ORIGINAL ARTICLE

Efficacy of Intravitreal Bevacizumab with Cryotherapy for Zone II Stage 3 + Retinopathy of Prematurity

Ali Kasiri[1]*, Foad Haghi[1], Mostafa Feghhí[1], Fereidon Farrahi[1], Hesam Hedayati[1], Mohammad Montazeri[2]

[1]Department of Ophthalmology, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, [2]Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Abstract

Objective: Vascular endothelial growth factor (VEGF), originally known as vascular permeability factor with different important roles in triggering vasculogenesis and angiogenesis. This protein has a pivotal role in retinopathy of prematurity (ROP). This study aims to evaluate the efficacy of VEGF inhibitor with cryotherapy for zone II Stage 3 plus ROP. **Methods:** In a prospective controlled clinical trial was performed on 6 infants, 12 eyes with zone II Stage 3 plus ROP. There was neurological visual impairment (NVI) in one eye. Under general anesthesia after confirmation of staging, prep and drape done cryotherapy of avascular retina in two rows combined with intravitreal injection of 0.625 mg bevacizumab in 0.025 ml was performed, and in one eye with iris neovascularization 0.625 mg intracameral bevacizumab injected too, all eyes were examined in 3 days, 1th, 4th, and 12th week after procedure. **Results:** Regression of NVI in 3 days and retinal neovascularization in 1 week period post operation. **Conclusion:** One session cryotherapy combined with intravitreal injection of 0.625 mg of bevacizumab can be effective in management of zone II Stage 3 plus ROP, more studies with more participants seems to be necessary.

Key words: Cryotherapy, intravitreal bevacizumab, prematurity, retinopathy

INTRODUCTION

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness worldwide. There is an abnormal proliferation of vessels in developing retina.[1] It affects the motor cortex, verbal, conceptual, and social development of the child.[2,3] It is characterized by proliferation of abnormal vessels in developing retina, such as diabetic and sickle cell retinopathies.[4,5] The international classification of ROP describes the progress and treatment method of the disease.[6,7] Vascular endothelial growth factor (VEGF), also known as vascular permeability factor, is a signal protein produced by cells that stimulate vasculogenesis and angiogenesis. It is a potent angiogenic factor and an essential growth factor for vascular endothelial cells. VEGF is up-regulated in many tumors, and its contribution to tumor angiogenesis is well defined the VEGF plays different important roles in ROP.[8] Destruction of cells due to hyperoxia causes the release of cell content and VEGF.[9] It causes the increase of fibrovascular tissue growth in peripheral retina specifically. These factors also exacerbate the growth of vessels in anterior and post segment.[9]

Treatments such as cryotherapy and laser therapy in suitable time causes decrease in VEGF, and neovascular proliferation, the treated patients, should be followed up carefully because cell destruction by cryotherapy and laser therapy may cause cell destruction and more release of VEGF.[10] The time of cryotherapy and laser therapy in patients with ROP is doubtful.[11] The time of development of complications in neovascular ROP is not exactly clear, and the exact time for cryotherapy and laser therapy is controversial.[12-16]

Address for correspondence:
Ali Kasiri, Department of Ophthalmology, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran E-mail: iranalikasiri343@gmail.com

Received: 12-05-2017
Revised: 22-05-2017
Accepted: 26-05-2017

The administration of anti-VEGF agents was useful in the treatment of different cancers, intravenous injection of bevacizumab in 2004 for the treatment of colon cancer and metastatic pulmonary cancer was successful.[17-21] The food and drug administration approved intravitreal bevacizumab injection for treatment of neovascular diseases of retina in 2006; it was used in age-related macular degeneration.[17-21] Ablative treatment employing cryotherapy and laser therapy in immature infants may stop the disease.[17-21]

According to the previous studies, there is not a suitable treatment for all patients, the disease may progress after cryotherapy and laser therapy in 10-15% of patients and retinal detachment may develop in 50% of patients with Stage 3 plus disease ROP.[9] Therefore, this study was aimed to evaluate the efficacy of intravitreal bevacizumab with cryotherapy for treatment of zone II Stage 3 plus ROP.

MATERIALS AND METHODS

In this prospective, controlled clinical trial study 6 patients, 12 eyes with zone II Stage 3 ROP were enrolled in the study. These patients were referred to Imam Khomeini Hospital of Ahvaz in 2010-2011; all patients had Hx of neonatal intensive care unit admission. There was not any systemic anomaly in all patients. One eye only had neurological visual impairment for 3 O'clock. The mean gestational age and weight were 28 weeks (26-35 weeks) and 1280 g (1150-1500 g), respectively.

All patients were examined under GIA by three retina specialists using indirect ophthalmoscope to confirm the staging of the disease first, then prep and drape was done using 5% betadine solution, blepharostat was placed, cryotherapy was performed to ablate the avascular retina in two rows with mild whitening of avascular retina, CO_2 gas was used for cryotherapy, then 0.625 mg of bevacizumab in 0.025 ml was injected in vitreous using a 30 gauge needle, 1.5 mm post to limbus, this dosage was selected because vitreous volume in infants is percentage of adults vitreous volume.

