Intravitreal Bevacizumab Injection in Advanced Retinopathy of Prematurity

Janejit Choovuthayakorn MD*,
Ubonrat Khiaocham MD*

** Department of Ophthalmology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*

Objective: *To report the efficacy of intravitreal bevacizumab injection for advanced retinopathy of prematurity (ROP) patients.*

Material and Method: *A retrospective chart review was performed for 19 advanced ROP patients (34 eyes), who had intravitreal bevacizumab injection between January 1, 2007 and July 31, 2009 at Chiang Mai University Hospital. The baseline characteristics including gestational age, postmenstrual age of first injection, anterior and posterior segment changes, and complications between treatments to 1-year followed-up were analyzed.*

Results: *The patients were divided into 2 groups according to the indications for treatment. Group 1, two patients (4 eyes), received initial intravitreal bevacizumab injection followed by laser photocoagulation due to aggressive posterior disease. Group 2, seventeen patients (30 eyes), received intravitreal bevacizumab injection due to persistence of the vascular activity after laser treatment. There were statistical significant difference between the two groups in terms of a mean gestation age, a mean birth weight, and a mean time for first intravitreal injection (p = 0.002, 0.008, and 0.007 respectively). However, there was no statistical significant difference between the two groups in terms of timing for resolution of vascular activity and retinal vasculogenesis across the laser scar (p = 0.172). One patients with aggressive posterior disease progressed to stage 4A ROP with successful anatomical attachment by pars plana vitrectomy. At 1-year follow-up, no other ocular or systemic side effects were observed. There was no statistical significant difference of a mean spherical equivalent between the two groups (p = 0.280).*

Conclusion: *Intravitreal bevacizumab injection is an effective procedure either as an adjuvant or initial treatment in advanced ROP cases.*

Keywords: *Intravitreal bevacizumab injection, Laser photocoagulation, Advanced retinopathy of prematurity*

J Med Assoc Thai 2012; 95 (Suppl. 4): S70-S75
Full text. e-Journal: *http://www.jmat.mat.or.th*

Retinopathy of prematurity (ROP) is a proliferative disorder of the retinal vasculature in premature infants. Due to medical advancement in neonatal care, the survival rate for extremely premature infants has increased in accordance with the number of ROP cases. The biphasic hypothesis for pathophysiology of ROP includes the first hyperoxic phase and the second retinal hypoxic phase, resulting in upregulation of vascular endothelial growth factor (VEGF) expression, neovascularization, or, in some cases, tractional retinal detachment[1,2].

Currently, the standard treatment for ROP is retinal ablation, resulting in downregulation of VEGF expression. Laser photocoagulation is attributable to fewer adverse effects over cryotherapy and has become the first line treatment in ROP[3-6]. Although studies have reported a decreasing progression of this disease, ablative retinal treatment is not absolutely effective in promoting the regression of ROP, especially in aggressive posterior (AP-ROP) form. Despite the treatment, the multicenter trial of cryotherapy for retinopathy of prematurity (CRYO-ROP) showed visual acuity of 6/60 or worse and unfavorable structural outcome in 44.7% and 30% of eyes respectively[7]. The multicenter trial of early treatment for retinopathy of prematurity (ET-ROP) showed the benefit of early treatment in type 1 prethreshold disease. Nevertheless, 65.4% of eyes treated early developed visual acuity of worse than 6/12[8,9].

With the availability of anti-VEGF drugs in this era, reports of alternative ROP treatment, with bevacizumab aiming to block excessive levels of VEGF already trapped within the vitreous cavity, have been published as monotherapy[10,11], combined with either

Correspondence to:
Choovuthayakorn J, Department of Ophthalmology, Faculty of Medicine 110 Intawaroros Road, Chiang Mai 50200, Thailand.
Phone: 053-945-512-3, Fax: 053-946-121
E-mail: janjitc@yahoo.com

laser photocoagulation[12-15], or vitrectomy[16,17]. Bevacizumab (Avastin; Genentech Inc, South San Francisco, CA, USA), is a completely humanized monoclonal antibody directed against all biological forms of VEGF. The present study was a noncomparative, retrospective, interventional case series which reported the outcomes of intravitreal bevacizumab injection in AP-ROP and in persistence neovascularization patients after conventional laser photocoagulation.

