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Research article

Efficacy of Intravitreal Bevacizumab Injection as a Primary Therapy for Stage 3+ Retinopathy of Prematurity

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Running title: Bevacizumabtherapy for Retinopathy of Prematurity

ABSTRACT

Purpose: To evaluate the efficacy and safety of intravitreal injection of bevacizumab as a primary therapy in patients with threshold disease,stage3retinopathy of prematurity (ROP)

Methods: The study included 64 eyes of 34 patients with severe active ROP (stage 3, threshold, or plus disease in zone II). For all we gave intravitreal injection of bevacizumab (0.625mg) after obtained written consent from the parents, including disclosure of the off-label use of the drug, its unknown safety and efficacy for this indication, and its unknown effects in children. In 30 patients both eyes and in 4 patients only one eye were affected.

Results: Sixty four eyes of 34 patients with stage 3 plus zone II ROP were enrolled in this study. In all eyes 3 days after injection, retinal vessels dilation, and tortuosity was decreased. No recurrence was observed during 6 to 12 months follow-up assessments.In one case, lens opacity was observed after 14 days and in onecase, the lens subluxation was observed after 3 weeks.

Conclusion: Intravitreal injection of bevacizumab is an easy and effective therapeutic approach for severe ROP.This treatment may be occasionally associated with complications such ascataract and lens subluxation.

Keywords: Retinopathy of prematurity, Treatment, Intravitreal injection, Bevacizumab

INTRODUCTION

Retinopathy of prematurity(ROP) is a neovascular retinal disorder of premature babiesbecause of retinal immaturity. Neovascularization leads to retinal traction, retinal detachment, hemorrhage, and a funnel shape retinal detachment. Neovascularization is mainly driven by vascular endothelial growth factor (VEGF)(1). Globally at least 50,000 children are blind from ROP (1). It is a leading cause of childhood blindness in the United States and other highly industrialized nations, occurring primarily in infants of low birth weight ≤1250 g(mean: 700 g)(1). The incidence of blindness in infants due to ROP is relatively low: about 1 case in 820 infants(2), because of good neonatal care and appropriate screening and treatment(1). The disorder is a major cause of childhood blindness in developing countries,manifesting in larger premature infants of birth weight ≤ 2000 g(mean, 1400 g). The worldwide prevalence of blindness due to retinopathy of prematurity is 50, 000(1).

Vascular endothelial growth factor (VEGF) plays an important role in the development of ROP (3, 13). If we could both up regulate and down regulate vascular endothelial growth factor we could prevent ROP. Bevacizumab (Avastin, Genentech Inc., South San Francisco, CA) is a humanized anti-VEGF monoclonal antibody(6). The Food and Drug Administration approved intravenous bevacizumab therapy in 2004 for the treatment of metastatic colon cancer; the drug works by reducing the size and number of new vessels feeding

metastases.(6)Off-label use of intravitreal bevacizumab therapy for ophthalmologic neovascular disorders began shortly thereafter.The drug has good results in treating many retinopathies with VEGF up-regulation, such asdiabetic retinopathy(9 –11), neovascular glaucoma(14)and ROP(1-3).

The present study aimed to evaluate the efficacy and safety of intravitreal injection of bevacizumab as a primary therapy in patients with threshold disease in stage III ROP and to detect local or systemic complications.

MATERIALS AND METHODS

This is a retrospective non randomized study conducted in patients with ROP who underwent bevacizumab treatment.The data were collected fromthe patients referred to the Ophthalmology department, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran which is the referral center for ROP in south west of Iran.The revised version of international classification for ROP was used to classify ROP(4). Inclusion criteria were 32 weeks of gestation or less and birth weight of 2000 g or less, and eyes with stage 3 ROP. Exclusion criteria were refusal of informed consent from a parent or guardian, any previous laser, cryotherapy or surgical procedure or presence of traction (stageIV).

The data were collected from January 2010 to December 2012.Medical records for patients with ROP who were treated with intravitreal injection of bevacizumab (IVB) were collected. Eachpatient's parent or legal guardian signed a consent form before the IVB including disclosure of the off-label use of the drug, its unknown safety, and efficacy for this indication and its unknown effects in children. The eligibility process for patients to be included in the study was establishedby the supervisor ophthalmologist and was confirmed by a second ophthalmologist.For stage 3 ROP, the indications for treatment werepatients whose retinopathy met the criteria of type 1 ROP used inthe ETROP study(2).Patients were treated when aplus or pre-plus sign was present. Patients with a follow-up lastingless than 6 months were excluded.

