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Refractive errors in premature infants with retinopathy of prematurity after anti-vascular endothelial growth factor (anti-VEGF) therapy

Refrakcione greške kod prevremeno rođene dece sa prematurnom retinopatijom nakon terapije antivaskularnim endotelnim faktorom rasta (anti-VEGF)

Milena S. Vujanović*, Gordana Lj. Stanković-Babić†, Ana Oros‡§, Gordana D. Zlatanović*†, Predrag Jovanović*†, Sonja P. Cekić*, Branislav Tomašević*, Jasmina M. Djordjević-Jocić*†

***Clinic for Eye Diseases, Clinical Center Niš, Niš, Serbia; †Faculty of Medicine, University of Niš, Niš, Serbia; ‡Clinic for Eye Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia; §Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia**

Abstract

Background/Aim. Retinopathy of prematurity (ROP) is a vasoproliferative retinopathy which affects the blood vessels of the retina during its development. The aim of this study was to evaluate the incidence and the degree of refractive errors in premature infants with severe ROP treated with anti-vascular endothelial growth factor (anti-VEGF) (bevacizumab). **Methods.** This prospective study included 21 patients (42 eyes) nine months old who received intravitreal injection of anti-VEGF therapy. The control group consisted of 45 patients (90 eyes) who were subjected to laser treatment. In cycloplegia each patient underwent retinoscopy, keratorefractometry, and A-scan ultrasonography. **Results.** Myopia was present in 47.62% of the eyes in the study group and in 33.33% of the eyes in the control group, but there were no statistically significant differences between these groups. Seven (16.67%) eyes in the study group and 17 (18.89%) eyes in the control group were discovered to have high myopia (SE–spherical equivalents < -3.0 D – dioptre). Clinically significant hypermetropia was higher in the study group (47.62%) than in the control group (34.44%), but with no statistically significant difference. In addition, high hypermetropia was significantly greater in the control group (15.56%) than in the study group (11.90%) ($p < 0.001$). Astigmatism was more common in the control group than in the study group (81.11% *vs* 71.43%, respectively), especially high astigmatism (56% *vs* 43%, respectively). Also the more common form of astigmatism was with the rule (WTR) both in the study and the control group (42.86% *vs* 55.56%, respectively). Anisometropia was significantly greater in the control group (24.44%) than in the study group (9.52%) ($p < 0.05$). The children from the study group had significantly greater lens thickness, and a shorter anterior chamber depth than children from the control group ($p < 0.01$). There was no significant difference in the axial length of the eye between the groups. **Conclusion.** At the 9-month follow-up myopia was present in the patients with severe ROP treated with anti-VEGF, but high myopia was present to a lesser degree than in the laser treated patients. This difference is possibly related to anterior segment development. Research into the longer-term refractive outcomes is necessary with observation of the biometric components, visual acuity, and the visual field in order to monitor the real effects of this therapy.

Key words:
retinopathy of prematurity; refraction, ocular; diagnostic techniques and procedures; myopia; astigmatism; vascular endothelial growth factors.

Apstrakt

Uvod/Cilj. Prematurna retinopatija (*retinopathy of prematurity*, ROP) je vazoproliferativna retinopatija koja deluje na krvne sudove retine tokom njenog razvoja. Cilj rada bio je proceniti učestalost i stepen refrakcionih anomalija kod prevremeno rođene dece sa teškom formom ROP, a koja su lečena anti-vaskularnim endotelnim faktorom rasta (anti-VEGF) (bevacizumab). **Metode.** Prospektivnom studijom obuhvaćeno je 21 dete (42 oka), starosti devet meseci, kod kojih je zbog teške forme ROP primenjena anti-VEGF terapija. Kontrolnu grupu činilo je 45 dece (90 očiju) kod kojih je primenjena laser fotokoagulacija. Kod svakog deteta nakon cikloplegije urađena je retinoskopija, keratorefraktometrija i A-scan ultrasonografija. **Rezultati.** Miopija je bila prisutna kod 47,62% očiju studijske grupe i kod 33,33% očiju kontrolne grupe, ali bez statistički značajne razlike između njih. Visoka miopija (stem ekvivalent – SE < -3.0 dioptrije – D) bila je zastupljena kod 16,67% očiju studijske grupe i kod 18,19% očiju kontrolne grupe. Klinički značajna hipermetropija bila je češća u studijskoj nego u kontrolnoj grupi (47,62% *vs* 34,44%). Visoka hipermetropija bila je mnogo zastupljenija u kontrolnoj grupi (15,56% *vs* 11,90%; $p < 0,001$). Astigmatizam, posebno visoki, bio je mnogo učestaliji u kontrolnoj grupi nego u studijskoj grupi. Najčešća forma astigmatizma u obe grupe bio je pravilan astigmatizam. Anisometropija bila je mnogo

