Original Article

Evaluation Of Melatonin Effects On Retinopathy Of Prematurity Prophylaxis

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Abstract

Background: According to the latest evidence, infants with gestational age < weeks (33 weeks and six days or less) or birth weight ≤ 2,000 grams are at risk of prematurity retinopathy (ROP) and should be screened. It is preventable in most cases and treatable if diagnosed on time; otherwise, the disease is progressive and quickly leads to blindness. In the final stages of the disease, treatment is complicated and, in some cases, impossible and expensive.

Therefore, this study was conducted to evaluate the early diagnosis and treatment of this disease and the prophylactic effect of melatonin.

Methods: This study was a clinical trial conducted on all preterm infants admitted to the neonate intensive care unit (NICU) ward of Akbarabadi and Ali Asghar hospitals of Iran University of Medical Sciences. Study information was given to the parents, and they were included in the study after obtaining written consent. These infants were randomly divided into two groups; for the first group, melatonin (3 mg/kg/day) was administered from day 7 of birth to the end of week 37, and the second group (control group) did not receive this drug. After completing the course, the two groups were evaluated and compared regarding the incidence of retinopathy prematurity.

Results: Sixteen neonates in two groups were included in this study. Between the two groups, there was not any significant difference in neonatal gender (P=0.6), mean gestational age (P=0.6), birth weight (P=0.7), average APGAR score in minutes 1 (P=0.3) and five (P=0.1), umbilical cord PH (P=0.8), mechanical ventilation and CPAP (P=0.4), other respiratory support (P=0.7), duration of hospitalization (P=0.7), final weight (P=0.7). 13.3% of neonates in the melatonin group and 36.7% of the control group had ROP. There was a significant difference in the incidence of ROP according to the study group (P=0.03). However, there was no significant relationship between the study group and the severity of neonatal ROP (P=0.9).

Conclusion: Our data suggested that treating preterm infants with melatonin could effectively reduce the incidence of ROP.

Keywords: Retinopathy of Prematurity, Premature Neonate, Melatonin.

Background

Retinopathy of retinal vascular disease often occurs in preterm infants. It can lead to a wide range of visual impairments, from minor defects modifiable to visual acuity to retinal detachment and blindness. It can be treated in most cases preventable case of early diagnosis and is progressive in the absence of an early diagnosis, and quickly leads to blindness (1). In these children, the retina has not evolved, and the effect of various factors, such as oxygen intake, may cause abnormal veins in the eyes. Not getting enough oxygen increases the risk of brain problems, and it may be necessary to prescribe oxygen with the doctor's opinion (2). Neonatal retinopathy can be evaluated four weeks after birth and at least a modified age of 33 weeks. Therefore, the first examination of the endangered infant is performed at this age. Follow-up examinations are also performed depending on the condition of the baby's eye. Fortunately, after the relative development of the baby's retina, the risk of developing retinopathy is zero (3). With a significant increase in the survival rate of preterm infants, which has increased from about 5% to more than 65% for infants weighing less than 1000g and more than 90% for infants weighing 1000-1500 grams in the last forty years, the number of infants with prematurity retinopathy will increase unless serious measures are taken to prevent the disease (1).

Melatonin (N-acetyl-5-methoxy tryptamine) is a hormone that is produced in the pineal gland (pineal) and helps regulate sleep-wake cycles in the body (4-6). It is also synthesized in the retina, lens, thymus, respiratory epithelium, skin, gastrointestinal tract (GI), bone marrow and other places (6). Also, Melatonin has shown various medicinal properties such as maintaining endothelial barrier function and maintaining vascular permeability (7,8), anti-inflammatory (9), anti-apoptosis (9-11) and reducing

oxidative stress (12,13).

A study on laboratory mice also showed that melatonin consumption could reduce the severity and incidence of retinopathy. Retinopathy is an eye condition that affects the retina and can lead to vision loss and decreased vision (14).

Studies have shown that using Melatonin for children is safe, has no side effects, and can be effective in treating some disorders in children (15). Also, in another study, infants receiving melatonin supplements showed no potential effects (such as nausea, diarrhea or abnormalities in sleep patterns) (16).

In a multicenter, double-blind clinical trial conducted by Garofoli and his team in 2020 on preterm Italian infants, while emphasizing the safety of Melatonin, its positive impact on neurosurgeon health protection and the development and improvement of rehabilitation of premature human infants was confirmed (17).

Considering the importance of the mentioned cases and the lack of previous studies on the effect of Melatonin on the prevention of retinopathy of prematurity (ROP) in newborns, this study aimed to investigate the effect of Melatonin in the prevention of ROP in newborns.

MATERIALS AND METHODS

Patients

This double-blind clinical trial study was conducted on all neonates admitted to NICU at two hospitals in Tehran (Ali Asghar children's hospital and Akbarabadi hospital) because of prematurity from October 2021 to March 2022. The sample size was calculated according to a recent study (18). In this protocol, the sample size is considered according to the neuroprotective effect of Melatonin. Therefore, in this study, considering the outcome and statistical power of 80% and the significance level of 95%, the required sample size was 26 patients for each group. 15% collapse was Designated, and 30 patients were countered as the final sample size for each group.

