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Efficacy of intravitreal bevacizumab for zone-II retinopathy of prematurity

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ABSTRACT.

Purpose: **To assess the effect of intravitreal bevacizumab for Type 1 retinopathy of prematurity (ROP) in zone II ROP.**

Methods: **We conducted a randomized clinical trial. Preterm infants with a gestational age less than 34 weeks or birthweight less than 2000 g were examined at 4 weeks chronological age or 31 weeks postmenstrual age (whichever was later). Preterm infants with Zone-II/Stage 2 or 3 and plus disease were included. Eligible infants were randomized to receive either conventional indirect laser therapy or intravitreal bevacizumab injections (0.625 mg/0.025 ml). The primary outcome was defined as treatment failure: ROP persistence or recurrence by 90 weeks postmenstrual age.**

Results: **Our study population comprised 79 infants (158 eyes) with Zone-II ROP. Randomly, 43 infants (86 eyes) were assigned to receive intravitreal bevacizumab and 36 infants (72 eyes) to receive conventional indirect laser therapy. All the infants were followed up at least until 90 weeks postmenstrual age. Stage-3 ROP recurred in nine eyes (10.5%) in the bevacizumab group and one eye (1.4%) in the laser group (p value = 0.018). In recurrent cases after the second treatment, ROP in eight of the nine eyes (88.8%) in the bevacizumab group and the eye in the laser group regressed.**

Conclusion: **Recurrence of neovascularization with bevacizumab monotherapy seems to be higher than that with conventional laser therapy among infants with Type 1 ROP in zone II ROP but reinjection of bevacizumab causes regression in most recurrent cases.**

Key words: bevacizumab – intravitreal injection – laser – retinopathy of prematurity

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Introduction

Retinopathy of prematurity (ROP) is a retinal vascular development disorder mainly affecting preterm infants. In developed countries, ROP now occurs mostly in extreme low birthweight infants. The incidence of ROP seems to have declined over the last few decades in these countries. In contrast, in middle-income countries, high rates of premature labour and increasing resuscitation of premature infants, in conjunction with suboptimal standards of care and lack of widespread screening schedules, have resulted in a new epidemic of ROP. Timely diagnosis and treatment are urgently needed to control this epidemic (Zin & Gole 2013).

Despite advances in the treatment of ROP, it remains the leading cause of potentially preventable blindness in children (Mantagos et al. 2009). In the past few decades, the treatment method has changed from cryotherapy in threshold ROP (Cryotherapy for Retinopathy of Prematurity Cooperative Group 1988) to ablative laser therapy in type-1 prethreshold ROP (Early Treatment for Retinopathy of Prematurity Cooperative Group 2003). The role of various factors such as vascular endothelial growth factors (VEGFs) and hypoxia-inducible factor 1a (HIF-1a) on the pathogenesis of ROP has been investigated (Good & Hardy 2001; Smith 2002; Chen & Smith 2007; Cavallaro et al. 2014). Similar to other retinal vascular disorders, the introduction of anti-vascular endothelial growth factors (anti-VEGFs) influenced the management of ROP. There are multiple case series assessing the effect of intravitreal bevacizumab in ROP. A prospective randomized controlled stratified multicentre trial compared bevacizumab monotherapy and laser therapy for Zone-I or Zone-II posterior Stage 3+ (i.e. Stage 3 plus disease) ROP (BEAT-ROP) (Mintz-Hittner et al. 2011). There is also a small trial where bevacizumab was given to one eye and laser therapy used in the other eye (Moran et al. 2014).

Given the possible effect of race and ethnicity on the treatment outcomes (Mintz-Hittner & Best 2009), we evaluated the results of intravitreal bevacizumab injections for Iranian infants with ROP needing treatment.

Patients and Methods

Our study was a randomized controlled non-masked prospective clinical trial comparing the efficacy of indirect laser

therapy and intravitreal bevacizumab injection in infants with Type 1 ROP in zone II ROP.

Preterm infants with a gestational age less than 34 weeks or birthweight less than 2000 g were examined at 4 weeks chronological age or 31 weeks postmenstrual age (whichever was later) by indirect ophthalmoscopy at the ROP Clinic of Farabi Eye Hospital (a tertiary referral hospital in Tehran, Iran) from September 2012 to September 2013. Preterm infants with Zone-II/ Stage 2 or 3 and plus disease were included.