Correspondence to: Milena S Vujanović, Clinic for Eye Diseases, Clinical Center Niš, 18 000 Niš, Serbia

češća u kontrolnoj grupi (24,44%) nego u studijskoj grupi (9.52%) ($p < 0.05$). U studijskoj grupi bila je značajno veća debljina sočiva i plića prednja očna komora nego u kontrolnoj grupi. U dužini oka nije bilo značajne razlike između očiju ispitivanih grupa. **Zaključak.** Kod bolesnika sa ROP, kod kojih je primenjena anti-VEGF terapija, kratkovidost je bila prisutna, ali visoka kratkovidost manje nego u grupi ispitanika lečenih laserom. Ova činjenica je verovatno u vezi sa razvojem prednjeg segmenta oka, te je za praćenje uticaja anti-VEGF terapije na razvoj refrakcionog statusa oka potreban duži vremenski period i veći broj ispitanika.

Ključne reči:
retinopatija kod prematurusa; oko, refrakcija; dijagnostičke tehnike i procedure; miopija; astigmatizam; faktori rasta endotela krvnih sudova.

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative retinopathy which affects the blood vessels of the retina during its development. The consequence of this process is a disturbance in the growth and development of the retina. The final result is blindness [1, 2]. ROP develops in two phases. In the first phase, hyperoxia leads to obliteration of immature retinal blood vessels. The consequence of the obliteration of the blood vessels is hypoxia and neovascularization growth in the second phase. This ischemia induces the vascular endothelial growth factor (VEGF) that stimulates the growth of new blood vessels leading to the destruction of the retinal architecture, vitreous body affecting and consequent blindness [3, 4].

The economic development of the country determines the possibility of ROP screening and treatment and consecutive ROP induced blindness. The incidence of blindness varies between 15% in developed countries, and 60% in middle-income countries [5, 6].

The destruction of the peripheral avascular retina by laser photocoagulation is still considered the gold standard of treatment [7, 8]. Different studies have found a high incidence of myopia in patients who have been subjected to laser treatment. Ablation of the peripheral avascular retina, caused by laser treatment, leads to inflammation and scar tissue formation with a higher reported incidence of refractive errors [9–13].

Over the last couple of years the use of intravitreal anti-VEGF therapy has become common in ROP treatment, and there have been positive results [14–17].

The aim of this study was to determine the incidence and degree of refractive errors in anti-VEGF treated premature infants with severe ROP.

Methods

This prospective study was performed over six months at the Ophthalmology Clinic in the Clinical Center, Niš, Serbia. It was approved by the institutional ethics committee and all the parents signed the agreement form for their children to participate in the study.

A total of 21 premature infants (42 eyes), nine months old, with severe ROP (ROP 3+) were included in the study group. They received a single intravitreal dose (0.625 mg) of bevacizumab in both eyes. The control group included 45 patients (90 eyes) with severe form of ROP (ROP 3+) treated by laser photocoagulation. The screening program was performed according to the guidelines published by the American Academy of Ophthalmology, American Academy of Pediatrics and American Association for Pediatric Ophthalmology and Strabismus [18]. The findings were classified according to the International Classification of ROP criteria (ICROP) [19]. The treatment was carried out according the recommendations of the Early Treatment for ROP study group (ET ROP) and Bavecizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) Cooperative Group [14, 20].

