	106	49.19 (95.370) p<0.001	<0.0001
Visit 4	105	1127.38 (152.93)	106	834.33 (241.533)	
Change from baseline to Visit 4	105	429.37 (115.309) p<0.001	106	146.61 (115.608) p<0.001	<0.0001
Protein/Energy Ratio					
Visit 1	105	0.04 (0.007)	107	0.03 (0.008)	
Visit 3	105	0.04 (0.009)	106	0.04 (0.010)	
Change from baseline to Visit 3	105	0.0 (0.008) p<0.001	106	0.0 (0.010) p=0.0005	<0.0001
Visit 4	105	0.04 (0.009)	106	0.04 (0.025)	
Change from baseline to Visit 4	105	0.01 (0.007) p<0.001	106	0.01 (0.024) p=0.0012	<0.0001

[Table/Fig-7]: Change in dietary nutrient intake and dietary P/E ratio (ITT population).
Visit 1: baseline, visit 2: day 15, visit 3: day 30, visit 4: day 90. BMI: Body mass index; D-only: Dietary advice only; ITT: intent-to-treat; T+D: Test product+Dietary advice. p-value is obtained by performing paired t-test within groups. p value* is obtained for change from baseline between two groups by performing repeated measures ANOVA; One patient in Control (D-only) group discontinued after Visit 2 due to withdrawal of consent

change in dietary nutrient intake significantly improved in the T+D group vs. D-only group, including carbohydrate {39.99 (19.396) vs. 13.19 (19.568) gm, p<0.0001}, protein {22.63 (8.340) vs. 8.82 (5.224) gm, p<0.0001}, fat {17.50 (13.214) vs. 7.83 (5.006) gm, p<0.0001}, and energy {429.37 (115.309) vs. 146.61 (115.608) Kcal, p<0.0001}. Mean (SD) change in P/E ratio significantly improved in T+D group vs. D-only group from baseline to EOS {0.01 (0.007), p<0.001 vs. 0.01 (0.024), p=0.0012} [Table/Fig-7].

Incidence of illness: In the ITT population, seven children of T+D group reported nine episodes of illness and 10 children of the D-only group reported 13 episodes of illness. Fever (n=13), cough (n=1), cold (n=5), viral infection/rashes (n=1), and upper respiratory tract infection (n=2) were reported as illnesses.

The efficacy results were similar in ITT, evaluable, and PP populations hence results were provided only for ITT population.

Safety: Overall, 14 AEs were reported in nine (8.3%) children in the T+D group and 13 AEs in 10 (9.2%) children in the D-only group. The most common AEs (>3%) in T+D group were fever (5/108, 4.6%), vomiting (4/108, 3.7%), and cold (3/108, 2.7%). None of these AEs were serious. All AEs were mild in intensity, except the AE of fever in one child in the T+D group, which was moderate in intensity [Table/Fig-8]. All AEs were considered as not related to the study intervention and had resolved by the EOS. No deaths were reported.

Characteristic	Intervention (T+D) group Mean (SD) (N=108)	Control (D-only) group Mean (SD) (N=108)
Children with any AE	9 (8.3%)	10 (9.2%)
All AEs		
Fever	5 (4.6%)	8 (7.4%)
Vomiting	4 (3.7%)	0
Cold	3 (2.7%)	2 (1.8%)
Diarrhea	1 (0.9%)	0
Cough	1 (0.9%)	0
Upper respiratory infection	0	2 (1.8%)
Rashes	0	1 (0.9%)
Discontinuation due to AEs	1 (0.9%)	0
AEs of mild intensity	8 (7.4%)	10 (9.3%)

[Table/Fig-8]: Adverse Events (AE) experienced in any group (Safety population). D-only: Dietary advice only; T+D: Test product+Dietary advice; AE: adverse event; Percentages are based on number of patients in respective treatment group in safety population

DISCUSSION

The rate of growth and development increases with age, impacting the nutritional requirement of children. According to the WHO growth standards for children of 0-5 years of age and Indian Academy of Paediatrics (IAP) (children of 5-18 years of age), the healthy height and weight should be roughly between the z-scores -1.96 and +1.96 [30-32]. Children belonging to weight-for-age z-scores between -1 and -2 may not fit into any definition of malnutrition but do require additional nutrition to maintain age appropriate weight as inadequate attention to their dietary needs may push them towards frank malnutrition. The impact of ONS is not well elucidated in nutritionally at-risk Indian children. This study was conducted to evaluate the impact of ONS on growth parameters, nutrient intake and frequency of illness in Indian children aged 4-6 years with weight-for-age z-scores between 1 and -2.

