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Comparison of Risperidone and Melatonin Effects in Methylphenidate Treated Children with Attention Deficit Hyperactivity Disorder for Treatment of Sleep Disorders

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Abstract

Objectives: Some studies reported a significant improvement in sleep parameters by melatonin therapy in children with ADHD. Utilizing risperidone along with stimulants is another pharmacologic approach for ADHD treatment. In this study we investigated the effect of melatonin and risperidone on sleep disorders in children with ADHD and compared their effectiveness as well.

Methods & Methods: 29 patient aged 6 years to 12 years old with ADHD were randomly divided into two groups based on file number: either received melatonin (3 mg to 6 mg) combined with Ritalin or received risperidone (0.25mg to 0.5 mg) combined with Ritalin in a single blind randomized clinical trial. Assessments were performed at baseline and were repeated at 2 and 4 weeks after beginning of the treatment.

Results: In risperidone group significant differences has been found in total score of sleep disorders (P=0.000), sleep onset and maintenance score (P=0.000), Sleep-wake transition disorders (P=0.000), but no significant differences in breathing (P=0.104), and hyperhidrosis (P=0.105) and excessive daytime sleepiness score (p=0.065), and in arousal group after 2 weeks (p=0.027) and after 4 weeks (p=0.150). comparison of melatonin group in different weeks (Base line with 2 and 4 weeks after treatment), show significant differences in total score of sleep disorders (P=0.000), sleep onset and maintenance score (P=0.000), Sleep-wake transition disorders (P=0.003), excessive daytime sleepiness (P=0.004), but no significant differences in breathing (P=0.068) and arousal (P=0.218) and hyperhydrosis score (P=0.336).

Conclusion: The results showed the equal effect of risperidone and melatonin. It can be concluded that the risperidone has the same effect of melatonin in the treatment of sleep disorders in children with ADHD.

Keywords: Risperidone; Melatonin; Treated, Sleep disorders

Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a common condition characterized by repetitive obstruction of the upper airway resulting in daytime sleepiness due to sleep fragmentation caused by an airway obstruction. There are several papers on the prevalence of OSAHS showing that 7% to 26% of men and 2% to 13% of women have an apnea-hypopnea index (AHI) of more than 15 events per hour [1-5]. In Japan, the prevalence of OSAHS in the male working population has increased over the past decade, being estimated at 22.3% in patients with moderate to severe sleep-disordered breathing (SDB) [6]. It is significantly correlated with cardiovascular morbidity and mortality [7,8]. For patients with moderate to severe OSAHS, standard treatment is the continuous positive airway pressure (CPAP) ventilation. Compliance with and tolerance of CPAP are not always favourable, whose adherence rate is low, being 40% to 83% [9,10]. In Japan, CPAP treatment is not covered by health insurance for OSAHS patients with AHI of less than 20 events per hour. Consequently, one of the oral appliances (OA), prosthetic mandibular advancement (PMA), is a solid alternative to manage patients with mild to moderate OSAHS.

PMA causes protrusion of the mandible and tongue and enlarges and stabilizes the upper airway during sleep. Although the PMA has been shown to be effective for patients with mild to moderate OSAHS, adherence is poor [11,12]. Studies on PMA treatment have indicated that about 75% of patients remained adherent after 12 months of treatment, which may decrease to 50% after 5 years. In the PMA treatment, there are several side effects including tooth pain, pain of the temporomandibular joint (TMJ), gum disease, and dry mouth. Therefore, PMA treatments are not indicated for use in all patients who prefer PMA to CPAP, who do not respond to CPAP, or who show failed treatment attempts with CPAP. It is consequently important to develop other treatment options besides PMA for sleep apnea. A newly developed intraoral pressure gradient therapy system (IPGT), the iNAP® Sleep Therapy System (Somnics Inc., Hsinchu, Taiwan), was introduced as an alternative treatment for OSAHS [13]. The feasibility

study explored the abilities and safety of the new device, the iNAP® Sleep Therapy System, for patients with OSAHS in our clinical sleep laboratory using full-night polysomnography.

