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The Effect of Treated Retinopathy of Prematurity in Premature Infants on Ocular Structural Outcomes

Z. Nezamdoost (MD)[1], A. Bayat (MD)[1], M. Arish (MD)[1], P. Najafi (BSc)[2], M. Mahjoob (PhD)[*3]

1.Al-Zahra Eye Hospital, Zahedan University of Medical Sciences, Zahedan, I.R.Iran.

2.Department of Optometry, Paramedicine Faculty, Mashhad University of Medical Sciences, Mashhad, I.R.Iran.

3.Health Promotion Research Center, Zahedan University of Medical Sciences, Zahedan, I.R.Iran.

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ABSTRACT

Background and Objective: Retinopathy of prematurity is a complex developmental disease of retinal vessels in premature infants. Improvements in preterm care services are associated with an increased risk of advanced stages of retinopathy of prematurity. The aim of this study is to investigate the effect of treated retinopathy of prematurity in premature infants on ocular structural outcomes.

Methods: This cross-sectional study was conducted on 962 infants with retinopathy of prematurity referred to Al-Zahra Ophthalmology Hospital from 2018 to 2021. Based on the severity of the disease, the patients were followed up or treated with laser and intravitreal injection. In treated retinopathy of prematurity, structural outcomes of the eye were recorded as favorable and unfavorable outcomes. The favorable outcome was considered as regression of plus and new vessels, and unfavorable outcomes were considered as lens opacity and retinal detachment. Birth weight, gender, gestational age, mechanical ventilation, duration of oxygen use, history of radiation therapy, sepsis, respiratory distress, blood transfusion, and age at diagnosis of retinopathy of prematurity were recorded and analyzed for each patient.

Findings: The mean birth weight and gestational age at birth were 1760.65±457.90 grams and 32.37±2.39 weeks. 869 eyes were untreated and 93 eyes were treated. The incidence of adverse outcomes in those who were treated was 5.37%. Logistic regression test showed that gestational age, birth weight, stage of disease and area of retinal involvement had a significant relationship with adverse treatment outcomes (p=0.001).

Conclusion: Based on the results of this study, in retinopathy of prematurity requiring treatment, lower gestational age, lower birth weight, more severe disease stage and more central involvement area should be considered as risk factors for adverse structural outcomes of treatment.

Keywords: *Retinopathy of Prematurity, Gestational Age, Birth Weight.*

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***Corresponding Author: M. Mahjoob (PhD)**
Address: Department of Optometry, School of Rehabilitation Sciences, Zahedan University of Medical Sciences, Zahedan, I.R.Iran.
Tel: +98 (54) 33295715. **E-mail:** mahjoob_opt@yahoo.com

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Introduction

Retinopathy of prematurity (ROP) is a retinal developmental disorder in premature infants, which is considered as a very serious complication in these infants (1). In humans, the development of retinal blood vessels begins during the fourth month of pregnancy and reaches the peripheral areas of the retina before birth (2). Therefore, the developmental stages of retinal vessels in premature babies are incomplete and include an initial phase of vascular loss followed by a second phase of vascular proliferation (2). Retinopathy of prematurity is a multifactorial disease, and gestational age and birth weight are the most important risk factors of the disease (2, 3). Intraventricular bleeding (4), various maternal factors (5), respiratory disorders (4), vitamin E deficiency (2), heart disease, increased blood carbon dioxide, decreased blood oxygen, blood transfusion (6), the amount of oxygen received and duration of ventilation are the other risk factors for retinopathy of prematurity (5).

More preterm infants who survive are at increased risk of developing advanced stages of retinopathy of prematurity. In countries with well-developed neonatal intensive care services, infants born before 28 weeks of age and weighing less than 1 kg at birth are at high risk of retinopathy of prematurity, and the prevalence of retinopathy of prematurity in these countries is approximately 5-8% (7). However, in areas where many aspects of neonatal intensive care and ophthalmology are not routinely available, older infants weighing up to 2000 g at birth and 37 weeks are also at risk of severe retinopathy of prematurity (8). The prevalence of retinopathy of prematurity has been reported up to 30% in middle-income countries (2, 7). The prevalence of retinopathy of prematurity in Iran has been reported as 23.5% (3, 9).

