UNIVERSA MEDICINA

pISSN: 1907-3062 / eISSN: 2407-2230

Univ Med 2024;43:44-50

DOI: http://dx.doi.org/10.18051/UnivMed.2024.v43:44-50

ORIGINAL ARTICLE

Factors that influence refractive errors in premature infants

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Date of first submission, October 31, 2023
Date of final revised submission, March 21, 2024
Date of acceptance, March 26, 2024

Cite this article as: Surasmiati NMA. Handayani AT, Sutyawan IWE. Factors that influence refractive errors in premature infants. Univ Med 2024;43:44-50

ABSTRACT

BACKGROUND
The prevalence of refractive errors is reported to be higher in children born preterm. Factors such as gestational age, birth weight, and retinopathy of prematurity status, have a significant impact on the refractive development in preterm infants. Prematurity and low birth weight affect the development of organ systems in infants, including the eyes. In addition to immature retinas, other eye conditions, such as refractive status, are also observed. This study aimed to determine the risk factors of refractive status, specifically refractive errors (spherical equivalent, astigmatism, and anisometropia) in premature infants at a tertiary hospital in Bali.

METHODS
A cross-sectional study was conducted involving 53 premature infants. This study collected samples from January to August 2023 at the Neonatal Intensive Care Unit of Prof. dr. IGNG Ngoerah General Hospital. Data regarding gender, gestational age, birth weight, retinal condition, spherical equivalent, and refractive disorders were collected. The relationship between risk factors and spherical equivalent, astigmatism, and anisometropia were analyzed using multiple regression analysis with statistical significance set at $p<0.05$.

RESULTS
Hypermetropia is the most common finding in premature infants, followed by myopia and astigmatism. The prevalence of myopia (9.4%) and astigmatism (5.7%) is also more common among newborns of gestational age ≤30 weeks ($p=0.024$). Chronological age was significantly associated with spherical equivalent ($\beta=0.424$; $p=0.019$).

CONCLUSION
In premature infants, chronological age was the risk factor of spherical equivalent. Other risk factors were not associated with the prevalence of refractive errors among premature infants.

Keywords: Refractive error, myopia, hypermetropia, astigmatism, birth weight, premature

INTRODUCTION

Premature infants pose special challenges due to their underdeveloped organs. Prematurity refers to infants being born alive before 37 weeks of gestation, while low birth weight (LBW) is defined as a birth weight of less than 2.500 grams. It is estimated that globally there were 13.4 million premature babies in 2020, with 900,000 children dying from complications of premature birth.[1,2] The incidence of preterm birth in Indonesia is approximately 15.5%.[3] Low birth weight is the result of either premature birth, intrauterine growth restriction, or both.[4] The younger the gestational age and the lower the birth weight, the more immature their visual system becomes.[5,6]

Premature infants who survive tend to face lifelong disabilities, including learning disabilities and problems with vision.[7,8] However, the advancements in neonatal care facilities increase the life expectancy of premature infants.[1] Detection of abnormalities caused by prematurity, including eye disorders, is being routinely performed.[9,10]

The physiological conditions of a shallow anterior chamber, high corneal curvature, and spherical lens in premature infants can cause refractive errors, such as myopia and astigmatism.[6,11,12] Similarly, a history of low birth weight is associated with a tendency to develop myopia due to growth disturbances affecting ocular geometry among children.[13,14] The gestational age at birth affects the incidence of refractive disorders and amblyopia. Preterm infants have a tendency to develop myopia and emmetropia compared to full-term infants.[11] Therefore, myopia is more common in premature and low birth weight infants.[14]

On the other hand, several studies have obtained different results where low birth weight and gestational age showed only minimal effects on refractive status.[15] The study of Hsieh et al. [16] showed that low gestational age and low birth weight led to an increased risk of myopia. Other studies also stated that premature babies are more likely to have refractive errors, particularly hypermetropia.[15,17] In contrast, a community-based observational study among children aged 5 - 16 years did not find any significant association between prematurity and prevalence of hypermetropia, although numerically hypermetropia was more common in the preterm group.[16] Anisometropia, defined as the difference in refractive errors between both eyes had also been frequently reported among newborn infants.[16] Refractive status in infants undergoes emmetropization within the first year of life, leading to normalization of refractive outcomes. [18] Therefore a new study is needed due to these conflicting results. This study aimed to determine the risk factors of refractive error status in premature infants.