Materials and Methods

Subjects

Subjects enrolled in this study were from outpatient clinic at the Child and Adolescent Psychiatric Division of Roozbeh Hospital, which is the university hospital of the Tehran University of medical sciences, located in Tehran, Iran. Inclusion criteria were (1) ages between 6 and 12 years old, inclusive; (2) diagnoses of ADHD according to DSMIV criteria (American Psychiatric Association, 2000); (3) receiving ritalin; (4) suffering from sleep disorders. Exclusion criteria included (1) presence of major depressive disorder, bipolar disorder, psychotic disorder, generalized anxiety disorder or other psychotic disorders; (2)Mental Retardation;(3)Drug intolerance;(4) any contraindications to the use of two drugs; (5) BMI above the 85th percentile. Subjects meeting diagnostic criteria for ODD were not excluded because of the high level of comorbidity of ODD in most ADHD populations, being present in around 30% to 60% of children with ADHD [12]. In this study 16 out of 29 ADHD patients had been diagnosed with ODD.

Study design

This study was a 28-day, randomized, single-blind clinical trial and parallel-arm comparison of melatonin and risperidone. The diagnosis of ADHD with or without comorbidity was achieved through clinical interview and CSI-4 (Child Symptoms Inventory-4) questionnaire which is a DSM-IV-referenced rating scale that screens for emotional and behavioral symptoms of childhood disorders.

To assess clinically significant improvement relative to baseline, we used the Clinical Global improvement (CGI-I) scales rated separately for symptoms of mania, depression, and ADHD. The CGI is rated on a 7-point scale that ranges from 1 (very much improved) to 7 (very much worse). Participants with ADHD had to have Scores 2 (much improved) on the CGI. In addition, socio-demographic information was collected from the parents. This research was approved by the Ethics Committee of Tehran University of Medical Sciences and written informed consent was filled with the participant's parents after full description of the study.

Medication schedule

In this study Subjects were randomly (1:1 ratio) allocated to receive either risperidone or melatonin for 4 weeks. Patients were randomized to a group according to the file number that was odd or even. For children who weighed less than 30 kg, melatonin was given at an initial dose of 3 mg at bedtime and for children upper than 30 kg; 3 mg to 6 mg was given. Besides, risperidone was given 0.25 mg to 0.5 mg for treating sleep problems. Parents were called weekly to monitor progress and discuss possible problems.

Assessment of efficacy and side effects

The parents filled in a 26-item sleep questionnaire(Sleep Disturbance Scale for Children)[13]. Assessments were performed at baseline and were repeated at 2 and 4 weeks after beginning of the treatment. Adverse events were recorded throughout the treatment period. Side effects were then compared between the two trial groups.

Data analysis

The two groups were compared using the X2 or Fisher exact test (categorical variables), Independent Sample t test and Repeated Measure ANOVA (continuous variables) using SPSS 20. Statistical significance was determined at $p<0.05$.

Results

Pretreatment patients characteristics

Fifty five patients were screened; 30 ADHD patients were eligible to participate in the study. One of the participants due to hypoglycemia excluded from the study. Afterwards from the remaining 29 patients, 15 were assigned to resperidone and 14 were assigned to melatonin. 10 female (4 and 6 were in the resperidone and melatonin group, respectively) and 19 male (11 and 8 were in the resperidone and melatonin group, respectively) were in the study. There were no statistically significant differences between the genders of two groups according to X2 test.

Patients' quantitative data such as age, body mass index, as well as baseline characteristics were analyzed in two trials before pharmacological intervention. Data analysis showed that there were no significant difference in age (P=0.24), body mass index (P=0.41), total score of sleep disorders (P=0.66), sleep onset and maintenance score (P=0.4), sleep disordered breathing (P=0.67), arousal disorders (P=0.63), sleep-wake transition disorders (P=0.98), excessive daytime sleepiness (P=0.58) and excessive sweating before intervention between two groups (Table 1). There were no significant differences between treatment groups in ODD ratio (P=0.34), and dose of Ritalin effects (P=0.793) in both risperidone and melatonin group.