In retinopathy of prematurity, the treatment options for severe cases of the disease are limited. However, currently suitable treatments include laser photocoagulation and intravitreal injection of Anti-VEGF (Anti-Vascular Endothelial Growth Factor) (8). In a study conducted on 339 infants with retinopathy of prematurity, it was shown that early treatment and greater gestational age at birth reduce the incidence rate of adverse ocular structural and functional outcomes (10). Furthermore, in another study that was conducted on 225 premature babies in threshold retinopathy of prematurity, they showed that the favorable treatment outcomes in the laser treatment group were 66%, while in the group treated with Anti-VEGF were 80% (11). Anti-VEGF is an emerging treatment option for retinopathy of prematurity, the use of which is increasing due to its short-term effectiveness and its safety level being similar to laser photocoagulation (12). Research has shown that laser treatment in infants with retinopathy of prematurity is associated with about 90% of favorable visual outcomes (13). However, it has been reported that after timely and complete treatment of retinopathy of prematurity in pre-threshold and threshold stages with laser in some patients, the disease progresses to more advanced stages (13). The presence of retinal and vitreous hemorrhage during or after laser therapy is associated with a higher rate of adverse outcomes (14). The advantages of using Anti-VEGFs include faster treatment, faster recovery of the disease, less destruction of the peripheral retina and less possibility of myopia and astigmatism (12, 15, 16). Considering the role of anti-VEGF drugs in the treatment of advanced stages of retinopathy of prematurity, it is reasonable to use these drugs as a potential treatment option for retinopathy of prematurity, especially for more severe cases of the disease (16, 17).

Despite significant progress in the treatment of retinopathy of prematurity, it is still one of the most common causes of vision loss in children (1). Considering that the improvement of care services for premature infants has led to an increase in the incidence of severe retinopathy of prematurity (18) and role of genetics and race on the occurrence of retinopathy of prematurity and even the results of treatment (19-21), this study was conducted to investigate the effect of treated retinopathy of prematurity on ocular

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structural outcomes in premature infants referred to Al-Zahra Ophthalmology Hospital in Zahedan, which is a tropical region in the southeast of Iran.

Methods

This retrospective cross-sectional study was conducted on infants referred to the ROP center of Al-Zahra Ophthalmology Hospital in Zahedan from 2018 to 2021 with the diagnosis of retinopathy of prematurity. This study was in accordance with the Declaration of Helsinki and was approved by the ethics committee of Zahedan University of Medical Sciences with the code IR.ZAUMS.REC.1401.230. Informed consent form was obtained.

In order to investigate the relationship between risk factors of retinopathy of prematurity and adverse outcomes of treatment, 962 cases with gestational age less than 36 weeks and birth weight less than 2500 grams were randomly selected. Exclusion criteria included lack of complete information in the patient's document, having other eye diseases such as cataracts and other retinal disorders.

All referred preterm infants had undergone complete ophthalmological examination using indirect ophthalmoscopy with +20D or +30D lens, and based on retinal involvement, retinopathy of prematurity was diagnosed by a retinal fellowship. The stage of the disease and the zone of retinal involvement were determined for each patient and the necessary treatment or follow-up was done for the patients. The stage of the disease refers to the appearance of the disease at the intersection of the vascular and non-vascular areas of the retina, which includes 5 stages: in the first stage, a boundary line is seen between the mature retinal area and the immature retina; in the second stage, the ridge has height and thickness; in the third stage, new abnormal blood vessels grow and multiply and are visible in the ridge; in the fourth and fifth stage, the retina is completely detached (22). Necessary criteria for the treatment of retinopathy included involvement in zone I in any stage of retinopathy of prematurity with plus, zone I in stage 3 with or without plus, and zone II in stage 2 or 3 with plus (23).

Depending on the condition of the disease, laser treatment or Anti-VEGF injection (Bevacizumab) or both treatments were performed for threshold condition and pre-threshold type. The followed up was done for three months after the treatment, and the ocular structural outcomes were recorded as favorable and unfavorable outcomes. The desired outcome in patients treated with laser and intravenous injection was defined as regression of plus and new vessels. Adverse outcomes were considered as lens opacity, posterior lens fibroplasia, macular elongation, and retinal detachment.

Gestational age at birth (weeks), birth weight (grams), gender, amount of mechanical ventilation (days), duration of oxygen use (days), history of radiation therapy, history of sepsis, history of respiratory distress, history of blood exchange and age at diagnosis of retinopathy of prematurity (week) were recorded for each patient.

