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Original Article

Comparing the Effects of Folic Acid and Cyproheptadine on Appetite, Weight, and ADHD Symptoms in Children with ADHD: A Randomized Clinical Trial

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Abstract

Background: Children with Attention Deficit Hyperactivity Disorder (ADHD) treated with methylphenidate may lose their appetite and body weight. In this study, an attempt was to compare the effects of folic acid with cyproheptadine on appetite, weight, and symptoms of attention deficit and hyperactivity in children with ADHD who are taking methylphenidate.

Methods: This was a randomized clinical trial performed on 7-12 year old children who were diagnosed with ADHD, treated with methylphenidate, and complained of appetite loss. In the first visit, anthropometric measurements were performed and then mothers completed the ADHD rating scale, Sleep Disturbance Scale for Children, and visual analogue scale for appetite. Then, the participants were randomly assigned to receive either cyproheptadine (4 *mg/day*), or folic acid (1 *mg/day*). All assessments were repeated after 8 weeks.

Results: Twenty-four children in the cyproheptadine group and 23 in the folic acid group (19 boys in each group) completed the study and statistical analyses were performed. The hyperactivity score significantly decreased in the folic acid group compared with the cyproheptadine group (p=0.035). However, the change in attention deficiency scores between groups was not significant. During the study, only girls in the folic acid group had significant body weight increase in contrast to other subgroups.

Conclusion: Improving hyperactivity symptoms in the folic acid group along with better growth especially in girls reveals the clinical superiority of folic acid over cyproheptadine.

Keywords: Appetite, Attention deficit disorder with hyperactivity, Body weight, Children, Cyproheptadine, Folic acid

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Introduction

Central Nervous System (CNS) stimulants including methylphenidate are among the first-line medications for treating Attention Deficit/Hyperactivity Disorder (ADHD) (1). Even when clinically positive responses are observed, some children may experience common side effects most notably abdominal discomfort, appetite suppression, and weight loss especially during the first weeks of the onset of medication (2). Different studies have shown loss of appetite, slower weight gain or weight loss (3), even growth retardation in stimulant-taking children compared with non-stimulant-taking or healthy controls (3,4). These undesirable effects are usually transient but still, families and medical teams are concerned about stimulants side effects so that some families are unwilling to put their children on stimulants or have poor compliance with stimulant therapy. Many studies suggest the advantages of adjunctive nutrition therapy versus monotherapies to overcome attention deficit/hyperactivity disorder.

Simultaneous use of micronutrients with psychiatric medications is common to improve the psychiatric symptoms. The micronutrients play role in various metabolic pathways in the brain as cofactors and impair innate metabolism to change the normal and efficacious procedure. Folic acid or vitamin B (9) is essential for neural tube development during the embryonic stage. This water-soluble vitamin is also necessary for brain function and improving mental health status. Folic acid deficiency leads to peripheral neuropathy, irritability, behavioral disorders, cognitive deficits, mental confusion, forgetfulness, loss of appetite, and poor growth (5). Some investigators had successfully administrated folic acid as an appetite stimulant in children (6). Ghanizadeh *et al* have augmented 5 *mg/day* folic acid to 10 to 20 *mg/day* methylphenidate and compared the effects with placebo. They concluded that folic acid could not add a beneficial effect to methylphenidate with regard to ADHD symptoms and quality of life (7). However, they did not assess the appetite and body weight changes during the study.

Cyproheptadine Hydrochloride (CH) is a first-generation FDA-approved antihistamine that is both a histamine and serotonin antagonist with few side effects such as appetite stimulation and transient drowsiness especially when one starts to take the medication for the first time (8,10). Cyproheptadine improves appetite suppression through the antiserotonergic effect on 5-HT2 receptors in the brain (11). Some clinicians have successfully used cyproheptadine as an appetite stimulant especially in children with malnutrition or weight loss (12,14). Kadkhoda Mezerji *et al* augmented 4 *mg* cyproheptadine to 5 *mg* increment of methyphenidate and compared the effects with placebo in children with ADHD. They did not observe a significant difference with regard to growth and response to treatment in the cyproheptadine group compared with placebo (15). Furthermore, the safety of cyproheptadine administration in children is approved by previous studies(16). Using different doses for longer duration may bring different outcomes. Furthermore, before the current study, there was not a clinical trial comparing the effects of folic acid with cyproheptadine in children with ADHD. Hence, in this study, their effects on appetite, weight, height, symptoms of attention deficiency, hyperactivity, and sleep disturbances in children with ADHD who are taking methylpheni date were compared.

