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Original research

# Comparison of intravitreal bevacizumab injection and laser photocoagulation for type 1 zone II retinopathy of prematurity

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## Abstract

***Purpose***: To compare the efficacy of intravitreal bevacizumab (IVB) injection with conventional laser photocoagulation in eyes with type 1 zone II retinopathy of prematurity (ROP).
***Methods***: Preterm infants with type 1 ROP in zone II (stage 2 or 3 ROP with plus disease) were randomly assigned to intravitreal injection of 0.625 mg/0.025 ml bevacizumab (Group 1) or laser photocoagulation (Group 2). Patients were followed weekly for 4 weeks and then biweekly till 90 weeks gestational age. Also, spherical and cylindrical refractive errors were compared at 90 weeks postmenstrual age (PMA).
***Results***: A total of 116 preterm infants (232 eyes) were treated and completed the follow-up period. IVB injection was done in 154 eyes (77 cases), and laser photocoagulation was done in 78 eyes (39 cases). ROP regressed after single IVB injection in 149 eyes (96.8%) and in 5 eyes (3.2%) after the second injection. Cataract developed in one eye (0.63%) after IVB injection. ROP regressed in 94.7% of treated eyes (76 eyes) in the laser photocoagulation group; however, retinal fold and traction developed in 2 eyes. Spherical and also cylindrical refractive errors had no significant difference.
***Conclusions***: Both IVB injection and laser photocoagulation are effective methods for the treatment of type 1 zone II ROP. However, re-treatment requirement may be higher in the IVB injection group. IVB re-injection is an effective option for re-treatment in persistent cases.


*Keywords:* Retinopathy of prematurity; Bevacizumab; Avastin; Laser photocoagulation; Zone II

## Introduction

Retinopathy of prematurity (ROP) is a multifactorial and potentially blinding disorder in premature infants[1,2] and is one of the major causes of visual impairment in children worldwide.[3,4] Although the pathogenesis of ROP is not completely understood, dis-regulation of vascular endothelial growth factor (VEGF) may lead to abnormal vasculogenesis and neovascularization and play a significant role in the pathogenesis of this disorder.[5,6] Therefore, in the recent years, intravitreal injections of the anti-VEGF have been used for the treatment of ROP.[7–9]

Laser photocoagulation has been the standard treatment of ROP for the last two decades, but a large area of peripheral retina is destroyed in the laser procedure.[3,4]

Bevacizumab (Avastin, Genetech Inc, South San Francisco, California, USA) is a recombinant humanized monoclonal antibody that is directed against all isoforms of VEGF and has been used off-label to treat many types of retinopathies with VEGF up-regulation and also to treat ROP. Some studies have shown that anti-VEGFs can be effective in the treatment of eyes with ROP,[10–12] but there has not been a large study that evaluates the efficacy of intravitreal bevacizumab (IVB) for the treatment of ROP in zone II.

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In this study, we compared the efficacy of IVB with laser photocoagulation for the treatment of preterm infants with type 1 zone II ROP.

## Methods

Between September 2013 and September 2015, preterm infants with a birth weight of ≤2000 g and a gestational age of ≤34 weeks were examined at a chronological age of 4 weeks or postmenstrual age (PMA) of 31 weeks, whichever was later. Preterm infants with type 1 zone II ROP (stage 2 or 3 ROP with plus disease) were enrolled in this prospective, randomized, non-masked study. Diagnosis of the ROP and the disease stage and zone was done by several expert vitreoretinal surgeons in the ROP Clinic of Farabi Eye Hospital. Infants with other ocular disorders such as congenital cataract, congenital glaucoma, or history of previous treatment for ROP were excluded.

Informed consent was obtained from the parents, and the benefits and side effects of each treatment were explained to them. This study was approved by the Ethics Committee of Eye Research Center, Farabi Eye Hospital.

Using computer-based randomization, patients were randomized into two groups with 2/1 ratio: IVB injection was done for patients in Group 1, and conventional laser photocoagulation was performed for cases in Group 2.

For IVB injection, in the operation room and after administration of anesthetic eye drop (tetracaine 0.5%), the eyes were prepared using 5% povidone iodine. After that, 0.625 mg/0.025 ml bevacizumab was injected into the vitreous cavity 1 mm behind the limbus using 29-gauge needle. In bilateral cases, IVB injection was done in both eyes during the same session.

For cases in Group 2, under general anesthesia, near confluent laser photocoagulation was applied to the avascular peripheral retina using diode indirect laser ophthalmoscope. Treatment was performed by several expert vitreoretinal surgeons in both groups.

Follow-up visits were performed one day after treatment and then weekly for 4 weeks, biweekly for 8 weeks, and monthly until 90 weeks PMA. Re-treatment was performed if persistent or recurrent disease was detected that was defined as the absence of the regression of neovascularization and plus disease 1 week following treatment or new extra-retinal fibrovascular proliferation with the peripheral retinal progression arrest through the follow-up time. Re-treatment for patients in Group 1 was re-injection of IVB, and for patients in Group 2 included additional laser ablation between the previous laser scars.

