Combine Intravitreal Bevacizumab Injection with Laser Treatment for Aggressive Posterior Retinopathy of Prematurity (AP-ROP)

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Objective*: To assess a new method the "Combine Treatment" consisted of diode laser photocoagulation and intravitreal bevacizumab for treatment of AP-ROP.*
Material and Method*: These retrospective and non-comparative case series study in twelve premature infants (7 Male, 5 Female) from ROP clinic with diagnosis of aggressive posterior retinopathy of prematurity (AP-ROP) based on indirect ophthalmoscopic examination were included in the present study. The "Combine Treatment" consisted of one treatment session in which diode laser photocoagulation was applied in the avascular zone (anterior and posterior to the presumed ridge include vascular nets up to the clear retina) followed by intravitreal injection of Bevacizumab (Avastin)®. Fundus photographs were obtained before and after the treatment using a wide-field digital pediatric imaging system (RetCam).*
Results: *Twenty-three eyes were treated with the "Combine Treatment". The rest were treated with only laser abrasion. All patients got favorable anatomical outcomes of all treated eyes. Proliferative tissue started regress 2 weeks after treatment and completed regress about 4.92 weeks (range; 3-7 weeks). There was neither progression of disease nor serious ocular or systemic complications. No further treatments were needed.*
Conclusion: *In the present study, one session of the "Combine Treatment" leads to favorable anatomical outcomes for patients with AP-ROP. This new approach prevents aggressive progression and offers hope of good future vision to patients. The authors hope that this new approach will be another choice of treatment to prevent aggressive progression of the disease and gain good vision in the future.*

Keywords: *Aggressive posterior retinopathy of prematurity (AP-ROP), Intravitreal bevacizumab, Combine treatment, Anti-VEGF*

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Retinopathy of prematurity (ROP) is a proliferative disorder of developing retina that continues to be a major cause of blindness of children in developed and developing country[1,2]. Blindness resulting from ROP may be prevented with the proper timely treatment. Most of ROP patients are associated with early gestational age and low birth weight[3]. The current theory about ROP is a biphasic disease consisting of an initial phase of oxygen-induced vascular obliteration followed by a period of hypoxia-induced vessel proliferation[4]. In most premature infants, retinal vascularization eventually resumes without significant sequelae. However, in some infants the prolonged time hypoxia experienced by an avascular retinal periphery causes an abnormal increase in vascular endothelial growth factor (VEGF) production[5,6]. Subsequently, at a time when intra-ocular VEGF levels would normally be declining late in the third trimester of pregnancy, abnormally high levels of VEGF are observed due to large areas of avascular retina and associated time hypoxia. The therapeutic efficacy of peripheral retinal ablation is defined in Retinopathy of Prematurity and Early Treatment ROP study[3,7]. A subset of patients with particularly aggressive (zone 1 cases) disease tends to progress early and rapidly to

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retinal detachment and blindness despite timely ablation[8-14]. Aggressive posterior retinopathy of prematurity (AP-ROP) is introduced in the revised retinopathy of prematurity classification[8] and is frequently associated with congestion of iris vessels, prominence of tunica vasculosa lentis, poor pupillary dilatation and vitreous haze (all of which can compromise the integrity of the examination and completeness of laser treatment). The advent of anti-VEGF drug has revised the possibility of treating selected cases of retinopathy of prematurity off-label with these medications. As VEGF is required in the developing retina for normal angiogenesis, the goal of treatment is to quench the excessive levels of VEGF in the vitreous rather than to penetrate retinal tissue. Futhermore, as VEGF activity is endogenously down-regulated around the time of the due date. The choice of bevacizumab is deliberated in an attempt to minimize the possibility of systemic complications. The molecular weight of bevacizumab is 149 kd, that of VEGF-trap (investigational) is 110 kd and that of ranibizumab (Lucentis; Genentech, Inc.) is 48 kd. Only 1: 1,000 of bevacizumab level in the treated eye has been shown (in rabbits) to be present in the non-treated eye or in the blood[15]. Since 2007, several articles have been reported regarding the use of bevacizumab for treatment of AP-ROP. Several studies reveal use 0.5-1.25 mg intravitreal injection[16-20]. No report shows ocular or systemic side effect because appropriate laser treatment is still progress to tractional retinal detachment in AP-ROP. Thus, the authors tried to do diode laser ablation combined with intravitreal bevacizumab in one session for treatment of AP-ROP to stop the progression.

