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Original Article

The effect of treatment with melatonin on primary school aged children with difficulty in initiation and maintenance of sleep

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ABSTRACT

Background. The present study was designed to evaluate the effect of melatonin on the sleep initiation, duration of sleep, quality of sleep and daily performance in healthy children suffering from insomnia.

Methods. This study was done as a double blind randomized clinical trial in the sleep clinic of Qods Hospital. Sixty healthy children between 7 and 12 years of age having sleep problems were chosen and randomly divided in interventional and placebo groups. Before the treatment, children's sleep habits questionnaire (CSHQ) was filled in both groups. Then, both groups were taught about sleep hygiene. Afterwards, the intervention group was treated with 3mg nocturnal dose of melatonin for one month and the other group with a placebo. Then, CSHQ was filled again for both groups. The intervention was Melatonin. The mean analyzed results of the variants in pre-test and post-test were compared and $p<0.05$ was regarded as significant.

Results. Results showed that Melatonin with no side effect is effective in improving: 1- The initiation and maintenance of sleep, 2- Sleep onset delay, 3- Sleep duration, 4- Sleep anxiety, 5- Nightly awakenings 6- Parasomnias and 7- daily performance; but is ineffective in bedtime resistance and sleep disordered breathing.

Conclusions. Our results indicate that melatonin is more effective than placebo in improving the initiation and maintenance of sleep and most of its subscales in primary school aged children.

Key words: difficulty in initiation and maintenance of sleep, primary school aged children, melatonin.

Difficulty in initiation and maintenance of sleep is observed in 15-25% of children and adolescents.[1] Insomnia is described as the decrease in daily performance due to sleep disturbances.[2] Children having insomnia suffer from fatigue, attention deficit, loss of concentration, irritability, loss of energy and anxiety. In chronic form, complications such as learning problems, decrease in school performance and depression do occur. Along with the problem, other family members' performance and sleep pattern are affected.[3]

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To evaluate the sleep problems, firstly, medical problems should be diagnosed and treated.[4] Then, sleep hygiene should be regarded in patients. Sleep hygiene practices comprises fixing the sleeping time and morning wake up time, fixing the amount of time expected for sleep appropriate to age, providing a restful and dark sleep environment, not being hungry at bed time, avoiding nicotine and caffeine compounds and including relaxation techniques before sleep, which is in turn composed of avoiding watching TV and playing computer and video games and encouraging to read before bed time.[5] Usually the steps above will lead to appropriate treatment, but in some resistant cases, drug therapy is necessary. To do this, benzodiazepines, antianxiety, antidepressants and antihistamines can be

used. But most of these drugs are not FDA approved for under 18 years of age.[4,6] For this reason, there is an increasing tendency to use natural hypnotics such as Melatonin for the treatment of insomnia in children. Naturally, the increase in the secretion of this hormone by pineal gland at night causes sleep within one to two hours. But contact electronic media and intense light, by changing the secretion amount of this hormone, could affect the initiation and maintenance of sleep and cause the corruption of natural sleep pattern and the beginning of sleep problems.[7] Exogenous melatonin causes the disruption of the body's internal clock to be resolved. In the past two decades, this drug has been used for the treatment of insomnia in children suffering from psychological disorders, ADHD, learning and developmental disorders and depression.[7,8] Nevertheless, it has been mostly used in children with concurrent somatic or psychological disorders, and its use for the treatment of sleep problems in healthy children otherwise, has been limited to only a small quantity and short term studies.[7-9] Besides, its exact dosage in children has not been yet specified and in different studies, a dosage range between 0.5 to 10 mg, 1 to 5 hours before sleep has been used.[9,10]

In 2001, Kayumov et al.[11] in a clinical trial, showed that melatonin without prolonging the duration of nightly sleep, significantly reduced the sleep onset delay and the amount of fatigue and sleepiness the following day.

In 2001, Takeuchi et al.[12] from Japan, compared the therapeutic effect of melatonin on REM sleep behavioral disorder with its choice drug clonazepam and showed that melatonin, quite similar to clonazepam, is strongly effective in improving the clinical symptoms of this parasomnia.

In 2001, Dodge and Wilson[13] in a double blind placebo controlled clinical trial, compared the therapeutic effect of melatonin in 20 children with developmental disorders with placebo. Significant decrease in sleep onset delay was seen, but the duration of sleep and the number of nightly awakenings did not change at all.

In 2001, Smits et al.[14] in a clinical trial, concluded that treatment of insomnia in children with 5 mg nocturnal dosage of melatonin significantly improves sleep onset delay and the duration of sleep. Only in one of the patients, mild generalized seizure occurred only once, but no other side effect was seen in the other patients.