The pupil wasdilated with 1.25% phenylephrine and 1% tropicamide before intravitreal injection, the infant wassedated and the eye or eyes were prepared in a standard fashion using 5%povidone/iodine, 0.625 mg (0.025 ml) ofbevacizumab was injected intravitreally via the pars plicata, through a 30-gauge needle1.5 mm from limbus. Considering the relatively long half-life of intravitreal bevacizumab (5 to10 days), the highly viscous preterm vitreous geland a definitive end point, completion of retinal vascularization, it is expected that a single injection of bevacizumab (half the dose typically administered intravitreally in adults for ocular neovascular disease) would be adequate to treat ROP(3).

After the injection,intraocular pressure and retinal artery perfusion were checked. The patients received topical antibiotic for 3 days.

Follow-up examinations were performed clinically by fundoscopyon the postoperative days1 and 3, weekly for 1 month, then monthly for one year.Disappearance or decrease in retinal vessel tortuosity and neovascularization, clearing of vitreous haze and flattening of the ridge and vascularization toward the peripheral retinawere important indicators of regression.If the eye did not respond positively to this treatment in 2to 3 weeks,was received another IVB of same dose.

RESULTS

Of 430 premature newborn who werereferred to the ophthalmology department of Imam Khomeini Hospital,Ahvaz Jundishapur University of Medical Sciences during 2010 to 2012,136 newborn had ROP.Sixty four eyes of 34 patients had stage3 zone 2ROP with plus that received IVB as the primary treatment and completed 1 year follow up. Sixty one eyes received a single dose of IVB 0.625 mg /0.025 ml, 2 eyes received two doses, and 1 eye received 3 doses.They were 20 males and 14 females. Mean birth weight in these infants was 1050 g, mean gestational age at birth was 28.7weeks, and mean age at the time of first injection was37weeks.

After injection neovascular activity reduction was observed in all the eyes (100%), 61eyes(95%) after single injection, 2eyes in one

patient(3%)after two injections with 3 weeks interval and 1eye (1.5%)after 3 injections with 3 weeks intervaland no additional laser treatment was required.All the 64 eyes remained stable during follow-up. No systemic side effects of bevacizumab were observed and no further treatment was necessary.After three months, unilateral cataract was seen in one patient and unilateral lens subluxation was seen in another patient.

DISCUSSION

In our study a single intravitreal injection of bevacizumab 0.625 mg/0.025 ml alone in 6th to 7th week post gestational age was effective in 61 eyes (95.3 %) of ROP stage 3,Zone 2.Also two injections was required in 2eyes(3%) and three injections was required in 1eye(1.5%) for complete resolution to occur and this was at 3 weeks interval from the previous injection if there are no signs of regression.Based on current study it seems regression of the disease is fastand a significant extent of regression and stabilization will be achievedwith sufficient IVB in stage 3 ROP. In contrast, In the children with lower birth weights and shorter gestational age, the disease were more aggressive and less responding to intravitreal bevacizumab injection which may be due to that VEGF load probably is high at this period of disease(3).

In our study the overall final success rate was 100% and this was comparable with Mintz-Hittner et al (3), Chung et al, (7) Lalwani et al, (8)Wu et al, (9) and kusaka et al(10).

Our clinical study showed increased efficacy of IVB, compared with conventional laser therapy (14). In addition conventional laser therapy is laborious and requires special training to administer, as well as expensive equipment, endotracheal intubation, and a location designated for the use of lasers. In contrast with Mintz-Hittner(3) that reported IVB is effective in infants with stage 3+ROP for zone I, but not zone II disease, our study showed IVB is effective for stage 3 + ROP in zone II.

A major ocular side effect in our study was cataract aloneand with lens subluxation that were observed in two patients that was compared with Beat-ROP study that reported 4 cases of complication, one case of corneal opacity and three cases of lens opacity with conventional laser therapy for zone II and no any ocular side effects attributable to the administration of bevacizumab, but the sample size of our study was too small to address the question of whether IVB is safe or not (3). However, infantile cataract and lens subluxation can be developedat any time during the first year of life (17).

In the Beat-ROP study five deaths were reported in the bevacizumab group and two in the laser group whereas in our study no death occurred. This could be due to lower birth weight and gestational age (mean birth weight =650, meangestational age =24 w) in the BEAT-ROP study compared to our study(mean birth weight =1050, mean gestational age =28.7 w)

The study did not assess safety and this is still an issue. Future studies in conjunction with neonatologists should address IVB effects on growth and mental development. However, further prospective, randomized, controlled clinical trials with larger number of enrolled patients are necessary to determine the best choice of therapy, as well as optimal dose and timing, the need for repeat treatments and the possibility of ocular or systemic complications.

CONCLUSION

IVB is an easy and effective modality of therapy for threshold disease ROP.Bevacizumab injection seems effective and well tolerated in stage3 ROP. Ocular complications could result from the injection of bevacizumab in pediatric eyes.

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