Vol. 2 No. 3 (2025)
ONLINE ISSN :3007-309X
PRINT ISSN :3007-3081
Journal of Medical & Health Sciences Review

EFFECT OF FOLIC ACID SUPPLEMENTATION ON APPETITE IMPROVEMENT IN PRE-SCHOOL CHILDREN – A RANDOMIZED CONTROLLED TRIAL

Amber Latif[1] , Hajra Javed[2], Sughra Wahid[3], Maliha Akhtar Qureshi[4]

[1],[2] Postgraduate Resident Paediatrics, Krl Hospital G-9 Islambabad
[3],[4] Consultant Paediatrics, Krl hospital G-9 Islambabad

ARTICLE INFO:

Keywords:
Appetite, CEBQ, Cyproheptadine, Growth percentile, Folic acid, Nutrition

Corresponding Author:
Amber Latif
Postgraduate Resident Paediatrics, Krl hospital G-9 Islambabad
Email
amberlatif332@gmail.com

Article History:
Submission: 20 june 2025
Acceptance: 12 July 2025
Published : 17 July 2025

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 50th 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 ≤ 0.05.

Results: Total fifty children included in the trial with mean age of 45.74±7.73 months including 21 (42%) girls and 29 (58%) boys having mean growth percentile of 28.14±7.8 and BMI of 15.78±0.33 kg/m^2 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.[1] The recommended daily allowance of folate in adults is 400µg which is equivalent to 240µg of folic acid.[2] 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.[3] 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.[4] It is also thought to exert healing effects on the gastrointestinal epithelium through various growth factors.[5] 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.[6]

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.[7] 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.[8] 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.[9]

The purpose of conducting this trail is to assess the positive effects of folic acid on appetite and consequently hemoglobin and child growth. This will help health care providers to device 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

ACTRN12625000084482.

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.[10] 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 trail.

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

years who were below the 50th 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 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, given as crushed half tablet of Myfol[R] 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).[11] 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 ≤ 0.05 was considered significant.

RESULTS

Total fifty children included in the trial with mean age of 45.74±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±7.8. At baseline, the BMI of these children was 15.78±0.33 kg/m^2. 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±13.19 out of a total 175 points at the beginning of trial. Similarly, the baseline hemoglobin was 9.68±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 ±SD)		45.96±8.19	45.52±7.40	0.843
Gender	**Male**	14(56%)	15(60%)	0.500
	Female	11(44%)	10(40%)	
Growth Percentile		27.84±6.31	28.44±9.19	0.789
BMI (mean kg/m^2 ±SD)		15.87±0.35	15.69±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±SD)		79.52±13.72	78.56±12.91	0.800
Hemoglobin (mean g/dL±SD)		9.74±0.69	9.63±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
Growth Percentile		37.52±5.80	36.96±8.35	0.784
BMI (mean kg/m^2 ±SD)		16.23±0.39	15.96±0.30	0.01
Meal Count per Day	**Two**	7(28%)	4(16%)	0.628
	Three	8(32%0	10(40%)	
	Four	5(20%)	7(28%)	
	Five	5(20%)	4(16%)	
CEBQ Score		112.16±21.34	104.92±14.66	0.169
Hemoglobin (mean g/dL ±SD)		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**	
Growth Percentile		27.84±6.31	37.52±5.80	<0.001	28.44±9.19	36.96±8.35	<0.001
BMI (mean kg/m^2 ±SD)		15.87±0.35	16.23±0.39	<0.001	15.69±0.28	15.96±0.30	<0.001
Meal Count per Day	**Two**	11(44%)	7(28%)	<0.001	11(44%)	4(16%)	<0.001
	Three	4(16%)	8(32%)		6(24%)	10(40%)	
	Four	4(16%)	5(20%)		3(12%)	7(28%)	
	Five	6(24%)	5(20%)		5(20%)	4(16%)	
CEBQ Score		79.52±13.72	112.16 ±21.34	<0.001	78.56±12.91	104.92 ±14.66	<0.001
Hemoglobin (mean g/dL ±SD)		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)