METHODS

Research design

This study was a cross-sectional study conducted at the tertiary Prof. dr. IGNG Ngoerah General Hospital, from January to August 2023.

Research subjects

A total of 53 premature infants who were referred for ROP screening in the Neonatal Intensive Care Unit (NICU) were included in the study. They underwent streak retinoscopy, followed by indirect fundus examinations, to evaluate the fundal and peripheral parts of the retina. The ROP screening is generally scheduled twice a week, on Mondays and Thursdays. The inclusion criteria were premature infants who were medically stable and could be weaned from the incubator to an infant warmer for examination. The infants referred for ROP screening who still required respiratory support from a high-flow nasal cannula and would be unstable during the screening were excluded from undergoing streak retinoscopy.

Data collection

All premature infants with a chronological age of more than two weeks and a gestational age of <30 weeks were included in the study. One drop of tropicamide 0.5% was administered to both eyes and this was repeated every 15 minutes to dilate the pupil for diagnostic purposes. After the baby was transferred to an infant warmer, the ophthalmologist gently applied a topical anesthetic (tetracaine hydrochloride 0.5%) and then placed a speculum on the infant's eye. The streak retinoscopy examination was conducted by one pediatric ophthalmologist expert (SR). Refractive errors were converted into the spherical equivalent (SE, defined as spherical errors and half of astigmatic error), astigmatic error, and anisometropia (defined as the absolute difference in SE of ≥1 diopter between the two eyes). Refractive abnormalities are classified as myopia (SE <-0.50 diopter), hypermetropia (SE ≥2

diopter), and astigmatism if the cylindrical power is greater than the spherical power, with the cylindrical power being ≥1 diopter.[19]

Statistical analysis

All data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corp, Armonk, NY, USA). All categorical data were analyzed using the Chi-square test. All numerical data were tested by the Shapiro-Wilk test to determine the normality of data distribution. Multiple linear regression analysis was used for analyzing the relationship between several risk factors with refractive outcomes. A p value of <0.05 was considered statistically significant.

Ethical clearance

The ethical clearance for this study was obtained from the Research Ethics Committee, Faculty of Medicine, Udayana University, with the registration number 1219/UN14.2.2.VII.14/LT/ 2023.

RESULTS

This study found that the mean gestational age among the premature infants was 31.22 ± 2.47 weeks, while the mean birth weight was 1520.0 ± 392.93 gram. Retinopathy of prematurity (ROP) was diagnosed after performing an indirect fundus examination to assess the peripheral retina. Four (7.5%) patients were found to have ROP, among whom two infants had emmetropia and two infants had hypermetropia. Anisometropia was found in more than one-fourth of all subjects (Table 1).

The most common refractive disorder in premature infants was hypermetropia, being present in the right eye in 26 infants (49.1%) and in the left eye in 29 infants (54.7%). The study sample demonstrated a myopia prevalence of less than 10%, which was comparable to the rate of astigmatism (Table 2).

Table 1. Characteristics of the research subjects (n=53)

Characteristic	Mean ± SD	n (%)
Gender		
Male		29 (54.7)
Female		24 (45.3)
Gestational age (mean ± SD, weeks)	31.22 ± 2.47	
GA ≤ 30		20 (37.7)
GA > 30		33 (62.3)
Chronological age (mean ± SD, weeks)	4.01 ± 2.28	
Post menstrual age (mean ± SD, weeks)	35.24 ± 2.42	
Birth weight (mean ± SD, gram)	1520.0 ± 392.93	
≤ 1500		30 (56.6)
1500-2500		21 (39.6
>2500		2 (3.8)
Retinopathy of prematurity (ROP)		
Present		4 (7.5)
Absent		49 (92.5)
Spherical equivalent RE (mean ± SD, diopter)	2.41 ± 2.52	
Spherical equivalent LE (mean ± SD, diopter)	2.34 ± 2.68	
Anisometropia		14 (26.4)
Astigmatism		3 (5.7)

Table 2. Distribution of refractive errors in the right eye and left eye

	RE (n %)	LE (n %)
Emmetropia	19 (35.8)	18 (34.0)
Myopia	5 (9.4)	4 (7.5)
Hypermetropia	26 (49.1)	29 (54.7)
Astigmatism	3 (5.7)	2 (3.8)
Total	53 (100)	53 (100)

RE = right eye; LE = left eye

The study also examined the distribution of refractive status based on gestational age and found that hypermetropia was more common in all gestational age groups (less than 30 weeks and more than 30 weeks of gestational age). Myopia and astigmatism were found among the premature infants with gestational age ≤30 weeks (p=0.024) (Table 3).