Informed consent for participation in the study was obtained from the parents. They were informed about the pros and cons of each treatment. The parents were told that infants in the study will be randomly assigned to one of two different treatment plans. The ethics committee of eye research centre, Farabi Eye Hospital, approved this study.

Infants with eye diseases other than ROP such as congenital cataract and glaucoma and infants with a history of prior treatment for retinopathy of prematurity were excluded from the study. All eligible infants (rather than eyes) were randomized to receive either conventional indirect laser therapy or intravitreal bevacizumab injection. Need for treatment was approved by at least two of three expert examiners. We took RetCam photographs before applying treatment. All treatments were performed during the 48 hrs after diagnosis.

Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) trial (Mantagos et al. 2009) and Early Treatment for Retinopathy of Prematurity (ETROP) trial (Good & Hardy 2001) suggested that the recurrence rates with conventional laser therapy would be up to 20% for Zone-II posterior disease. The recurrence rates after intravitreal bevacizumab monotherapy are different between studies available by now. It was 5% in BEAT-ROP trial (Mintz-Hittner et al. 2011). Assuming the power of 80% and p value of 0.05%, we calculated that a sample of 73 eyes per treatment group would be required to detect a statistically significant difference in the rate of the primary outcome between the two treatment groups.

IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp, Armonk, NY, USA), was used to perform statistical analyses. A p value of less than 0.05 was considered to indicate statistical significance. Two-sample *t*-test was used to evaluate whether the two groups of infants assigned to different treatments were similar before treatment with respect to risk factors for retinopathy of prematurity such as birthweight, gestational age and duration of supplemental oxygen therapy. Two-sample *t*-test was used to compare the results between two groups.

Intervention

(1) Bevacizumab group: all the intravitreal bevacizumab injections were performed in the operating room at a dose of 0.625 mg/0.025 ml under topical anaesthesia (Tetracaine 0.5%). This is the same dose of bevacizumab used in nearly all published studies; although there are reports of injecting lower doses such as 0.375 mg/0.03 ml (Harder et al. 2014). The injection site was in the inferotemporal or inferonasal quadrants, 1.5–2 mm from the limbus. The tip of a 29-gauge needle was oriented perpendicular to the floor (rather than the globe centre as in injections in adults) to lower the risk of crystalline lens damage. In bilateral cases, both eyes were injected at the same day. Infants received sulphacetamide 10% eye drop q6 hrs for 3 days after injection.
(2) Laser group: the infants in this group received indirect laser ablation (wavelength = 640 nm) to the peripheral avascular area. All laser therapies were performed by the same surgeon. Laser therapy was performed under general anaesthesia by default. If general condition of infant was not suitable for general anaesthesia, laser therapy was performed under topical anaesthesia with sedation. The entire avascular retina was treated in the standard method; which is applying laser spots to the avascular area separated by one-half burn width (about 800 spots).

Follow-up

The infants were re-examined at day 1 after treatment. The next follow-up visits were held weekly for 4 weeks, biweekly for 8 weeks and then monthly until 90 weeks postmenstrual age. Infants suspected to have disease persistence or recurrence were followed more vigorously (every 3 days). All infants also visited at 54 and 90 weeks postmenstrual age.

We took RetCam photographs of all infants before treatment and retreatment (if needed), 1 week after the initial treatment and at 54 weeks postmenstrual age. All follow-up visits were performed by three retina specialists; all had great expertise in the field of ROP (surgeons performing the treatments were not among them). Treatment and retreatment were applied if at least two examiners recommended it.

Outcomes

The primary outcome was the rate of treatment failure. Treatment failure was considered as ROP persistence or recurrence.

Persistence of ROP was defined as the absence of the regression of neovascularization and plus disease 1 week after treatment. Recurrence of ROP was defined as new extraretinal fibrovascular proliferation with the arrest of the anterior progression of the retinal vasculature during the follow-up period.

Persistent vascular tortuosity, especially after intravitreal bevacizumab injection, without other indicators of disease activity was not considered as a sign of treatment failure.

Retreatment for those who received laser therapy was additional laser ablation and for those who received intravitreal bevacizumab injections was reinjection of the drug. In laser retreatment, more laser spots were added between the previous laser scars (about 200 spots).

