

Intravitreal Bevacizumab Injection as a Primary Therapy for Threshold Disease (ROP) in Al Qassim Region

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Abstract

Purpose: To evaluate the efficacy and safety of intravitreal injection of bevacizumab without laser as primary therapy in patients with threshold disease in difficulties or lack of facilities for laser as Al Qassim region.

Patients and methods: The study included eighteen eyes of nine patients with moderate to severe active ROP (stage III, threshold, or plus disease in zones I and II). For all we gave intravitreal injection of bevacizumab without laser 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.

Results: Of 18 eyes enrolled in the study, all have completed 1-year follow-up. Mean birth weight in these infants was 1235 gm, mean gestational age at birth was 28.8 weeks, and mean age at the time of injection was 1.5 months. All eyes showed complete resolution of neovascular plus disease. No patient developed any ocular or systemic complications. In all cases, the ERG and VEP were within normal at 1 year.

Conclusions: Intravitreal injection of bevacizumab is an easy, safe and effective modality of therapy for threshold disease ROP especially in presence of difficulties for laser photocoagulation.

Keywords: Retinopathy of prematurity; Intravitreal injection; Bevacizumab

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness worldwide and an association with prematurity was identified [1]. In recent years, cryotherapy and laser therapy have been used with limited success. Although these ablative treatments reduce the incidence of blindness by 25% in infants with severe disease, visual acuity post-treatment remains considerably impaired [2].

Endo laser is difficult to perform through occluded media caused by corneal or lens opacities or through narrow pupil [2].

Vascular endothelial growth factor (VEGF) plays an important role in the development of ROP. Recently it has been shown that serum VEGF levels are elevated in cases of ROP. It is thought that VEGF is responsible for an increase in vascular permeability, the suppression of genetically programmed endothelial cell apoptosis and the promotion of neovascularization in ROP. With the recognition of VEGF's role, interest has grown in the use of anti-VEGF agents to treat ROP [3].

Bevacizumab is an anti-VEGF monoclonal antibody. Intravitreal bevacizumab injections have recently gained popularity as a potential treatment for several intraocular neovascular diseases without known serious ocular systemic adverse events [4].

Studies using bevacizumab in combination with laser treatment for the treatment of ROP in stage 1 with encouraging results have recently been published [5,6]. In ROP One potential roadblock to use of intravitreal bevacizumab is the risk of systemic complications.

Other risk factors for ROP have been identified in literature include septicemia, congenital infections, ventilatory support, blood transfusions, intracranial hemorrhage, asphyxia and vitamin E deficiency [7].

Our study aimed to evaluate the efficacy and safety of intravitreal injection of bevacizumab without laser as primary therapy in patients with threshold disease in stage III in case of difficulty to do and to

detect local or systemic complications and to study risk factors for ROP.

Patients and Methods

This prospective non randomized study included eighteen eyes of nine patients with moderate to severe active ROP (stage III, threshold, or plus disease in zones I and II). We 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.

All patients received a single dose of intravitreal bevacizumab 0.625 mg /0.025 ml (half of the adult dosage) through a 30-gauge needle after anterior chamber paracentesis under general anesthesia. The procedure was performed in the operating room with standard aseptic precautions.

Inclusion criteria were 32 weeks of gestation or less and birth weight of 1300 g or less. All eyes had stage 3 ROP were at a high risk of permanent vision loss and had a decreased likelihood of improvement with conventional laser therapy alone. The ROP stage and plus disease were defined on the basis of the international classification scheme [1]. Exclusion criteria were refusal of informed consent from a parent or guardian, any previous laser, cryo or surgical procedure and presence of traction (stage IV).

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The peripheral neovascular activity was evaluated in each eye before the injection by indirect ophthalmoscopy.

As ROP has a multifactor etiology, the variables studied were sex, birth weight, gestational age, fifth minute Apgar score, nutritional status at birth, intrauterine growth curve in addition to the use of supplementary oxygen, mechanical ventilation, intracranial hemorrhage, prophylactic and/or therapeutic indomethacin and blood transfusions [8,9].

Gestational age was estimated according to maternal history, obstetric echography if taken during the first trimester of pregnancy and was confirmed by physical examination of the newborns themselves.

All of the newborn infants were examined by fontanelle ultrasound at the end of the first week postpartum for diagnosis of intracranial hemorrhages.

Follow-up examinations were performed clinically by fundoscopy and ultrasonography at postoperative day 1, weekly for 1 month, then monthly for 1 year. Changes in tortousity and dilatation of retinal vessels were evaluated. Regression of neovascularization, clearing of vitreous haze and flattening of the ridge were important indicators of the early signs of regression and if it happened we did not give another injection. But if these signs did not happen in addition to persistence of vascular changes, tortousity and dilatation after one month from the injection we gave another injection of same dose with systemic and ocular monitoring along with neonatal and pediatric neurological examinations. Outcome measures at 1 year post-injection included progression of ROP and any adverse events. With flash electroretinogram (ERG) or flash visual evoked potential (VEP) 6 month post injection.