Table 3. Distribution of refractive error based on gestational age and birth weight

Right Eye		≤1500 grams	>1500 grams	Total	Left Eye		≤1500 grams	>1500 grams	Total
GA ≤30	N	6(30.0)	1(5.0)	7(35.0)	GA ≤30	N	5(25.0)	1(5.0)	6(30.0)
weeks	M	2(10.0)	2(10.0)	4(20.0)	weeks	M	2(10.0)	2(10.0)	4(20.0)
	H	7(35.0)	1(5.0)	8(40.0)		H	8(40.0)	1(5.0)	9(45.0)
	A	1(5.0)	0 (0.0)	1(5.0)		A	1(.05)	0 (0.0)	1(5.0)
Total		16(80.0)	4(20.0)	20(100.0)			16(80.0)	4(20.0)	20(100.0)
GA >30	N	6(18,2)	6(18,2)	12(36.4)	GA >30	N	6(18.2)	6(18.2)	12(36.4)
weeks	M	0 (0.0)	1(3.0)	1(3.0)	weeks	M	0 (0.0)	0 (0.0)	0 (0.0)
	H	8(24.2)	10(30,3)	18(54.5)		H	8(24.4)	12(36.4)	20(60.6)
	A	0 (0.0)	2(6.1)	2(6.1)		A	0 (0.0)	1(3.0)	1(3.0)
Total		14(42.4)	19(57.6)	33(100.0)	Total		14(42.4)	19(57.6)	33(100.0)

Values are expressed as n (%); N=normal; M=myopia; H=hypermetropy; A=astigmatism; GA= gestational age
*% according to gestational age and laterality

Table 4. Multiple regression analysis of major risk factors contributing to refractive outcomes in preterms

Contributing factors	SE OD			SE OS			Astigmatism			Anisometropia		
	β	Beta	p value	β	Beta	p value	β	Beta	p value	β	Beta	p value
Age	0.324	0.293	0.064	0.424	0.361	0.019*	-0.015	-0,148	0.365	-0.007	-0.039	0.813
Sex	-0.271	-0.052	0.712	-0.652	-0.121	0.369	0.027	0,058	0.695	-0.104	-0.128	0.395
Gestational age	0.171	0.167	0.386	0.355	0.326	0.084	0.019	0,202	0.319	0.032	0.192	0,352
Birth weight	0.002	0.285	0.126	0.001	0.216	0.226	0.000	-0,174	0.370	0.000	-0.167	0.,397
ROP	0.324	0.034	0.806	0.066	0.007	0.961	0.048	0,055	0.709	-0.026	-0.017	0.910

SE: Spherical equivalent; OD: oculus dexter ; OS: oculus sinister; β: regression coefficient
*p<0,05 statistically significant

Birth weight was divided into two categories: ≤1500 grams and >1500 grams. In all birth weight categories, hypermetropia was the most frequent refractive error in both the right and left eyes (Table 3).

The study investigated the relationship between major risk factors and refractive outcomes. This study found that an increase of one week in chronological age significantly corresponded to an increase of 0.424 diopters in SE value for the left eye (β=0.424; p=0.019) (Table 4).

DISCUSSION

Retinopathy of prematurity is a vasoproliferative retinal disorder in premature infants and the leading cause of preventable childhood blindness.[20,21] This study found 4 infants (7.5%) with ROP, which is consistent with the fact that in Indonesia, the incidence of ROP in 2016-2017 was 7% among infants with a gestational age of 28-32 weeks.[22] Premature infants are babies born alive before reaching a gestational age of 37 weeks, while low birth weight (LBW) refers to a birth weight of <2500 grams. Both of these conditions are screening criteria for examining the ocular posterior segment for signs of ROP. The National ROP Task Force and Prof. dr. IGNG Ngoerah General Hospital established the criteria of LBW ≤1500 grams or gestational age ≤34 weeks for ROP screening. Screening can also be done on infants with higher birth weights or older gestational ages with additional risk factors of ROP, including high oxygen saturation for more than one week, repeated transfusions, sepsis, respiratory diseases, history of apnea, asphyxia, younger gestational age, bronchopulmonary dysplasia, patent ductus arteriosus, and a family history of prematurity or ROP.[23] Low birth weight negatively affects organ growth during the developmental period, including morphology and eye function, thus resulting in long-term implications for refractive abnormalities in adulthood. [5,6,13]

