

ORIGINAL ARTICLE

The Effect of Melatonin on Sleep Disorders in Children with Cerebral Palsy A Randomized Clinical Trial

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Abstract

Objectives

Cerebral palsy (CP) is one of the most common causes of serious physical disability in childhood and is a persistent movement disorder before the age of three. This disorder can negatively affect both the child and their family. In recent years, the use of melatonin as a safe, effective, and cheap drug has been expanding in improving the sleep disorders of these children. Therefore, this study aimed to investigate melatonin's effect on sleep disorders in children with CP.

Materials & Methods

This double-blind clinical trial was conducted on children aged 2 to 12 years with CP who were referred to the pediatric neurology clinic for sleep problems. The participants were included in the study by convenience sampling. After obtaining informed consent from parents, patients were divided randomly into two intervention (melatonin) and control (placebo) groups. In the intervention group, patients received oral melatonin tablets, and in the control group, patients received a placebo (3 mg oral lactose) 30 minutes before going to sleep.

Results

The results of this study showed no significant relationship between age and gender with sleep disorders in children with CP ($P < 0.05$). A significant effect of melatonin on sleep disorders was found in children with CP. The greatest effect of melatonin is the time required to start falling asleep. Melatonin was associated with decreased time needed to fall asleep and increased sleep duration.

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Conclusion

The results of the study demonstrated that sleep disorders are prevalent among children with CP. Therefore, proper and timely treatment of these children is crucial. According to the present study's findings, melatonin effectively improves the time of falling asleep and these children's sleep duration.

Keywords: Melatonin, Sleep Disorder, Cerebral Palsy

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Introduction

Cerebral palsy (CP) is a set of developmental disorders causing activity limitations due to non-progressive disturbances, lesions, or abnormalities in the developing fetal or infant's brain (1). CP can lead to neurological, motor, shortness, deformities, and functional limitations (2). This disease is usually associated with many disorders in sensory, cognitive, and communication functions. Children with physical-motor disabilities are among the most different children with special needs, and CP is one of the most common disabilities in childhood and adolescence (3). Taking care of these children is of particular importance due to their physical disabilities. This group of children is prone to sleep disorders. Those disorders can negatively affect the child and their families (4).

Adequate sleep in children plays a crucial role in the growth and development of children and is associated with improved attention span, learning, and memory. Approximately 40% of children with CP have sleep disorders (5). The incidence and severity of sleep disorders in children with CP depend on the severity of their

brain damage and the type of CP. Bilateral spastic CP and quadriplegia have the greatest impact on the quality of life and sleep of those children (6). Sleep disorders are divided into two categories: dyssomnia and parasomnia. In children with CP, sleep can be affected by several factors, including muscle spasms, musculoskeletal pain, and reduced ability to change body position during the night (7). Considering that this problem can be controlled to some extent with drugs, it seems logical to use new non-pharmacological methods to solve the sleep problems of these children. In the conducted studies, no specific intervention to improve sleep disorders in children with CP has been reported, and only melatonin has been introduced as a drug to improve sleep disorders in children with CP (8). Melatonin (N-acetyl-5-methoxytryptamine) is a molecule derived from tryptophan, a Chronobiotic hormone. This hormone, secreted from the pineal gland, is a vital element for regulating the sleep-wake cycle (9). The production and secretion of melatonin in children and adults starts at night and reaches its peak between 2 and 4 in the morning (10). Other non-specific tissues, such as the retina, also secrete melatonin. It has an essential effect in creating circadian rhythms due to the impact of light

on the eyes (11). In addition, cells and organs such as astrocytes, glial cells, lymphocytes, digestive tubes, ovary, placenta, and skin can also produce melatonin to some extent (12). On the other hand, despite the great effect of melatonin on treatment-resistant seizures in children, in a few cases, this drug has led to an increase in seizure activity in children with severe neurological disabilities. Due to these factors, there remains a lack of agreement concerning the application of melatonin in patients with CP. Therefore, the current study investigated melatonin's effect on sleep disorders in children with CP.

Materials & Methods

This double-blind clinical trial was conducted on children aged 2 to 12 years with CP referred to the pediatric neurology clinic in Mashhad, department of neurology, with complaints of sleep problems. The study included the participants by convenience sampling from July 2018 to May 2019. The inclusion criteria included children aged 2-12 years with CP and complaints of sleep disorders. Exclusion criteria include the patient's or their parents' dissatisfaction with participating in the study and the presence of side effects of melatonin medication during the treatment period. Thus, after obtaining informed consent from parents and doing the exclusion and inclusion criteria, 13 patients were removed. Finally, fifty children with CP participated in this study, and there was no fall in the participant number and no side effects during one month of the study, as mentioned in the consort flow diagram (Figure 1). The following patients were randomly divided into control and intervention groups.