Material and Method

A retrospective chart review was performed to identify the ROP patients treated with intravitreal bevacizumab injection between January 1, 2007 and July 31, 2009 at Chiang Mai University Hospital. The patients were divided into 2 groups according to the indications for treatment: 1) AP-ROP patients with poor pupillary dilation or media opacities precluding standard laser treatment, 2) patients with persistent neovascular activity despite complete laser treatment. The data from medical records were analyzed, including those for gestational age (GA), birth weight (BW), ROP staging, postmenstrual age (PMA) at first treatment, timing of full involution and/or development of retinal detachment, ocular complications and cycloplegic refraction at 1-year follow-up period. Informed consent was obtained from parents or legal guardians after thoroughly discussing the off-label, potential of local or systemic risks and complications of bevacizumab injection. All injections were performed in the operating room under topical anesthesia. The eyes were prepared by 0.5% proparacaine hydrochloride ophthalmic solution and 5% povidone-iodine. Bevacizumab at 0.625 mg (0.025 mL) was then injected inferotemporally into the vitreous cavity 1 mm behind the limbus under surgical microscope. The retinal artery perfusion was checked by an indirect ophthalmoscope. Antibiotic eye drops were prescribed for every 6 hours for 1 week. The patients were followed-up at day 1, then at 1, 2, 4 and 8 weeks, 6 and finally at 12 months. The present study was approved by the intuitional review board of the Faculty of Medicine, Chiang Mai University, Thailand.

Statistical analysis

The frequency, mean and standard deviation (SD) were used to summarize the results between two groups. Mann-Whitney U test was used to compare means between two groups. P-value was set at 0.05 for significant.

Results

The 19 infants (34 eyes; 9 males and 10 females) were included in the present study. A mean gestational age was 27.82 $\pm$ 3.51 (range; 20 to 32) weeks, mean birth weight was 1,049.68 $\pm$ 286.03 (range; 600 to 1,890) g and mean PMA at the time of intravitreal injection was 38.26 $\pm$ 3.26 (range; 32 to 44) weeks. All infants were treated by two surgeons (JC and UK). The patients in group 1, two patients (4 eyes), had stage 3 zone 1 ROP (AP-ROP). They received intravitreal bevacizumab injections as the initial treatment due to opacities of the media and poor dilation of the pupil, followed by laser treatment within 1 week. This subgroup of patients had a mean gestational age (GA) of 22.00 $\pm$ 2.31 (range; 20 to 24) weeks, a mean birth weight of 675.00 $\pm$ 86.60 (range; 600 to 750) g, a mean PMA at the time of intravitreal treatment of 33.50 $\pm$ 1.73 (range; 32 to 35) weeks. Three eyes showed resolution of vascular activity and improvement of pupillary dilation within 24 hours. The retinal vessels were seen across the laser scar with a mean PMA of 45.00 $\pm$ 3.46 (range; 42 to 48) weeks. One eye progressed to stage 4A retinal detachment and anatomical attachment developed after successful lens-sparing vitrectomy performed at PMA of 39 weeks.

Group 2, seventeen patients (30 eyes), 3 patients (6 eyes) had stage 3 zone 1 ROP, 14 patients (24 eyes) had stage 3 zone 2 ROP. They were received intravitreal bevacizumab injection after persistent vascular activity even though complete near confluent laser photocoagulation was performed. This subgroup of patients had a mean gestational age (GA) of 28.79 $\pm$ 2.87 (range; 20 to 32) weeks, a mean birth weight of 1,113.89 $\pm$ 269.12 (range; 600 to 1,890) g, a mean PMA at the time of intravitreal treatment of 39.11 $\pm$ 2.82 (range; 34 to 44) weeks. All eyes showed resolution of vascular activity. The retinal vessels were seen across the laser scar with a mean PMA of 43.68 $\pm$ 2.49 (range; 40 to 48) weeks. The patient characteristics are shown in Table 1. The statistic showed significant difference between 2 groups in terms of a mean GA, a mean BW and a mean time for intravitreal injection ($p = 0.002$, 0.008, and 0.007 respectively). However, there was no statistical significant difference in terms of timing for resolution of vascular activity and retinal vasculogenesis across the laser scar ($p = 0.172$).

At 1-year follow-up, none of the patients received re-injection. There were no ocular or systemic adverse events observed. All eyes had attached retina with a mean spherical equivalence of -0.79 $\pm$ 1.84 (range; -5.25 to +5.00) diopters (D) and a mean cylindrical

equivalence of -0.56 ± 0.57 (range -1.50 to 0.00) D. There was no statistical significant difference of a mean spherical equivalent between the two groups (p = 0.280).

