

Does Intravitreal Bevacizumab Injection for Retinopathy of Prematurity Treatment Arrest Anterior Segment Development?

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Abstract

Purpose: To determine intravitreal bevacizumab (IVB) effect on ocular development by comparing refractive and biometric outcomes of intravitreal bevacizumab (IVB) and laser photocoagulation for treatment of retinopathy of prematurity (ROP).

Methods: A prospective nonrandomized interventional comparative study was conducted in a referral hospital for ROP management. All patients who received either single IVB or diode laser photocoagulation were enrolled. Cycloplegic refraction and biometry was performed before treatment and at the corrected age of 9 months.

Results: The IVB group included 17 patients (28 eyes; gestational age (GA): 28.54 ± 2.2 weeks) and the laser group included 17 patients (34 eyes; GA: 28.53 ± 1.6 w). GA, BW and corrected age at the end of follow-up was statistically similar between the two groups. Eyes in IVB group had significantly longer axial lengths and thinner lenses at final visit ($p=.037$ and $p=.002$).

Conclusions: Following IVB treatment of ROP, eye development in general and crystalline lens in particular are less affected compared to laser treatment. This supports the idea that anterior segment arrest which was first described for laser therapy of ROP occurs minimally with IVB if at all.

Keywords: Retinopathy of Prematurity; Intravitreal Bevacizumab; Diode Laser photocoagulation; Refraction; Biometry

Abbreviations: IVB: Intravitreal Bevacizumab; ROP: Retinopathy of Prematurity; GA: Gestational Age; ETROP: Early Treatment of ROP study; VEGF: Vascular Endothelial Growth Factor; AL= Axial Length; ACD= Anterior Chamber Depth; LT= Lens Thickness; V= Vitreous Cavity

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disease of preterm neonates which may result in severe complications if left untreated in high risk patients. In 2001 Early Treatment of ROP study (ETROP) showed significant benefit of laser photocoagulation in eyes with type 1 prethreshold ROP [1]. Since then, laser photocoagulation of the avascular retina using either transpupillary or transscleral approach is the standard of care for type 1 ROP [2-6]. In recent years, the use of anti-vascular endothelial growth factor (VEGF) agents mainly bevacizumab, has been increasingly popularized for the treatment of various ocular neovascular diseases including ROP [7-11]. Promising results have been reported for IVB injection in ROP especially in patients with severe or aggressive posterior ROP [12].

Previous studies have shown that ROP patients show significant myopia (55.2 to 80.04% in age group under 3 years old) after laser photocoagulation [13-15]. It is well established that myopia associated with prematurity and conventionally treated (cryo- or laser therapy) ROP is not fully explainable by axial length changes. In fact, it may be a result of a disruption of emmetropization called anterior segment arrest consisting of corneal steepening, anterior chamber depth reduction, and lens thickening [16-19]. Recently, a few studies have reported less myopia after intravitreal bevacizumab (IVB) injection in ROP patients in comparison to laser photocoagulation or combination treatments [20-25]. Gelonek et al. [25] speculated that IVB minimally disrupts anterior segment development, hence less myopia. However biometric effects of anti-VEGF agents on ocular growth have not been fully evaluated in a pre- and post-treatment model. Current study was conducted to compare the refractive

errors and biometric indices before and after single IVB injection and conventional laser therapy for ROP.

Methods

In this prospective comparative study, from March to September 2013, all premature infants who were scheduled to undergo either diode laser photocoagulation or IVB injection for the treatment of type 1 ROP in Rassoul Akram Hospital, Iran, Tehran were eligible for this study. Informed consent was obtained from the parents of all infants enrolled in the study, fully describing the treatment modalities and ultrasonography technique. Iran University Eye Research Center Ethics Committee approved the study. Screening and management of all patients were performed by retinal specialists (MMP and AS) in accordance to the guidelines of the American Association for Pediatric Ophthalmology and Strabismus [26] and the revised guidelines of the International Committee for the Classification of Retinopathy of Prematurity [27]. For prethreshold disease in zone I or posterior zone II, an intravitreal injection of 0.625 mg bevacizumab (Avastin; Genentech Inc, San Francisco, California, USA) was performed [10]. Infants with prethreshold disease in anterior zone II, received transscleral diode laser photocoagulation of avascular retina [28]. Patients who did not respond to primary monotherapy and needed further intervention were excluded. Also, eyes with media opacity including cataract, corneal opacity and vitreous hemorrhage, and those with other ocular diseases including glaucoma, and congenital vitreoretinal diseases were excluded.