Procedure

At first, the patient's demographic information (age and gender), type of sleep disorder (sleeping disorder, sleep duration and depth or lightness of sleep), and medications used were recorded. After fully explaining the research plan to the families of these children and obtaining informed consent, the children who met the inclusion criteria were divided into two intervention and control groups. A randomized block method with sealed envelopes was used to randomize people into two study groups. In the intervention group, patients received oral melatonin tablets 30 minutes before sleep. In the control group, patients received a placebo (3 mg oral lactose) 30 minutes before sleep. The duration of treatment in both groups was one month because the drug's effect was established within one month. In the first two nights of the study, the quality and depth of sleep were examined in both groups without receiving any medication.

From the third night onwards, both groups received medicine, and then the quality and depth of sleep at the end of the month were compared with the first two nights (without receiving medicine). In addition, the actigraphy method used quantitative criteria to check the quality and depth of sleep accurately. It was checked by smart wristwatches made by Xiaomi (China), which work based on the frequency of hand movements. In the actigraphy method, patients wear a smart device, such as a wristwatch, and then go to sleep. During sleep, the device objectively records sleep parameters and average motor activity.

Data analysis

Appropriate tables and graphs were used to describe the data. Qualitative variables were reported as

frequency (percentage), and quantitative variables were reported as mean and standard deviation. After checking the normality of variables, paired t-test and independent t-test were employed to compare quantitative variables, and the chi-square test was used to compare qualitative variables between two groups. The data collected in the checklists were entered into SPSS software version 22. A significant level of 5% was considered.

Ethical considerations

The information of all patients was kept confidential. The study was conducted following all relevant guidelines, including the Declaration of Helsinki and ethics research committees of the University of Medical Sciences. The project was carried out after being approved by the Research Council of the Faculty of Medicine, receiving the code of ethics, and receiving IRCT number.

Results

Finally, fifty patients were included in the study and were randomly divided into two control and intervention groups. There were 13 boys in the control group and 16 boys in the intervention group (mean age: 11 ± 2 in the control group and 16.9 ± 3 in the intervention group). There were also 12 girls in the control group and nine girls in the intervention group (mean age: 11 ± 2 in the control group and 16.9 ± 3 in the intervention group). According to the data, there is no significant relationship between children's sleep disorders with their gender ($P=0.39$) and age ($P=0.4$). Children are shown separately by type of CP, and it was found (Table 1) that 12 patients (48%) had quadriplegia in the control group and 11 in the intervention group.

During the research period, 19 children (76%) in the control group and 15 (60%) in the intervention group received other medications. Six children (24%) from the control group and ten (40%) from the intervention group did not take any medication. However, these two groups had no statistically significant difference ($P=0.225$).

According to the previous history of patients, 19 patients (76%) had seizures in the control group, and 15 (60%) had an old history of seizures that were not statistically significant ($P=0.225$). Furthermore, there was no seizure recurrence during this study.

Table 2 shows the data of the paired t-test in both control and intervention groups before and after the intervention to compare the average of four variables (time required to start sleep, length of sleep, depth of sleep, and lightness of sleep), where, statistically a significant difference was found between the groups in terms of four variables ($P>0.05$).

The average difference between the groups using the independent t-test showed a statistically significant difference between the groups (Table 3, $P<0.05$). According to Tables 2 and 3, the greatest effect of melatonin in both control and intervention groups is on the time needed to start sleeping. Additionally, deep and light sleep duration has increased in children of both intervention and control groups.

Discussion

CP is one of the most common causes of serious physical disability in childhood. This group of children is prone to sleep disorders. Those disorders are associated with adverse effects on children and

The Effect of Melatonin on Sleep Disorders in Children with Cerebral Palsy

Table 1: Children by types of cerebral palsy

Variable		Control	Intervention	P-value
Cerebral Palsy	Quadriplegia	12 (48%)	11 (44%)	0.999
	Diplegia	7 (28%)	7 (28%)	
	Hemiplegia	5 (20%)	5 (20%)	
	Extra pyramidal	1 (4%)	8 (8%)	

Table 2: Comparison of the average of four sleep variables

Variable Mean ± standard deviation		control group	P-value Mean ± standard deviation	Intervention group	P-value
Time needed to start sleeping (seconds: minutes: hours)	Before intervention	35:532:39:58±	0.001<	48:4302:32±	0.001<
	After the intervention	35:12±2:33:36		45:27±01:52:48	
Sleep duration (seconds: minutes: hours)	Before intervention	58:3404:03:19 ±	0.001<	46:5703:38:33±	0.001<
	After the intervention	59:33±04:11:12		46:37±04:34:50	
Deep sleep (seconds: minutes: hours)	Before intervention	16:2351±	0.001<	11:2146:48±	0.001<
	After the intervention	17:48±55:09		14:25±71:04	
Light of sleep (seconds: minutes: hours)	Before intervention	46:3403:12:09±	0.001<	38:4602:51:45±	0.001<
	After the intervention	46:2703:15:14±		03:24:08±	

