



Evaluation of Melatonin Supplementation in Children with Atopic Dermatitis at Aboreesh Hospital, Egypt

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Abstract

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease commonly associated with poor sleep efficiency. Lower nocturnal melatonin secretion was significantly associated with sleep disturbance in the children with AD, which is a major factor leading to an impaired quality of life (QOL). Evaluation of melatonin role in management of AD associated with sleep disorders to improve quality of life (QOL). Randomized clinical trial used double blind placebo pre and post experimental for intervention group with 43 children in each group who were recruited from dermatology outpatient clinic Aboreesh Hospital. This study included children with AD aged from (5-15) years and involving at least five % of total body surface area. Patients were randomly allocated into Melatonin group and Placebo group. Full history was taken and full general and dermatological examination using scoring atopic dermatitis index were done. Serum melatonin and IgE levels were assessed before and after melatonin supplementation. There was significant difference between pre and post regarding serum Melatonin and IgE except in blood level of melatonin in placebo group. As regard serum level of melatonin become 14pg/ml while before study was 59 pg /ml. But at placebo group started 25.5pg/ml and become 17pg/ml. IgE showed significant difference in pre and post study, as it was 132 before melatonin and become 24 after supplementation of melatonin while in placebo group drop from 129 to 27. There was significant improvement in total eczema score in post study markedly from 69 to two in Melatonin group and from 72 to three in Placebo group. Melatonin supplementation is a safe and effective way to improve the sleep-onset latency and disease severity in children with AD.

Keywords: Atopic dermatitis, Melatonin, SCORAD, QOL, IgE, Family practice

1 Introduction

Atopic eczema (atopic dermatitis (AD)) is a chronic inflammatory itchy skin condition that develops in early childhood in the majority of cases. It is typically an episodic disease of exacerbation (may occur as frequently as two or three per month) and remissions and in some cases it maybe continuous [1]. Health promotion has been defined as “the process of enabling people to increase control over their health and its determinants, and thereby improve their health”. One of the most important determinants of quality of life (QOL) is coetaneous body image of patient, so skin diseases are one of the most important factors which influences on it [2]. Poor sleep efficiency is common in children with AD and can be predicted by the Scoring Atopic Dermatitis index. Melatonin and IgE might play a role in the sleep disturbance [3]. Eczema is known to adversely affect daytime behavior. It is unclear whether this is a direct effect or mediated by the effect of eczema on sleep quality [4]. Healthcare professionals should adopt a holistic approach when assessing a child's atopic eczema at each consultation, taking into account the severity of the atopic eczema and the child's quality of life,

including everyday activities and sleep, and psychosocial wellbeing. There is not necessarily a direct relationship between the severity of the atopic eczema and the impact of the atopic eczema on quality of life [5].

Melatonin is the main product secreted by the pineal gland during the night it has a great functional versatility including the regulation of circadian and seasonal immune responses by regulation of the T helper 1 & 2 (TH1 & 2) balance and cytokine production. Effects of melatonin in different autoimmune diseases aren't clear [6]. Melatonin deficiency and increase serum IgE play a significant role in the sleep disturbance [7]. AD also called in Clinical Medicine atopic eczema is an increasing common childhood multi-factorial and chronic inflammatory skin disease [8]. The immune-pathological basis of AD is complex, but it is known that it is mediated by a TH1/TH2 biphasic inflammatory response that involves several cytokines, such as IL-4 IL-5, IL-13 and IFN- γ . Regarding to melatonin and atopic dermatitis a first report shown evidences of a dysfunction of the melatonin secretion in patients with atopic eczema, possibly due to a partially reduced activity of the sympathetic nervous system, which is involved in the control of melatonin secretion, it was shown an elevation of salivary melatonin in patients with AD. By contrary, in the phases of disease outbreaks it has been documented a reduction in the serum levels of both melatonin and B-endorphin. It has been reported that melatonin

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suppresses the development of at dermatitis-like skin lesions. It has been shown that melatonin related to the inflammatory response associated with contact hypersensitivity and that melatonin treatment attenuated the delayed-type hypersensitivity (DTH) [6]. The use of melatonin is supported by National institute for Health and Care Excellence (NICE) in their Clinical Guideline on the diagnosis and management of chronic fatigue syndrome in children. Within that Guideline it stated that melatonin may considered for children and young people who have sleep disorder [9].