Materials and Methods

Study design

This was a parallel double-blind randomized clinical trial with a 1:1 allocation ratio with no important changes to the method after trial commencement.

Subjects

This clinical trial was performed in a child and adolescent psychiatric clinic on children diagnosed with ADHD by a child and adolescent psychiatrist. Children aged 7-12 years, diagnosed with the combined form of ADHD based on DSM-5 criteria and treated with methylphenidate (Ritalin;1 *mg/kg*) prescribed by a child and adolescent psychiatrist who had complaint of appetite loss were included.

Exclusion criteria were children with a history of major prenatal complications such as prematurity, low birth weight (reported by parents), any past or present psychosis, co-morbid Tourette syndrome, autism spectrum disorders, or other persistent developmental disorders. Furthermore, usages of narcotics, confounding drugs, or dietary supplements during the past two months were among our exclusion criteria.

The sample size was determined with SigmaPlot 12 sample size calculator in type I error α=0.05 and with a power of 1-β=0.80 to detect 5 *kg* mean difference between groups with a standard deviation of 5.4 based on a pilot study. Accordingly, the sample size of 20 patients in each group was calculated to be sufficient. But, the sampling was continued to compensate for the loss to follow-up, which is common in clinical trials.

Study procedure

The structured interview and clinical judgment of the child and adolescent psychiatrist were carried out to determine ADHD diagnosis and the children were invited to participate in the study after describing the study's process and possible benefits, and side effects. Parents of 56 children who met the inclusion criteria signed the informed consent forms. After the assent of children, they were randomized using the permuted block randomization to receive either cyproheptadine (4 *mg/day*) or folic acid (1 *mg/day*). Randomization and allocation concealment both were done by a third-party. The treatments were blinded to patients, researchers, and the person who analyzed the data by coding the pills. Twenty-eight patients were allocated to cyproheptadine and 28 patients to the folic acid group. The study was approved and licensed by the clinical ethics review board of Tehran University of Medical Sciences (Letter No. 132308). This study was also registered in Iranian Registry of Clinical Trials (Clinical trial registration number:IRCT201203167462N5).

In the first visit, personal and socio-demographic questionnaires, ADHD Rating Scale, Sleep Disturbance Scale for Children (SDSC), and visual analogue scale for appetite were completed by mothers; anthropometric measurements in the standard situation were then performed. Height (in *centimeters* to nearest 0.5 *cm*) and weight (in *kilograms* to nearest 0.1 *kg*) were measured by a trained dietitian. Weight was measured by accurate bascule (Seca GmbH, Germany) while patients were in minimal clothing and height was measured by Seca wall height gauge (Seca GmbH, Germany) while subjects were standing without shoes in the standard position. All the assessments were repeated after 8 weeks. The study protocol was assessed by every-2-week phone calls and also in a visit at week 4. Furthermore, patients were asked to take their pills every session and their compliances were assessed by pill count. Poor compliances less than 70% were caused to dropout in research.

Outcomes

In this study, visual analogue scale was used as a subjective indicator of appetite alteration and the children's weight change was considered as a rapid somatic marker of the change in appetite as the main outcomes. Furthermore, to test the clinical relevance of supplementation, attention deficiency, hyperactivity, and sleep disturbance scores were compared between the two groups as the secondary outcomes.