Refractive errors and biometry indices were obtained under cycloplegic condition approximately 30 minutes after instillation of topical Tropicamide (Mydrax; Sina Darou, Tehran, Iran), 3 times with an interval of 5 minutes. Measurements were performed immediately before treatment, and at the age of 9 month.

Handheld retinoscopy was performed by two of the three expert examiners (RA, JK and MSS), masked to the planned treatment. If their results disagreed by more than 0.5 Diopters (D), refractions were repeated and the discrepancy was resolved. Spherical equivalent (SE) ≤ -0.5 and ≤ -5.00 D was considered as myopia and high myopia, respectively [29, 30].

Biometry was performed in supine position with the lid speculum in situ via A-scan contact mode ultrasonography (OcuScanRxP; Alcon Lab, Dallas, TX, USA). Measured indices included axial length (AL), anterior chamber depth (ACD), lens thickness (LT), and vitreous cavity length (V). All scans were performed by a single investigator (JK). After instillation of topical Tetracaine 0.5% (Anestocaine; Sina Darou, Tehran, Iran), 10 subsequent scans were recorded in Auto-save mode. Scans were repeated until standard deviation of less than 0.1 was achieved. Care was taken to apply minimum pressure on the cornea during ultrasonography.

Data analysis was done using SPSS software (version 16, SPSS, Inc., Chicago, IL, USA). T tests (paired t test when applicable) and Chi square test were used for analysis of continuous and categorical variables, respectively. P values less than 0.05 were considered statistically significant.

Results

A total of 34 neonates including 17 patients (28 eyes) in the IVB group and 17 patients (34 eyes) in the laser groups were studied. Table 1 shows demographics of the patients. Birth age, birth weight, follow up duration and corrected age at the end of follow-up were similar between the two groups; however, patients in IVB group received therapy significantly earlier ($p < 0.001$). All patients in the study responded to treatment in terms of resolution of ROP, no recurrence of ROP and no detachment/hemorrhage after treatment.

Table 1: Characteristic of study participant.

Characteristic	IVB group	Laser therapy group	P value
Patients, n	17	17	
eyes, n	28	34	
Sex			0.82†
Female n (%)	14 (50)	18 (52.9)	
Male n (%)	14 (50)	16 (47.1)	
Gestational age (weeks)	28.54±2.2	28.53 ± 1.6	0.99‡
Birth weight (gr)	1222±366	1142±387	0.41‡
Postmenstrual Age at first measurement (weeks)	35.7±2.1	39.14± 2.9	0.000‡
Postmenstrual Age at last measurement (weeks)	67.64±8.8	67.28±5.4	0.85‡

Categorical data are presented as n (%)

Continuous data are presented as mean ± standard deviation.

P < 0.05 (significant differences between the two groups)

† Chi square test

‡ T test

Results of refractive error measurements are summarized in Table 2. At baseline examination, a marginally significant difference was found in the mean SE between the 2 groups (-3.37 ± 4.68 Diopters [D] in the IVB group and -1.5± 3.97 D in the laser group, p: 0.08) and prevalence of myopia was significantly higher in IVB group (71.04% vs. 35.55%; P= 0.004). At final exam, refractive error in the IVB group and laser therapy group was -1.02 ± 2.96 D vs. -0.12 ± 2.28 D (P = 0.18) and the rate of myopia in IVB group decreased to 50%, while no significant change was observed in the laser group (38.24%, P=0.36). Finally the absolute

change in SE was not significantly different between the 2 groups (P=0.3).

Table 3 shows the biometric measurements. At baseline, no significant difference was found between the two groups in any of the biometric measurements. At final exam, eyes in the IVB group had significantly higher AL and V measurements and shallower ACD and shorter LT measurements compared to the laser group (p=.037, p=.017, p=.002 and p=.002). The biometric changes after treatment were significantly different between the two groups in AL, LT and V measurements (P=0.002, P=0.007 and P<0.000).