Comparison of the therapeutic effects (efficacy measure)

The results of SDSC sleep questionnaire were analyzed using ANOVA with repeated measures at baseline, 2 and 4 weeks after the treatment. Data analysis showed that there were no significant difference between two groups in total score of sleep disorders (P=0.339), sleep onset and maintenance score (P=0.212), sleep disordered breathing (P=0.187), arousal disorders (P=0.404), Sleep-wake transition disorders (P=0.858), excessive daytime sleepiness (P=0.349) and excessive sweating (p=0.349).

In a comparison of risperidone group in different weeks(Base line with 2 and 4 weeks after treatment),significant differences has been found in total score of sleep disorders (P=0.000), sleep onset and maintenance score (P=0.000), Sleep-wake transition disorders (P=0.000),but no significant differences in breathing (P=0.104), and hyperhidrosis (P=0.105) and excessive daytime sleepiness score| (p=0.065), and in arousal group after 2 weeks (p=0.027) and after 4 weeks (p=0.150).

Comparison of melatonin group in different weeks (Base line with 2 and 4 weeks after treatment), show significant differences in total score of sleep disorders (P=0.000), sleep onset and maintenance score (P=0.000), sleep-wake transition disorders (P=0.003), excessive daytime sleepiness (P=0.004), but no significant differences in breathing (P=0.068) and arousal (P=0.218) and hyperhydrosis score (P=0.336) (Table 2). No statistically significant differences had been observed between the two groups in any of the side effects (Table 3).

Variables		Resperidone group(N=15)	Melatonin group (N=14)	Statistical analysis
Gender	Female	4	6	χ2(1)=0.840, P=0.359
	Male	11	8	
ge (Mean ± SD)		8.6 ± 1.8	9.5 ± 2.21	t(27)=1.2, P=0.24
Body mass index(Mean ± SD)		27.88 ± 34.33	20.15 ± 6.08	t(27)=-0.83, P=0.41
Total score of sleep disorder(Mean ± SD)		51 ± 9.89	49.57±7.1	t(27)=-0.44, P=0.66
sleep onset and maintenance score(Mean ± SD)		17.27 ± 3.71	18.14 ± 2.8	t(27)=0.71, P=0.48
sleep disordered breathing		3.87 ± 1.68	3.64 ± 1.01	t(27)=-0.43, P=0.67
arousal disorders(Mean ± SD)		3.67 ± 1.29	3.43 ± 1.34	t(27)=-0.49, P=0.63
Sleep-wake transition disorders(Mean ± SD)		11.4 ± 4.29	11.36 ± 4.07	t(27)=-0.03, P=0.98
excessive daytime sleepiness(Mean ± SD)		11.2 ± 4.04	10.43 ± 3.39	t(27)=-0.55, P=0.58
excessive sweating(Mean ± SD)		3.6 ± 2.85	2.57 ± 1.65	t(27)=-1.18, P=0.25

Table 1: Demographic and background data of participant in the study of comparing risperidone and melatonin effect on sleep disorders in children with ADHD.

	Comparison of baseline with second week		Comparison of baseline with fourth week		Comparison of second week with fourth week	
variables	t(14)	P	t(14)	P	t(14)	P
Total Sleep disorder score	5.848	<0.000	9.28	<0.000	2.878	0.013
Disorders of initiating and maintaining sleep	5.983	<0.000	10.001	<0.000	2.447	0.029
Sleep Breathing Disorders	1.989	0.068	2.28	0.04	1	0.336
Disorders of arousal	1.472	0.169	1.295	0.218	1	0.336
Sleep wake Transition Disorder	3.191	0.007	3.702	0.003	1.343	0.202
Disorders of excessive somnolence	2.299	0.01	3.44	0.004	1.735	0.106
Sleep Hyperhydrosis	1	0.336	1	0.336	-	-

Table 2: Comparison of melatonin receiving group in the different weeks.