Statistical analyses

Stata 11.1 software was used to analyze the data. The normality of data distribution was checked first. Similarities of categorical and quantitative variables at baseline were tested with chi-square, Fisher's Exact test, or independent sample t-test. Mean differences in quantitative variables between groups were compared using the independent sample t-test. Intention-To-Treat (ITT) Informed consent: Written consent forms were obtained from parents and oral assents were attained from children. The study was approved and licensed by Clinical Ethics Board of Tehran University of Medical Sciences (Letter No.132308). Clinical trial registration number: IRCT201203167462N5

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Results

From 28 participants in each group, four children in the cyproheptadine group and 5 in the folic acid group lost to follow-up or voluntarily left the study or were excluded due to irregular drug consumption. Eventually, 24 children in the cyproheptadine group and 23 in the folic acid group (19 boys in each group) completed the study and their data was used for statistical analysis (Figure 1). The mean age of participants in the cyproheptadine group was 8.8± 2.7 years and in the folic acid was 8.6±2.2 years. Socio-demographic variables were not different between the two groups at baseline (Table 1).

Mean weight change was not significantly different between the two groups with a p-value=0.668 (Table 2). Subgroup analysis showed that girls in the folic acid group gained more weight comparing with other subgroups (Figure 2). Height increase was not significantly different between the two groups with a p-value=0.248 (Table 2). The height growth pattern was similar in both groups and was different between genders. A remarkable response of body height to both supplements in girls was observed; in fact, their height increase was more (Figure 3). The attention deficiency scores significantly decreased in both groups but the mean changes were not significantly different between the folic acid and cyproheptadine groups (Table 2). The mean change in hyperactivity score±SD during the study in the folic acid group was -3.5±5.4 (95%CI:-5.9 to-1.2) and in the cyproheptadine group was -1±3.9 (95% CI:-2.6 to 0.6). Hyperactivity score significantly decreased more in the folic acid group compared with the cyproheptadine group (p=0.035) (Table 2).

Mean change in appetite scores decreased in folic acid recipients but increased in cyproheptadine recipients but the difference between groups was not significant. Mean change in sleep disturbance scores was not significantly different either in or between groups (Table 2).

Table- 1 Characteristics of demographic variables at baseline

Age	Folic acid 8.6±2.2	Cyproheptadine 8.8±2.7	p value
Gender Male Female	 19 4	 19 5	0.631
Father education Under Graduated Graduated Post Graduated	 11 5 7	 19 2 3	0.262
Mather education Under Graduated Graduated Post Graduated	 11 8 4	 16 7 1	0.252
Economic status Low Middle High missing	 4 16 0 3	 9 9 1 5	0.121

Table- 2 Comparison of mean change in weight (kg), height (cm), attention deficiency score, hyperactivity score, appetite score, and sleep disturbance score between groups using two-sample t-test