The most frequent refractive status obtained in this study for premature infants is hypermetropia, both in the right eye and the left eye, based on refractive status distribution by gestational age and birth weight, despite the fact that hypermetropia has been known to be more common among term newborns. This result is in accordance with the studies conducted by Katsan and Adakhovskaia,[17] Mao et al.,[15] and Dervisogullari et al.[24] The refractive status changes with the increase in axial length and the flattening of the cornea and lens. Physiologically, newborn babies experience hypermetropia until they are 6-8 years old, which is followed by the change towards myopia until around the age of 16. This process of emmetropization refers to a combination of changes in refractive power in the anterior segment and changes in axial length so that the eyes become emmetropic.[18]

Our study found that myopia and astigmatism occurred in infants with gestational age <30 weeks although none of the four ROP patients were myopic. The small number of subjects could contribute to this unreliable finding. However, the study by Katsan and Adakhovskaia [17] found that ROP infants who underwent laser therapy and regressed also have a higher prevalence of hypermetropia. Myopia is commonly found among premature infants, especially in ROP following cryotherapy.[16] One of the risk factors of myopia is a history of prematurity and low birth weight,[14,18] and is related to the steeper corneal curvature and the thicker lens in preterm infants with ROP, such that the incidence of myopia and astigmatism is rather high.[25]

This study showed that more than one-fourth of the subjects were anisometropic; thus, long-term follow-up studies are suggested to monitor the progression of anisometropia during the emmetropization process, as the premature infants' eyes continue to grow during the early stages of life.[11,26] Anisometropia is defined as the difference in refractive errors between both eyes and more commonly at earlier ages. The anisometropia tends to regress as the emmetropization begins to occur.[27]

In our study, we found a significant relationship between chronological age and SE value, where a larger chronological age will result in an increase in SE. This finding is similar to those of Wang et al.,[6] Semeraro et al. [11], and Ozdemir et al.[19] Mature babies generally have hypermetropia, while premature babies with ROP tend to have myopia, so these findings are related to gestational age and chronological age. However, the myopia will change as gestational age increases. Infants with low gestational age and low birth weight also have smaller spherical equivalent values, where spherical equivalent correlates with increasing postmenstrual age (PMA).[12]

This study is expected to provide the baseline data for observing the development of the

refractive status of premature infants, in order to identify the long-term relationship between refractive status in adulthood and prematurity. The limitation of this study is that the measurement of axial length was not carried out, although it is an important indicator of refractive status. Further research should use axial length as one variable for investigation.

The findings in this study emphasize the clinical implication that refractive error screening should be comprehensively performed along with ROP screening, such that its result may become baseline data to monitor refractive error progression among prematurely born infants.

CONCLUSION

The most common refractive disorder in premature infants is hypermetropia. Myopia occurs in infants with lower gestational age and birth weight. There was a significant correlation between chronological age and spherical equivalent, in which increased chronological age contributes to greater SE.

Conflict of Interest

Competing interests: No relevant disclosure

Acknowledgement

The authors thank the neonatal nurses and ophthalmology residents of Prof. dr. IGNG Ngoerah General Hospital for their cooperation and excellent suggestions in this study.

Funding

This research was funded by DIPA PNBP Udayana University TA-2023 in accordance with the Research Implementation Assignment Agreement Number B/1.428/UN14.4.A/PT.01.03/ 2023.

Author Contributions

NMAS contributed to study concept and design, data collection and assembly, statistical analysis, and manuscript writing. ATH contributed to data analysis and interpretation, and manuscript writing. NWES contributed to data collection and data analysis and interpretation. All authors reviewed the manuscript, approved the final manuscript, and take public responsibility for the content of the manuscript submitted to Universa Medicina.

Data Availability Statement

The datasets generated and/or analyzed during the study are available upon request from the corresponding author.

Declaration of Use of AI in Scientific Writing

Nothing to declare

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