Refractive errors were diagnosed in cycloplegia induced by topical administration of one drop of Atropin solution 0.25% twice per day for three days. The refractive error was measured in the vertical and horizontal meridian in both eyes and was recorded to the nearest dioptre (D) using streak retinoscopy. Keratorefractometry was performed by an automated keratorefractometer. Ultrasound biometry and the estimated axial length (AL), anterior chamber depth (ACD) and lens thickness (LT) were measured. The results were recorded in the form of spherical equivalents (SE, spherical plus half of the cylinder power). Clinically significant myopia was defined as SE ≤ -1.0 D, and high myopia as less than -3.0 D (in the process of emmetropization et the age of 9 months only low myopic errors tend to show a hyperopic shift, but myopic as less than -3.0 D shows a tendency to further increase). Hyperopia was clinically significant when SE is greater than +3.0 D and high when greater than +4.0 D. Anisometropia was defined as significant when the difference between the eyes was 1 D (cyl) or more, and high if 2 D or more. Astigmatism was recorded as a negative cylinder, and defined as clinically significant (1 D cyl or more) and as high (2 D cyl or more). For analysis of the axis of astigmatism, three classes were recorded: with the rule (WTR 0°–15° and 165°–180°), against the rule (ATR 75°–105°), and oblique (O 16°–74° and 106°–164°).

Continuous variables were presented as mean values, standard deviations and medians, while categorical variables were presented as frequencies and percentages. The normality of distribution of continuous variables was assessed by the Shapiro-Wilk test. Differences in continuous variables between the two independent study groups were analyzed by Student's *t*-test for independent samples in case of normal distribution of variables, and Mann-Whitney test in case of deviation from the norm. We used Kruskal-Wallis test to determine the significance of the differences in the continuous variables between the groups with regard to their deviation from the norm. The differences in the frequencies of categorical variables between the groups were compared by means of χ^2-test, and if necessary we used Fisher's correction. The statistical significance was determined at the level of $p < 0.05$. Statistical analysis was performed using SPSS 15.0.

Results

Among the examined 66 prematurely born children with severe ROP (ROP 3+), 36 (55%) were male and 30 (45%) female. Their birth history, including their gestational age (GA) and birth weight (BW) by groups is shown in the Table 1.

The mean spherical equivalent in the study group of children treated with anti-VEGF was -0.50 D (range -8.13 to 3.5 D), and in the control group of children treated with laser photocoagulation it was -0.20 D (range -12.88 to 7.88 D). Myopia (SE ≤ -1.0 D) was observed in 20 (47.62%) eyes in the study group and in 30 (33.33%) eyes in the control group, but there were no statistically significant differences between these groups. Seven eyes (16.67%) in the study group and 17 (18.89%) eyes in the control group were discovered to have high myopia (SE < -3.0 D). The incidence of emmetropia (SE ≥-1.0 D but < +3.0 D) was lower in the study group [2 (4.76%)] than in the control group [28 (31.11%)] ($p < 0.001$). Clinically significant hyperopia (SE ≥ +3.0 D) was higher in the study group (20; 47.62%) than in the control group (31; 34.44%), although there was no statistically significant difference (Table 2). Also, high hyperopia (SE > +4.0 D) was significantly lower in the study group (11.90%) than in the control group (15.56%; $p < 0.001$).

The astigmatism incidence was lower in the children with severe ROP treated with anti-VEGF [30 (71.43%)] than in those treated with laser photocoagulation [73 (81.11%)]. The more common form of astigmatism was with-the-rule (WTR) astigmatism, with no statistical significant difference between the groups [18 eyes (42.86%) *vs* 50 eyes (55.56%)]. The incidence of oblique astigmatism was lower in the study group than in the control group [7 eyes (16.67%) *vs* 19 eyes (21.11%)]. Astigmatism against-the-rule (ATR) was most frequent in the patients treated with anti-VEGF therapy [5 eyes (11.90%)] (Table 3).

The median value of astigmatism in the study group was -0.50 ± 3.59 Dcyl and in the control group it was -0.27 ± 3.90 Dcyl. High astigmatism (≥ 2.0 Dcyl) was most common in the patients of the control group [41 eyes (56%)] (Table 4).

Anisometropia has significantly lower incidence in the study group 4 (9.52%) than in the control group 22 (24.44%) ($p < 0.05$) (Table 5).

Table 1

Demographic characteristics of the 66 study patients

Characteristics of patients	LFC treated sROP	Anti-VEGF treated sROP
Patients, n	45	21
male, n (%)	23 (51)	12 (57)
female, n (%)	22 (49)	9 (43)
GA (weeks), $\bar{x}$ ± SD	30 ± 4	29 ± 4
BW (g), $\bar{x}$ ± SD	1,200 ± 500	1,175 ± 425

LFC – laser photocoagulation; sROP – severe retinopathy of prematurity; GA – gestational age; BW – birth weight; VEGF – vascular endothelial growth factor.