Table 3: Comparison of the mean difference of the groups using independent t-test

Variables	Control Group	Interventional Group	P-value
The time difference required to start sleeping	03:21±06:21-	15:37±39:21-	<0.001
The difference in sleep duration	04:28±07:52	31:28±56:16	<0.001
The difference in depth of sleep	03:36±04:09	09:19±24:16	<0.001
The difference in lightness of sleep	03:13±03:04	25:43±33:02	<0.001

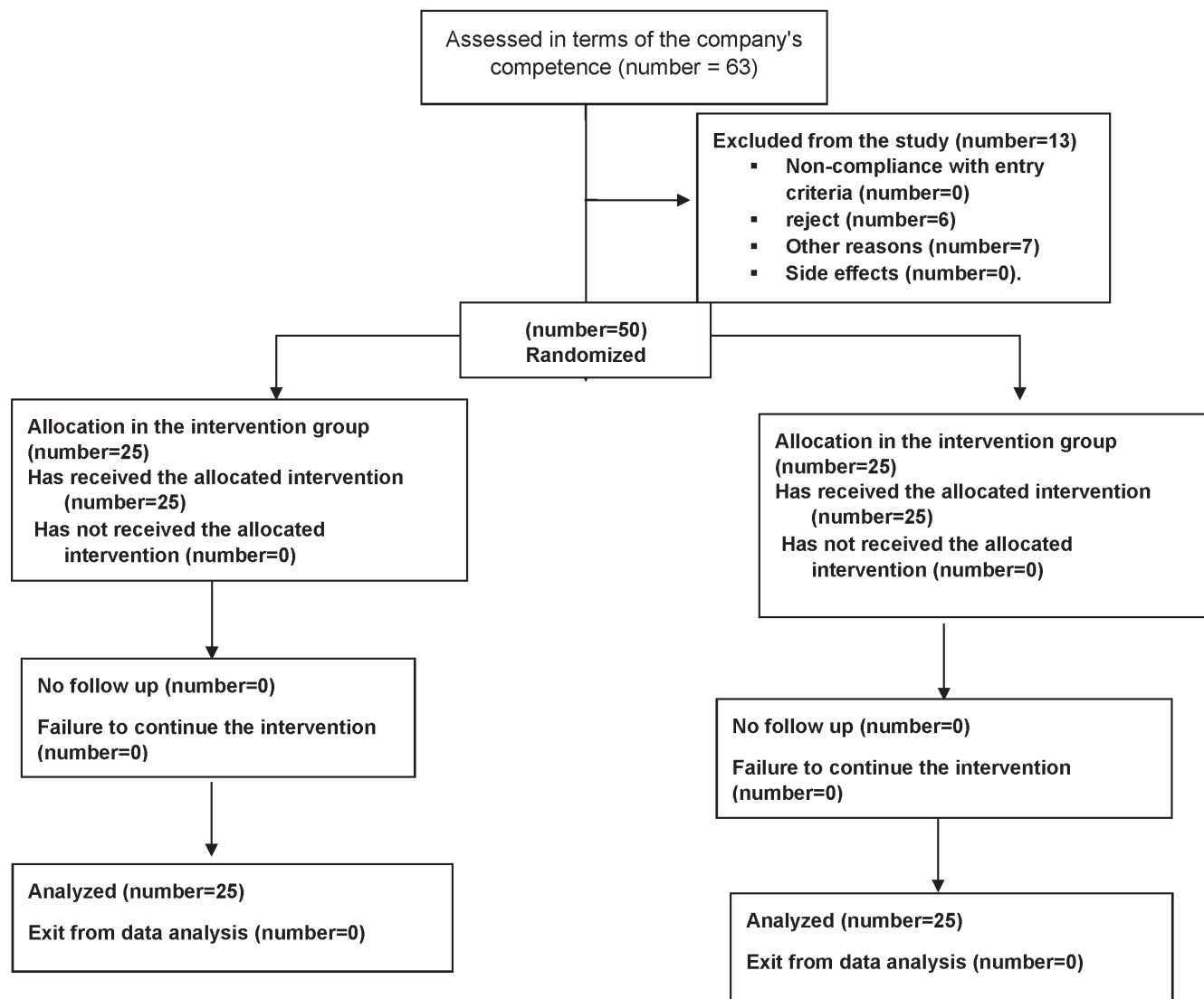


Figure 1. CONSORT flow diagram

their families. In recent years, the use of melatonin has been expanding as a safe, effective, and inexpensive drug in improving the sleep disorders of these children (13). Therefore, this study aimed to investigate melatonin’s effect on sleep disorders in children with CP. In this study, the mean age based on months was 38.6 ± 11.29 in the control group and 41.96 ± 16.99 in the intervention group. Most control and intervention group participants were boys (52% in the control group vs 64% in the intervention group). The study demonstrated no significant relationship between children’s sleep

disorders and gender ($P=0.39$).