		Folic acid (N = 23)				Cyproheptadine (n = 24)				
		Within group				Within group				
		Pre (Mean ± SD)	Post (Mean ± SD)	p value Paired t-test	Mean change ± SD	Pre (Mean ± SD)	Post (Mean ± SD)	p value Paired t-test	Mean change ± SD	Between groups p- value (independent t-test)
Weight (*kg*)	Boys	28.22± 6.50	28.68± 7.53	0.135	0.46 ± 0.29	29.97± 11.96	30.38± 11.98	0.097	0.40 ± 0.23	0.876
	Girls	28.87± 10.41	29.87± 10.49	0.016	1 ± 0.20	25± 0.86	25.5± 1.7	0.422	0.5 ± 0.86	0.348
	Total	28.33 ± 7.03	28.89 ± 7.85	0.036	0.55 ± 1.19	29.35± 11.28	29.77 ± 11.30	0.059	0.41 ± 1.02	0.668
Height (*cm*)	Boys	125.47± 24.11	126.86± 23.65	<0.001	1.39 ± 1.03	134.23± 15.73	135.23± 15.48	<0.001	1 ± 0.921	0.209
	Girls	130.62± 23.82	133.75± 21.65	0.063	3.12 ± 2.17	122 ± 1.73	125 ± 3.46	0.095	3 ± 1.73	0.938
	Total	126.36 ± 23.60	128.06 ± 22.99	<0.001	1.69 ± 1.40	132.70 ± 15.25	133.95 ± 14.88	<0.001	1.25 ± 1.20	0.248
Attention deficiency	Boys	14.84 ± 4.64	11.94 ± 5.46	0.010	- 2.89 ± 4.42	15.61 ± 7.56	12.42 ± 5.32	0.014	-3.19 ± 5.47	0.852
	Girls	14.75 ± 5.31	10.25 ± 4.27	0.361	- 4.5 ± 8.38	7.33 ± 4.61	7.33 ± 1.15	1.00	0 ± 3.46	0.429
	Total	14.82 ± 4.68	11.65 ± 5.22	0.006	-3.17 ± 5.09	14.58 ± 7.71	11.79 ± 5.26	0.017	-2.79 ± 5.31	0.802
Hyperactivity	Boys	14.47 ± 4.27	12.21 ± 4.39	0.048	- 2.26 ± 4.66	13.90 ± 6.33	12.61 ± 6.74	0.168	-1.28 ± 4.12	0.243
	Girls	18.25 ± 5.37	8.5 ± 1.91	0.032	- 9.75 5.18	7.33 ± 1.15	8.33 ± 2.88	0.422	1 ± 1.73	0.009
	Total	15.13 ± 4.58	11.56 ± 4.28	0.004	-3.56 ± 5.46	13.08 ± 6.32	12.08 ± 6.50	0.228	-1 ± 3.95	0.035

Appetite	Boys	13.68 ± 3.59	13.05 ± 3.79	0.089	-0 .63 ± 1.53	12.09 ± 3.65	11.66 ± 4.88	0.571	-0.42 ± 3.41	0.813
	Girls	13.5 ± 1	11.25 ± 1.5	0.018	- 2.25 ± 0.95	12.33 ± 0.57	12.66 ± 1.15	0.422	0.33 ± 0.57	0.009
	Total	13.65 ± 3.26	12.73 ± 3.54	0.010	-0.91 ± 1.56	12.12 ± 3.41	11.79 ± 4.57	0.614	-0.33 ± 3.1	0.437
Sleep disorder score	Boys	46.15 ± 14.73	45.15 ± 14.11	0.527	-1 ± 6.76	42.38 ± 14.04	43.09 ± 13.54	0.718	0.71 ± 8.96	0.502
	Girls	46.25 ± 12.81	50.75 ± 6.13	0.328	4.5 ± 7.72	34 ± 5.19	33.33 6.35	0.422	0.66 ± 1.15	0.312
	Total	46.17 ± 14.14	46.13 ± 13.14	0.976	-0.04 ± 7.08	41.33 ± 13.48	41.87 ± 13.18	0.754	0.54 ± 8.37	0.797