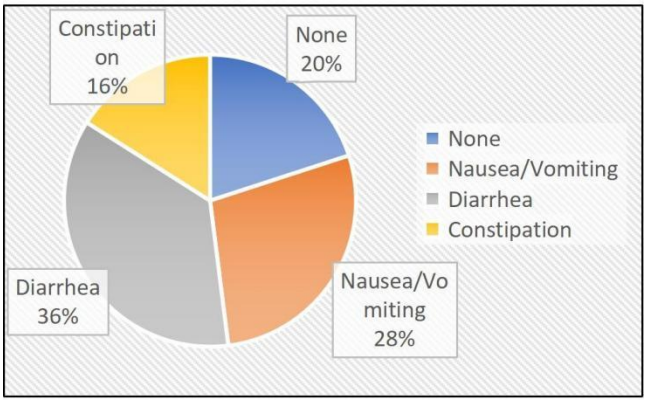

Figure 1: Side Effects of Folic Acid in Group-A children (n=25)

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.[12] 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.[13] 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.[14] 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.[15] 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.[16]

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.[17] 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.[18] In other studies, Dossa et a found no statistical significant change in appetite, weight and growth in children receiving either folic acid or placebo.[19]

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.[20] 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.[21]

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.

Acknowledgement

Authors extend their sincere appreciation to parents and guardians of the children for consenting for study. We appreciate the help of all the colleagues, registrars and house officers for assistance in data collection and analysis. We also acknowledged the help of consultants, nursing staff and laboratory staff to help in data collection, patient care and authentic laboratory tests.

Conflict of Interest None
Funding Nil
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

REFERENCES

1. Michels KB, Binder AM. Impact of folic acid supplementation on the epigenetic profile in healthy unfortified individuals – a randomized intervention trial. Epigenetics. 2024 Dec 31;19(1):2293410. https://doi.org/10.1080/15592294.2023.2293410
2. Shulpekova Y, Nechaev V, Kardasheva S, Sedova A, Kurbatova A, Bueverova E, et al. The Concept of Folic Acid in Health and Disease. Molecules. 2021 Jun 18;26(12):3731. https://doi.org/10.3390/molecules26123731
3. Ali MA, Hafez HA, Kamel MA, Ghamry HI, Shukry M, Farag MA. Dietary Vitamin B Complex: Orchestration in Human Nutrition throughout Life with Sex Differences. Nutrients. 2022 Sep 22;14(19):3940. https://doi.org/10.3390/ nu14193940
4. Koksal E, Ayaz A, Kucukerdonmez O, Bilgili N. Nutritional status in school children: Deficiencies in iron, folic acid and Vitamin B12. Scientific Research and Essays. 2011 Sep;6(21):4604–10. https://doi.org/10.5897/SRE11.930
5. Ajeigbe K, Aibangbee K, Saeed S, Ajeigbe O, Onifade A. Folic acid protects and heals gastric mucosa: role of acid output, inflammatory cytokines, angiogenic and growth factors. The Journal of Basic and Applied Zoology. 2022 Mar;83(1):15. https://doi.org/10.1186/s41936-022-00280-z
6. Harrison ME, Norris ML, Robinson A, Spettigue W, Morrissey M, Isserlin L. Use of cyproheptadine to stimulate appetite and body weight gain: A systematic review. Appetite. 2019 Jun 1;137:62–72. https://doi.org/10.1016/j.appet.2019.02.012
7. Vaivada T, Akseer N, Akseer S, Somaskandan A, Stefopulos M, Bhutta ZA. Stunting in childhood: an overview of global burden, trends, determinants, and drivers of decline. The American Journal of Clinical Nutrition. 2020 Sep;112:777S-791S. https://doi.org/10.1093/ajcn/ nqaa159.
8. Soofi SB, Khan A, Kureishy S, Hussain I, Habib MA, Umer M, et al. Determinants of Stunting among Children under Five in Pakistan. Nutrients. 2023 Aug 7;15(15):3480. https://doi.org/10.3390/nu15153480
9. THE 17 GOALS | Sustainable Development [Internet]. [cited 2024 Oct 3]. Available from: https://sdgs.un.org/goals
10. Naila NN, Mahfuz • Mustafa, Hossain • Muttaquina, Arndt • Michael, Walson JL, Nahar B, et al. Nutrition during the early life cycle Improvement in appetite among stunted children receiving nutritional intervention in Bangladesh: results from a community-based study. European Journal of Clinical Nutrition. 2021;75:1359–67. https://doi.org/10.1038/s41430-020-00843-9
11. Sleddens EF, Kremers SP, Thijs C. The Children's Eating Behaviour Questionnaire: factorial validity and association with Body Mass Index in Dutch children aged 6–7. The International Journal of Behavioral Nutrition and Physical Activity. 2008;5:49. https://doi.org/10.1186/1479-5868-5-49
12. Riahi F, Tashakori A, Vanani GS. Effects of Folic Acid on Appetite in Children with Attention Deficit Hyperactivity Disorder (ADHD) Treated with Methylphenidate: A Randomized Double-Blind Clinical Trial. Iran J Med Sci. 2018 Jan;43(1):9–17. PMID: 29398747
13. Nisar YB, Aguayo VM, Billah SM, Dibley MJ. Antenatal Iron-Folic Acid Supplementation Is Associated with Improved Linear Growth and Reduced Risk of Stunting or Severe Stunting in South Asian Children

