Original Article

Efficacy of Intravitreal Bevacizumab for the Treatment of Zone I Type 1 Retinopathy of Prematurity

Reza Karkhaneh[1,2], MD; Hamidreza Torabi[1,3], MD; Alireza Khodabande[1,2], MD
Ramak Roohipoor[1,2], MD; Mohammad Riazi-Esfahani[1,2], MD

[1]Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Ophthalmology, Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Ophthalmology, Baqiyatallah University of Medical Sciences, Tehran, Iran

Abstract

Purpose: To describe the efficacy of intravitreal bevacizumab for the treatment of type 1 retinopathy of prematurity (ROP) in zone I.

Methods: Preterm infants with type 1 ROP in zone I (zone I ROP, any stage with plus disease or zone I ROP, stage 3 without plus disease) were enrolled in this prospective study. Intravitreal bevacizumab (0.625 mg/0.025 ml) was injected under topical anesthesia. Patients were followed weekly for 4 weeks and then biweekly till 90 weeks gestational age.

Results: Seventy eyes of 35 patients with type 1 ROP in zone I were enrolled. At a gestational age of 90 weeks, ROP regressed with complete or near-complete peripheral retinal vascularization, in 82.9% of eyes after a single injection and in 92.9% of eyes after up to two injections. In five eyes (7.1%), ROP progressed to stage 4B or 5, so surgical management was required. There were no major complications such as endophthalmitis, cataract, or vitreous hemorrhage after injection.

Conclusion: Intravitreal bevacizumab injection is an effective method for the management of patients with Zone I ROP requiring treatment; however, some cases may progress to more advanced stages and require surgical management. Close monitoring for recurrence or progression is necessary. Eyes with persistent zone I ROP may progress to advanced stages when treated with intravitreal bevacizumab injection and re-treatment may be needed.

Keywords: Retinopathy of Prematurity; Zone I; Intravitreal Bevacizumab, Anti-vascular Endothelial Growth Factor; Treatment

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INTRODUCTION

Retinopathy of prematurity (ROP) remains one of the leading causes of visual impairment in extremely premature infants.[1,2] Because of improvement in the survival rate of premature patients, the incidence of ROP has increased.[3]

Correspondence to:
Hamidreza Torabi, MD. Department of Ophthalmology, Baqiyatallah University of Medical Sciences, Mollasadra St., Vanak Square, Tehran 14376, Iran.
E-mail: Dr_hamidrezatorabi@yahoo.com

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In severe cases of ROP, peripheral retinal neovascularization develops and may lead to retinal traction, retinal detachment and hemorrhage.[1] In the 1980s, cryotherapy was suggested for the treatment of ROP, but nowadays peripheral laser photocoagulation is preferred.[3] Laser photocoagulation is a destructive method that leads to visual field constriction in zone I ROP.[1]

Retinal neovascularization is driven mainly by vascular endothelial growth factor (VEGF), so intravitreal anti-VEGF therapy may be effective in the treatment of ROP [4]. Bevacizumab (Avastin; Genentech Inc, South San Francisco, California, USA) is a recombinant humanized monoclonal antibody that is directed against all isoforms of VEGF [5]. Bevacizumab is effective in the treatment of many retinopathies that are associated with VEGF upregulation such as neovascular age-related macular degeneration,[5-7] proliferative diabetic retinopathy,[8,9] neovascular glaucoma,[10,11] and retinal vascular occlusion.[12,13] The Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) study showed that intravitreal bevacizumab (IVB) is more effective than laser photocoagulation in patients with Zone I retinopathy of prematurity.[14]

However, there have been few studies assessing anatomical and functional outcomes following IVB treatment for Zone I ROP.

The current study aims to determine the efficacy of IVB in the treatment of Zone I ROP.

METHODS

This study was a prospective interventional case series performed in the ROP Clinic of Farabi Eye Hospital (a tertiary referral hospital in Tehran, Iran). Preterm infants with a birth weight of 2000 g or less and a gestational age of 34 weeks or less were examined, beginning at a chronologic age of 4 weeks or postmenstrual age of 31 weeks, whichever was later. Preterm infants with type 1 zone I ROP (any stage with plus disease or with zone I ROP, stage 3 without plus disease) were enrolled. Infants with congenital cataract, congenital glaucoma, history of any other ocular diseases, or history of previous treatment for ROP, were excluded from the study.

The benefits and side effects of treatment were explained to the parents and informed consent was obtained from them. The ethics committee of Eye Research Center, Farabi Eye Hospital, approved this study.