The primary outcome was the rate of ROP regression that was defined as regression of neovascularization and plus disease with complete or near complete vascularization of peripheral retina or complete vascularization of non-ablated retina in the laser eyes.

At 90 weeks of PMA, cycloplegic refraction was performed manually using a streak retinoscope in both groups. Cycloplegia was achieved using 3 instillation of homatropine 2% with 5 min intervals. Refraction was performed 30 min after instillation of the last drop.

Statistical analysis was performed using SPSS version 22.00 (IBM Corp, Armonk, NY, USA). *P*-value less than 0.05 was considered statistically significant.

## Results

A total of 232 eyes from 116 preterm infants with type 1 zone II ROP were treated and finally completed the follow-up period. IVB injection was done in 154 eyes from 77 cases (66.4%), and laser photocoagulation was done in 78 eyes from 39 cases (33.6%). The mean PMA, birth weight, and PMA at the time of treatment had no significant difference between the two groups (Table 1).

From 154 eyes in Group 1, regression of ROP and complete or near complete retinal vascularization was seen after single IVB injection in 149 eyes (96.8%). Additional IVB injection was required in 5 eyes (3.2%) due to persistent ROP. Re-injection was performed at a mean of 6.01 ± 1.27 weeks after the first IVB injection. No eye required surgical procedure in this group.

Finally, in all of cases in this group, regression of ROP was achieved, and vascularization appeared complete on clinical examination at 90 weeks of PMA after one or two IVB injections.

In Group 2, the use of laser photocoagulation resulted in regression of ROP in 76 (97.4%) eyes. Retinal fold and traction developed in 2 eyes (2.6%) from 2 consecutive patients in whom the encircling band was implanted in 2 eyes. No patient required re-treatment.

Overall, complete vascularization of non-ablated retina and ROP regression was seen in all cases in Group 1 and in 97.3% of eyes in Group 2 ($P = 0.20$).

At 90 weeks PMA, the mean spherical power was +1.47 ± 2.43 diopter (D) and +1.84 ± 2.22 D in Group 1 and Group 2, respectively ($P = 0.36$). The mean cylindrical power

Table 1
Comparison of mean postmenstrual age (PMA), birth weight, and PMA at treatment between the two study groups.

| | IVB injection group | Laser photocoagulation group | *P* value |
|---|---|---|---|
| Number of eyes | 154 | 78 | |
| Birth weight (grams) | 1232 ± 318 | 1273 ± 273 | 0.23 |
| Gestational age (weeks) | 28.75 ± 1.86 | 28.32 ± 2.11 | 0.41 |
| Stage 2/stage 3 (number of eyes) | 12/142 | 6/72 | 0.56 |
| Mean PMA at treatment | 37.10 ± 2.65 | 36.65 ± 2.83 | 0.71 |

IVB: Intravitreal bevacizumab; PMA: Postmenstrual age.

was 0.88 ± 0.8 D in Group 1 and 0.99 ± 0.8 D in Group 2 ($P = 0.43$).

The major ocular complication that was associated with IVB injection was cataract formation in one eye (0.63%) from a total of 159 injections (including first and re-injections).

## Discussion

In this study, we found that IVB injection is as effective as conventional laser photocoagulation for the treatment of type 1 zone II ROP. Regression of ROP and complete or near complete retinal vascularization was seen in 96.8% of cases after single IVB injection and in all cases after one or 2 injections. No eye required a surgical procedure in this group. The major ocular complication was cataract formation which was seen only in one eye. Likewise, laser photocoagulation resulted in the regression of ROP in 97.4% of subjects. However, rare complications such as retinal fold and traction developed in 2 eyes in which encircling band was implanted, and no patients required re-treatment.

At 90 weeks PMA, there was no significant difference between the two groups regarding the amount of spherical and cylindrical refractive error.

This study is a continuum of our previous study in which we compared the efficacy of IVB injection (86 eyes) and laser photocoagulation (72 eyes) for the treatment of type 1 zone II ROP from September 2012 to September 2013.[13] In that study, we showed that re-treatment was required in 9 eyes (10.5%) of the IVB injection group and one eye (1.4%) in the laser photocoagulation group. In 8 eyes (from 9 eyes), ROP regressed after second IVB injection, and pars plana vitrectomy was required in only one eye after the second injection due to dense pre-retinal hemorrhage. Surgical treatment was not needed in any case in the conventional laser photocoagulation group. At the end of our previous study, we performed the present study with completely different cases but similar methods. In comparison with our previous study, second IVB injection was required in fewer cases (3.2%) in the present study and no cases led to surgical intervention in the IVB injection group. Also, more cases resulted in retinal fold and retinal detachment in the laser photocoagulation group in the current study.