Secondary outcomes were comprised of need for surgery (either scleral buckling or 3-port pars plana vitrectomy) and situation of the retinal periphery by 54 weeks postmenstrual age.

Results

Eighty-five infants met the criteria. Parents of six infants were reluctant to be enrolled in the study (most were afraid about the possible complications of bevacizumab injection). Seventy-nine infants (158 eyes) randomized. Fortunately, no death or loss to follow-up occurred. Table 1 shows some characteristics of enrolled infants.

Table 1. Characteristics of the infants enrolled in the study.

	Bevacizumab group	Laser group	p value
Number of eyes	86	72	
Gender (male) – per cent	46.51	52.77	0.48
Gestational age – weeks	28.37 ± 1.96	28.50 ± 1.99	0.68
Birthweight (mean ± SD) – g	1133 ± 344	1202 ± 321	0.19
Duration of hospitalizations from birth to treatment – week	10.29 ± 3.9	10.39 ± 4.1	0.10
Stage 2/Stage 3 (no of eyes)	3/83	4/68	0.70

Table 2. Outcome of the eyes after treatment.

	Bevacizumab group	Laser group	p value
Retreatment	9 (10.5%)	1 (1.4%)	0.018
Surgery	1 (1.2%)	0	0.54
Time between treatment and retreatment (weeks mean ± SD)	5.07 ± 1.66	3	0.290

By a computer-based randomization, 43 infants (86 eyes) were assigned to receive intravitreal bevacizumab and 36 infants (72 eyes) to conventional indirect laser therapy.

All the infants (86 eyes in the bevacizumab group and 72 eyes in the laser group) were followed up at least until 90 weeks postmenstrual age.

No major ocular complication (cataract, endophthalmitis, vitreous haemorrhage or retinal detachment) occurred after treatment. Subconjunctival haemorrhage was noted in some of the infants treated with intravitreal bevacizumab.

Disease activity (severity of venous tortuosity and arterial dilation) declined in all eyes at first post-treatment visit. After this initial partial disease control, Stage-3 ROP recurred in nine eyes (10.5%) in the bevacizumab group and one eye (1.4%) in the laser group (p value = 0.018) (Table 2). Retreatment was performed at a mean of 5.07 ± 1.66 weeks after the first treatment in the bevacizumab group and 3 weeks in the laser group (p value = 0.290). After the second injection, ROP in eight of the nine eyes (88.8%) in the bevacizumab group regressed. Retreatment (applying more laser burns between previous burns) also caused regression of ROP in the eye with recurrence in the laser group.

One eye in the bevacizumab group and no eye in laser group needed surgery (p value = 0.54). Three-port pars plana vitrectomy was performed in that infant because of dense preretinal haemorrhage. (In ultrasonography, the retina was attached preoperatively.)

At 54 weeks postmenstrual age, 17 eyes (20.7%) in the bevacizumab group had regressed ROP on fundoscopy and the retina was fully vascularized but 65 eyes (79.3%) eyes in this group had an avascular area in Zone-III (despite ROP regression). At 90 weeks postmenstrual age, 37 eyes (45%) had still avascular area in retinal periphery.

The mean of birthweight in the infants with and without ROP recurrence (either in the bevacizumab or in the laser group) was 856 g and 1185 g, respectively (p value = 0.001).

There was a significant anisometropia (cyclorefraction at 90 weeks postmenstrual age) between the eyes of an infant who had vitrectomy in his right eye (−7.50 −1.25*30 OD versus −1.75 OS).

Discussion

In our study, there was a statistically significant difference between intravitreal bevacizumab injection and indirect laser therapy among the Zone-II ROP infants in terms of need for retreatment. Recurrence of ROP requiring retreatment was more prevalent in the bevacizumab group. Nine of the 86 eyes in the bevacizumab group and one of the 72 eyes in the laser group needed retreatment (p value = 0.018). Eight of the nine eyes in the bevacizumab group, who received a second injection, finally had regressed ROP, but one eye needed pars plana vitrectomy. Consequently, laser therapy was associated with less recurrence compared with bevacizumab, following a single application of treatment.