Material and Method

A retrospective review to premature infants was approved by the Queen Sirikit National Institute of Child Health Review Board. Inclusion criteria included preterm babies with AP-ROP diagnosed according to the International Classification of Retinopathy of Prematurity and treated from January 2010 to October 2010). They were referred patients and hadn't been treated before. All the process was done under general anesthesia and sterile technique. Avcascular retina was treated with a diode laser in a near confluent pattern extending ora serrata to the anterior ridge or neovascular tissue. After laser photocoagulation with diode laser, the procedure of intravitreal bevacizumab was done under microscope using tooth forceps to stabilize the eye in injected 0.02 ml = 0.5 mg bevacizumab at temporally behind the lens. The needle entered the sclera through the conjunctiva = 1.0 mm behind the limbus and the dose was injected approximately two thirds of the length of the needle and was emptied completely into the central vitreous (the surgeon must carefully avoid touching the crystalline lens during the entire procedure). Then the needle was pulled out and stopped leakage using cotton tip to pressure at the needle site for fifteen seconds. No eye patch was needed. All patients were prescribed ophthalmic antibiotic drops given every 6 hours for 7 days. After laser treatment, the infants were examined every 1 or 2 weeks until the infant reached a post-conceptual age of 50 weeks. The anatomic outcomes at 1, 2, 4, 6, 8 and 10 weeks were evaluated by fundus examination. Some cases were photographed by the RetCam Imaging System (Clarity Medical Systems, Pleasanton, CA) immediately before and after (1 week, 2 weeks, 1 month and 2 months) the unilateral or bilateral single injection combined with laser photocoagulation.

Results

The present retrospective, non-comparative case series of 23 eyes of 12 patients diagnosed with aggressive posterior retinopathy of prematurity (AP-ROP) included 7 males and 5 females (Table 1) during a 10 month period. All infants with AP-ROP had zone 1 plus disease in all four quadrants and 360o of avascular retina (Fig. 1). They underwent combine treatment (laser photocoagulation with diode laser delivered through the indirect ophthalmoscope system with intravitreal bevacizumab) within 48 hours of AP-ROP diagnosis. The mean birth weight and gestational age were 1,275 gm (range; 750-1,600 gm) and 30 wk (range; 26-35 wk) respectively. The mean post conceptional age and chronological age at treatment were 35.83 wk (range; 32-43 wk) and 5.83 wk (range; 1-10 wk) respectively. All 23 eyes were treated successfully with one time combine treatment. Twenty-one eyes (91.3%) regressed with normal retinal anatomy (Fig. 2), only 2 eyes (8.7%) dragged disc with flat macular area. The mean regression time following combine treatment was 4.92 wk (range; 3-7 wk). Proliferative tissues started to regress around 2 wk after combine treatment. There were no cases of trauma to ocular structures and any evidence of endophthalmitis. No early or late systemic complication attributed to bevacizumab treatment has been recorded within 2 to 9 months of follow-up.

Discussion

Aggressive posterior retinopathy of prema-

Table 1. Summary of data for infants receiving combine laser ablation with intravitreal bevacizumab treatment for aggressive retinopathy of prematurity in zone

Case	Sex	Stage	Zone	Birth Weight (g)	Gestational Age (wk)	Injected eye	Age at treatment (wk)	Length of follow-up (wk)	Outcome
1	Female	3	1	1,360	32	OU	36	40	Regress
2	Male	3	1	750	26	OS	36	40	Regress
3	Male	3	1	1,350	35	OU	43	32	Regress
4	Female	2	1	1,175	28	OU	34	18	Regress
5	Female	2	1	1,520	33	OU	34	15	Regress
6	Male	3	1	1,405	30	OU	34	13	Dragged disc OD, regress OS
7	Male	3	1	1,300	29	OU	36	30	Regress
8	Male	3	1	1,270	30	OU	36	11	Dragged disc OS, regress OD
9	Female	3	1	1,250	27	OU	32	20	Regress
10	Female	3	1	1,330	33	OU	39	23	Regress
11	Male	3	1	955	28	OU	35	13	Regress
12	Male	2	1	1,640	29	OU	34	13	Regress
Mean				1,275	30		35.83		

OU = both eye, OD = right eye, OS = left eye, Regress is normal anatomical retinal vessel and retinal structure