In 2003, Smits et al.[15] in another similar study on 62 children with chronic idiopathic disorder of the initiation of sleep, showed that melatonin significantly improved the sleep onset and sleep wake-up time.

In 2011, Sánchez-Barceló et al.[16] in a study, reported numerous applications for melatonin in pediatrics even other than treatment of insomnia.

In 2012, Eckerberg et al.[17], in another interesting study finally concluded that daily administration of low dose of melatonin in the evening, even if the students in the last two-day of the weekend, continue abnormal sleep habits, can improve sleep duration and promote conscious state of the students during school hours.

In 2013, Ferracioli-Oda et al.[2] in a meta-analysis study concluded that melatonin reduces sleep onset delay, increases total sleep duration and improves the overall sleep quality.

The aim of this study was to evaluate the effect of Melatonin on the sleep

initiation, duration of sleep, quality of sleep and daily performance in healthy children suffering from insomnia.

Material and Methods

Study Design and Patients

This study was a randomized double blind clinical trial. Our samples were chosen from primary school students (7 to 12 years old, boys and girls) referred to the sleep clinic of Qods Hospital with the complaint of sleep problems. This hospital is the only center equipped with a sleep clinic in the Qazvin province of Iran.

The research was reviewed and approved by ethics committee of Qazvin University of Medical Sciences. The ethic number was 28/20/4329. All participants involved in the study signed an informed written consent. Also, this trial was registered with the Iranian Registry of Clinical Trials. The registration number was IRCT 2015111225008N1.

The number of samples in our study was 60. Sample size calculation was performed. According to study conducted by van Geijlswijk et al.[18], mean value and standard deviation considered as below: sleep initiation in treatment group with melatonin and control group were 24.1±20.2 and 48.3±36.1, respectively. Based on the following formula, 30 participants were computed in each group. We considered 0.05 for value of alpha, corresponding to a 95% level of confidence for avoiding a type I error, and 0.80 for value of beta, to detect a large effect size.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 (S_1^2 + S_2^2)}{(\mu_1 - \mu_2)^2}$$

Participants (60 patients) were randomly allocated to intervention (n = 30) or to control group (n = 30). We used a specialized internet software application for randomization of participants.

In every 60 of these patients (i.e. the intervention and control group) and their parents sleep hygiene was asked. These children should have been physically and mentally healthy with the only problem of sleep disturbances, so they were examined by the physician, their underlying diseases, physical and psychological, ruled out and then randomly divided into intervention and control groups.

Inclusion criteria

Patients after interview and examination by the pediatric sleep medicine, were included in the study if they possessed the DSM-IV criteria for insomnia.

Exclusion criteria

Include the following: 1. Children with underlying neurological disorders, 2. children with psychological disorders including ADHD, 3. children with underlying organic problems including chronic cardiac, pulmonary, kidney and blood disorders, 4. history of drug use during the recent month including antibiotics, antihistamines and sedatives, 5. clear visible clinical symptoms suggestive of anemia. After assessing inclusion and exclusion criteria, all children were randomly divided into intervention and control groups.

Interventions

The 30 patients in the intervention group, were given Melatonin tablets (manufactured by Weber Nature Company) at a dosage of 3 mg at night and the 30 patients in the control group, were given placebo pills (taken from the pharmacy of Dr. Nozari in Qazvin). The administration of medication type was double-blind and the blinding of the medication to patients was carried by a pharmacist (Dr. Nozari) at the Qazvin university without the notice of the researchers. Both patients and control groups were blinded during the intervention. Medication intervention was of 4 weeks duration. All children were required to take medications at 7 pm. During the period of drug administration, none of the groups had the right to use another drug.

Measurement and statistical analysis tools

Our measuring tools in this study, was the Farsi translation of children's sleep habits questionnaire (CSHQ) Once before the treatment, and the second time at the end of the one month treatment, CSHQ was filled by the individuals in both groups by asking questions from their parents, so as to be used as pre-test and post-test scoring, by which the therapeutic response could be measured in both groups. Obtaining an overall score equal to or greater than 41 on this questionnaire indicates a sleep

disorder.[19,20] In our study although the basic sampling was done based on DSM IV criteria, the mean score of sleep disorders before the treatment was 56.57 for the intervention group and 53.96 for the control group, which suggests the existence of sleep disorders in both groups before intervention. Also, during the period of drug administration, parents were required to complete a sleep log every day for a month, to record bedtime, sleep onset, sleep duration, number of nightly awakenings after sleep, in other words to complete the 'evaluation of sleeping and waking hours' questionnaire.