In the BEAT-ROP (Mintz-Hittner et al. 2011) study, four of 78 eyes (5.1%) with Zone-II posterior ROP which received intravitreal bevacizumab and nine of 80 eyes (11.2%) with Zone-II posterior ROP which received conventional laser therapy had disease recurrence before 54 weeks postmenstrual age. There was no statistically significant difference between the two groups. Two eyes in the bevacizumab group and no eye in the laser group needed vitrectomy.

The difference in results between our study and BEAT-ROP may be due to patient enrolment. Whereas in the BEAT-ROP study, only infants with 'posterior' Zone-II disease were enrolled, our study also included infants with anterior Zone-II, Stage 3 plus disease.

Another explanation for superiority of laser therapy in our study may be the great expertise of surgeons applying laser. All had the experience of at least 15 years in the field of ROP. The results of laser therapy are absolutely dependent on the quality and quantity of laser burns. Inexperienced surgeons usually leave some area untreated. These skipped areas raise the possibility of treatment failure and disease recurrence.

Based on the results of our study and the current insufficient data about the systemic safety of anti-VEGFs in infants, it seems that use of bevacizumab in treating Zone-II ROP should be confined to centres lacking the facilities for conventional laser therapy.

Another interesting finding in our study was a statistically significant lower birthweight in the infants with treatment failure (Zone-II ROP). The mean of birthweight in the infants with and without ROP recurrence was 856 g and 1185 g, respectively (p value = 0.001). It shows that infants with lower birthweights should be followed up more vigorously.

Although the rate of retreatment was higher in the bevacizumab group, no eye in this group had retinal detachment at 54 weeks postmenstrual age. It may show that the reinjection of bevacizumab will control ROP in most recurrent cases. (The indication of surgery for the only eye that required

pars plana vitrectomy in the bevacizumab group was preretinal haemorrhage with attached retina). Thus, the results of intravitreal bevacizumab may become more similar to those of laser therapy if patients are followed up appropriately and reinjected as needed.

Seventy-nine per cent and 45% of the eyes in the Zone-II group who received bevacizumab had avascular areas in Zone-III at 54 and 90 weeks postmenstrual age, respectively. In fact, one of the major drawbacks of treating ROP by anti-VEGFs is persistence of peripheral avascular retina for an undetermined time. Tahija et al. (2014) performed fluorescein angiography on 20 eyes with a history of intravitreal bevacizumab injections for ROP. All the neonates had regression of Zone-I or posterior Zone-II ROP at the time when fluorescein angiography was performed. The median of IVB-FA interval was 87.5 weeks. Eleven eyes (55%) had incomplete peripheral retina vascularization. Of these 11 eyes, nine (82%) had fluorescein leakage at the junction of vascular–avascular retina. The authors concluded that although intravitreal bevacizumab can be very effective in causing the regression of Zone-I and posterior Zone-II ROP, ophthalmologists should remain cautious as avascular peripheral retinas may persist even many years after treatment.

Ittiara et al. (2013) reported bilateral exudative retinal detachment one year after an intravitreal bevacizumab injection in a 25-week postmenstrual age premature infant with ROP. They concluded that regular follow-up after intravitreal injections of bevacizumab for ROP should be continued until either the retina is fully vascularized or peripheral ablation is performed.

The clinical importance of long-lasting peripheral retinal avascularity after intravitreal bevacizumab injection has yet to be known. Until then, infants treated with bevacizumab monotherapy should be followed up until retina became fully vascularized (sometimes up to 2 years). Based on our experience, it is not necessary to ablate the avascular retina in a silent eye with well-regressed ROP.

There was a significant anisometropia in infant in whom pars plana vitrectomy was performed. Significant myopic shift (6–8 dioptres) was noted in the eye that underwent deep vitrectomy. Changes in the axial length after deep vitrectomy may be the reason.

Conclusion

Although intravitreal bevacizumab injection for ROP has been popularized among paediatric ophthalmologists, the recurrence of neovascularization with bevacizumab monotherapy seems to be higher than that with conventional laser therapy among infants with Type 1 ROP in zone II ROP. The reinjection of bevacizumab causes regression in most recurrent cases. The peripheral retina will remain avascular for a long period after the injection; therefore, regular long follow-up is warranted for infants treated by intravitreal bevacizumab.

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