



## EFFECT OF FOLIC ACID SUPPLEMENTATION ON APPETITE IMPROVEMENT IN PRE-SCHOOL CHILDREN

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### ABSTRACT

**Objective:** To observe the effect of folic acid supplementation on appetite improvement in pre-school children

**Study Design:** Randomized Control Trial

**Place and Duration of Study:** Department of Pediatric, KRL Hospital, Rawalpindi, Pakistan, November 2024 to June 2025.

**Methodology:** Fifty children of age 3-5 years with who were below the 50<sup>th</sup> percentile on the growth chart enrolled. Children were divided in to two groups A and B, each consisting of 22 children. Group A patients were to receive folic acid in a dose of 200µg/day while Group B was given a placebo in the form of a glucose capsule. Variables including number of meals, Child Eating Behavior Questionnaire (CEBQ) score, weight, growth percentile and hemoglobin levels were checked at baseline and at 3-month for improvement in these parameters. Means were compared between both groups with a significant p-value of  $\leq 0.05$ .

**Results:** Total fifty children included in the trial with mean age of  $45.74 \pm 7.73$  months including 21 (42%) girls and 29 (58%) boys having mean growth percentile of  $28.14 \pm 7.8$  and BMI of  $15.78 \pm 0.33$  kg/m<sup>2</sup> at baseline. The studied variables such as appetite, BMI, growth percentile, CEBQ score and hemoglobin when compared across groups showed no significant differences between the groups at the end of 3 months. However, intragroup comparison showed significant improvement in these whether the patient took folic acid or placebo.

**Conclusion:** Folic acid appears to improve appetite but insignificantly differ from the effects of other dietary measure and lifestyle modifications.

## INTRODUCTION

Folic acid or Vitamin B9 is the synthetic form of folate which is an essential in various transfer / methylation reactions involved in the synthesis of DNA and RNA bases.<sup>(1)</sup> The recommended daily allowance of folate in adults is 400µg which is equivalent to 240µg of folic acid.<sup>(2)</sup> Average bioavailability of folic acid is around 85% whereas folate from natural sources has a bioavailability of only 50%, thus dietary intake is less than the recommended intake in routine for most.<sup>(3)</sup> Folic acid, by virtue of its effect on cell growth, thought to mediate its stimulatory effect on appetite. Exact mechanism is however unclear and this effect is still debatable.<sup>(4)</sup> It is also thought to exert healing effects on the gastrointestinal epithelium through various growth factors.<sup>(5)</sup> Children require an abundant supply of nutrients because of their rapid growth. Poor appetite is often attributable to acute infections and micronutrient deficiencies such as iron and folic acid. A large number of people visiting the pediatric out-patient department in our public healthcare set ups report that their children don't like to eat as much as they should and are found on the lower end of the spectrum on the growth charts with some having failure to thrive as well. Instead of using appetite stimulants such as cyproheptadine, it is often beneficial to use the micronutrient supplements such as folic acid for improving appetite in children.<sup>(6)</sup> Pakistan faces significant challenges with childhood malnutrition, including high rates of stunting and micronutrient deficiencies, particularly folic acid deficiency. Nearly 40% of children under the age of 5 years in Pakistan show a stunted growth.<sup>(7)</sup> This is largely attributable to the majority of population belonging to the lower socioeconomic class and prevailing harsh economic conditions in the country. A child cannot reach his or her full physical and intellectual potential because of nutrient deficiencies.<sup>(8)</sup> Poor dietary intake and food insecurity further exacerbate these issues, especially in pre-school children. Given the

lack of local research on this topic, conducting this study in Pakistan would provide valuable data for cost-effective public health strategies aimed at addressing malnutrition, aligning with national health priorities and the global Sustainable Development Goal to end hunger and improve nutrition.<sup>(9)</sup>

The purpose of conducting this trial is to assess the positive effects of folic acid on appetite and consequently hemoglobin and child growth. This will help health care providers to devise a dietary plan for pre-school children and guide parents as well.