In addition, during this period, researchers had weekly telephone contacts with all the patients in the two groups to be sure of drug consumption and to ask about possible adverse drug reactions and the effect of the drug on child's sleep based on the parents' observations.

The hypotheses of the study include the following:

1) The main hypothesis: Treatment with melatonin in primary school aged children with difficulty in initiation and maintenance of sleep, generally improves the sleep disorder.

2) First sub-hypothesis: Treatment with melatonin in primary school aged children with difficulty in initiation and maintenance of sleep, improves sleep onset. (It should be noted that the sleep onset is measured with two sub-scales of bedtime resistance and sleep onset delay.)

3) Second sub-hypothesis: Treatment with melatonin in primary school aged children with difficulty in initiation and maintenance of sleep, improves their sleep duration.

4) Third sub-hypothesis: Treatment with melatonin in primary school aged children with difficulty in initiation and maintenance of sleep, improves their sleep quality. (It should be noted that the quality of sleep is evaluated with four subscales of sleep anxiety, nightly awakenings, parasomnias, and breathing problems during sleep.)

5) Fourth sub-hypothesis: Treatment with melatonin in primary school aged children with difficulty in initiation and maintenance of sleep, improves their daily performance.

6) Fifth sub-hypothesis: Side effects of the prescribed Melatonin in primary school aged children with difficulty in initiation and maintenance of sleep, influences their treatment process.

In any case, in this way, the intervention and placebo groups were compared with each other from the viewpoint of sleep onset, sleep duration, sleep quality and daily performance improvement as well as possible adverse drug reactions, so that the differences among the melatonin and placebo-treated groups could be compared and declared. Then, the collected data were statistically analyzed with the SPSS version 18 software. The statistically significant number was considered at less than 0.05. The paired t-test was used to compare differences at before and after treatment in each groups, and between groups comparisons were made by independent student t-test.

Results

The overall mean age of the patients was 9.59 with a standard deviation of 2.03. The mean age of the patients in the intervention group was 9.79 with the standard deviation of 2.02, minimum age was 6 years and maximum was 12 years; in the placebo group 9.38 with a standard deviation of 2.05, minimum age was 7 years and maximum was 12 years. There was no statistically significant difference between two groups in terms of age ($P>0.05$).

All the children in both groups had parents with college education. The final results of our study has been shown in Table I, in which you can see all the variables' mean scores in pre-test and post-test in both the groups.

As it is observed, there is no significant difference before treatment for all the variables between the two groups.

On the other hand, except for bedtime resistance and sleep disordered breathing, based on the scoring system of CSHQ, the post- treatment mean scores show significant decrease between two groups after treatment with melatonin ($p<0.05$). But for the two variables of bedtime resistance and sleep disordered breathing, the mean score increased and insignificantly decreased, respectively, p value > 0.05.

Also, Table II shows results from paired t-test between before and after treatment in melatonin group. Results show that after treatment with melatonin, all variables have improved significantly except bedtime resistance.

Discussion

Thus, the findings of our study indicate that treatment with melatonin in primary school children, is in general effective in improving the difficulty in initiation and maintenance of sleep, reducing sleep onset delay, improving sleep duration, reducing sleep anxiety, reducing nightly awakenings, improving parasomnias, and improving daily performance.

Treatment with melatonin in primary school children, is not effective in improving bedtime resistance, and reducing sleep disordered breathing. In our study, melatonin did not have any side effects.

Table I. Comparison of mean scores of sleep disorder variables according to CSHQ , in placebo and melatonin groups.

	Before treatment		p-value	After treatment		p-value
	Placebo group	Melatonin Group		Placebo group	Melatonin Group	
Total	53.96±4.46	56.57±8.44	0.24	49.20±5.53	39.23±7.62	0.001
Bed time resistance	11.33±1.71	11.27±2.73	0.76	11.53±1.91	12.43±2.05	0.07
Sleep onset delay	1.63±0.67	2.2±0.85	0.63	2.33±0.77	1.37±0.67	0.001
Duration of sleep	4.90±1.16	4.73±1.20	0.61	4.13±1.38	4.11±0.99	0.001
Sleep anxiety	6.87±1.46	6.97±1.90	0.32	6.23±1.22	4.93±1.68	0.001
Nightly awakenings	3.90±0.88	4.20±1.35	0.76	3.50±0.9	2.60±1.16	0.002
Parasomnias	9.63±1.08	9.07±1.63	0.51	8.97±1.45	7.80±1.49	0.001
Sleep disordered breathing	4.97±1.10	5.43±1.36	0.93	4.90±1.49	5.20±1.52	0.87
Daily performance	10.87±2.58	10.80±3.39	0.46	9.97±2.30	9.25±3.56	0.002

CSHQ: Children's Sleep Habits Questionnaire

Table II. Comparison of mean scores of sleep disorder variables according to CSHQ before and after in the melatonin intervention group.

