Dietary intake, growth and development of children with ADHD in a randomized clinical trial of Ritalin and Melatonin co-administration: Through circadian cycle modification or appetite enhancement?

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Objective: It is postulated that ritalin may adversely affect sleep, appetite, weight and growth of some children with ADHD. Therefore, we aimed to evaluate melatonin supplementation effects on dietary intake, growth and dev elopment of children with ADHD treated with ritalin through circadian cycle modification and appetite mechanisms .
Method: After obtaining consent from parents, 50 children aged 7-12 with combined form of AD/HD were randomly divided into two groups based on gender blocks: one received melatonin (3 or 6 mg based on weight) combined with ritalin (1mg/kg) and the other took placebo combined with ritalin (1mg/kg) in a double blind randomized clinical trial. Three-day food record, and standard weight and height of children were evaluated prior to the treatment and 8 weeks after the treatment. Children's appetite and sleep were evaluated in weeks 0, 2, 4 and 8. Hypotheses were then analyzed using SPSS17.
Results: Paired sample t-test showed significant changes in sleep latency (23.15±15.25 vs. 17.96±11.66; p=0.047) and total sleep disturbance score (48.84±13.42 vs. 41.30±9.67; p=0.000) before and after melatonin administration, respectively. However, appetite and food intake did not change significantly during the study. Sleep duration and appetite were significantly correlated in melatonin group (Pearson r=0.971, p=0.029). Mean height (138.28±16.24 vs. 141.35±16.78; P=0.000) and weight (36.73±17.82 vs. 38.97±17.93; P=0.005) were significantly increased in melatonin treated children before and after the trial .
Conclusion: Administration of melatonin along with ritalin improves height and weight growth of children. These effects may be attributed to circadian cycle modification, increasing sleep duration and the consequent more growth hormone release during sleep.

Keywords: *Attention Deficit Disorder with Hyperactivity, Diet, Growth and Development, Melatonin, Ritalin,*

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Central nervous system (CNS) stimulants including ritalin have been safely used for many years in treating attention deficit hyperactivity disorder (ADHD) and have always been among the first-line medications in the pharmacotherapy of ADHD. Nevertheless, approximately 30% of those who take stimulant drugs either do not show clinically significant improvement or do not tolerate them(1). Even when clinically positive responses are observed, some children may experience some common side effects (2,3). Sleep disturbances, insomnia, abdominal discomfort, and appetite suppression are among the most common stimulant side effects. These undesirable effects are usually transient (2) but still a concern for families and medical team. As a result of these side effects, some families are unwilling to consider treatment with a stimulant or will discontinue their children treatment. So far, many efforts have been made to replace stimulant drugs with non-stimulants (2, 4-9), or adjunct them to herbal (3, 6, 9) or food supplements (10, 11). Nevertheless, stimulants are still among the first-line treatment for managing ADHD.

Different studies have shown slower weight gain (12, 13) even loss of BMI (14) and growth retardation (12-14) in stimulant-taking children compared to non-stimulant taking and healthy children. Evidences imply that pineal gland substance moderates growth both in humans and rats (15). Serotonin and its pineal derivative, melatonin, have also been implicated as the stimulus for growth hormone secretion after the onset of slow-wave (non-rapid eye movement, NREM) sleep in normal humans.

According to the safety study of melatonin administration in children (16), we decided to examine its effects on dietary intake, growth and development of children with ADHD who are taking ritalin through circadian cycle modification and appetite mechanisms.

Materials and Method

Participants

Children aged 7-12 years who were newly diagnosed with the combined form of ADHD by a child and adolescent psychologist were recruited into the initial stage of this study. Children with history of major prenatal complications such as prematurity, low birth weight (reported by parents), any past or present psychosis, comorbid tourette syndrome, celiac, phenylketonuria, autism, or other persistent developmental disorders were excluded. Furthermore, usages of narcotics, confounding drugs or dietary supplements during past two months were among our exclusion criteria.

Written consent forms were obtained from parents and oral assents were attained from children. Parents of 60 ADHD children who met the inclusion criteria signed the consent forms**.** Eight children (25%) in the placebo group and 2 (7.25%) in the melatonin group dropped out of the study voluntarily or were excluded due to irregular drug consumption. Eventually, 26 children in the melatonin group and 24 in the placebo group completed the study.