Discussion

Laser photocoagulation is the standard treatment for ROP at present. However, it is not a suitable procedure in some situations such as haziness of the ocular media, presence of exudative retinal detachment, or presence of tractional fibrovascular membrane, which may delay the treatment and lead to retinal detachment in advanced ROP cases[18]. The authors showed that intravitreal injection of bevacizumab, either as an adjuvant to laser treatment or as primary treatment, effectively decreased retinal vascular activity in ROP. Regression of tunica vasculosa lentis, reducing iris vascular engorgement, and improving pupillary dilation were seen within 24 hours, which was in accordance with other authors[12,13]. Chung et al reported regression of these anterior segment signs from day 1 and clearly observed at 1 week post-injection[19]. Recently, the recurrence vascular activity of ROP after intravitreal bevacizumab injection has been reported. Mintz-Hittner et al, BEAT-ROP study, have reported that the recurrence activity of ROP occurred in more patients of the laser group than in the bevacizumab group[10]. Thus appropriate follow-up schedule is necessary after treatment. With small numbers of patients, the authors revealed no retinal vascular reactivity and none received re-intravitreal bevacizumab injection. VEGF also plays an important role in normal retinal vasculogenesis. Anti-VEGF treatment in very premature patients is still of major concern. With a mean PMA of 38.3 weeks at the time of intravitreal bevacizumab injection, the involution of neovascularization and development of retinal vessels across the laser scar were shown in all cases.

The vitreous level of VEGF in eyes with ROP was found to be significantly higher in vascular active ROP[20]. Decreasing of unbound VEGF concentration in ROP eyes after intravitreal bevacizumab injection produced successful as adjunctive therapy for advanced ROP cases[21]. Nevertheless, anti-VEGF reduces the angiogenesis component and simultaneously accelerates the contraction of fibrous membrane components, which may aggravate tractional retinal detachment[16,22]. The authors reported development of stage 4A ROP in one patient after 4 weeks of intravitreal bevacizumab injection. Therefore, use of anti-VEGF in stage 4 and 5 ROP patients should be taken with caution[22].

In terms of post-laser photocoagulation refraction, Axer-Siegel et al reported a mean spherical equivalence of -1.5 D in the threshold ROP cases, and Connolly et al reported a mean spherical equivalent of -4.48 D[23,24]. With limited follow-up period, the authors revealed an early refractive outcome with a mean spherical equivalence -0.79 D and a mean cylindrical equivalence of -0.56 D after initial and adjuvant intravitreal bevacizumab injection which was lower than laser treatment reported by Axer-Siegel et al and Connolly et al. Nevertheless, with changing of refraction in young children, the refraction should be compared in a longer follow-up period. The authors also reported none of ocular or systemic adverse reactions were observed. The information from the present study should be carefully determined.

Limitations of the present study were the small numbers of patients, a nonrandomized, noncontrolled retrospective nature, and a short follow-up period for only one year. Therefore, the present study had no long term assessment of neurodevelopmental outcomes and safety profile of intravitreal bevacizumab injection.

Conclusion

Intravitreal anti-VEGF injection is an effective alternative treatment for ROP that under investigation. The major benefit of anti-VEGF is the acute suppression of a pathologically high level of VEGF, thus limiting tissue destruction and permitting visualization of the fundus especially for AP-ROP. However, VEGF is essential for retinal and neuronal differentiation. The effects of bevacizumab should be carefully monitored in a long term follow-up to assess possible complications in adolescence or adulthood. Without the data from large randomized clinical trials with adequate power, the treatment should be strictly justified.

What is already known on this topic

Retinopathy of prematurity (ROP) is a biphasic pathogenesis proliferative disease. Laser photocoagulation is the standard treatment for ROP in the past with further progression in some groups of patients despite treatment.

What this study adds

Vascular endothelial growth factor is one of the intrinsic factors leading to the disease development. Intravitreal anti-vascular endothelial growth factor injection is the treatment under investigations. The

Table 1. Demographic data of patients (19 infants: 34 eyes)

	Group 1	Group 2	p-value
Number of patients (eyes)	2(4)	17(30)	
Stage 3 zone 1	2(4)	3(6)	
Stage 3 zone 2	0	14 (24)	
Sex (male /female)	1/1	8/9	0.966*
Mean GA (weeks) ± SD	22.0 ± 2.3	28.8 ± 2.9	0.002*
Mean BW (grams) ± SD	675.0 ± 86.6	1,113.0 ± 269.1	0.008*
Mean age at injection (weeks) ± SD	33.5 ± 1.7	39.1 ± 2.8	0.007*
Mean age at resolution (weeks) ± SD	45.0 ± 3.5	43.7 ± 2.5	0.172*
Mean refraction at 1 year (Diopters) ± SD	1.7 ± 3.1	1.2 ± 1.0	0.278*
Sphere	1.9 ± 3.3	-0.9 ± 1.4	0.170*
Astigmatism	-1.2 ± 0.25	-0.5 ± 0.6	0.710*
Spherical equivalent	1.7 ± 3.1	-1.4 ± 1.3	0.280*

Group 1 = Aggressive posterior retinopathy of prematurity patients with intravitreal bevacizumab injection as an initial treatment
Group 2 = Persistent neovascular activity patients with intravitreal bevacizumab injection as an adjunctive treatment
GA = Gestation age, BW = Birth weight, SD =Standard deviation,
*$p < 0.05$ = clinically significance

authors reported the efficacy of intravitreal bevacizumab injection in aggressive posterior ROP and in unsuccessful laser photocoagulation ROP patients. Intravitreal bevacizumab injection is alternative treatment with careful justification in advanced ROP cases.

