Intravitreal Bevacizumab (Avastin) Added to Conventional Therapy for Threshold ROP

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Abstract

***Purpose*:** To study the effects of adding intravitreal bevacizumab (Avastin) to conventional LASER treatment on regression of retinal neovascularization in threshold ROP.

***Methods*:** Intravitreal injection of bevacizumab (1.25 mg) in one eye of each of three newborns with threshold ROP was performed in addition to laser treatment. The other eye of each patient was treated with laser alone. Changes in retinal neovascularization, its regression and unfavorable anatomical outcome were assessed on fundus photographs by Retcam and frequent funduscopy. ERG was performed four months after injection.

***Results*:** ROP regressed in both eyes at the same time. There were no differences in normal retinal vascularization. We had no adverse effects due to injection including cataract, endophthalmitis or vitreous hemorrhage. We didn't observe any differences in ERG between two eyes.

***Conclusion*:** Intravitreal injection of bevacizumab seems to have no adverse effect in newborns with threshold ROP. There were no differences in regression of neovascularization between two eyes. It is recommended to perform more studies in order to assess its effect.

***Keywords*:** retinopathy of prematurity, treatment, bevacizumab

Iranian Journal of Ophthalmology *2007;19(4):34-38*

Introduction

Retinopathy of prematurity (ROP) is still a major cause of blindness in children[1] despite current treatment of late-stage ROP.

Although laser photocoagulation or cryotherapy of the retina reduces the incidence of blindness by suppressing the neovascular phase of ROP, the visual outcome after treatment often is poor.[2]

ROP is a two-phase disease beginning with delayed retinal vascular growth after premature birth.[2] ROP was first described in the late 1940 and was associated with excessive oxygen use.[3]

Vascular endothelial growth factor (VEGF) is an important oxygen–regulated factor.

Blood vessel growth is dependent on both IGF-1 and VEGF.[4] The discovery of VEGF and ICG-1 and the important roles that theses factors play in the development of ROP is a step forward in our understanding of the pathogenesis of the disease.[4]

It seems that intervening medically in the disease process may prevent destructive neovascularization.

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Received: December 28, 2006
Accepted: April 26, 2007

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In this study we are going to study the effects of intravitreal bevacizomab (Avastin) in addition to conventional laser treatment on regression of retinal neovascularization in threshold ROP and assessment of its possible burden on normal development in neonates.

Methods

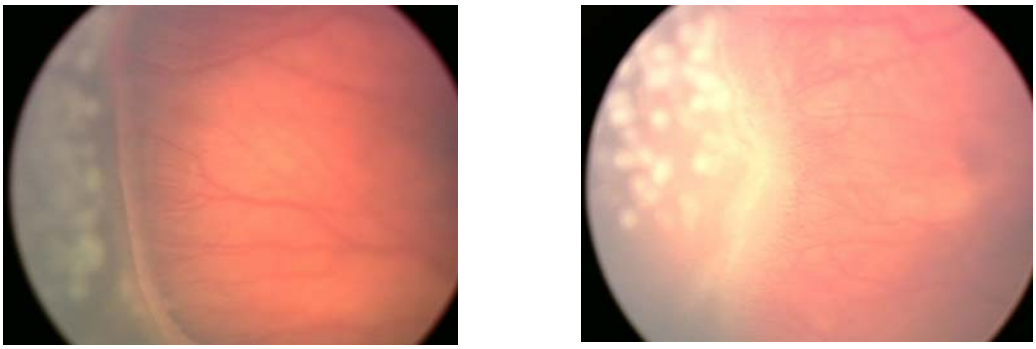
After obtaining parental consent, off-label intravitreal injections of bevacizumab (Avastin, Genentech) were administered.

Three newborns with bilateral threshold ROP, received unilateral intravitreal bevacizumab (1.25 mg) in addition to conventional laser therapy in avascular zones of both eyes (Figure 1). They were three male neonates with a gestational age of 28, 26 and 29 weeks and birth weight of 1000, 750 and 1100 g respectively. They were referred at 32, 33 and 32 weeks of conceptional age respectively. The history of mechanical ventilation and blood transfusion in patient number 1 and phototherapy in patient number 1 and 2 were positive. They had threshold ROP (stage III with plus disease in zone I & II) in both eyes and LASER therapy was performed to avascular area in both eyes of each patient.

Intravitreal injection of bevacizumab (Avastin) was performed in the amount of 0.05 ml by a 30 gauge needle through pars plicata and intraocular pressure was lowered by performing AC tap at the limbus. Intravitreal injection was done for left eye of each patient. We evaluated the patients in the days 2, 7, 14, 21, 60 and 120 postoperatively.