## METHODOLOGY

This study was conducted as an open label, randomized clinical trial in the Pediatric Outpatient department of KRL hospital, Islamabad, Pakistan from 11 November 2024 to 15 June 2025 . Approval was obtained beforehand from the Ethical Review committee of the hospital and permission was also sought from the parents of children at the time of enrollment using an informed written consent form. The trial was registered at the Australian New Zealand Clinical Trial Registry via registration number

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The power of the study was kept at 80% and level of significance was chosen to be 0.05 with a 95% confidence interval. The sample size was calculated using the WHO sample size calculator. We used the reported pre and post nutritional intervention milk consumption in children reported by Naila et al and it came out to be 36.<sup>10</sup> Keeping the drop out at 15%, we adjusted the sample size to 44. Convenience sampling technique was used and all children presenting to the pediatric OPD with trivial illnesses such as acute upper respiratory tract infection or a diarrheal illness and meeting the inclusion criteria were enrolled in the trial.

**Inclusion Criteria:** All children presenting to the pediatric OPD, between the ages 3 and 5

years who were below the 50<sup>th</sup> percentile on the growth chart were enrolled.

**Exclusion Criteria:** Children having any chronic condition such as celiac disease, diabetes mellitus, neoplasia or anemia were excluded from the study.

Children were divided into two groups A and B, each consisting of 22 children. Group A patients were to receive folic acid in a dose of 200µg/day, given as crushed half tablet of Myfol<sup>R</sup> while Group B was given a placebo in the form of a glucose capsule. Compliance to the drug was ensured by counselling the parents and empty strips or packets of tablets were seen at each monthly follow up. Data was collected using a specialized questionnaire designed for the trial which also included the Child Eating Behavior Questionnaire (CEBQ).<sup>11</sup> This questionnaire was filled at baseline and at 5 months follow-up of the patients. Primary outcome of the trial was to observe any improvement in the appetite at 3-month using the CEBQ. Secondary outcomes included improvement in the nutritional status as seen by change in the BMI, percentile on growth chart and change in hemoglobin. Side effects of folic acid therapy were also noted. Data were entered in Statistical Package for Social Sciences software version 25. Normality of the data was checked using Kolmogorov Smirnov test. Mean was calculated for quantitative variables like age, CEBQ score, BMI and hemoglobin of the children whereas frequencies and percentages were calculated for qualitative variables and expressed as figures and tables. The Null hypothesis was “there is no difference in appetite following folic acid supplementation as compared to placebo”. Means were compared using independent samples t test or paired samples t test while ordinal variables were compared using Mann Whitney U test and categorical variables were compared using Chi square test. A p-value of  $\leq 0.05$  was considered significant.

## Results

Total fifty children included in the trial with mean age of  $45.74 \pm 7.73$  months including 21 (42%) girls and 29 (58%) boys. On the growth chart, these children had a mean growth percentile of  $28.14 \pm 7.8$ . At baseline, the BMI of these children was  $15.78 \pm 0.33$  kg/m<sup>2</sup>. The meal count per day in 22(44%) of these children was two meals per day while only 7(14%) had a meal count of four per day. On the Child Eating Behavior Questionnaire, the enrolled children scored  $79.04 \pm 13.19$  out of a total 175 points at the beginning of trial. Similarly, the baseline hemoglobin was  $9.68 \pm 0.80$  g/dL in these children. The characteristics of the experimental and control groups compared against each other at baseline have been summarized in the table-I.

*Table-I. Baseline Characteristics of Experimental and Control Groups (n=50)*

Variable		Experimental Group (A) (n=25)	Control Group (B) (n=25)	p-value
Age (mean months $\pm$ SD)		45.96 $\pm$ 8.19	45.52 $\pm$ 7.40	0.843
Gender	Male	14(56%)	15(60%)	0.500
	Female	11(44%)	10(40%)	
Growth Percentile		27.84 $\pm$ 6.31	28.44 $\pm$ 9.19	0.789
BMI (mean kg/m <sup>2</sup> $\pm$ SD)		15.87 $\pm$ 0.35	15.69 $\pm$ 0.28	0.049
Meal Count per Day	Two	11(44%)	11(44%)	0.889
	Three	4(16%)	6(24%)	
	Four	4(16%)	3(12%)	
	Five	6(24%)	5(20%)	
CEBQ Score (mean $\pm$ SD)		79.52 $\pm$ 13.72	78.56 $\pm$ 12.91	0.800
Hemoglobin (mean g/dL $\pm$ SD)		9.74 $\pm$ 0.69	9.63 $\pm$ 0.91	0.639

The above-mentioned parameters when compared across groups at the end of 3-month showed improvement in appetite, growth percentile, weight and hemoglobin although these improvements were statistically insignificant differences when compared between both the groups (Table-II).