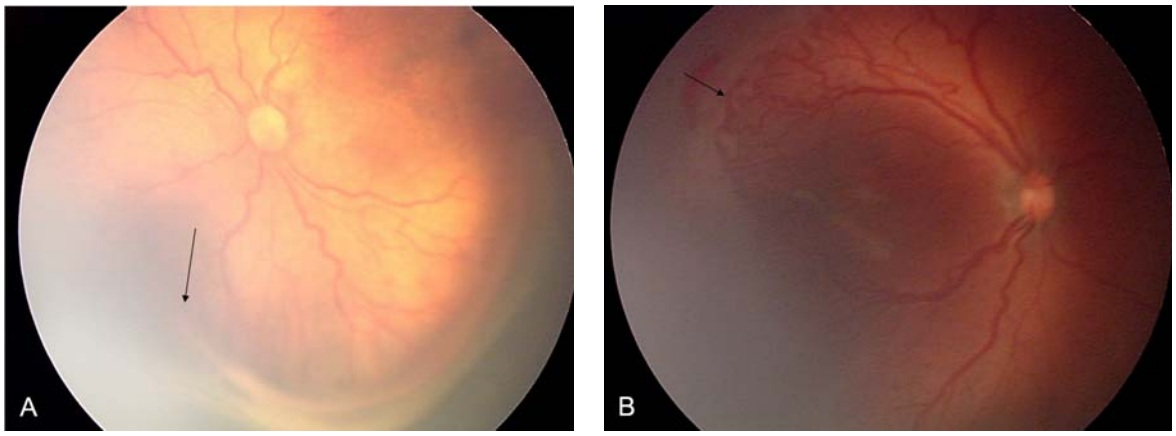

Fig. 1 Case 10 A, Nasal retina (of right eye) demonstrates severe stage 3 retinopathy of prematurity in zone 1 with severe plus disease and extremely thick extrafibrovascular proliferation at 10 weeks of life. Case 3 B, Temporal retina (of left eye) demonstrates severe stage 3 retinopathy of prematurity in zone 1 with plus disease, a small area of vitreous hemorrhage superotemporally, and extremely thick extraretinal fibrovascular proliferation at 8 weeks of life

turity is usually found in premature infants of low birth weight and progresses at an accelerated course. Treatment screening for early detection of zone 1 retinopathy of prematurity, together with prompt treatment (within 48 hrs), of these high risk eyes is necessary. In several developing countries recent reports have suggested that severe retinopathy of prematurity affects much larger and heavier infants than their Western counter parts[21-26]. The results of the present study is similar to the study of Sanghi et al (India)[27], which found that the mean birth weight and gestational age were 1,259.66 gm (range; 600-2,000 gm) and 29.75 wk (range; 26-36 wk) respectively. The mean gestational age and birth weight in the present study

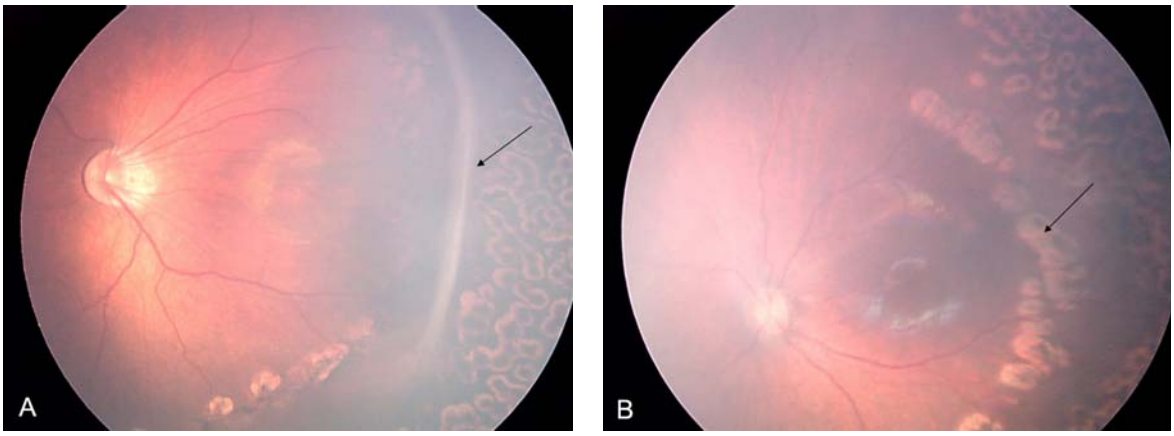

Fig. 2 Case 10 A, One month post "Combine Treatment" demonstrates fibrous remnants in vitreous at nasal side, laser scar and continued anterior vascularization. Case 3B, Two month post "Combine Treatment" demonstrates confluent laser scar and normal retinal vascularization

are higher than the Western studies of atypical posterior retinopathy of prematurity[12,28,29]. Thus, some infants would miss screening if using the American screening guidelines for retinopathy of prematurity, which recommended that infants $\leq$ 1,500 gm birth weight or $\leq$ 32 wk of gestational age must be screened. In developing countries, unmonitored oxygen saturation and lack of awareness of risk factors in the peripheral center contribute to retinopathy of prematurity in the heavier cohort of babies[30,31].