Table 2

Refractive errors in the patients with sROP treated with anti-VEGF and laser

Refractive errors	LFC (n = 90)	antiVEGF (n = 42)
	n (%)	n (%)
Myopia	30 (33.33)	20 (47.62)
High myopia	17 (18.89)	7 (16.67)
Emmetropia	28 (31.11)*	2 (4.76)
Hyperopia	31 (34.44)	20 (47.62)
High hyperopia	14 (15.56)*	5 (11.90)

***$p < 0.001$.**

n – number of eyes; LFC – laser photocoagulation; VEGF – vascular endothelial growth factor; sROP – severe retinopathy of prematurity.

Table 3

Types of astigmatism according to axis

Astigmatism type	LFC (n = 90)	anti-VEGF (n = 42)
	n (%)	n (%)
Astigmatism presence	73 (81.11)	30 (71.43)
WTR	50 (55.56)	18 (42.86)
ATR	4 (4.44)	5 (11.90)
Oblique	19 (21.11)	7 (16.67)

n – number of eyes; WTR – with the rule; ATR – against the rule; LFC – laser photocoagulation; VEGF – vascular endothelial growth factor.

Table 4

Distribution of astigmatism

Astigmatism distribution	LFC (n = 90)	Anti-VEGF (n = 42)
	n (%)	n (%)
From 1 Dcyl to 2 Dcyl	32 (44)	17 (57)
≥ 2 Dcyl	41 (56)	13 (43)

n – number of eyes; LFC – laser photocoagulation; Dcyl – dioptre cylinder; VEGF – vascular endothelial growth factor.

Table 5

Distribution of anisometropia

Anisometropia distribution	LFC (n = 45)	Anti-VEGF (n = 21)
	n (%)	n (%)
Anisometropia, n (%)	22 (24.44)	4 (9.52)*
≥ 1 D to < 2 D	11 (12.22)	2 (4.76)
≥ 2 D	11 (12.22)	2 (4.76)

***p < 0.05.**
n – number of eyes; LFC – laser photocoagulation;
D – dioptre; VEGF – vascular endothelial growth factor.

The biometric characteristics of the eyes of premature infants with severe ROP, treated with laser photocoagulation or anti-VEGF therapy are given in Table 6. The children from the study group had significantly greater lens thickness, and shorter anterior chamber depth than those from the control group ($p < 0.01$). The values of the other biometric characteristics did not show statistically significant differences between the study and the control groups.

Table 6

Biometric characteristics of the study and control groups

Biometric characteristics	LFC (n = 90)	Anti-VEGF (n = 42)
	$\bar{x} \pm$ SD (median)	$\bar{x} \pm$ SD (median)
ACD (mm)	2.90 ± 0.40 (3.01)	2.81 ± 0.37 (2.89*)
LT (mm)	3.96 ± 0.32 (3.90)	4.34 ± 0.66 (4.09*)
AL (mm)	19.77 ± 1.47 (19.47)	19.93 ± 1.24 (19.72)
CR (mm)	7.68 ± 0.23 (7.65)	7.80 ± 0.37 (7.69)

***p < 0.01.**
n – number of eyes; ACD – anterior chamber depth; LT – lens thickness; AL – axial length; CR – corneal curvature; LFC – laser photocoagulation; VEGF – vascular endothelial growth factor.