Side effect	Melatonin group	Riper done group	P-value (Fisher exact test)
Headache	0 (0%)	1 (7.14%)	0.483
Abdominal pain	0 (0%)	2 (14.29%)	0.224
Morning Somnolence	2 (13.33%)	1 (7.14%)	1
Increased appetite	2 (13.33%)	0 (0%)	0.483

Table 3: Analysis of side effects in both risperidone and melatonin group.

Discussion

Attention Deficit-Hyperactivity Disorder (ADHD) is the most common psychological disorder in childhood with estimated prevalence of 5.29% worldwide and 10% in Iran [14,15]. The results of this study indicate that there is no significant difference between

risperidone and melatonin in the treatment of sleep disorders in children with ADHD.

The clinician who visit the ADHD children usually focus on improving hyperactivity, attention deficit and impulsiveness. Since the correlation between ADHD and sleep disorder was approved [16,17], it is clear that they should pay enough attention to manage their concomitant sleep disorders.

The effective intervention approaches for ADHD is a combination of different therapeutics strategies including, parent training, cognitive-behavioral and medical therapy by stimulants [18]. Stimulants as the most effective medications for the treatment of ADHD effectively alleviate the symptoms (poor attention, distractibility, hyperactivity and restlessness) [19]. There are a limited number of studies regarding to quality and quantity of sleep in children with ADHD. At present available research results indicate that melatonin can be effective medication in the treatment of insomnia [20].

The results of this study are consistent with the results of previous studies on the effect of melatonin on sleep disorders of ADHD patients. Smits et al. in a double-blind, placebo-controlled study indicated that short-term melatonin administration was relatively safe and significantly more effective than placebo in patients with sleep onset insomnia [21]. Heijden et al. investigated the effect of melatonin treatment on sleep and quality of life. They indicated that melatonin could enhance total asleep time in children with ADHD and chronic sleep onset insomnia [22]. In a double blind randomized clinical trial in Iran with co-administration of melatonin and ritalin significant changes in sleep latency and total sleep disturbance score had been shown in children with ADHD [23].

The effect of risperidone on the quality of sleep has been reported in some studies. For example, Jacobsen [24] reported an improved quality of sleep following treatment with risperidone in affective illness and obsessive-compulsive disorder. In contrast, Daniel et al. [25] reported that patients complained of more insomnia with risperidone and more sedation with clozapine.

It is noteworthy that no statistically significant differences had been observed between the two groups in any of the side effects. Therefore, it can be concluded that the risperidone has the same effect of melatonin in the treatment of sleep disorders in children with ADHD. Since the beneficial effects of melatonin on sleep disorder treatment of patients with ADHD has been proven, the results showed the equal effect of resperidone and melatonin. This prospective follow-up study evaluated a small group of 29 children. A number of issues remain for further investigation. Long-term efficacy and safety of both risperidone and melatonin should be examined in children with ADHD. Additionally, further research is needed with the larger number of subjects and control group to evaluate the clinical impact of risperidone and melatonin.

Limitations

The current research had a number of limitations. It was implemented in 6 years to 12 years. Therefore, these results can be generalized only to adolescent 6 years to 12 years old of Tehran. They could not be generalizable to other geographical areas due to cultural, social, and economic differences.