The study was approved and licensed by Clinical Ethics Board of Tehran University of Medical Sciences (Letter No. 31807).

Procedure

In the first visit, personal and socio-demographic questionnaires, diagnosis tests for ADHD (ADHD Rating Scale, based on diagnostic criteria for DSM-IV), SDSC (Sleep Disturbance Score for Children) and appetite questionnaires were completed by mothers; anthropometric measurements in standard situation were then performed. Height (in centimeters) and weight (in kilograms) were measured by a trained dietitian. Weight was measured by accurate bascule (seca762, seca gmbh & co. kg • Hammer Steindamm 9 – 25 • 22089 Hamburg • German) while patients were in minimal clothing and height was measured by Seca wall height gauge (seca 206, seca gmbh & co. kg • Hammer Steindamm 9 – 25 • 22089 Hamburg • German) while subjects were standing without shoes in standard position.

Furthermore, in the first visit, a trained dietitian provided mothers with instructions regarding portion sizes, and trained them to make a 3-day food record on what their children consume. Three day food records were to be completed at home over two non-sequential weekdays, and one day on a weekend, with the days being assigned according to a computerized randomization table. Parents were required to record all food and beverages (including snacks, gum, candy, and etc.) consumed by their children. They were required to deliver the 3-day food record one week later in the second visit. Meanwhile, inclusion and exclusion criteria were assessed and eligible participants were entered in to the second phase of the study.

At the second phase, children were divided in to two groups in a double blind permuted block randomized allocation design based on gender blocks. One group took melatonin (3 or 6mg based on weight: 3mg in children under 30kg and 6mg in children above 30kg according to Kristiaan and colleagues(17)) combined with Methylphenidate (Ritalin) (1mg/kg), and the other group took placebo combined with ritalin (1mg/kg). Methylphenidate, (10mg Ritalin tablets, Basel, Switzerland), melatonin (3mg capsules, Nutricentury, Canada) Placebo (starch capsule, Made by Institute of Medicinal Plants, Tehran, Iran) were used in this study.

ADHD rating scale, SDSC, and appetite questionnaires were completed by mothers at baseline (before treatments at the first visit), and were repeated at 2, 4, and 8 weeks after the treatments. Anthropometric assessments and 3-day food record were done at baseline and were repeated 8 weeks after the interventions. At the end of study, stimulant drug side effects questionnaire was completed by mothers; then, side effects were compared between the two study groups.

Statistical Analysis

SPSS 17 software was used to analyze the data. Kolmogorov Smirnov test was used for assessing the normality of data distribution. Changes in the mean of quantitative variables before and after the treatment were assessed using paired sample t-test. Differences in quantitative variables between groups were compared using independent sample t-test. Qualitative variables were compared between the two groups using Chi-Square and Fisher's Exact Test. Pearson correlation and general linear model have been used where necessary. To track changes of means in appetite and sleep duration at baseline, 2, 4, and 8 weeks after the intervention, ANOVA with repeated measures was used.

Food data processes

Dietary intakes provided in the three-day food records were entered into the computer nutrient database (Food Processor II®, ESHA Research, Salem, Oregon) that was modified to include domestic foods. If a particular brand consumed by a subject was not in the nutrient database, the closest brand of the food or beverage was

selected as a substitute. Three-day food record was analyzed based on all standard macro- and micro-nutrient parameters performed by Food Processor II, and printout reports were made for each subject. Reported data from the printouts were then entered into the SPSS database.

Results

Fifty subjects completed the study (36 boys and 14 girls) with mean age of 9.22±1.76 years. Mean age differences between melatonin and placebo groups was not statistically significant (9.57±1.65 vs. 8.83±1.82 respectively; P=0.138). Group receiving melatonin included 26 patients (19 boys and 7 girls), and the group receiving placebo included 24 patients (17 boys and 7 girls).

No statistically significant difference was observed between the two groups regarding gender distribution (p=0.786, Fisher's Exact Test).

All demographic variables including family income levels, parents' educational levels, children's birth order, children's delivery type, and parents' relationship were similarly distributed between the two groups. Data on anthropometric variables in both groups at the beginning and after the intervention and paired samples test results are listed in table 1. Based on independent sample t-test, no significant difference was detected between recipients of melatonin and placebo groups in terms of anthropometric measurements before intervention.