Patients were randomly divided into the groups of intervention (melatonin treatment) and control (no treatment).

Inclusion criteria: All premature neonates with gestational age (GA) < 32 weeks with the parent's consent and no congenital, genetic, or metabolic anomalies exist.

Exclusion criteria: Intraventricular hemorrhage (grades 3 & 4), parent's tendency for left the study, gastrointestinal complications (such as necrotizing enterocolitis), neonatal asphyxia, less than 14 days of melatonin consumption, positive blood culture, any drug side effect, hypotension needing vasopressors.

Intervention and Measurements

In this study, patients were randomized through a random number table and divided into two groups: group 1(intervention): in this group, 3 mg/kg/day of Melatonin was consumed in patients, group2 (control), only routine treatment was prescribed.

Melatonin 5 mg tablets belonged to VANA Darou Gostar under the license of Nutralab/Canada. They started with 3 mg/kg daily (17) from 7 days of age and before the age of 32 weeks and up to 37 weeks, the transition from phase 1 to phase 2 retinopathy prematurity was administered (19). The results were calculated in 37 and 44 weeks, at the end of the drug administration period and the end time of retinal development.

Patients' information (Gender, GA, Birth weight, date of study entry, length of study, perinatal history, respiratory support specification) was collected in the prepared questionnaire.

Neonatal eye examinations were done by retinal fellowship and with an ophthalmoscope.

Statistical analysis

The results of this study were analyzed by SPSS software (IBM, version 19). Quantitative data were analyzed using the descriptive program and presented as Mean ± SD. Crosstabs and Chi-Square tests were used to compare the percentages or frequencies between the two groups. Comparing the mean of parametric data between cases and controls was analyzed using an independent student sample t-test. In this study, $p< 0.05$ was considered statistically significant.

RESULTS

Sixteen neonates in two groups (treated with melatonin and control group) were included in this study. 50% of neonates in the melatonin group and 43.3% of the control group were males (Table 1). There was no significant difference between the two groups regarding neonatal gender (P=0.6).

Table 1. Gender of neonates

Variable			Group		Total	P value
			melatonin	control		
gender	Boy	Count	15	13	28	0.6
		%	50.0%	43.3%	46.7%	
	Girl	Count	15	17	32	
		%	50.0%	56.7%	53.3%	
Total		Count	30	30	60	
		%	100.0%	100.0%	100.0%	

Overall, infants in the treatment and control groups were hospitalized at 11.32 ± 59.40 days and 12.17 ± 58.53 days, respectively. There was no statistically significant difference between the two groups (P=0.7).

The mean gestational age of infants in the treatment group was 1.1 ± 29.1 and in the control group was 1.3 ± 29.3 weeks. There was no significant difference between the two groups (P=0.6). Infants in the melatonin group had an average birth weight of 83.3 ± 1130.33 grams, and infants in the control group had an average weight of 86.2 ± 1117.66 grams. There was no statistically significant difference between the two groups regarding their birth weight (P=0.7).

The mean of 1 & 5 minute APGAR scores were 0.81 ± 6.53 and 0.50 ± 8.46 in the melatonin group and 0.83 ± 6.70 and 0.49 ± 8.63 in the control group. There was no significant difference between the two groups (P=0.3, and P=0.1, respectively).

Also, the evaluation of umbilical cord blood PH in the treatment and control group was 0.03 ± 7.22 and 0.02 ± 7.21, respectively, which did not show any significant difference (P=0.8).

Infants in the melatonin group underwent invasive and mechanical ventilation for an average of 2.59 ± 7.18 days, and in the control group, 2.78 ± 7.68 days.

In addition, the infants in the melatonin group underwent CPAP for an average of 4.33 ± 10.50 days, and the control group underwent CPAP and respiratory support for 11.7 ± 8 days.

There was no statistically significant difference between the two groups of neonates regarding mechanical ventilation, CPAP and other respiratory support (P=0.4 and P=0.7, respectively).

Demographic data of patients' information is summarized in Table 2.