*Table-II. Comparison of Experimental and Control Groups at the end of trial period (n=50)*

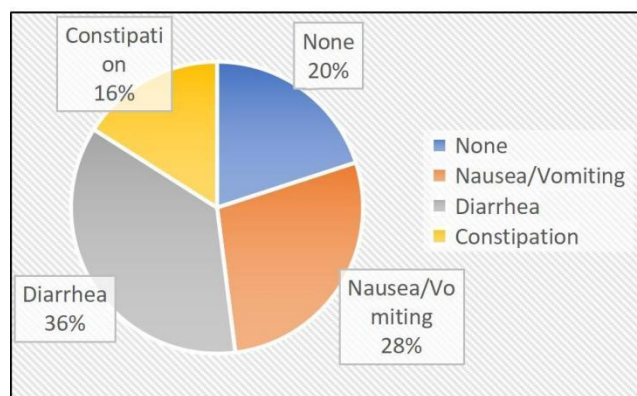
Variable	Experimental Group (A) (n=25)	Control Group (B) (n=25)	p-value
<b>Growth Percentile</b>	37.52±5.80	36.96±8.35	0.784
<b>BMI (mean kg/m<sup>2</sup> ±SD)</b>	16.23±0.39	15.96±0.30	0.01
<b>Meal Count per Day</b>	<b>Two</b>	7(28%)	0.628
	<b>Three</b>	8(32%)	
	<b>Four</b>	5(20%)	
	<b>Five</b>	5(20%)	
<b>CEBQ Score</b>	112.16±21.34	104.92±14.66	0.169
<b>Hemoglobin (mean g/dL ±SD)</b>	10.25±0.66	9.90±0.88	0.122

However, intragroup comparison showed that there was a significant improvement in these parameters whether the patient took folic acid or placebo (Table-III).

*Table-III. Intragroup Comparison of baseline and 3-month characteristics (n=50)*

Variable	Experimental Group (A) (n=25)		-p-value	Control Group (B) (n=25)		p-value
	Baseline	3-month		Baseline	3-month	
<b>Growth Percentile</b>	27.84±6.31	37.52±5.80	<0.001	28.44±9.19	36.96±8.35	<0.001
<b>BMI (mean kg/m<sup>2</sup> ±SD)</b>	15.87±0.35	16.23±0.39	<0.001	15.69±0.28	15.96±0.30	<0.001
<b>Meal Count per Day</b>	<b>Two</b>	11(44%)	<0.001	11(44%)	4(16%)	<0.001
	<b>Three</b>	4(16%)		6(24%)	10(40%)	
	<b>Four</b>	4(16%)		3(12%)	7(28%)	
	<b>Five</b>	6(24%)		5(20%)	4(16%)	
<b>CEBQ Score</b>	79.52±13.72	112.16±21.34	<0.001	78.56±12.91	104.92±14.66	<0.001
<b>Hemoglobin (mean g/dL ±SD)</b>	9.74±0.69	10.25±0.66	<0.001	9.63±0.91	9.90±0.88	<0.001

The side effect profile of the children receiving folic acid (n=25) included nausea/vomiting in 7(28%) children, diarrhea in 9(36%) and constipation was reported by 4(16%) children. (Figure-1)



*Figure 1: Side Effects of Folic Acid in Group-A children (n=25)*

## Discussion

This trial demonstrate that both the folic acid and placebo groups showed significant intragroup improvements in appetite scores, growth percentiles, and hemoglobin levels over the 3-month period. It was noted that appetite following 3-months of folic acid improved resulting in increased body weight and hemoglobin levels. Riahi et al observed in his study that appetite significantly improved at week 6 and 8 in children who were given folic acid supplementation as compared to those who were given placebo. Also, appetite slope dropped continuous without folic acid supplementation in studied cohort.<sup>12</sup> Similarly, Nisar et al also showed that folic acid improved appetite in female during pregnancy and preschool children consequently improving body weight, hemoglobin levels and growth as well.<sup>13</sup> Change in growth percentile was observed in this study from 27.84±6.31 and 28.44±9.19 at baseline which increased at 3-months of folic acid following improvement in appetite 37.52±5.80 and 36.96±8.35 in group-A and group-B respectively.