2 Materials and Methods

2.1 Study design

This study is randomized clinical trial used double blind placebo pre and post experimental for intervention group. This study was carried out through a period of nine months from the 1st of March 2017 to the end of October 2017.

2.2. Ethical approval

Official permissions were obtained from the family medicine department, pediatric department, the director of the outpatient clinic and the scientific ethical committee of the collage. An informed consent was obtained from every patient before filling the questionnaires. They were reassured about the strict confidentiality of any obtained information, and that the study results would be used only for the purpose of research.

2.3 Participants

Eighty-six children were included in this study. Children were recruited from dermatology outpatient clinic Aboreesh Hospital, Faculty of Medicine, Cairo University in the period nine from the 1st of March 2017 to the end of October 2017. All included children had AD, skin changes above five % of body surface area and sleep insufficiency subjective complaint. Children with systemic illness, blood disease, hormonal disorders, congenital anomalies and children documented sleep disorders or neuro-psychiatric-disorders were excluded from the study.

2.4 Sample size & sampling

As effect size of treated agents' melatonin (18.6%) with confidence level 95% and power 80%. sample was 43 children in each group of total 86 children. Patients were randomly allocated into Melatonin group and Placebo group.

2.5 Intervention & data collection

Melatonin three mg/day or placebo were administrated by subjects one hour before bed time for four weeks. Placebo was manufactured by the same drug company manufacturing melatonin. Dosage was once daily for four weeks. Patient arranged by electronic coding each patient in each group represented by number. Melatonin and placebo were arranged by a pharmacist coding all the container by specific number and letter coding only was known by him. At the end of the result he translates the coding. There was no drop out. All the children patients were submitted to the following after parental approval:

2.6 A structured interviewing questionnaire

(a) Personal history: name, age, sex, residence. Level of consciousness, appearance (color) and vital signs subjective symptoms of sleep disturbances children and parents (main care giver) completed pediatric sleep evaluation questionnaire to evaluate subjective symptoms of sleep disturbances the questions included problems with sleep initiation. (Taking 30 minutes to fall asleep) or maintenance (waking up for at least

one time per night), difficulty falling asleep after waking up at night, or difficulty waking up in the morning. (b) Compliant: main symptom that necessitates the medical advice. (c) Present history: Onset, course, duration of AD, lesions, pattern of spread, symptoms and sleep pattern. (d) Past History: development, nutrition, vaccination, disease, operations, drugs and exposure to allergen and dietary recall. (e) Family History: consanguinity, allergic diseases (skin allergy -Bronchial asthma).

2.7 Clinical Examination

Full general and dermatological examination was done using SCORAD scale which is a useful tool for assessing AD widely used, the Sleep Disturbance Scale for Children (SDSC) and QOL questionnaire, this questionnaire aims to measure how much skin problem have affect child daily life. Scoring system in this study includes Eczema Score Consists of three sub score, Extent: After give each affected body part its own weighted score summation done, Intensity: give score (from 0-3) according to degree of intensity then summation, Subjective: estimated by patient for sleep loss and irritability (from 0-10) then summation Final score by $(\text{extent} / 5) + ((7 \times \text{intensity}) / 2) + \text{subjective}$ If < 25 mild $25-50$ moderate > 50 sever. Quality Scoring system: After summation of each item (from 0-3) and total score we considered $> 60\%$ impacted Sleep scoring system: After summation of each item (from 1-5) and total score we considered $> 60\%$ impacted.