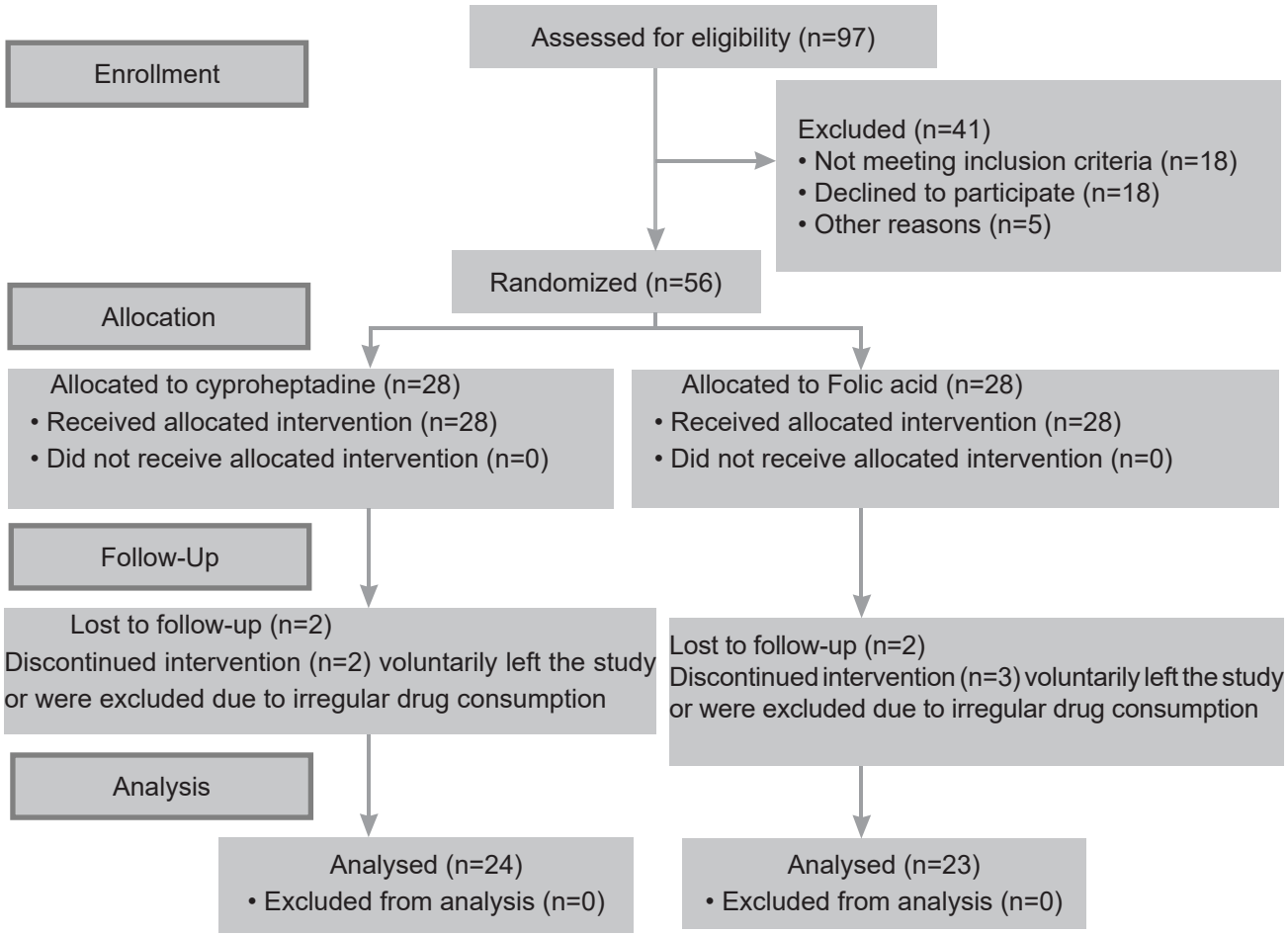

Figure 1: Flow Diagram of study; CONSORT 2010.

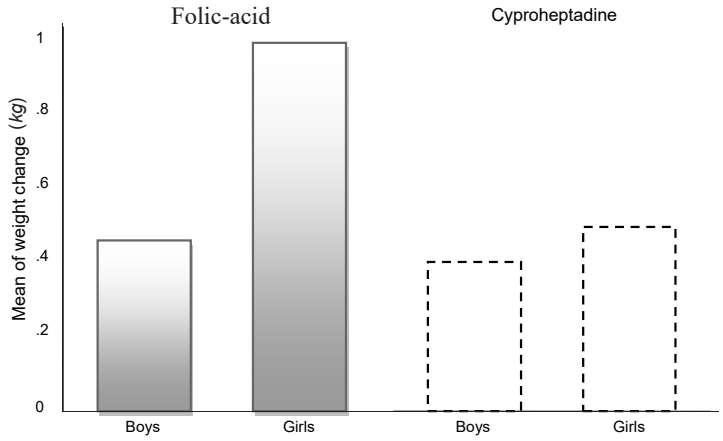

Figure 2: Bar chart of comparison of mean change in body weight between groups by gender.