Acknowledgment

The authors wish to thank Chanphet Butsabongphaiwan, Patthama Gakum, and Jiraporn Wongsirimaeteekul for their nursing care assistance.

Potential conflict of interest

None.

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การฉีดยา bevacizumab เข้าวุ้นตาทารกคลอดก่อนกำหนดที่มีจอตาผิดปกติในรายที่มีอาการรุนแรง

เจนจิต ชูวุฒยากร, อุบลรัตน์ เขียวฉ่ำ

วัตถุประสงค์: *เพื่อรายงานประสิทธิภาพของการใช้ยา bevacizumab ฉีดเข้าวุ้นตาทารกคลอดก่อนกำหนดที่มีจอตาผิดปกติในรายที่มีอาการรุนแรง*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาย้อนหลังจากเวชระเบียนของทารกคลอดก่อนกำหนดที่มีจอตาผิดปกติในรายที่มีอาการรุนแรงจำนวน 19 คน (34 ตา) ที่ได้รับการรักษาด้วยการฉีดยา bevacizumab เข้าวุ้นตาระหว่างวันที่ 1 มกราคม พ.ศ. 2550 ถึงวันที่ 31 กรกฎาคม พ.ศ. 2552 ณ โรงพยาบาลมหาราชนครเชียงใหม่ โดยทำการเก็บรวบรวมข้อมูลทั่วไป ข้อมูลทางจักษุวิทยา และภาวะแทรกซ้อนอื่น ๆ ตั้งแต่เริ่มการรักษาจนเมื่อติดตามผลการรักษาครบ 1 ปี*

ผลการศึกษา: *เมื่อพิจารณาตามข้อบ่งชี้ในการรักษาพบว่าสามารถแบ่งผู้ป่วยออกเป็น 2 กลุ่มคือ กลุ่มแรกจำนวน 2 คน (4 ตา) ได้รับการรักษาโดยการฉีดยา bevacizumab เข้าวุ้นตาตั้งแต่เริ่มแรกและตามด้วยการยิงเลเซอร์ภายใน 1 สัปดาห์ กลุ่มที่ 2 จำนวน 17 คน (30 ตา) ได้รับการฉีดยา bevacizumab เข้าวุ้นตาหลังจากการรักษาโดยเลเซอร์แล้วไม่สามารถทำให้ภาวะหลอดเลือดที่ผิดปกติฝ่อลงได้หมด ทารกในกลุ่มแรกมีค่าเฉลี่ยอายุแรกคลอด ค่าเฉลี่ยน้ำหนักแรกคลอด และค่าเฉลี่ยอายุที่ได้รับการฉีดยา bevacizumab เข้าน้ำวุ้นตาน้อยกว่าทารกในกลุ่มที่สองอย่างมีนัยสำคัญ (p = 0.002, 0.008 และ 0.007 ตามลำดับ) อย่างไรก็ตามผู้ป่วยทั้งสองกลุ่มมีระยะเวลาในการถดถอยของโรคและมีการพัฒนาระบบหลอดเลือดจอตาไปจนถึงจอตาส่วนริมไม่แตกต่างกันอย่างมีนัยสำคัญ (p = 0.172) ผู้ป่วยกลุ่มแรกจำนวน 1 คน (1 ตา) มีการดำเนินโรคแย่ลงจนเกิดจอตาลอกในระยะ 4A แต่สามารถผ่าตัดรักษาให้จอตากลับมาอยู่ในกายวิภาคเดิม เมื่อติดตามผลการรักษาครบ 1 ปี ไม่พบรายงานภาวะแทรกซ้อนทางจักษุวิทยาและทางร่างกายอื่น ๆ โดยทารกทั้งสองกลุ่มมีค่าสายตาไม่แตกต่างกันอย่างมีนัยสำคัญ (p = 0.280)*

สรุป: *การฉีดยา bevacizumab เข้าวุ้นตาเป็นวิธีการรักษาที่มีประสิทธิภาพทางเลือกหนึ่งในการรักษาทารกคลอดก่อนกำหนดที่มีจอภาพผิดปกติที่มีข้อบ่งชี้คือไม่สามารถใช้เลเซอร์รักษาในขั้นต้นได้ และในผู้ป่วยที่ได้รับการรักษาโดยเลเซอร์แล้ว ไม่สามารถควบคุมให้หลอดเลือดที่ผิดปกติฝ่อลงได้หมด*