2.8 Laboratory investigations

Five-milliliter peripheral venous blood samples were withdrawn at 9 A.M. from placebo group and melatonin group subjects, then blood was allowed to clot and then centrifuged at $8000 \times g$ for 5 min to separate the serum which was stored at -80°C until used for estimation of: (a) melatonin level in all subjects before and after supplementation by ELISA and (b) total serum IgE level in all subjects before and after supplementation.

2.8 Statistical analysis

Results were expressed as mean \pm standard deviation (SD) for normally distributed data (Total SCORAD, Quality of life score and Sleep disorders score) and median interquartile range (IQR) for not normally distributed data (Serum Melatonin and IgE). Comparison of different variables between groups was performed using unpaired t test in normally distributed data (Total SCORAD, Quality of life score and Sleep disorders score) or Mann Whitney U test in not normally distributed data (Serum Melatonin and IgE). Pair-wise comparison (pre- versus post-assessment) within the same group for different variables was performed using paired t test in normally distributed data (Total SCORAD, Quality of life score and Sleep disorders score) or Wilcoxon Sign Rank test in not normally distributed data (Serum Melatonin and IgE). Statistical Package for Social Sciences (SPSS) computer program (version 20 windows) was used for data analysis. P value ≤ 0.05 was considered significant and < 0.01 was considered highly significant.

3 Results

The present study included 86 subjects that were divided into two groups: placebo group (n=43) and melatonin group (n = 43). Age of patients ranged from 5 to 15 with a mean of 5.23 and 5.46 years respectively, Placebo group included 18 (41.9%) males and 25 (58.1%) females and the melatonin group included 24 (55.8%) males and 19 (44.2%) females. There were no significant differences between the placebo group and melatonin group regarding age and sex ($P = 0.12$, P

= 0.19) respectively (Table 1). The Total SCORAD, Quality of life score, Sleep disorders score, Serum Melatonin and IgE showed a highly significant reduction ($P = 0.001$) within both groups, while it showed non-significant differences between both groups post- Supplementation ($P > 0.05$). Comparing both groups pre- Supplementation revealed a statistically highly significant increase in Serum Melatonin ($P = 0.001$) in favor of the Melatonin group (Table 2).

4 Discussion

Numerous epidemiologic and clinical studies within the past decade have demonstrated that genetic, environmental, and immunological factors all affect AD development as well as its clinical picture, degree of severity, and course in addition to the classic predictors of AD development such as family history and urban environment. Recently recognized predictors of disease course and severity include onset of AD signs and symptoms before 12 months of age and the presence of FLG gene mutations and concomitant IgE sensitization early in life. The environment continues to be a topic of great interest in the quest to better understand the pathologic pathways in AD [10].

Main Outcomes and Measures: The primary outcome was AD severity evaluated using SCORAD index, with scores ranging from (0-103) and greater scores indicating worse symptoms. Secondary outcomes included sleep variables measured by SDSC subjective change in sleep and dermatitis, sleep variables, serum melatonin and IgE levels. Clinical trials investigated the supplement of melatonin in

human patients with AD were so limited studies from 2012 up till now. The present study aimed to evaluate role of melatonin in treatment of AD associated with sleep disorders in children between (5-15) years. At the same time the present study showed impact of atopic eczema on QOL and sleep disorders by using quality score and sleep disorder score. Distribution among the two groups was 44.2% female in Melatonin group while male percentage was 55.8%. However female in Placebo group was 58.1% and male percentage was 41.9%. There was no significant difference in age distribution between both groups with mean age 5.5 years. Age group in the current study was chosen (5-15) as age of school entry child can take tablet at bed time, and can be examined easy. That was limited to human adult (>18 years of age) [11]. Similarly, the study conducted in Taiwan for the same purpose, the age group was (1-18) year. However, the study conducted in France chose age group of (7-14) year in evaluation of role of melatonin in AD in children [12]. Regarding laboratory results serum melatonin was 58.8 ± 57.5 pg/ml in Melatonin group and 25.5 ± 17.8 in Placebo group; significantly higher in Melatonin group. While serum IgE was 129.5 ± 43.2 & 132.8 ± 47.5 in Placebo & Melatonin groups respectively with no significant difference between both groups. As regard the mean extent of eczema score in pre supplementation of the drug, there was no significant difference between two groups with mean extent score 59.3 ± 22.0 & 54.5 ± 29.2 in Placebo & Melatonin groups respectively.