One patient with iris neovascularization received intracameral 0.625 mg of bevacizumab additionally; at the end of procedure one drop 5% betadine was installed in the eye for 1 min. The eye was examined by indirect ophthalmoscope for possible intra-operative complications. The patients were treated with topical chloramphenicol eye drops QID for 4 days. All patients were examined on 3 days, 1st, 4th and 12th week after the procedure to evaluate the condition of retina and abnormal vessels. All of the study procedures and the potential benefits and risks were clearly explained to the participants and their parents and then, the parents of children filled and signed a written consent form on the participation in the study. For data analyses, a statistical package of SPSS (version 16) with Chi-square test was used.

RESULTS

Retinal vessel tortuosity was decreased significantly and iris neovascularization improved 3 days after injection, and retinal neovascularization was disappeared in all patients after 1 week. Descriptive data of cases illustrated in Table 1.

There was no ROP in all patients after 4 weeks. A small preretinal hemorrhage developed in one patient, which was absorbed in 3 weeks. There was no sign of endophthalmitis or increased intraocular pressure in the follow-up assessments.

DISCUSSION

There was zone II Stage 3 plus disease ROP in all eyes, iris neovascularization was present in one eye, cryotherapy and intravitreal injection of bevacizumab were performed for all eyes. The eye with iris neovascularization received intracameral bevacizumab too.

Neovascularization of iris and vessel tortuosity and dilation were resolved after 3 days. Retinal neovascularization regressed after 1 week. According to the previous studies, cryotherapy and laser therapy may be insufficient for cure, and the disease may progress in 10-15% of patients, and retinal detachment may develop in 50% of Stage 3 plus disease ROP patients.[9]

Since the effect of cryotherapy may be insufficient for treatment of ROP, intravitreal injection of bevacizumab was done at the time of cryotherapy. In one study in 2007, patients were divided into three groups. The first group was treated with intravitreal bevacizumab, and in the second group one eye of each patient was treated with laser therapy and intravitreal bevacizumab injection in the same eye, and in the third group both eyes of each patient were treated with laser therapy and intravitreal bevacizumab injection. The findings of this study demonstrated that the neovascularization regressed in all groups no systemic complication was noted.[22] There are four studies in literature; that shows an intravitreal injection of bevacizumab was effective in regression of fibrovascular tissue in ROP patients.[23] In one eye which laser therapy was not successful, 7 days after injection of intravitreal bevacizumab vascular tissue regressed but tractional retinal detachment develops due to contraction of fibrotic tissue.[24]

In another study, 13 eyes were enrolled; retinal detachment developed in 4 eyes after intravitreal injection of bevacizumab and all of them were treated by deep vitrectomy.[10] VEGF is necessary for normal vascularization in growing infants, and anti-VEGF properties can be harmful for normal vascularization.[25] Pediatric oncologist used systemic bevacizumab injection for treatment of soft tissue malignancies in 20 patients.(kind and reference) The administration of the drug was every 2 weeks, to control the effect Of bevacizumab on growth plate of long bones,

Table 1: Descriptive data of cases

Sex	Zone	Stage	Iris neovascularization	Weight of birth	GA	Age in injection	Sepsis	PDA	ICH
Female	II	3b	+	1250	35	40	-	-	-
Male	II	3b	-	1500	32	39	-	-	-
Male	II	3b	-	1150	29	40w	-	-	-
Male	II	3b	-	1300	28	38	-	-	-
Female	II	3b	-	1256	27	36	-	-	-
Female	II	3b	-	1150	26	34	-	-	-

ICH: Intracranial hemorrhage, PDA: Patent ductus arteriosus, GA: Gestational age

X-ray films were obtained from tibia and fibula every 2 weeks.[25]

This study shows that systemic administration of bevacizumab in doses <15 mg/kg is tolerated well without any side effect, no hypertension and cardiopulmonary side effects were noticed in this study.[25] Similarly, Autrata *et al*. showed that cryotherapy and laser therapy destroyed the retinal tissue and the concentration of VEGF during the study period was significantly reduced which in turn enhanced the therapeutic efficacy of the combined approach in ROP.[26] The findings of our study support this finding indicating effective therapeutic efficacy of combined cryotherapy with laser therapy for treatment of Stage 3 plus ROP.

CONCLUSION

This study tried to evaluate the efficacy of intravitreal bevacizumab with cryotherapy for treatment of zone II Stage 3 plus ROP in the rat model. The results showed that combining cryotherapy with intravitreal injection of bevacizumab could rapidly inhibit the VEGF activity and therefore, significantly improved the therapeutic effect of the combined treatment approach in ROP. However, further controlled studies are needed to reach a decisive conclusion on the efficacy of cryotherapy combined with intravitreal bevacizumab in the treatment of zone II Stage 3 plus ROP.