Table 2: Refractive error measurements before treatment and at age of 9 month.

	IVB group	Laser therapy group	P value
refraction at first measurement (Diopters)			
sphere	-2.87±4.45	-1.13±3.78	0.10†
cylinder	-1.00±0.47	-0.75±0.57	0.03†
spherical equivalent	-3.37±4.68	-1.5±3.97	0.08†
refraction at final measurement (Diopters)			
sphere	-0.34±2.92	0.63±2.44	0.18†
cylinder	-1.37±1.09	-1.51±0.90	0.58†
spherical equivalent	-1.02±2.96	-0.12±2.28	0.18†
SE change	+2.34±4.47	+1.36±4.12	0.37†
Myopia* at first measurement (%)	71.04	35.55	0.004‡
Myopia* at final measurement (%)	50	38.24	0.36‡
High myopia* at first measurement (%)	32.14	17.65	0.19‡
High myopia* at final measurement (%)	7.14	5.88	0.84‡

Categorical data are presented as n (%)

Continuous data are presented as mean ± standard deviation.

P < 0.05 (significant differences between the two groups)

†T test

‡ Chi square test

* Spherical equivalent (SE) ≤ - 0.5 and ≤ - 5.00 D was defined as myopia and high myopia, respectively.

Table 3: Biometric measurements before treatment and at the age of 9 month.

	IVB group	Laser group	P value
first measurement (mm)			
AL	16.76±0.47	17.02±0.69	0.06†
ACD	2.48±0.38	2.52±0.38	0.68†
LT	3.96±0.21	3.99±0.19	0.58†
V	10.24±0.56	10.48±0.66	0.11†
final measurement (mm)			
AL	20.07±1.16	19.46±1.02	0.037†
ACD	2.95±0.45	3.21±0.36	0.017†
LT	3.78±0.26	3.99±0.21	0.002†
V	13.30±1.44	12.2±0.96	0.002†
changes in biometric indices (mm)			
AL	3.29±0.97	2.35±1.15	0.002†
ACD	0.43±0.69	0.64±0.45	0.19†
LT	-0.22±0.33	-0.007±0.23	0.007†
V	3.04±1.37	1.67±0.88	<0.000†

Categorical data are presented as n (%)

Continuous data are presented as mean ± standard deviation.

AL= Axial Length; ACD= Anterior Chamber Depth; LT= Lens Thickness; V= Vitreous Cavity

†T test

In bivariate correlation analysis, SE change in the laser group correlated significantly to axial and vitreous cavity length changes (p=0.005 and p=0.006). No significant correlation between SE and biometric changes were found in IVB group.

In multivariate analysis, no significant association was found between SE changes and the treatment modality (p=0.46), AL changes (p=0.56), ACD changes (p=0.49), LT changes (p=0.08), V

changes (p=0.49), GA (p=0.56) and BW (p=0.74).

Discussion

Although there are few reports of more hyperopic changes following laser treatment of ROP [31] most recent studies comparing IVB and laser monotherapy or combination therapies show a myopic preponderance in laser therapy (Table 4).

Table 4: Studies evaluating Refractive and biometry outcome of IVB.

Study	year	Design	Therapy	Patients (eyes)	Age (Month)	GA (Week)	BW (Gram)	Ref (Diopter)	Biometry
Axer-Siegel et al. [37]	2011	Retro	IVB IVB+Laser	10 8	24	24 to 27	660	+ 0.5 -7.25	N/A
Harder et al. [20]	2012	Pro	IVB OD OS	6 (12)	10.5±12.7	24.8 ±1.2	627 ±116	-0.27±4.09 1.54 ±2.19	N/A
		Retro	Laser OD OS	10 (20)	11.5±1.0	25.1±1.9	732±226	-6.25±5.31 -4.20±5.92	
Harder et al. [22]	2013	Retro	IVB Laser	12 (23)	11.4 ± 2.3	25.2 ± 1.6	622 ±153 717± 197	-1.04 ± 4.24 -4.41± 5.50	N/A
Martinez-Castellanos et al. [23]	2013	Pro	IVB	13	12 36	28.66	1061	-1.09 -1.25	AL: 22.38 ACD: 2.86 LT: 3.91
Chen et al. [24]	2014	Retro	IVB IVB +Laser	40 17	24	26.6 ± 1.7 24.7± 2.2	879± 212 732± 127	- 0.98 ± 4.05 - 2.40 ± 3.13	AL: 21.30±0.78 AL: 21.44±1.44
Geloneck et al. [25]	2014	Pro	Zone I IVB	52	30	N/A	N/A	-1.51 ± 3.42	N/A
			Laser	35				-8.44 ± 7.57	
			Zone II posterior IVB	58				-0.58 ± 2.53	
			Laser	66				-5.83 ± 5.87	