Results from this study depicted that children in the T+D group receiving ONS+dietary advice showed significant change in all the anthropometric measurements, weight-for age z-score and mean rate of weight gain (observed as early as at day 15) compared to similar children in the D-only group. These findings were consistent with the previous studies conducted in children with picky-eating behaviours [13,33]. The gain in mean height was significantly higher even with short study duration in the T+D group (about 1 cm) than in the D-only group (about 0.5 cm). However, this gain in height was inadequate to maintain or improve the z-score compared with the WHO growth standards [30]. It needs to be noted that height is the last anthropometry parameter to respond to any intervention. Thus, no significant difference was observed in height-for-age z-score over 3 months. This is evidenced by a study conducted in preschool children (at risk of undernutrition), ONS showed significant improvement in height after 24 weeks of supplementation, which suggests that long term studies are required to note significant differences in height [34].

The picky eating behaviour noticed in children belonging to this age group makes it difficult to deliver complete nutrition essential for their growth. To meet the dietary nutrient requirements for healthy growth and development at an early age, it is recommended to include plenty of grains, fruits, vegetables, and high levels of complex carbohydrates in children's diet [27]. The challenge posed by picky eating behaviour of children can be overcome with the use of a nutritionally balanced supplement which would help bridge the nutrient delivery gap thereby optimising the growth and development of the child [3,13,21-25,27]. In this study, significant improvement was noted in dietary nutrient intake in the T+D group compared to D-only group. Mean change in energy intake from baseline to EOS was much higher in the T+D group than D-only group. As per Food and Agriculture Organisation/ WHO/United Nations University (FAO/WHO/UNU) report and Torun B et al., report on dietary P/E ratios, high quality protein diets have lower P/E ratios i.e., recommended or safe P/E ratios [35,36]. This study demonstrated a lower P/E ratio in T+D group this could be due to the improved quality and quantity of proteins provided by ONS. The lower P/E ratio in T+D group can also be due the fact that both energy and protein intake improved on consumption of ONS whereas the energy intake improvement in D-only group was comparatively less.

Evidence suggests a strong association between poor nutritional status and impaired immunity and decreased resistance to infections [2,13,37,38]. This study is consistent with the findings of several other studies that demonstrated positive effect of ONS in reducing infections or number of sick days [13,33,37]. Children in T+D group experienced less episodes of illness than D-only group. The strengths of this study include study population, as healthy children have rarely been studied in Asian countries, comprehensive dietary assessment, high compliance and low number of dropouts.

Limitation(s)

Limitations of the study include relatively short study duration and a relatively small sample size. Also, there were no follow-up visits conducted to see continued effect of ONS on said parameters. Secondly, this was a non-blinded, open-label study therefore, there may have been bias in administration of test product and parents recording dietary intake data in the diary. However, the high compliance (>80%) observed in the study was supported by high energy intake and significant improvement in anthropometry parameters. Long term studies are suggested to understand the impact of ONS and dietary advice on bone quality and height.

CONCLUSION(S)

Use of ONS combined with dietary advice helps improve growth, nutrient intake and reduce frequency of illness in 4-6 years old nutritionally at risk children. Considering India's health economic and clinical burden of childhood undernutrition and associated health problems, long-term studies are warranted.

Acknowledgement

We thank Dr. Nandan Joshi and Dr. Madhavi Marathe for their valuable inputs and guidance during designing of the study

protocol (Nutricia International Pvt. Limited), Nigar Malik (B. Pharm), SIRO ClinPharm (funded by Nutricia International Pvt Ltd, India) for writing assistance and editorial support. The authors thank the study patients without whom this study would not have been accomplished, and also thank the investigator site team for their support in this study. This research was funded by Nutricia International Pvt Ltd, India.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Apr 01, 2021
- Manual Googling: Aug 19, 2021
- iThenticate Software: Sep 10, 2021 (14%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Mar 26, 2021**
Date of Peer Review: **Jun 29, 2021**
Date of Acceptance: **Aug 23, 2021**
Date of Publishing: **Nov 01, 2021**