	Before treatment	After treatment	p-value
Total	56.57±8.44	39.23±7.62	<0.001
Bed time resistance	11.33±1.71	11.53±1.91	0.1
Sleep onset delay	1.63±0.67	2.33±0.77	<0.001
Duration of sleep	4.90±1.16	4.13±1.38	0.001
Sleep anxiety	6.87±1.46	6.23±1.22	0.003
Nightly awakenings	3.90±0.88	3.50±0.90	<0.001
Parasomnias	9.63±1.08	8.97±1.45	<0.001
Sleep disordered breathing	4.97±1.10	4.90±1.49	0.09
Daily performance	10.87±2.58	9.97±2.30	<0.001

CSHQ: Children's Sleep Habits Questionnaire

About the main hypothesis of our research, it should be noted that our findings are in line with the studies of Eckerberg et al.[17], Sánchez-Barceló et al.[16], Coppola et al.[21], Smits et al.[14], van Geijlswijk et al.[18], and Kayumov et al.[11]

All of them in their studies concluded that treatment with melatonin generally improves insomnia. In addition, Ferracioli-Oda et al.[2] too, in 2013 showed that melatonin reduces sleep onset delay, increases total sleep duration and improves overall sleep quality.

About the first sub-hypothesis of our research (effect of melatonin treatment on bedtime resistance and sleep duration), our findings are similar to the studies of Kayumov et al.[11], Smits et al.[14,15], Coppola et al.[21], Armour and Paton[22], Eckerberg et al.[17], Buscemi and Witmans.[23] All of them in their studies concluded that treatment with melatonin improves sleep onset.

About the second sub-hypothesis of our research (effect of melatonin treatment on improvement of sleep duration), our findings are in line with the studies of Smits et al.[14,15], Eckerberg et al.[17], Ferracioli-Oda et al.[2] They all concluded that treatment with melatonin increases sleep duration. Eckerberg et al.[17] in their study in 2012, finally concluded that daily administration of low dose melatonin in the evening, even if the students continue abnormal sleep habits in the last two days of the weekend, can improve sleep duration and promote students' conscious state during school hours. But our findings are not in line with the findings of Dodge and Wilson[13] and Armour and Paton.[22] But it should be noted that they studied the melatonin therapeutic effect on children with developmental disorders.

About the third sub-hypothesis of our research (effect of melatonin treatment on sleep quality), our findings are in line with the studies of van Geijlswijk et al.[18] and Takeuchi et al.[12] They also in their studies, concluded that Melatonin improves the sleep quality of the patients. Therefore, van Geijlswijk[18] suggested using the minimum dosage of melatonin i.e. 0.05mg/kg 1 to 2 hours before bed time for the treatment of the nocturnal insomnia in children due to initiation of sleep. Also, Ferracioli-Oda et al.[2] in their meta-analysis in 2013, emphasized the improvement of sleep quality after melatonin treatment. But our findings are not in line with Buscemi and Witmans' study.[23] Of course, it should be noted that they studied the Melatonin therapeutic effect on children with developmental disorders.

About the fourth sub-hypothesis of our research (effect of melatonin treatment on daily performance in school), our findings were similar to the studies of Kayumov et al.[11], and Eckerberg et al.[17] Their research results also showed that after melatonin administration for the treatment of sleep disorders, patients did not have sleepiness during the day and their daily performance increased. Eckerberg et al.[17] also emphasized that melatonin as well as increasing the duration of nightly sleep, promotes the students' conscious state during school hours.

And finally, about the fifth sub-hypothesis of our research (side effects of melatonin treatment), fortunately, in our study, melatonin caused no side effect on the patients; and this is in line with the studies of Smits et al.[14], Coppola et al.[21], and Buscemi et al.[23]

Of course, we should recall that in the study of Smits et al.[14] one of the patients had a period of mild generalized seizure which was not repeated for the second time.

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Ethical approval

The research was reviewed and approved by ethics committee of Qazvin University of Medical Sciences. The ethic number was 28/20/4329.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: SJ; data collection: SR; analysis and interpretation of results: SJ, SR, ZY; draft manuscript preparation: SJ, SR, ZY, MS. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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