SPSS version 26 was used for data analysis. To determine the relative factors of the ocular structural outcomes, logistic regression test was used. Independent t-test was used to investigate the difference between quantitative variables in two groups of favorable outcomes and unfavorable outcomes, and Mann-Whitney test was used for qualitative variables. P-value<0.05 was considered significant.

Results

In this study, 962 patients with retinopathy of prematurity (521 boys and 441 girls) were examined. In each patient, if there was retinopathy of prematurity in both eyes, the eye with sever involvement was

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chosen, and if there was equal involvement in both eyes, the right eye was chosen. The gestational age at the time of birth of the infants was 32.37±2.39 weeks and the birth weight were 1760.65±457.90 grams.

Among the 962 eyes examined, 93 eyes were treated and the rest (869 eyes, 90.4%) were controlled without treatment and with regular follow-ups. Gestational age at birth, birth weight, duration of oxygen treatment, age of disease diagnosis, history of blood transfusion and history of respiratory distress were significantly different in patient with and without treatment (p<0.001) (Table 1).

Out of 93 treated eyes, 28 eyes were treated with laser and 23 eyes were treated with intravitreal anti-VEGF injection and 42 eyes were treated with both. Out of the eyes that were treated, 5 eyes had an unfavorable outcome of the treatment (2 eyes had lens opacity and 3 eyes had retinal detachment). Therefore, the rate of unfavorable outcomes in patients who were treated was estimated at 5.37%.

The independent t-test showed that there is a significant difference in the mean birth weight in the two groups of unfavorable outcomes and favorable outcomes of treatment (p=0.035). Other investigated variables were not significantly different in two groups (Table 2).

The logistic regression analysis for all eyes with retinopathy of prematurity showed that gestational age and birth weight have a significant relationship with the unfavorable outcomes of treatment (p=0.034); lower gestational age and lower birth weight have the higher the probability of an unfavorable outcome (gestational age: Odd ratio= 0.77, 95% confidence interval: 0.61-0.98 and birth weight: Odd ratio= 0.99, 95% confidence interval: 0.99-1.00).

Table 1. Comparison of the investigated parameters in premature infants in two groups without needing treatment and treated group

Parameters	Without needing treatment group Mean±SD or Number(%)	Treated group Mean±SD or Number(%)	p-value
Gestational age (weeks)	32.65±2.28	30.02±2.37	<0.001
Birth weight (grams)	1796.61±468.97	1349.60±388.54	<0.001
Duration of oxygenation use (days)	2.35±3.02	5.43±7.39	<0.001
Duration of mechanical ventilation (days)	1.97±0.4	1.90±0.93	0.194
Age at diagnosis (weeks)	37.61±3.81	35.95±2.32	<0.001
History of radiation therapy			
Yes	681(78.5)	74(79.6)	0.804
No	187(21.5)	19(20.4)	
History of respiratory distress			
Yes	589(67.9)	92(98.9)	<0.001
No	279(32.1)	1(1.1)	
History of sepsis			
Yes	46(5.3)	5(5.4)	0.975
No	822(94.7)	88(94.6)	
History of blood transfusion			
Yes	108(12.4)	38(40.9)	<0.001
No	760(87.6)	55(59.1)	

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Table 3 shows the percentage of eyes with retinopathy of prematurity in different stages and zone of involvement in two groups with favorable outcome and unfavorable outcome. The logistic regression analysis showed that the stage of the disease and the zone of involvement have a significant relationship with the unfavorable outcomes of the treatment (p=0.001); the more severe the stage of the disease and the more central area of involvement have the higher the probability of the occurrence of an unfavorable outcome (stage of the disease: Odd ratio= 8.68, 95% confidence interval: 3.44-12.89, zone of involvement: Odd ratio= 0.155, 95% confidence interval: 0.05-0.48).