Continuous data are presented as mean ± standard deviation.

AL= Axial Length; ACD= Anterior Chamber Depth; LT= Lens Thickness; N/A=Not Available; OD= Right Eye; OS= Left Eye; Pro=Prospective; Ref=Refractive Outcome; Retro=Retrospective; Thx= Therapy; V= Vitreous Cavity

Whether the observed myopic shift is attributable to the allocated treatment or the severity of the disease has been a matter of controversy, however, the follow up of the BEAT- ROP clinical trial [10,25] the only large randomized prospective study in the field, demonstrated that the higher degree and frequency of myopia in laser treated eyes (compared to the eyes who received IVB) did occur in spite of no significant difference in myopia severity.

In a process called emmetropization a relatively wide distribution of refractive error in full term newborns, gets narrower toward hyperopia in the first few years of life [30,32]. In this process, vitreous cavity length elongation is balanced by reduction of corneal curvature (from 51 to 44 D), crystalline lens power (by getting thinner) [33]. Myopia associated with prematurity and conventionally (cryo- or laser therapy) treated

ROP is not fully explained by axial length, but it is a result of an emmetropization disruption called anterior segment arrest consisting of corneal steepening, anterior chamber depth reduction, and lens thickening [16-19]. Although Geloneck et al. [25] speculated that IVB minimally disrupts anterior segment development; effect of anti-VEGF agents on ocular growth is not fully evaluated.

In the present study despite the initially higher prevalence of myopia among IVB group (71%) in comparison to laser therapy group (35.55%) before treatment, the frequency decreased to 50% at the age of 9 month in IVB group while no significant change was observed in laser therapy group (38.2%). On the other side, biometry results demonstrated that although the eyes in IVB group were initially marginally smaller than those in the laser group, they finally had significantly larger size. At

a concordant trend lens thickness in IVB group significantly decreased leading to less frequency of myopia in this group. Such a significant reduction in lens thickness was not observed in the laser group. These observations support the idea that the crystalline lens development (the expected lens thinning) continues following IVB treatment of ROP while it is arrested by laser therapy. This is in consistence with a previous study which suggests that high myopia associated with ROP is primarily a reflection of inappropriately higher lens thickness and power [34]. To the best of our knowledge, it is for the first time that a study reports the refractive and biometric indices of eyes before and after undergoing treatment for ROP.

It has been proposed that anterior segment growth may be slowed by decreased levels of local growth factors as a result of delayed migration of vessels to oraserrata (in premature neonates) alongside photoreceptors maturation arrest [35,36]. It is also known that laser therapy stops retinal vessel development, while vessels continue to develop beyond neovascular ridges upto the oraserrata after IVB injection [10]. This may partly explain the pathophysiology of the so-called anterior segment arrest following the laser therapy; however, further experimental investigation is needed.

The present study has several limitations. Although randomization would avoid analytical concerns inherent to the non-randomized design, investigators believed it would be unethical to randomize ROP patients, regardless of their stage of the disease, to the two treatment group. In the current ROP protocol applied in this reference hospital, ROPs in zone I and posterior zone II are treated with IVB and ROPs in anterior zone II are offered the laser treatment. Additionally enrolled infants in the present study have notably higher birth weight and gestational age compared to some studies which may also contribute to the smaller degree of myopia observed in the pretreatment examination in this study compared to other reports. Finally for the investigators a relatively short follow-up was considered an acceptable trade-off for the prospective design.

Despite these limitations, current study is the first to report pre- and post-treatment biometric and refractive indices of eyes treated for ROP and its results further support the theory that IVB does not halt anterior segment development in ROP patients as laser therapy does.

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