Less than Two Years of Age: A Pooled Analysis from Seven Countries. https://doi.org/10.3390/nu12092632
14. Namdari M, Abadi A, Taheri SM, Rezaei M, Kalantari N, Omidvar N. Effect of folic acid on appetite in children: Ordinal logistic and fuzzy logistic regressions. Nutrition. 2014 Mar;30(3):274–8. https://doi.org/10.1016/j.nut.2013.08.008
15. Mohammadi MR, Mostafavi SA, Hosseinzadeh P, Nojoumi M, Asadian-Koohestani F. Comparing the Effects of Folic Acid and Cyproheptadine on Appetite, Weight, and ADHD Symptoms in Children with ADHD: A Randomized Clinical Trial. JIMC. 2022 Jan 24 [cited 2025 Jan 26]; https://doi.org/10.18502/jimc.v4i4.8473
16. Mostafavi SA. Children with ADHD: A Randomized Clinical Trial. Journal of Iranian Medical Council All rights reserved. 2021;4(4):257–65. http://dx.doi.org/10.18502/jimc.v4i4.8473
17. Hassanzadeh-Rostam Z, Kazemi A, Akhlaghi M. Effect of Multivitamin-Mineral Supplements Is Transient in Preschool Children With Low Appetite and Growth Failure. http://dx.doi.org/101177/1941406414543183. 2014 Jul;6(6):345–50. https://doi.org/10.1177/1941406414543183
18. Stoltzfus RJ, Chway HM, Montresor A, Tielsch JM, Jape JK, Albonico M, et al. Low Dose Daily Iron Supplementation Improves Iron Status and Appetite but Not Anemia, whereas Quarterly Anthelminthic Treatment Improves Growth, Appetite and Anemia in Zanzibari Preschool Children. Journal of Nutrition. 2004;134(2):348–56. https://doi.org/10.1093/jn/134.2.348
19. Dossa RAM, Ategbo EAD, Raaij JMAV, Graaf CD, Hautvast JGAJ. Multivitamin-multimineral and iron supplementation did not improve appetite of young stunted and anemic Beninese children. Journal of Nutrition. 2001;131(11):2874–9. https://doi.org/10.1093/jn/131.11.2874
20. Hatamizadeh N, Eftekhar H, Shafaghi B, Mohammad K. Effects of folic acid on preschool children's appetite: Randomized triple-blind clinical trial. Pediatrics International. 2007 Oct;49(5):558–63. https://doi.org/10.1111/j.1442-200X.2007.02421.x
21. Taneja S, Chowdhury R, Kvestad I, Bhandari N, Strand TA. Vitamin B 12 and/or folic acid supplementation on linear growth: a 6-year follow-up study of a randomised controlled trial in early childhood in North India. British Journal of Nutrition. 2023;129:1172–9. https://doi.org/10.1017/S0007114522002343