IVB (0.625 mg in 0.025 ml of solution) injection was performed in the operating room under topical anesthesia. In cases that needed bilateral injection in the same session, each eye was injected using a separate vial of bevacizumab. All infants received sulfacetamide 10% eye drop every 6 hours for 3 days after the injection.

Patients were examined one day after injection. Follow-up visits were scheduled weekly for 4 weeks, and then biweekly until postmenstrual age of 90 weeks.

The primary outcome was the rate of ROP regression after IVB injection. Regression of ROP was defined as improvement in plus disease and neovascularization.

Examinations at all follow-up visits were performed by three retina specialists with experience in the field of ROP (KR, RR, and RM). Retreatment was performed if at least two examiners recommended it on the basis of the following criteria: neovascularization or plus disease existing after 4 weeks or new extraretinal fibrovascular proliferation.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp, Armonk, NY, USA).

RESULTS

Seventy eyes of 35 patients with Zone I ROP were enrolled into this study. All patients were followed- up at least until 90 weeks postmenstrual age (PMA). No death or loss to follow-up occurred during the course of the study.

The mean gestational age and birth weight were 27.6 ± 1.8 weeks and 1089.1 ± 307.2 g respectively. Plus disease was present in all eyes. Stage 2 disease was noted in two of 70 eyes (2.9%) and 68 eyes (97.1%) had stage 3 ROP.

The mean PMA at initial injection was 35.6 ± 2.7 weeks. At 90 weeks PMA, complete regression of ROP was observed in 58 eyes (82.9%) after a single IVB injection.

In 12 eyes (17.1%) reinjection was required because of persistent or recurrent neovascularization at a mean of 6.2 ± 1.24 weeks after the first treatment. ROP regressed after reinjection in seven eyes. Thus, ROP regressed completely in 92.9% of eyes with zone I ROP after a single or two IVB injections.

In spite of reinjection, the disease progressed to advanced stages requiring surgery in five eyes at a mean of 51.7 ± 4.31 weeks PMA. The surgical procedures were pars plana vitrectomy in four eyes and scleral buckling in one eye.

Retina was attached at 90 weeks PMA in all cases. At this age, complete peripheral retinal vascularization was observed in 41 eyes out of the 65 eyes with ROP regression (63.1%). Twenty-four eyes (36.9%) still had an avascular area in the retinal periphery, without any signs of disease activity.

Subconjunctival hemorrhage occurred in a few cases after injection, but no major complications such as endophthalmitis, cataract, or vitreous hemorrhage were reported.

DISCUSSION

This study showed that treatment with intravitreal bevacizumab is effective for regression of ROP in eyes

with type 1 ROP in zone I. Of the eyes with zone I ROP, 82.9% regressed after a single IVB injection, and 12 eyes (17.1%) needed reinjection. Overall, 92.9% of eyes had favorable structural outcomes after one or two injections of IVB. Five eyes (7.1%) progressed to retinal detachment and required surgical management.

The intravitreal concentration of VEGF is highly elevated in advanced ROP and this factor have a major role in the development of retinal neovascularization in ROP eyes.[13,15] Therefore, decreasing the intravitreal VEGF level may be a good therapeutic option for the treatment of ROP.[1] Bevacizumab is a monoclonal antibody that binds VEGF and blocks it and is increasingly used in the treatment of ROP worldwide.

In the present study, we used 0.625 mg bevacizumab, the same dose used in the BEAT-ROP study, which is half the adult dose.[14]

In the BEAT-ROP study, Mintz-Hittner and his associates showed that IVB injection provided a significant benefit in the treatment of eyes with zone I ROP.[14] In the BEAT-ROP study, late recurrent disease was observed in two of 62 eyes with zone I disease.[14]

Previous studies have reported that anatomical outcomes of zone I ROP are poor. O'Keefe et al reported that 17 of 24 eyes (70.8%) with zone I ROP that were treated with laser photocoagulation developed retinal detachment.[16] Kychenthal et al reported that 17 of 48 eyes (35.4%) with anterior zone I ROP and all nine eyes (100%) with posterior zone I ROP that were treated only with laser photocoagulation progressed to retinal detachment.[17] It seems that IVB injection can improve the prognosis of eyes with zone I ROP. Progression to stage 4 or 5 was seen in 7.1% of eyes in our study. Mintz-Hittner et al showed that a single injection of bevacizumab prevented progression to retinal detachment in all 22 eyes with zone I or posterior zone II ROP that were treated with IVB injection, without the need for laser ablation.[18]