Table1. Anthropometric variables of children with Attention Deficiency and Hyperactivity Disorder (ADHD) at baseline and after 8 weeks of intervention in Melatonin and Placebo groups; results are in Mean ± SD and p-values are reported separately for each group based on paired samples t-test comparing before and after intervention values

Variable	†Melatonin group	P-value	‡Placebo group	P-value
Height (Cm)				
B.I	138.28±16.24		133.78±14.81	
A.I	141.35±16.78	0.51	135.89±15.55	0.62
Weight (Kg)				
B.I	36.73±17.82		32.73±14.74	
A.I	38.97±17.93	0.65	33.60±17.14	0.84
BMI (Kg/m²)				
B.I	19.20±4.40		18.28±4.74	
A.I	19.54±4.94	0.79	18.43±4.85	0.91

B.I: Before Intervention;
A.I: After Intervention;
†Subjects: 26 (19 boys and 7 girls);
‡Subjects: 24 (17 boys and 7 girls)

Table2. Energy, macronutrients and relevant micronutrients in Attention Deficiency and Hyperactivity Disorder (ADHD) at baseline and after intervention in Melatonin and Placebo groups; results are in Mean ± SD, paired samples t-test showed no significant differences comparing before and after intervention mean values.

Variable	† Melatonin group	‡ Placebo group
Energy(Kcal)		
B.I	1699.61±400.8	1596.0±243.14
A.I	1705.47±443.8	15340±308.28
Carbohydrate(g)		
B.I	213.23±51.96	199.26±41.51
A.I	212.44±60.41	195.28±48.38
Protein(g)		
B.I	49.37±13.3	43.87±14.11
A.I	48.83±11.7	45.48±14.65
Total Fat(g)		
B.I	77.86±25.2	74.61±12.92
A.I	79.15±25.0	68.76±15.97
Zn (mg)		
B.I	5.58±1.51	5.26±1.55
A.I	5.54±1.41	5.20±1.64
Fe (mg)		
B.I	9.63±3.38	7.80 ±2.71
A.I	10.22±3.84	7.97±2.89
Omega-3 (mg)		
B.I	0.029±0.13	0.0047±0.019
A.I	0.018±0.05	0.0059±0.024

B.I: Before Intervention;
A.I: After Intervention;
† Subjects: 26 (19 boys and 7 girls);
‡Subjects: 24 (17 boys and 7 girls)

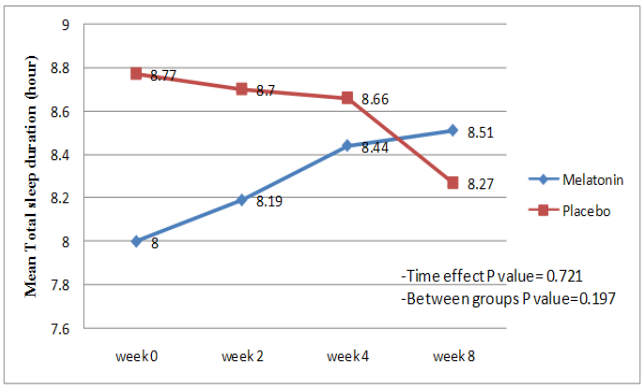

Figure 1 Mean total sleep duration (hour) of two trial groups based on SDSC sleep questionnaire at baseline, 2, 4, and 8 weeks after the treatment using ANOVA with repeated measures.

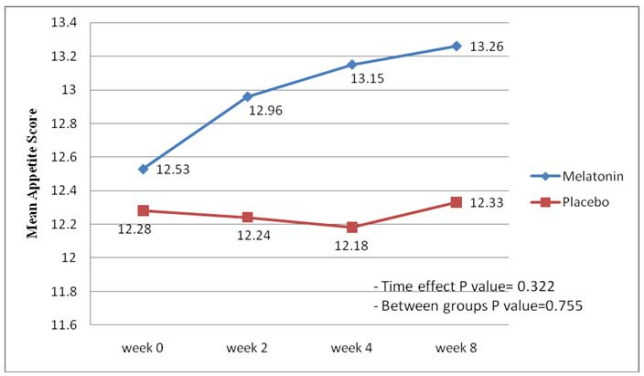

Figure 2 Mean total appetite score of two trial groups based on appetite questionnaire at baseline, 2, 4, and 8 weeks after the treatment using ANOVA with repeated measures

Moreover, at the end of the intervention, the differences in height, weight and body mass index (BMI) were not statistically significant between the two groups.