Various studies have been done in this regard. The findings of a study conducted by Romeo DM. et al. on the sleep of 165 children with CP was consistent with the present study. It is concluded that no significant relationship exists between age and gender in sleep disorders in children with CP (6). The study conducted by Wayte et al. on 100 children with CP reported a significant relationship between gender and sleep disorders in children with CP, and most boys with CP suffered from sleep disorders (14). The difference in the current

research results can be attributed to the higher number of samples in both boys and girls, leading to clearer and more specific results.

In the current study, no statistically significant relationship was found between age and sleep disorders in children with CP ($P=0.4$). Such results were also obtained in the study of Romeo DM. et al. and the study of Mol et al. (6, 13).

Most of the children in both groups of this study (48%) were suffering from spastic quadriplegic CP, followed by spastic diplegic cerebral palsy (28%), spastic hemiplegic CP (20%), and extrapyramidal CP (4%), indicating that quadriplegic CP was more common among the study's patients. In the study conducted by Romeo et al., it was shown that sleep disorders are more common in children with CP of the quadriplegic type (6,15). In the study conducted by Dalvand H. et al., most children with CP and sleep disorders had quadriplegia, which was consistent with the results obtained in the present study. The results obtained in the mentioned study indicated that initiating and maintaining sleep disorders were the most prevalent (9).

In the present study, during the research period, the control (76%) and intervention (60%) groups of children used other drugs, especially antiseizure medications. In the study conducted by Newman CJ. et al., about 17.3% of children with CP had seizures and used antiepileptic drugs (16).

The greatest effect of melatonin in the intervention group in this study was on the time required to initiate falling asleep. The average time needed to initiate falling asleep in the present study was reduced to 39.3 minutes in the control group and 6.6 minutes in the intervention group. The length of sleep in both groups increased after the

intervention. The average length of sleep in the control group increased from 243 to 251 and from 218 to 274 minutes in the intervention group.

In the present study, children experienced deeper sleep after the intervention, and the average depth of sleep increased from 46 to 71 minutes in the intervention group. The lightness of sleep has increased in the study's intervention group. The duration of both deep and light sleep increased in children of intervention groups. These sleep depth and duration changes significantly differ from the control group ($P<0.05$).

In a study conducted by Jan M. et al., the average sleep duration of children with disabilities (both mental and physical) increased from 6.8 hours to 7.9 hours after using melatonin. (17) In the study conducted by Jan JE. et al. indicated that fast-release melatonin was most effective when there was only delayed sleep onset, but controlled-release melatonin was more beneficial for sleep maintenance. (18)

In this study, 23% of patients in the control and 18/5% in the intervention group had epilepsy and used antiseizure medication. However, during this study, none had seizures or other side effects. Another study conducted by Newman CJ. et al. on children with CP with sleep disorders, sleep onset, and sleep retention disorders were found to be more common. In the mentioned study, about 17.3% of children had epilepsy. Indicatively, both medical and environmental factors can be capable of affecting sleep disorders in children with CP (16).

A study by Wasdell evaluated the efficacy of controlled-release melatonin (5 mg) in treating delayed sleep phase syndrome of children with neurodevelopmental disabilities in a 3-month

open-label study, and the dose of drug used was increased until positive results appeared. Based on the study results, the length of sleep time and the time required to start sleeping in these children were improved significantly by about 30 minutes ($P < 0.05$) (19). This research, like the present study, showed that treatment with melatonin has been effective in improving the sleep of these children and reducing family stress.

In Conclusion

This study revealed that the effect of melatonin on sleep disorders in children with CP of any type was significant. The greatest effect of melatonin was on the time required to start sleep. That was dramatically reduced by using melatonin. Furthermore, this drug has increased the depth and duration of sleep. Thus, seemingly, melatonin is a safe drug with minimal side effects and also cheap and easily accessible to treat sleep disorders in CP. Lastly, we need a large sample size and a longer follow-up period to establish this hypothesis to recommend this drug.

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Author's Contribution

Hamid Reza Goldouzi: writing-original draft, project administration. Javad Akhondian: statistics consultant, formal analysis. Mehran Beiraghi Toosi: statistics consultant, formal analysis.

Hassan Mahrad Majd: investigation, writing & editing, methodology. Shima Shekari: writing-review & editing. Meisam Babaei: supervision, conceptualization, writing- review & editing.

Conflict of Interest

None declared

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