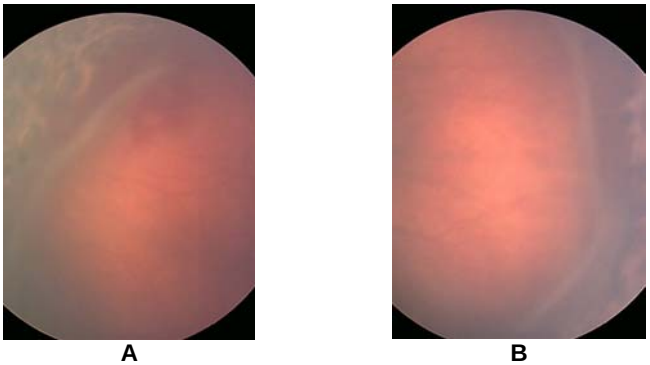
Changes in retinal neovascularization and normal vascular development were assessed by Ret-Cam and indirect ophthalmoscopy. At the end of follow-up (4 months after injection) ERG was performed in order to assess retinal function & comparing two eyes.

ROP regressed in both eyes of each patient (between day 14th & 21st after laser treatment) at the same time (Figure 2). We had no adverse effects due to injection including cataract, endophthalmitis or vitreous hemorrhage and none of the injected eyes had unfavorable structural outcome during 4 months of follow-up. There was no impediment of normal vascular development (Figures 3) or differences in ERG between two eyes (Figures 4).



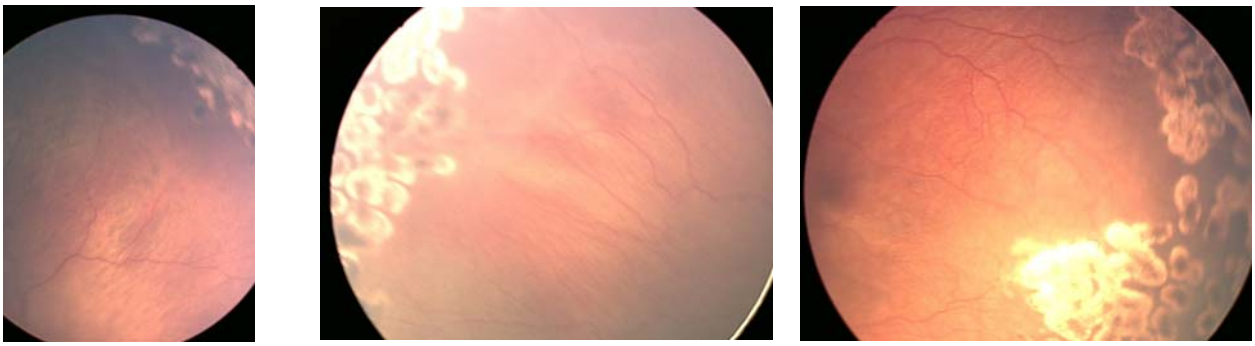
A B

Figure 1. Patient number 1:A & 2:B
Showing laser therapy to avascular zone in day 1



A B

Figure 2. Patient number 1
Showing regression of neovascularization in both eyes in day 14



A B C

Figure 3. Patient number 1:A & 2:B,C
Showing normal vascular development in both eyes in day 90