Independent sample t-test showed that the mean weight increment in melatonin treated children was higher than placebo group (2.24 vs. 0.87 kilogram؛ P=0.376). Furthermore, mean height growth was more in melatonin group compared to placebo group (3.07cm vs. 2.11؛ p=0.339).

The study groups were not significantly different from one another in terms of energy, macronutrients and micronutrients in the beginning and at the end of the intervention (table 2). Furthermore, based on independent sample t-test, between group differences were not significant in terms of energy, macro-and relevant micronutrients.

Paired sample t-test showed significant changes in sleep latency (23.15 minutes ±15.25 vs. 17.96 minutes ±11.66; p=0.047) and total sleep disturbance score (48.84±13.42 vs. 41.30±9.67; p=0.000) in children taking melatonin before the treatment and 8 weeks after trial. P-value for sleep duration was near significant (p=0.06) but appetite change during the study was not significant. None of these variables changed significantly during the study in the placebo group.

Appetite was significantly correlated with total sleep duration (Pearson r=0.971, p=0.029) in melatonin group. General linear model test has been done and B=1.33 was attained, the constant was 1.94, β was significant at 0.05 level, t(1)=5.71, p=0.029. Regression equation: y=1.94+1.33x

ANOVA with repeated measure was used to track changes of means in sleep duration (figure 1) and appetite (figure 2) at baseline and 2, 4, and 8 weeks after the intervention.

At the end of the 8th week of the trial, stimulant drug side effects questionnaire was completed voluntarily by mothers. Twenty patients in the melatonin group and 18 in the placebo group completed this questionnaire.

The mean scores of side effects were 11.35±8.81 in the melatonin group and 10.16±9.05 in the placebo group. The difference was not statistically significant (p=0.686).

Discussion

Total calorie intake, and macronutrients are among factors which may influence children's height and weight (18). In addition, some studies have reported the effects of zinc, iron, and omega-3 fatty acids on appetite, growth and development of children (19-23). Results of the current study (table 2) did not show any significant differences in within groups or between groups before and after the treatment in terms of micronutrients, macronutrients and calorie intake. Furthermore, age, gender and all demographic variables including family income levels, parents' educational levels, children's birth order, children's delivery type and parents' relationship were similarly distributed between the two groups by randomization. Therefore, slightly better growth in melatonin groups could not be due to calorie, macro- and micronutrients intake alterations or other controlled variables. We can infer that changes in sleep, appetite, height and weight could be a result of melatonin supplementation.

Height increased significantly within both groups in our study (table 1). Weight increased significantly in children taking melatonin, but this increase was not significant in recipients of placebo (table 1). These changes were not significant when we removed placebo effects by comparing both groups with independent sample t-test. Even though increments in height and weight are clinically apparent in melatonin group, not detecting statistically significant changes in between groups may be due to small sample size, short study duration and/or low melatonin dose.

During this study, taking 3 or 6 mg of melatonin decreased sleep latency and total sleep disturbances

while it increased total sleep duration. Appetite score rose (figure 2) as total sleep duration increased (figure 1) in the melatonin group. However, these clinically important effects on appetite were minute and could not affect the total calorie intake. Therefore, the theory of melatonin effects on dietary intake and consequently on height and weight through the appetite promotion mechanism is not supported by this study. To our best knowledge, no study on humans had been formerly carried out to investigate melatonin effects on appetite and calorie intake.

Valcavi R. and colleagues (24) showed that melatonin stimulates growth hormone release as well as growth hormone responsiveness to growth hormone-releasing hormone (GHRH) secretion. Our results in height and weight promotion in melatonin group are confirmed by Vacavi study results. Van Cauter E. and colleagues (25) revealed that sleep exerts modifying effects on release of hormones, regulation of serum glucose and cardiovascular and systemic functions. Throughout slow wave sleep (SWS), the anabolic growth hormone is released meanwhile the catabolic stress hormone cortisol is inhibited leading to synthesis of complex molecules, which promotes weight and height in growing children (25).

Thus, administration of melatonin along with ritalin may slightly improve height, weight, growth and development of ritalin-taking children with ADHD. These effects may be mostly attributed to circadian cycle modification, less sleep disturbances, increased sleep duration and the consequent more growth hormone release during sleep.

Conflict of Interest

Authors declare no conflict of interest related to this work.

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