REFERENCES

1. Wheatley CM, Dickinson JL, Mackey DA, Craig JE, Sale MM. Retinopathy of prematurity: Recent advances in our understanding. Arch Dis Child Fetal Neonatal Ed 2002;87:F78-82.
2. Mets MB. Childhood blindness and visual loss: An assessment at two institutions including a 'new' cause. Trans Am Ophthalmol Soc 1999;97:653-96.
3. Piccioni A, Lanners J, Goergen E, editors. Early rehabilitation in retinopathy of prematurity children (0-4 years). Progress in Retinopathy of Prematurity. Proceedings of the International Symposium on Retinopathy of Prematurity; 1997.
4. Earl AP, Arnall P, Dalel LP. Retinopathy of Prematurity. Messoouri: Mosby; 1472-5.
5. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter Trial of Cryotherapy for Retinopathy of Prematurity: Ophthalmological outcomes at 10 years. Arch Ophthalmol 2001;119:1110-8.
6. Multicenter trial of cryotherapy for retinopathy of prematurity. Preliminary results. Cryotherapy for retinopathy of prematurity cooperative group. Arch Ophthalmol 1988;106:471-9.
7. Palmer EA, Flynn JT, Hardy RJ, Phelps DL, Phillips CL, Schaffer DB, *et al.* Incidence and early course of retinopathy of prematurity. The cryotherapy for retinopathy of prematurity cooperative group. Ophthalmology 1991;98:1628-40.
8. Stone J, Itin A, Alon T, Pe'er J, Gnessin H, Chan-Ling T, *et al.* Development of retinal vasculature is mediated by hypoxia-induced vascular endothelial growth factor (VEGF) expression by neuroglia. J Neurosci 1995;15:4738-47.
9. Early Treatment For Retinopathy Of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: Results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol 2003;121:1684-94.
10. O'Keefe M, Lanigan B, Long VW. Outcome of zone 1 retinopathy of prematurity. Acta Ophthalmol Scand 2003;81:614-6.
11. Pediatrics AA. Screening examination of premature infants for retinopathy of prematurity. Pediatrics 2006;117:572-6.
12. Averbukh E. The evidence supporting the early treatment for Type 1 retinopathy of prematurity needs further evaluation. Arch Ophthalmol 2005;123:406.
13. Chiang MF, Jiang L, Gelman R, Du YE, Flynn JT. Interexpert agreement of plus disease diagnosis in retinopathy of prematurity. Arch Ophthalmol 2007;125:875-80.
14. Coats D, Saunders R. The dilemma of exercising clinical judgment in the treatment of retinopathy of prematurity. Arch Ophthalmol 2005;123:408-9.
15. Jalali S, Essuman VA, Thomas R. Clinical application of the revised indications for the treatment of retinopathy of prematurity. Arch Ophthalmol 2005;123:407-8.
16. Vander JF, McNamara JA, Tasman W, Brown GC.

Revised indications for early treatment of retinopathy of prematurity. Arch Ophthalmol 2005;123:406-7.
17. Multicenter trial of cryotherapy for retinopathy of prematurity. One-year outcome-Structure and function. Cryotherapy for retinopathy of prematurity cooperative group. Arch Ophthalmol 1990;108:1408-16.
18. Nagata M. Treatment of acute retrolental fibroplasia with xenon arc photocoagulation. Jpn J Ophthalmol 1972;16:131-43.
19. Nagata M, Kobayashi Y, Fukuda H, Suekane K. Photocoagulation for the treatment of the retinopathy of prematurity. Jpn J Clin Ophthalmol 1968;22:419-27.
20. Payne JW, Patz A. Treatment of acute proliferative retrolental fibroplasia. Trans Am Acad Ophthalmol Otolaryngol 1972;76:1234-46.
21. Yamashita Y. Studies on retinopathy of prematurity. III. Cryocautery for retinopathy of prematurity. Jpn J Clin Ophthalmol 1972;26:385.
22. Shah PK, Narendran V, Tawansy KA, Raghuram A, Narendran K. Intravitreal bevacizumab (avastin) for post laser anterior segment ischemia in aggressive posterior retinopathy of prematurity. Indian J Ophthalmol 2007;55:75.
23. Lalwani GA, Berrocal AM, Murray TG, Buch M, Cardone S, Hess D, *et al*. Off-label use of intravitreal bevacizumab (avastin) for salvage treatment in progressive threshold retinopathy of prematurity. Retina 2008;28:S13-8.
24. Kusaka S, Shima C, Wada K, Arahori H, Shimojyo H, Sato T, *et al*. Efficacy of intravitreal injection of bevacizumab for severe retinopathy of prematurity: A pilot study. Br J Ophthalmol 2008;92:1450-5.
25. Glade Bender JL, Adamson PC, Reid JM, Xu L, Baruchel S, Shaked Y, *et al*. Phase I trial and pharmacokinetic study of bevacizumab in pediatric patients with refractory solid tumors: A Children's Oncology Group Study. J Clin Oncol 2008;26:399-405.
26. Autrata R, Krejcírová I, Senková K, Holoušová M, Doležel Z, Borek I. Intravitreal pegaptanib combined with diode laser therapy for stage 3 retinopathy of prematurity in zone I and posterior zone II. Eur J Ophthalmol 2012;22:687-94.

Source of Support: Nil. **Conflict of Interest:** None declared.