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References

1. Konofal E, Lecendreux M,Cortese S, (2010) Sleep and ADHD. Sleep Med 11: 652-658.
2. Association A.P. Diagnostic and statistical manual of mental disorders DSM-IV-TR Fourth Edition (Text Revision) Author: American Psychiatr. 2000.
3. Owens J, Sangal BR, Sutton KV, Bakken R, JA, et al. (2009). Subjective and objective measures of sleep in children with attention-deficit/ hyperactivity disorder. Sleep Med 10: 446-456.
4. Efron D, Lycett K, Sciberras E (2014) Use of sleep medication in children with ADHD. Sleep Med 15: 472-475.
5. Mark W, Lawrence B, Ronald T, George D, Marian E, et al. (2011) Pediatrics AAO Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. ADHD: Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics 128: 1007-1022.
6. Stein MA,Weiss M, Hlavaty L (2012) ADHD treatments, sleep, and sleep problems: Complex associations. Neurotherapeutics 9: 509-517.
7. Heijden V, Kristiaan B, Marcel G, Someren EV, Ridderinkhof KR, et al. (2007) Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. J Am Acad Child Adolesc Psychiatry 46: 233-241.
8. Weiss MD, Michael BW, Bomben MM, kathleen, Freeman RD (2006) Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia. J Am Acad Child Adolesc Psychiatry 45: 512-519.
9. Aman MG, Binder C, Turgay A (2004) Risperidone effects in the presence/absence of psychostimulant medicine in children with ADHD, other disruptive behavior disorders, and subaverage IQ. J Child Adolesc Psychopharmacol 14: 243-254.
10. Leysen JE, Janssen PM, Megens AA, Schotte A (1994) Risperidone: A novel antipsychotic with balanced serotonin-dopamine antagonism, receptor occupancy profile, and pharmacologic activity. J Clin Psychiatry. 55: 5-12.
11. Lind CCK, Carchedi CLR, Staudenmeier LJJ (2005) Atypical Presentations of Atypical Antipsychotics. Psychiatry (Edgmont) 2: 32-39.
12. Biederman J, Newcorn J, Sprich S (1991) Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. The Am J Psychiatry 148: 564-577
13. Bruni O, Salvatore O, Vincenzo G, Romoli M, InnocenzI M, et al. (1996) The sleep disturbance scale for children (sdsc) construct ion and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. J Sleep Rrs 5: 251-261.
14. Hendriksen J, Peijnenborgh W, Aldenkamp A, Vles H (2015) Diagnostic overshadowing in a population of children with neurological disabilities: A cross sectional descriptive study on acquired ADHD. Eur J Paediatr Neurol 1-4.
15. Meftagh SD, Najimi A, Mohammadi N, Ghanizadeh A, Rahimi C, et al. (2014) The most effective intervention for attention deficit-hyperactivity disorder: Using continuous performance test. Psychiatria Danubina 26: 165-171.
16. Betancourt F, Leon DJYJ, Jimenez BC (2006) Attention deficit hyperactivity disorder and sleep disorders. Revista de neurologia 42: 37-51.
17. Weiss MD, Salpekar J (2010) Sleep problems in the child with attention-deficit hyperactivity disorder. CNS drugs 24: 811-828.

18. Johnston C, Hommersen P, Seipp C (2008) Acceptability of behavioral and pharmacological treatments for attention-deficit/hyperactivity disorder: Relations to child and parent characteristics. Behav Ther 39: 22-32.
19. Dusan K, Amanda K, Maria G, Lucy C, Cassidy S, et al. (2008) Treatment of adults with attention-deficit/hyperactivity disorder. Neuropsychiatr Dis Treat 4: 389-403.
20. Holvoet E, Gabriëls L (2012) Disturbed sleep in children with ADHD: Is there a place for melatonin as a treatment option. Magazine for psychiatry 55: 349-357.
21. Smits MG, Nagtegaal EE, Heijden J, Anton ML, Kerkhof A, et al. (2001) Melatonin for chronic sleep onset insomnia in children: A randomized placebo-controlled trial. J Child Neurol 16: 86-92.
22. Heijden KBV (2007) Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. J Am Acad Child Adolesc Psychiatry 46: 233-241.
23. Mostafavi SA, Mohammadi RM, Hosseinzadeh P, Eshraghian MR, Akhondzadeh S (2012) 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? Iran J Psychiatry 7: 114-119.
24. Jacobsen FM (1995) Risperidone in the treatment of affective illness and obsessive-compulsive disorder. J Clin Psychiatry 56: 423-429
25. Daniel DG. Different side effect profiles of risperidone and clozapine in 20 outpatients with schizophrenia or schizoaffective disorder: A pilot study. Am J Psychiatry (1995).