Table 1: Age and sex distribution between both groups

	Placebo group (n = 43)	Melatonin group (n = 43)	p- value
Age (Mean +SD)	5.2321	5.4647	0.12
Sex distribution N (%)			
Male	18 (41.9%)	24 (55.8%)	0.19
Female	25 (58.1%)	19 (44.2%)	

p-value: level of significance

Table 2: Descriptive and inferential statistics for all dependent variables at different measuring periods at both groups

		Placebo group (n = 43)	Melatonin group (n = 43)	P value*
Total SCORAD	Pre-Supplementation	71.95 ± 11.98	68.77 ± 22.27	0.413 ^{NS}
	Post-Supplementation	3.42 ± 5.79	2.22 ± 5.21	0.238 ^{NS}
	P value**	0.001 ^{HS}	0.001 ^{HS}	
Quality of life score	Pre-Supplementation	18.34 ± 9.74	16.72 ± 7.25	0.079 ^{NS}
	Post-Supplementation	1.60 ± 1.95	1.48 ± 4.46	0.914 ^{NS}
	P value**	0.001 ^{HS}	0.001 ^{HS}	
Sleep disorders score	Pre-Supplementation	55.51 ± 21.67	53.06 ± 18.74	0.413 ^{NS}
	Post-Supplementation	27.25 ± 3.02	29.3 ± 14.24	0.075 ^{NS}
	P value**	0.001 ^{HS}	0.001 ^{HS}	
Serum Melatonin	Pre-Supplementation	25.5 (17.89)	58.84 (57.58)	0.001 ^{HS}
	Post-Supplementation	17.69 (18.8)	14.3 (4.72)	0.254 ^{NS}
	P value**	0.001 ^{HS}	0.001 ^{HS}	
IgE	Pre-Supplementation	129.5 (43.21)	132.84 ± 47.52	0.08 ^{NS}
	Post-Supplementation	27.21 (19.21)	24.32 (18.2)	0.58 ^{NS}
	P value**	0.001 ^{HS}	0.001 ^{HS}	

* Inter-group comparison; ** intra-group comparison of the results pre- and post-Supplementation.

^{NS} $P > 0.05$ = non-significant, ^{HS} $P < 0.01$ = highly significant, P = Probability.

AD impacts sleep by different ways; Itching, Irritability and disturbed circadian rhythm and also it impacts QOL with different results in variable studies [13]. Sleep disturbance has also been reported to have a major influence on the QOL of AD patients and there was significant correlation between sleep quality and QOL in children. Thus, the use of QOL indices, AD patients and care-givers have the potential to experience greater satisfaction with treatment [14].

The total eczema score in both Placebo & Melatonin groups was 71.9 ± 11.9 & 68.7 ± 22.2 respectively with no significant difference. As regard sleep pattern in both groups by using SDSC, results were similar scores with no significant difference as Melatonin group was 53.0 ± 18.7 and Placebo group was 55.5 ± 17.6 . The QOL in both groups was affected estimated by quality score that calculated using QOL questionnaire that were 16.7 ± 7.2 in Melatonin group and 18.3 ± 9.7 in Placebo group with no significant difference between two groups pre intervention. These findings were agreed with the results reported by Ca'mfferman et al., who found that sleep not impacted significantly while disturbed sleep is reported in 47%–60% of patients and is a major factor leading to an impaired quality of life [4].