Namdari et al conducted ordinal and fuzzy logistic regression analysis on folic acid effect on appetite and concluded that folic acid and sufficient serum folate levels had significant positive effect on appetite in pediatric group. Also it was observed on basis of fuzzy regression analysis, employment status of mothers was noted be risk factor of poor appetite in preschool children.<sup>14</sup> The results

showed that improvement in appetite, weight, growth percentile and CEBQ score at the end of 3-months showed no significant differences between the groups. However, intragroup comparison showed significant improvement in these parameters whether the patient took folic acid or placebo.

In a RCT, Mohammadi et al explained that there was some but statistically insignificant improvement in appetite and body weight gain increase in children who received folic acid supplementation as compared to those who were given cyproheptadine. He also observed that folic acid group had reduced hyperactivity score in ADHD children as compared to cyproheptadine.<sup>15</sup> Similar results were explained by Mostafvi et al that folic acid decreased hyperactivity score, improved appetite, body weight and hemoglobin levels in pre-school children.<sup>16</sup>

This study observed that folic acid had transiently positive effect on appetite of preschool children but this change noted to be statistically insignificant in comparison to placebo effect. Hassanzadeh et al observed in a RCT that multi-vitamin including folic acid transiently increased the appetite and weight in preschool children with impaired growth secondary to poor dietary intake.<sup>17</sup> Stolfutz concluded similar results that low dose folic acid supplementation in preschool children transiently improved appetite and weight but not corrects the anemia with no sustained long term benefits without side effects.<sup>18</sup> In other studies, Dossa et al found no statistical significant change in appetite, weight and growth in children receiving either folic acid or placebo.<sup>19</sup>

Hatamzadeh et al concluded that at 3-4 weeks folic acid supplementation improved appetite as compared to children receiving placebo (mean difference of appetite score: 1.7; 95% CI: 0.1-3.4;  $p=0.04$ ). But at 7-8 week of study, there was no significant difference in overall appetite and also weight gain was insignificant in both groups.<sup>20</sup> Similarly positive effect of vitamin B12 on children growth was observed but no significant change in appetite, weight and growth in

children receiving folic acid alone by Taneja et al.<sup>21</sup>

These findings suggest that the effect of folic acid supplementation on appetite improvement in children remains inconclusive. The significant improvements in the placebo group highlight the importance of non-pharmacological factors, such as caregiver involvement and dietary monitoring, in influencing outcomes.

### **Conclusion**

Folic acid supplementation improved appetite and subsequently BMI and growth percentile also but these improvements were statistically insignificant from the effects of placebo or other dietary measures and lifestyle modifications. The non-pharmacological factors including behavioral habits, caregiver involvement and dietary monitoring contributed towards improvement in appetite in placebo children.

### **Limitations**

Conducting the study at a single center and a limited sample size are amongst the major limitations of the study. The effect of dietary and environmental elements, ethnicity and genetics as possible confounding factors were not taken into account for underlying cause of low appetite and improvement at 3-month. The social-economic status of parents and working status of mother was also not inquired in current study. The results therefore cannot be generalized to other demographics or healthcare environments. To better understand the potential role of folic acid in appetite regulation and growth, longer-duration trials with larger sample sizes are warranted, with careful control for baseline differences between groups.

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**Conflict of Interest**     None

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**Author's Contribution:**

The authors confirm the contribution to the paper as follows:

: Conception and study design, data acquisition, manuscript writing, analysis and interpretation, final approval

: Conception and study design, analysis and interpretation, critical review and final approval

: Data acquisition, manuscript writing, analysis, critical review and final approval

: Study design and data acquisition, analysis and interpretation, critical review and final approval

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