Discussion

Our results are somehow different from the results of several previously published studies in which the prevalence of myopia is significantly lower in eyes treated with anti-VEGF therapy [16, 17, 21–24]. In the present study, the most frequent refractive error in both groups was myopia, although high myopia (SE< -3.0 D) was more common in the laser-treated group. Hypermetropia was more common in the anti-VEGF group, but high hypermetropia was more common in the laser treated group ($p < 0.001$). In the BEAT-ROP clinical trial a greater prevalence of myopia, especially very high myopia (≤ -8.0 D), was found in the eyes that received peripheral laser therapy than in eyes that received the intravitreal anti-VEGF therapy [22]. Harder at al. [17] reported that the refractive error was less myopic in the anti-VEGF group than in the laser treated group (17% *vs* 54%, respectively), especially for high myopia (9% *vs* 42%, respectively). Chen at al. [21] recorded a lower incidence of high myopia and more frequent emmetropia in the eyes of children treated with bevacizumab than those treated with laser therapy. Furthermore, Hwang at al. [23] found anti-VEGF treatment to be associated with less myopia than panretinal photocoagulation. Martínez-Castellanos et al. [24] are also of the opinion that anti-angiogenic therapy is associated with lower myopia. The possible reasons for the somewhat different results in our study can be found primarily in the stricter border for high myopia (SE< -3.0 D) than that used by other authors (SE < -5.0 D or SE < -8.0 D), in addition to which our patients were younger, aged nine months. We used atropine solution 0.25% for cycloplegia, but in other studies, cyclopentolate solution 1% was used, or a combination with tropicamide solution 0.5%. We chose this range for high myopia because the age of our subjects was lower, they were 9 months of age opposed to other studies in which the age of subjects ranges from 2 to 2 and a half years. It is well-known that the refractive error abnormalities of ROP patients have been found to be present early in infancy and persist into adulthood [25]. Wang et al. [26] showed that the rapid progression of myopia in eyes with severe ROP has a critical period of 1.3 years and that the later progression of myopia slower. Myopia present in a 9-month-old child with the history of severe ROP is associated with long-term myopia and carries a high risk of developing into high myopia. The true nature of myopia in preterm infants, as well as its progression, is not well-understood. It is believed that it results from the influence of three etiological factors: prematurity, severity of ROP, and changes due to the different therapies applied [22]. In normal development, most eye growth takes place in the first year of life: the refractive state changes as the axial length increases and the cornea and lens flatten. However, prematurity may affect the emmetropization process of ocular development in the postnatal stage, the so-called myopia of prematurity (MOP) [22, 25]. This myopia is nonaxial, consisting of the steeper cornea, shallower anterior chamber and increased lenticular thickness. This suggests that severe ROP and/or its treatment may result in arrested development of the anterior segment. During the rapid eye growth at an early age, all these abnormal biometric parameters may come together and result in the significant progression of myopia in eyes with severe ROP [5, 25, 27]. In the present study we found significantly greater lens thickness and shorter anterior chamber depth, especially

in the group treated with anti-VEGF ($p < 0.01$), but there were no statistically significant differences in axial length and corneal curvature. Our results are similar to the results of other authors regarding the biometric characteristics of eyes with severe ROP [5, 27, 28].

One possible explanation for the progression of myopia in a severe form of ROP treated with laser is the growth signals hypothesis. It has been shown that the peripheral retina in the eyes of very preterm infants will vascularize or differentiate only to the location of the anterior termination of the endothelial cell precursors at birth. Thus, the retinal vessels may never reach the *ora serrata*. Because of this, the arrested maturation of the photoreceptors decreases the levels of the local growth factors required for signaling the pathways involved in anterior segment development. Intravitreal anti-VEGF therapy allows continued development of the retinal vessels beyond the neurovascular ridges, which is minimal or absent following laser treatment. It is possible that this development could allow continued expression of the local growth factor and the signaling pathways necessary for a more normal anterior segment with minimal myopia [5, 14, 22].

In the present study, we found that the prevalence of astigmatism was greater in the laser treated group, especially high astigmatism. Also in both groups, the most common type of astigmatism was with-the-rule (WTR). These results agree with the results of other authors [29–31]. Astigmatism has been known to be associated with ROP, but the exact mechanism of this astigmatism in prematurity and ROP is not completely understood. Corneal curvature (CR) is one of the determinant factors in refractive error. It is usually steep in newborn infants and even steeper in premature infants [31]. In our study we noted that the cornea was steeper in the laser-treated group than in the anti-VEGF group, but not statistically significant. Most of the eyes in our and other studies showed WTR astigmatism, which can usually be explained by the larger number of laser spots in the temporal part of the retina in the laser treated eyes, and which can lead to changes in the corneal curvature in the horizontal axis [28-31]. However, there is still no good explanation for frequent WTR astigmatism in eyes treated with anti-VEGF therapy.

Our results, in accordance with the results of the other authors, show that anisometropia is significantly greater in the laser treated group (12.22%), especially for high anisometropia. This can be explained by an imbalance in the severity of the disease between the eyes and/or that laser treatment may not be done in both eyes identically.

This is supported by the finding of Geloneck at al. [22] that myopia increases by -0.14 D for every 100 laser spots.

The limitations of this study are the small number of patients and its short duration.

Conclusion

Our study confirms that severe ROP treated by anti-VEGF therapy causes less incidence of high myopia (SE < -3.0 D), less value of astigmatism and anisometropia, which means the less possibility of amblyopia and strabismus incidence.

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