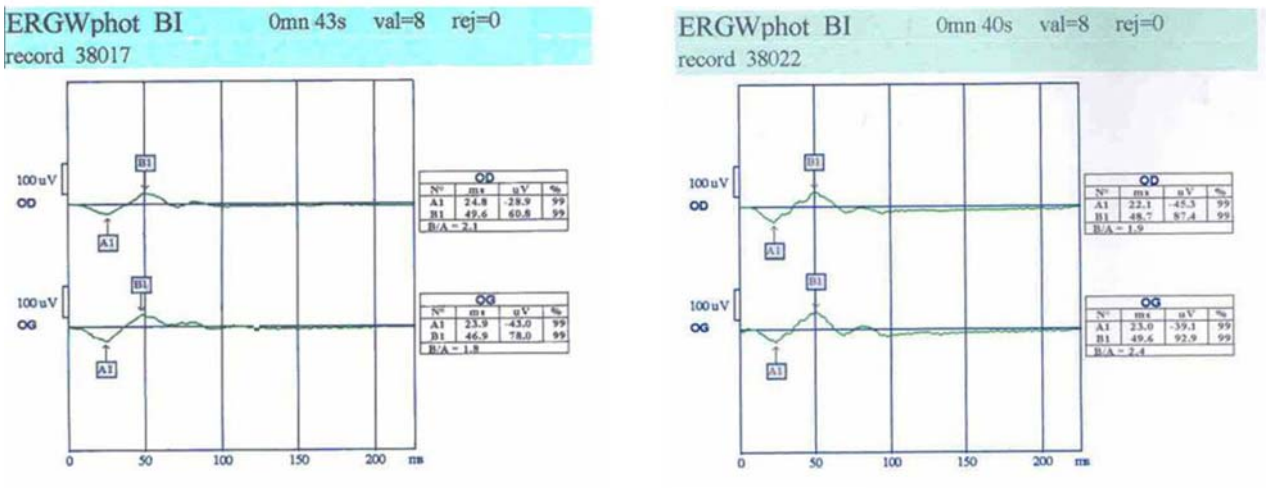


Figure 4. Patient number 2 & 3
Showing normal ERG in both eyes in day 120

Discussion

Retinopathy of prematurity (ROP) is a major cause of blindness in children in the developed and developing world despite current treatments[1] and its incidence seems to be increasing each year.

Although ablation treatment, laser photocoagulation or cryotherapy of the retina, reduces the incidence of blindness by 25% to 50%, the visual outcome after treatment are often poor.[2] Even with timely treatment of threshold retinopathy of prematurity with cryotherapy or laser, ROP still progresses in 15% to 30% of eyes, resulting in retinal detachment and blindness.[5]

In ROP, the first phase involves the premature termination of normal retinal vascular growth after premature birth, producing an avascular peripheral retina. In the second phase, the hypoxic state of the peripheral retina leads to a retinal neovascularization response,[6,7] the second phase occurs at about 32-34 weeks' post menstrual age. This phase of ROP is similar to other proliferative retinopathy.

Phase II of ROP is driven by vascular endothelial growth factor (VEGF), an inducible cytokine and a vascular endothelial cell mitogen.[6,7] The central role of VEGF in ocular neovascularization has also been demonstrated by other investigation in other animal models.[8] Normal blood vessel growth is also partly VEGF dependent. After premature birth, supplemental oxygen interferes with normal VEGF driven vascular development. Afterwards, VEGF is elevated due to hypoxia in the vitreous of patients with retinal neovascularization.[9,10] VEGF activates

some proteases leading to production of TGF ß, which by itself causes more proliferations to occur.

The discovery of VEGF and IGF-1 and the important roles that these factors play in the development of ROP is a step forward in our understanding of the pathogenesis of the disease.[4] These studies suggest a number of ways to intervene medically in the disease process, and also it should be noted that timing is critical to any intervention, since the two phases of the disease require very different approaches.

Inhibition of either VEGF or IGF-1 early after birth can detrimentally alter normal blood vessel growth and may aggravate the disease, whereas inhibition at the second neovascular phase might prevent destructive neovascularization[4] and fibrous proliferation (and ultimately prevention of tractional retinal detachment).

Avastin is an intravenously delivered recombinant humanized monoclonal antibody currently approved for the treatment of advanced colorectal cancer.[11] The use of a specific antagonist of an angiogenic factor as strategy to treat proliferative diseases was proposed more than 30 years age.[12]

The dramatic findings of Rosenfeld, Fung and Puliafito demand that further studies be done to assure safety and confirm treatment benefits.[13] Intravitreal avastin has been used successfully for post laser anterior segment ischemia in aggressive posterior ROP[14] and also for salvage treatment in threshold ROP[15] and they achieved regression of neovascularization secondary to ROP, similar to cases of PDR or AMD complicated by vitreous hemorrhages.

There are some studies that have been done to test intravitreal toxicity of bevacizumab (Avastin) and they concluded that histologic and ERG results suggest that there is no significant measurable retinal toxicity.[16-18] Our study is compatible with the previous ones showing no changes in ERG in neonates.

It is important to note that as ROP may progress to its cicatrical stage in a short period of time, we can consider medical drugs such as anti-VEGF to have permanent effects on disease process even with one dose of drug administration. In other proliferative diseases such as diabetic retinopathy that are permanent systemic diseases multiple injections may be needed to have a long-lasting effect.

Conclusion

There's always a debate on the usage of avastin in ROP, postulating that this drug might impede normal vascular development; but as it was mentioned in our study normal retinal vascularization developed in the same way in all of the eyes.

The results that have been observed following the intravitreal injection of bevacizumab are provocative, but our study is limited due to a small number of cases and further study of the safety and efficacy of intravitreal bevacizumab in treatment of ROP is warranted.

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