In their retrospective single center study, Kabataş et al. treated 128 preterm infants with type 1 ROP by three different treatment options including IVB (Group 1), intravitreal ranibizumab (IVR) (Group 2), or laser photocoagulation (Group 3).[10] They found that all those treatment options were equally effective on regression of ROP with low recurrence rates and no anterior segment complications. These results are similar to the current study in which we found nearly the same results in regression of ROP in the two study groups. However, reported posterior segment complications in their study groups were different from observed complications in our study. In one case of the laser photocoagulation group, bilateral exudative retinal detachment was noted, which successfully resolved following treatment by intravenous steroid. Also, bilateral macular ectopia was noted in one case in the laser photocoagulation group, which was partly similar to the current study.

Cryotherapy was suggested as a treatment modality for ROP in the 1980s; however, nowadays, laser photocoagulation is the standard treatment.[14] Laser photocoagulation leads to the destruction of peripheral retina, and normal retinal vascularization cannot be achieved.[9] Intravitreal injection of anti-VEGF is another treatment option for ROP.[15] Compared to laser photocoagulation, intravitreal injection of anti-VEGFs required less equipment and fewer skills and can be performed without general anesthesia.[16–20]

The BEAT-ROP trial was the first prospective randomized study that evaluated the efficacy of bevacizumab for the treatment of ROP.[11] The BEAT-ROP trial showed that in comparison to laser therapy, IVB injection led to favorable outcomes in patients with zone I ROP, but not in eyes with zone II disease.[11] Unlike the BEAT-ROP study, this study showed that IVB injection is an effective method for the treatment of patients with ROP in zone II; however, re-treatment may be required in some cases.

IVB blocks only the VEGFs that present in the vitreous cavity but not the VEGFs continuously produced by avascular retina. Therefore, ROP may progress or recur after initial regression following IVB injection.[21] Persistent ROP was detected in 3.2% of the eyes after IVB injection in the current study. We used re-injection of IVB as a re-treatment, and regression happened in all of them. Karkhaneh et al. used IVB injection for treatment of patients with type 1 ROP in zone I.[22] They showed that re-treatment was needed in 17.1% of cases, which is more than re-treatment requirement in cases with ROP in zone II in the present study. Also, 7.1% of eyes with zone I ROP progressed to retinal detachment after re-treatment with IVB injection in their study. Therefore, re-treatment with IVB injection in persistent or recurrent cases with ROP in zone II is more effective than cases with ROP in zone I.

The only major complication of IVB injection in our study was cataract formation that occurred in one eye (0.63%). Yetik and coworkers evaluated the efficacy of IVB injection for the treatment of ROP.[12] They reported that no serious ocular complications were seen following a total of 253 IVB injections. Wu and coworkers reported cataract formation in 1% of eyes following IVB injection for ROP.[9]

CRYO-ROP and ET-ROP trials and some other studies reported that myopia and high myopia increased significantly after ablation of peripheral retina for the treatment of ROP.[23–27] Gelonek et al. compared the refractive outcomes following IVB injection and laser photocoagulation.[28] They reported that in cases with posterior zone II ROP at age of 2.5 years, the mean spherical equivalent was −0.58 ± 2.53 D and −5.83 ± 5.87 D after IVB injection and laser photocoagulation, respectively ($P < 0.001$). In our study, the refractive outcomes in both IVB injection and laser photocoagulation groups were more hyperopic than Gelonek et al. results, albeit, the follow-up period was shorter in our study. In the current study at 90 weeks PMA, the mean spherical power was +1.47 ± 2.43 D and +1.84 ± 2.22 D in Group 1 and Group 2, respectively, which had no statistically significant difference.

This result was parallel to findings of Gunay and coauthors who assessed three treatment options, IVB, IVR, and laser photocoagulation, for 134 infants with ROP and found insignificant differences in both mean spherical equivalent as well as axial length among their study groups.[29] This also corresponded to findings of Kuo and coauthors who did not find significant differences in post-procedure refraction among treated ROP cases with either IVB or laser photocoagulation in longer follow-up.[30]

Hong et al. showed that plasma concentration of VEGF decreased significantly after IVB injection for the treatment of ROP and did not return to pre-injection levels until 8 weeks following treatment.[31] VEGF is an important factor for organ development in infants especially during vasculogenesis and neurogenesis.[32,33] Therefore, potentially, IVB injection may lead to systemic complications or organ development abnormality. No death or systemic complications were observed in the IVB injection group in this study, but longer studies are required.

Several previous studies described that peripheral vascular arrest may happen following intravitreal injection of anti-VEGFs for ROP which is diagnosed with fluorescein angiography.[34,35] We did not detect this because we did not do fluorescein angiography.

The major limitation of our study was that we did not use fluorescein angiography to detect the progression of vascularization. The extent of vascularization is typically overestimated in clinical examination as infants grow and struggle against scleral indentation, and fluorescein angiography is needed to recognize completeness of vascularization.

In conclusion, this study demonstrated that both laser photocoagulation and IVB injection are effective modalities for the treatment of eyes with zone II ROP; however, retreatment may be required in some cases after IVB injection. Also, re-injection of IVB is effective for persistent or recurrent cases with ROP in zone II. Close monitoring and careful follow-up until complete retinal vascularization is necessary. Further studies with a longer period of follow-up may prove necessary to confirm findings of the current study.

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