Results

Of 18 eyes enrolled in the study, all have completed 1-year follow-up. They were 5 males and 4 females. Mean birth weight in these infants was 1235 gm, mean gestational age at birth was 28.8 weeks

and mean age at the time of injection was 1.5 months (Table 1). And risk factors in (Table 2)

Out of the eighteen eyes, all had stage 3 ROP and ten had stage 3 plus disease, Zone 2 was most commonly involved (12 eyes), with 6 eyes involving zone 1, involving zone 3. Tortousity and vessel dilatation were apparent before therapy. After injection, reduced neovascular activity was observed in all the eighteen (100%) eyes, twelve eyes (66.66%) after single injection, four eyes (22.22%) after two injection with 4 weeks interval and 2 eyes (11.11%) needed three injections with 4 weeks interval between each injection. All the eighteen eyes remained stable during follow-up. No systemic side effects of bevacizumab were observed and no further treatment was necessary. In all cases, the ERG and VEP were within normal at 1 year (Figure 1, Figure 2).

Discussion

The number of infants with ROP is increasing likely due to better medical management of premature infants worldwide. Another reason is that more infants are now eligible for ROP screening. Guidelines recently changed to recommend screening in premature infants 30 weeks or less post-menstrual age or compared to 28 weeks or less that be recommended previously [1]. Our study was done for weight equal to or less than 1300 grams with mean 1235 grams and age of 32 weeks or less with mean 28.8 weeks.

Intravitreal injection of bevacizumab is advantageous in eyes with rigid pupils or hazy media, or in sick babies in whom laser would be difficult to administer or in places in where there is no endolaser like our hospital.

In our prospective study single intravitreal injection of bevacizumab 0.625 mg/0.025 ml alone in 6th to 7th week post gestational was effective in 12 eyes (66.66%) of ROP stage 3 zone 1 or 2. This was comprable with Chung et al [5] and Lalwani et al. [6] in stage 1 ROP and retrospective studies on stage 3 ROP as Wu et al. [10] and kusaka et al. [11].

Case n°	Sex	Eye	Stage & plus disease	Zone	Time of inj in wk	N° of inj	inj Interval in wk
1	M	OU	3+	II	6	2	4
2	M	OU	3+	II	7	1	-
3	M	OU	3	I	7	1	-
4	F	OU	3+	II	7	1	-
5	F	OU	3	II	6	1	-
6	M	OU	3+	II	6	2	4
7	F	OU	3+	II	6	3	4
8	M	OU	3	I	7	1	-
9	F	OU	3	I	6	1	-

Table 1: characteristics and treatment of eighteen eyes with ROP by intravitreal bevacizumab injection.

Case n°	Sex	Birth weight in gm	Gestational age in wk	5 th minutes Apgar	Mechanical ventilation	Intracranial haemorrhage	Blood transfusion
1	M	1060	26	7	+ve	-ve	-ve
2	M	1250	28	8	+ve	-ve	+ve
3	M	1300	32	8	+ve	-ve	-ve
4	F	1190	26	7	+ve	-ve	+ve
5	F	1280	28	7	+ve	-ve	-ve
6	M	1270	29	8	+ve	+ve	-ve
7	F	1200	28	8	+ve	-ve	-ve
8	M	1270	31	7	+ve	-ve	-ve
9	F	1300	31	8	+ve	-ve	-ve

Table 2: Systemic risk factors for each patients.

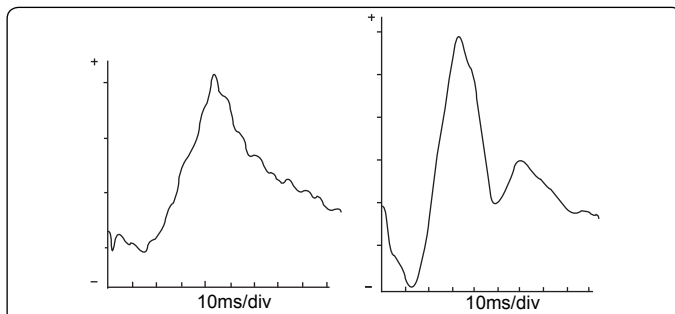


Figure 1: Flash ERG (left) at one month preinjection with low amplitude a wave and latency of 44.52 ms and (right) at 6 months post injection with developed a and b- wave with latency 34.90 ms.

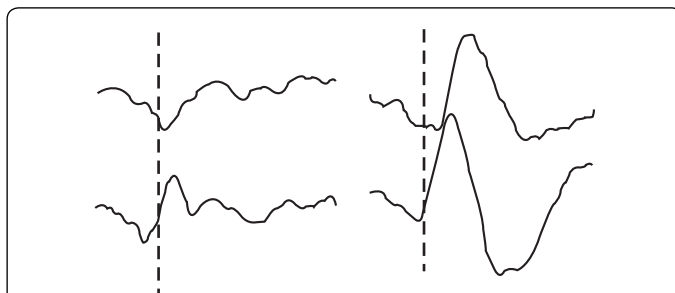


Figure 2: Flash VEP (left) at one month preinjection and (right) at 6 months post injection.