Wu et al treated 17 eyes with Zone I ROP with IVB injection; none of the eyes progressed to stage 4 or 5 ROP after treatment.[1]

In a retrospective study, Gunay M et al compared the 2-year outcomes following IVB (48 eyes) and laser photocoagulation (30 eyes) for the treatment of aggressive posterior ROP.[19] They reported that three eyes in the IVB group and two in the laser group required re-treatment. Retinal examinations at an adjusted age of two years revealed successful retinal vascularization in the bevacizumab group and stable retinal findings in the laser group. A higher rate of progression to retinal detachment in the current study may be due to different genetic factors resulting in different response rates. We included only patients with zone I ROP that had a high chance of progression to advanced stages of ROP and poor prognosis, this contradicts the inclusion criteria of many studies, which enrolled preterm infants with both zone I and zone II ROP.

Yoon JM and co-workers compared the efficacy of conventional laser photocoagulation, combined IVB injection and zone I sparing laser photocoagulation, and IVB with deferred laser treatment in the treatment of 101 eyes with type 1 retinopathy of prematurity in zone I.[20] They reported that IVB with concomitant or deferred laser therapy resulted in favorable anatomical outcomes without recurrence or the need for retreatment.

Yetik et al treated 238 eyes with pre-threshold, threshold, or aggressive posterior ROP with IVB injection.[21] They reported that regression of ROP was observed in 95.4% of eyes after the first injection. Reinjection was performed in 11 eyes (4.6%) and four eyes required a third injection. In their study, complete regression of ROP occurred in 95.4% of eyes after a single injection, in 98.2% of eyes after the second injection and in 100% of eyes after a third injection. Zone I disease accounted for 140/238 (58.8%) of cases, whereas zone II disease was present in 98 of 238 (41.2%) cases. We compared the efficacy of IVB to that of laser photocoagulation for the treatment of type 1 zone II ROP in another study.[22] Eighty six eyes with zone II ROP underwent intravitreal bevacizumab injection. Reinjection was performed in 10.5% of eyes because of persistent or recurrent disease and only one eye needed surgery for pre-retinal hemorrhage. In the present study, we repeated IVB injection for persistent disease but progression to advanced stages with retinal detachment happened in 7.1% of eyes. Therefore, re-treatment with IVB can be performed in cases with persistent or recurrent ROP; however, treatment failure is higher in eyes with zone I ROP compared to eyes with zone II ROP.

Laser photocoagulation alone or in combination with IVB injection can be used as a re-treatment procedure in persistent cases with zone I ROP, as in this study, 7.1% of eyes progressed to retinal detachment after re-treatment with IVB alone. On the other hand, previous studies showed that progression to retinal detachment occurred in more than 70% of eyes with zone I ROP treated only with conventional laser photocoagulation.[16,17] Therefore, re-treatment with laser photocoagulation alone may not be effective for prevention of the progression of zone I ROP. Further studies are required to establish the preferred method for retreatment in persistent or recurrent cases.

Laser photocoagulation is a destructive procedure that ablates the peripheral retina and can contribute to visual field constriction, especially in eyes with zone I ROP.[23-25] IVB injection is a simple procedure that takes less time, requires no special equipments, and can be performed without general anesthesia.

IVB blocks the VEGF that is already present in the vitreous cavity, but not the VEGF produced continuously by the avascular retina; besides, VEGF is not the only growth factor up-regulated in eyes with ROP, therefore, ROP may continue to progress after IVB injection.[26]

Close monitoring with fundus examination should be performed every one to two weeks until complete regression of ROP. Re-treatment, especially in zone I ROP, is necessary if persistent retinal neovascularization is observed.

There were no cases of cataract formation or postoperative endophthalmitis in our study. Wu et al reported cataract formation in 1% of cases after IVB injection and reported no cases of endophthalmitis.[1] In the study by Harder et al, no ocular side-effects were reported after IVB injection in 57 eyes with ROP.[27]

Sato and associates showed that in patients with ROP, serum concentration of bevacizumab increased and serum concentration of VEGF decreased after intravitreal injection of 0.5 or 1 mg of bevacizumab.[28] Therefore, blocking the systemic VEGF has the potential risk of systemic side effects. No systemic side effects were observed until 90 weeks of PMA in the current study, but studies with longer follow-ups are needed.

In conclusion, IVB injection is an effective method in the treatment of patients with zone I type 1 ROP; however, some cases may progress to advanced stages and require surgical management. Close monitoring and re-treatment in persistent cases until complete retinal vascularization is mandatory.

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Conflicts of Interest

There are no conflicts of interest.

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