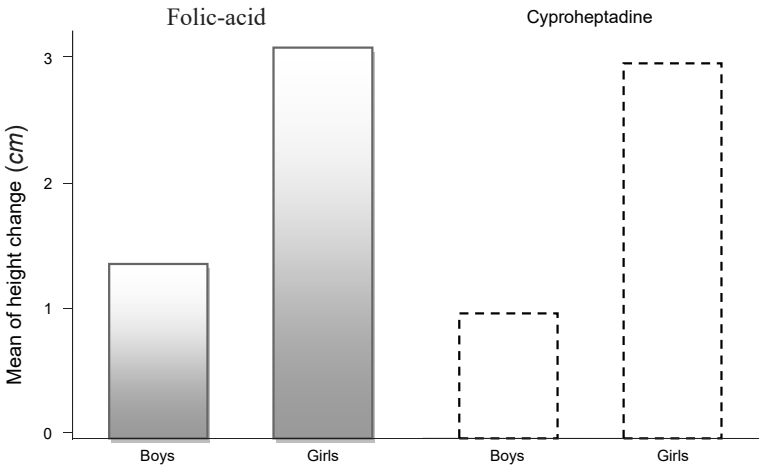

Figure 3: Bar chart of comparison of mean change in height between groups by gender.

Discussion

In this study, two commonly used appetite boosters in ADHD children treated with methylphenidate complaining of appetite loss were used. The purpose was to evaluate which of them can better alleviate the appetite suppression side effect of methylphenidate.

Unlike the cyproheptadine group, children in the folic acid group significantly gained weight during the study. However, the mean change in body weight (*kg*) between the two groups using the independent sample t-test was not statistically significant. The comparison with subgroup analysis by gender was repeated. A remarkable and significant response of bodyweight to folic acid in girls (Figure 2) was observed. Medeiros *et al* (17) found that children on the folic acid supplementation significantly gained more weight than those on placebo. The chief mechanism of enhancing growth by folic acid has not yet been proved but it has been claimed that the indirect effect of induced appetite rationally follows by an improvement of growth velocity. Better response to folic acid in girls subgroup may be due to possible folic acid deficiency in girls around puberty (18).

The comparison of mean change in height (*cm*) between groups using the independent sample t-test showed that children in the folic acid group slightly but not significantly gained more height than the cyproheptadine group. The comparison with subgroup analysis by gender was repeated. A remarkable response of body height to both supplements in girls (Figure 3) was observed. This may be due to the height growth in girls related to puberty and age. Najib *et al* (19) showed beneficial effects of cyproheptadine on body mass index in undernourished children

compared to the control group. But our study was the first study that compared the efficacy of folic acid with cyproheptadine for appetite and growth in children with ADHD.

In our study, no significant difference was found between groups regarding sleep disturbance; however, the sleep disturbance score was less in the cyproheptadine group which may be due to its hypnotic effects. Similarly, Kadkhoda Mezerji *et al* did not find a significant difference regarding the Pittsburgh Sleep Quality Index between children receiving the cyproheptadine and the placebo 15. In our study, folic acid significantly decreased the hyperactivity (but not attention deficiency) in children with ADHD compared with the cyproheptadine. Ghanizadeh *et al* in an eight-week randomized double-blind placebo-controlled clinical trial of co-administration of folic acid and methylphenidate in patients with ADHD did not find any significant difference in ADHD symptoms in the folic acid group compared with the placebo which is in contrast with our result (7). Different doses may be responsible for different results.

The generalizability of the results of this study is limited to children with ADHD treated with methylphenidate. The current study was relatively small in sample size and the results may be susceptible to random effect error. Not having a control group, and food records, short-term follow-up, and imbalance in gender distribution that may affect sub-group analysis are among the limitations.

Conclusion

Significant improvement of hyperactivity symptoms in the folic acid group along with better growth especially in the girls' subgroup suggests the clinical superiority of folic acid over cyproheptadine. This suggests the possible beneficial effects of folic acid with stimulants in growth of adolescents with ADHD. Further research should be carried out in this field to confirm the findings.

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Conflict of Interest

All authors declare no commercial or noncommercial conflict of interest related to this work.

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