Post intervention analysis demonstrated that serum level of melatonin became 14.3 ± 4.7 pg/ml in Melatonin group but at placebo group became 17.6 ± 18.8 pg/ml. Melatonin level started high at the morning nine AM in children who have AD. After supplementation of melatonin three mg before bed time serum level of melatonin significantly decreased it seems that external melatonin alters circadian rhythm. As standard treatment of eczema was resumed, also course of eczema was remission and exacerbation. IgE decreases spontaneously, the present study IgE showed significant difference in pre and post study with mean 24 after supplementation of melatonin 24.3 ± 18.2 in Melatonin group while in Placebo drop to 27.2 ± 19.2 . Of course significant improvement but with no difference between Placebo and Melatonin that indicates that melatonin gives no difference of statistically value. While other data conducted in 2014 suggested that melatonin inhibits development of atopic eczema and reduces total serum IgE [15]. Equally important that was significant improvement in total eczema score in post study markedly from (69 to 2) in Melatonin group and Placebo from (72 to 3) in P group. This indicates that melatonin have a role but limited or unclear. Together with total sleep score drop from (53 to 29) in Melatonin group and from (55.5 to 27) in Placebo group. Then quality score improved from (17 to 1) and from (18 to 2) in Melatonin and Placebo groups respectively.

Both group scores improved but other study showed that melatonin has significant influence as the following; in France a study conducted showed melatonin supplement for short period at bed time give dramatic response by decreasing ASOL (awaking sleep onset latency). Also in that study analyzed plasma melatonin concentration before and after supplementation, results showed plasma melatonin concentrations were significantly higher with a recovery in the circadian rhythm and actual sleep time was significantly longer with substantial reduction in sleep onset, latency and night awakenings [12]. Furthermore, sleep score significantly improved in study conducted in China using three mg melatonin daily at bed time for four weeks [16]. Also, in agreement with study evaluated the QOL in 101 AD patients compared with healthy controls and showed that patients with AD had reduced DLQI scores compared to controls ($p < 0.0001$) [13]. In contrary with the study recently evaluated the effectiveness of melatonin supplementation in children with AD and demonstrated that it is a safe & an effective way to improve sleep-onset latency (sleep-onset latency shortened by

21.4 min after melatonin treatment compared with after placebo; $P = 0.02$) and disease severity by SCORAD (SCORAD decreased by 9.1 compared with after placebo; $P < 0.001$) [7]. On the other hand, there was no significant difference between quality and sleep score in post study in Placebo and Melatonin group.

6 Implications for research and/or practice:

Further studies are required to explore the mechanisms of action of melatonin and clinical implications, could serve as a useful evaluating tool in management of AD. It is important that clinicians evaluate the severity of AD and ask general questions about itching, sleep, impact on daily activities, and persistence of disease during each patient visit and follow-up with the complaint of sleep disturbance. Family physician should screen for sleep disorders with AD. Management of sleep disturbance in AD should focus on adequate disease control of AD as well as possible medical interventions to help improve sleep. The pathophysiology of sleep disturbance in AD is extremely complex, and further research is needed to better understand the interplay of the immune system, circadian rhythm, and environmental factors implicated in both AD and sleep. AD has been found to be associated with impaired QOL. While some patients and families are better able to cope than others. So health education about triggers factors and protective mechanisms is indicated in cases of atopic dermatitis in primary care.

5 Conclusion

Melatonin supplementation is a safe and effective way to improve the sleep-onset latency and disease severity in children with AD. But study conducted was limited so further studies are needed.

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Ethical issue

Authors are aware of, and comply with, best practice in publication ethics specifically with regard to authorship (avoidance of guest authorship), dual submission, manipulation of figures, competing interests and compliance with policies on research ethics. Authors adhere to publication requirements that submitted work is original and has not been published elsewhere in any language.

Competing interests

Authors declare there is no conflict of interest regarding the publication of paper.

Authors' contribution

All authors of this study have a complete contribution for data collection, data analyses and manuscript writing.

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