Table 2. Comparison of the demographic and clinical characteristics between cases and control groups

Variables	group	N	Mean	SD	Minimum	Maximum	P value*
gestational age	melatonin	30	29.13	1.1	27	32	0.6
	control	30	29.30	1.3	27	32	
birth weight	melatonin	30	1130.33	83.3	920	1230	0.7
	control	30	1117.66	86.2	900	1250	
1st min Apgar	melatonin	30	6.53	0.81	5	8	0.3
	control	30	6.70	0.83	5	8	
5th min Apgar	melatonin	30	8.46	0.50	8	9	0.1
	control	30	8.63	0.49	8	9	
cord blood pH	melatonin	30	7.22	0.03	7.20	7.30	0.8
	Control	30	7.21	0.02	7.20	7.29	
mechanical ventilation	melatonin	30	7.18	2.59	1	11	0.4
	control	30	7.68	2.78	2	11	
CPAP/respiratory supports	melatonin	30	10.50	4.33	6	20	0.7
	Control	30	8.00	11.78	7	20	

Evaluation of ROP incidence in both groups showed that 13.3% of neonates in the melatonin group and 36.7% of neonates in the control group had this complication. There was a statistically significant difference between the two groups regarding the incidence of ROP, so the incidence of this complication was significantly higher in the control group (P=0.03). There was no significant difference in ROP severity between the two groups. (Table 3).

Table 2. ROP incidence & severity between melatonin and control group

Variable	Group	Total	P value

			melatonin	Control		
ROP	yes	Count	4	11	15	0.03
		%	13.3%	36.7%	25.0%	
	no	Count	26	19	45	
		%	86.7%	63.3%	75.0%	
Total		Count	30	30	60	
		%	100.0%	100.0%	100.0%	
ROP severity	stage I	Count	2	3	5	0.9
		%	50.0%	27.3%	33.3%	
	stage II	Count	2	6	8	
		%	50.0%	54.5%	53.3%	
	stage III	Count	0	2	2	
		%	0.0%	18.2%	13.3%	
Total		Count	4	11	15	
		%	100.0%	100.0%	100.0%	

DISCUSSION

This study aimed to investigate the relationship between Melatonin and ROP incidence in preterm infants. Infants in the intervention group were given Melatonin (3 mg/kg/day). The final evaluation results showed that the incidence of ROP (13.3% in the intervention group versus 36.7% in the control group) was significantly lower in melatonin users. This finding can be promising for the effect of this safe drug on ROP prophylaxis and paves the way for further studies.

A study conducted by Katarina et al. to evaluate the effect of external Melatonin on the blood-retinal barrier and vitreous oxidative status in rats with oxygen-induced retinopathy (OIR) and its prospects in the treatment and prevention of premature retinopathy. It was shown that exogenous Melatonin helps stabilize the blood-retinal barrier in OIR due to its vascular formation inhibitor and potent antioxidant activity (20).

Currently, a large number of studies have been devoted to the protective role of Melatonin in various diseases of the neonatal period. Very encouraging results have been obtained from studying the effect of Melatonin on neonatal diseases such as chronic pulmonary disease, perinatal brain injury and necrotizing enterocolitis (21).

Treating ocular diseases using Melatonin alone or in combination with other medications requires serious investigations. Moreover, Melatonin prophylactic treatments in different eye oxidative disease risk groups are an essential research topic related to vision preservation. Clinical trials using Melatonin will likely reduce the severity of eye diseases.

There was no stage III disease in the melatonin-treated group, and 50% of infants had ROP stage I and 50% had ROP stage II, but in the control group, more than 70% of neonates had ROP with stage III (13.3% stage III). Despite the lack of statistically significant differences, probably due to the low number of newborns with this disorder, this finding is of great importance. Because as the disease stage increases, treatment becomes more complex and invasive, subsequent complications and the risk of blindness increase. Therefore, Melatonin has been able to reduce the risk of higher clinical stages progression and prevent long-term and irreparable complications of the disease. In order to get definitive conclusions in this regard, studies with higher sample sizes of patients with ROP and in different stages of it are needed to determine the exact effect of Melatonin on the progression of the disease and prevent this complication in the high stage.

CONCLUSION

In general, this study's results showed that treating preterm infants with Melatonin could effectively reduce the incidence of ROP. The low toxicity of Melatonin (115) and the ability to simultaneously influence several pathogeneses of ROP allow considering Melatonin and its analogues as a potential drug for the prevention of ROP in the clinic, which of course, requires a further comprehensive study of the effectiveness of its use. Although further studies with higher sample sizes, with different doses of Melatonin and investigation of possible side effects of the drug, are needed to confirm the use of endogenous antioxidant supplements such as Melatonin in damaged retinal tissue, the results of this study show that the therapeutic outcome of this drug is.

LIMITATIONS OF THE STUDY

Issues with samples and selection, the insufficient sample size for statistical measurements, lack of previous research studies on the topic, time constraints, recall and observational bias.

DECLARATIONS

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Iran University of Medical Sciences. Informed consent was obtained from the study participants. Registration ID in Iranian Registry of Clinical Trials (IRCT): (IRCT20211226053528N2).

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analyzed during the current study are not publically available due to patient confidentiality but are available from the corresponding author on reasonable request.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors have no potential conflict of interest to disclose.

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AUTHORS' CONTRIBUTIONS

NK, NK, AV, ZV and HK provided insight into the design and draft of the study, interpreted the data, performed statistical analysis, wrote and edited the manuscript, and revising the manuscript. All authors have read and approved this version to be published.

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