Two injections was required in our study in four eyes (22.22%) and three injections was required in 2 eyes (11.11%) for stage 3 plus zone 2 for complete resolution to occur and this was at 4 weeks interval from the previous injection if there are no signs of regression. So our observations, from the current study there seems to be faster regression of the disease and a greater extent of regression and stabilization in more term babies with less preinjection severity of the disease. while in less birth weight and less gestational age babies 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 but this needs further study to proof.

Published data demonstrate that ROP is primarily linked with low gestational age and birth weight [9]. Our study confirmed that these were the significant risk factors for ROP. The other risk factors for ROP were not significant in our study as all babies were in mechanical ventilation for period which is statistically not significant > 0.05 between the patients and only one case got intracranial haemorrhage which disappeared spontaneously after one month with 5th minutes Apgar score were nearly same for all.

In our study the overall final success rate was 100% and this was comparable with intravitreal bevacizumab in other studies [5,6,10,11]. In comparison with success of treatment of ROP stage 3 by the use of other methods of treatment cryotherapy and when treated with laser photocoagulation 87.5% [12] -92% [13] and cryotherapy (40%) [12]. so success rate was higher in our study than both laser and cryotherapy.

In our study there were no local or systemic adverse effects even with multiple injections and this were comparable with other studies [5,6,10,11]. So intravitreal injection with an anti-VEGF agent might also avoid complications that can be seen with laser such as the onset of visual field loss, macular burn, or anterior segment ischemia.

Regarding the long-term efficacy in our study, ERG and VEP findings were within normal at 1 year follow up and this was comparable with other studies [5,6,10,11].

Conclusions

Intravitreal injection of bevacizumab is an easy, safe and effective modality of therapy for threshold disease ROP especially in presence of difficulties for laser photocoagulation. Less gestational age and less birth weight are of higher risk to develop ROP. However, further prospective, randomized, controlled clinical trials with larger number of enrolled patients are necessary to determine the best choice of drug, as well as optimal dose and timing, the need for repeat treatments and the possibility of ocular or systemic complications.

References

1. International Committee for the Classification of Retinopathy of Prematurity (2005) The International Classification of Retinopathy of Prematurity Revisited. *Arch Ophthalmol* 123: 991-999.
2. Chen J, Smith LE (2007) Retinopathy of prematurity. *Angiogenesis* 10: 133-140.
3. Sears JE (2008) Anti-vascular endothelial growth factor and retinopathy of prematurity. *Br J Ophthalmol* 92: 1437-1438.
4. Mathew MR, Fern AI, Hill R (2002) Retinopathy of prematurity: Are we screening too many babies? *Eye (Lond)* 16: 538-542.
5. Chung EJ, Kim JH, Ahn HS, Koh HJ (2007) Combination of laser photocoagulation and intravitreal bevacizumab (Avastin) for aggressive zone I retinopathy of prematurity. *Graefes Arch Clin Exp Ophthalmol* 245: 1727-1730.
6. Lalwani GA, Berrocal AM, Murray TG, Buch M, Cardone S, et al. (2008) label use of intravitreal bevacizumab (Avastin) for salvage treatment in progressive threshold retinopathy of prematurity. *Retina* 28: S13-S18.
7. Graziano RM, Leone C (2005) Problemas oftalmológicos mais frequentes e desenvolvimento visual do pré-termo extremo. *J Pediatr (Rio J)* 81: S95-S100.
8. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M (1996) A United States national reference for fetal growth. *Obstet Gynecol* 87: 163-168.
9. Chiang MF, Arons RR, Flymm JT, Starren JB (2004) Incidence of retinopathy of prematurity from 1996 to 2000. Analysis of a comprehensive New York State patient database. *Ophthalmology* 111: 1317-1325.
10. Wu WC, Yeh PT, Chen SN, Yang CM, Lai CC, et al. (2010) Effects and Complications of Bevacizumab Use in Patients with Retinopathy of Prematurity: A Multicenter Study in Taiwan. *Ophthalmology*.
11. Kusaka S, Shima C, Wada K, Arahori H, Shimojyo H, et al. (2008) Efficacy of intravitreal injection of bevacizumab for severe retinopathy of prematurity: a pilot study. *Br J Ophthalmol* 92: 1450-1455.
12. Noonan CP, Clark DI (1996) Trends in the management of stage 3 retinopathy of prematurity. *Br J Ophthalmol* 80: 278-281.
13. Seiberth V, Linderkamp O, Vardarli I, Knorz MC, Liesenhoff H (1996) Diode laser coagulation of stage 3+ retinopathy of prematurity. *Ophthalmologie* 93: 182-189.