Table 2. Comparison of the investigated parameters in two groups of favorable outcome and unfavorable outcome in treated retinopathy of prematurity

Groups / Parameters	Favorable outcome Mean±SD	Unfavorable outcome Mean±SD	p-value
Gestational age (weeks)	30.01±2.36	28.08±1.09	0.046
Birth weight (grams)	1350.70±396.37	1330.02±233.45	0.035
Duration of oxygenation use (days)	3.60±3.58	5.53±7.57	0.571
Duration of mechanical ventilation (days)	1.89±0.95	2.0±0.08	0.878
Age at diagnosis (weeks)	35.87±2.32	37.40±1.94	0.863

Table 3. The number of eyes in different stages and zone of involvement in two groups of favorable outcome and unfavorable outcome of treatment

Groups	Stage of the disease Number(%)					Zone of involvement Number(%)		
	1	2	3	4	5	1	2	3
Without needing treatment	760(78.8)	97(11.2)	4(0.5)	4(0.5)	0(0)	6(0.7)	40(4.7)	813(94.5)
Treated								
Favorable outcome	11(12.5)	42(47.7)	35(39.8)	0(0)	0(0)	14(15.9)	41(46.6)	33(37.5)
Unfavorable outcome	0(0)	1(20)	1(20)	2(40)	1(20)	2(40)	1(20)	2(40)

Discussion

The results of this study showed that 5.6% of infants with retinopathy of prematurity who needed treatment had unfavorable ocular structural outcomes such as lens opacity and retinal detachment. Adverse treatment outcomes are significantly related to gestational age, birth weight, stage and zone of retinal involvement.

In this study, out of 962 patients with retinopathy of prematurity, 869 patients recovered without the need for treatment, and the incidence of spontaneous recovery was 88.2%. According to the results of this study, gestational age, birth weight, duration of oxygen use, history of blood exchange, stage of the disease and zone of involvement are considered as risk factors in retinopathy of prematurity requiring treatment, and there was a significant difference in these factors between the group that recovered without treatment and the group that needed treatment. In line with the results of this study, in a study conducted on 93 infants with retinopathy of prematurity, it was shown that sepsis and blood transfusion play an important role in

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retinopathy of prematurity that requires treatment (6). Also, birth weight and gestational age in retinopathy of prematurity requiring treatment are known as independent risk factors (20).

In retinopathy of prematurity, the treatment options for severe cases of the disease are limited, but currently suitable treatments include laser photocoagulation and injection of Anti-VEGFs. In this study, 93 eyes were treated with laser or Anti-VEGF injection or both treatments. Out of all treated eyes, 5 eyes had an unfavorable structural outcome of the treatment in the form of 2 eyes with lens opacities and 3 eyes with retinal detachment. Therefore, the number of favorable outcomes in the patients who were treated was estimated at 63.94%. In a similar study conducted in Iran, they showed that among 326 eyes that were treated, the favorable outcome of the treatment was 94%, which is almost similar to the favorable outcome reported in the present study (24). Considering that both studies were conducted in Iran, a possible reason for the consistency between our results and this study could be the role of race on the therapeutic outcomes of retinopathy of prematurity. Previous studies showed that race can affect the therapeutic outcomes of retinopathy of prematurity (19-21). Another possible reason for the alignment of the results of these two studies could be the similarity in the study inclusion criteria. The inclusion criteria in this study, like the present study, were birth weight less than 2500 grams and gestational age less than 36 weeks (24).

Our results showed that lower gestational age, lower birth weight, higher stage of disease and central involvement zone have a significant relationship with unfavorable treatment outcomes. In a study conducted on patients with posterior retinopathy of prematurity with and without intravitreal hemorrhage, they reported a success rate of 91% in the group without hemorrhage and 12.5% in the group with hemorrhage and stated that although age and weight have a significant relationship with unfavorable outcomes of treatment, intravitreal hemorrhage should be considered as an important clinical sign in unfavorable prognosis (14). Although intravitreal hemorrhage was not investigated in the present study, our results also showed that lower birth weight and lower gestational age increase the probability of unfavorable treatment outcomes. In another study, the worse prognosis of photocoagulation laser treatment was shown in more central zone of the disease (involvement in zone 1) (25), which was consistent with our results. Since central involvement zone and the more severe stage of the disease indicate the greater severity of the disease, it seems reasonable that in higher severity, the unfavorable outcomes of the treatment are more than in mild stage of the disease, and the consistency of our results with the previous studies has confirmed this issue.

One of the limitations of this study is the small sample size in the group with unfavorable outcome, which requires more studies with larger sample size.

In general, the results of this study showed that most of the eyes with retinopathy of prematurity recover without the need for treatment, however, in the group that receives treatment, lower gestational age, lower birth weight, more severe stage of the disease, and a more central zone of involvement should be considered as risk factors of the unfavorable outcome of treatment.

Conflict of Interest: There is no conflict of interest.

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