Peripheral laser retinal ablation is expected to prevent unfavorable structural and visual outcome for zone 1 cases. But, some studies have reported high unfavorable outcome[7] (such as early progressing retinopathy of prematurity and rapid retinal detachment) despite timely ablation[8]. Several small case series have documented the use of intravitreal bevacizumab in eye with AP-ROP[32-34]. Chang et al[16] used combine intravitreal bevacizumab and laser for aggressive zone 1 retinopathy of prematurity demonstrating regression of retinopathy of prematurity. In the present study, early and aggressive confluent laser photocoagulation with intravitreal bevacizumab all AP-ROP infants mitigates relentless progression to retinal detachment. Intravitreal bevacizumab has a rapid effect in flat neovascularization plus disease. Anti-VEGF therapy causes regression of abnormal vessels and the advancement of normal retinal vessels. Thus early combine treatment shows success in treatment of zone 1 AP-ROP in the present study. Randomized, prospective and clinical trials designed to evaluate the short-term safety of intravitreal bevacizumab in retinopathy of prematurity infants is shown in BLOCK-ROP and BEAT-ROP phase 1 study. The mission of the BLOCK-ROP and BEAT-ROP study is multicenter prospective longitudinal cohort study. Phase 1 is administering a single-dose intravitreal bevacizumab in one or both eyes of infants who have zone 1 or posterior zone 1 AP-ROP cases. There is no ocular or systemic event in Phase 1 and currently both study groups proceed to phase 2. Unlike other ocular neovascular conditions (such as exudative Aging Macular Degeneration and Proliferative Diabetes Retinopathy) where there is continual release of VEGF[35,36], ROP is a single burst of VEGF that promotes neovascularization[36]. Therefore, repeat injections would likely be unnecessary if the intravitreal injection could be administered at the correct time. Since 11 infants in the present study had bilateral injection, the authors were unable to observe any contra-lateral effects. The only infant who received unilateral combine treatment (case 2) had already demonstrated regression of AP-ROP in the contra-lateral eye and contra-lateral effect. In such a case, it would be difficult to assess because it was possible that eyes with zone 1 AP-ROP might have increased breakdown of the blood-retinal barrier which, in turn, caused more susceptibility to systemic anti-VEGF than others. By the way, the authors did not observe any systemic effect. Even through, early combine treatment laser photocoagulation and intravitreal bevacizumab showed success in the present study, but the long term systemic complications are considered following the single injection of a small dose into the vitreous cavity. Based on the valid evidence-based data (BLOCK-ROP, BEAT-ROP study) and its efficacy and safety, Bevacizumab

alone for retinopathy of prematurity stage 3 may become not only just an adjunct to laser therapy or vitrectomy, but also primary treatment replacing laser therapy as standard of care. The most disadvantage of laser treatment is retinal scar and destructive therapy. Laser treatment requires wide pupil dilation and good surgical skill. Some institutes perform laser treatment under general anesthesia. Furthermore, due to costly laser equipment, some institutes do not provide laser treatment. On the other hand, leaving no scar and requiring only needle and syringe with no special surgical skills, intravitreal anti-VEGF can be performed in any institute. However, anti-VEGF can accelerate the contraction of fibrous membranes resultant worsening of retinal detachment and should have more data for long- term systemic side effect. The present preliminary results is a small case series of 23 eyes, warrants a prospective randomized, controlled, multicenter clinical trials.

Conclusion

AP-ROP in the present study was formed in babies who may be heavier and more mature than other studies from developed countries. Combine aggressive confluent laser photocoagulation with intravitreal bevacizumab can be slow vasculaogenesis and maximized outcomes in AP-ROP excluded (ROP stage 4, 5).

Potential conflicts of interest

None.

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การรักษาด้วยเลเซอร์ร่วมกับการฉีดยา bevacizumab ในน้ำวุ้นตา ในผู้ป่วยทารกคลอดก่อนกำหนดที่มีภาะหลอดเลือดจอประสาทตาเจริญผิดปกติชนิดรุนแรง (aggressive posterior retinopathy of prematurity)

เบญจวรรณ วุฒิวรวงศ์, อุษา ฐิติรัตน์สานนท์, ชัยรัตน์ เสาวพฤทธิ์, ไอรีน ศุภางคเสน, บังอรรัตน์ เกยุราพันธุ์, อัจฉรา อัมพรพฤติ, จินดา ภู่มงกุฎชัย, สุนิสา เทพหัสดิน ณ อยุธยา.

วัตถุประสงค์: *เพื่อศึกษาการรักษาผู้ป่วยทารกคลอดก่อนกำหนดที่มีหลอดเลือดจอตาเจริญผิดปกติอย่างรุนแรง (Aggressive Posterior Retinopathy of Prematurity)*

รูปแบบการวิจัย: *การศึกษาเก็บข้อมูลย้อนหลัง*

วัสดุและวิธีการ: *การศึกษาในผู้ป่วยทารกคลอดก่อนกำหนดจำนวน 12 ราย (ทารกชาย 7 คน, ทารกหญิง 5 คน) จากคลินิกจอตาผู้ป่วยทารกคลอดก่อนกำหนด ที่ได้รับการวินิจฉัยว่ามีภาวะหลอดเลือดจอตาเจริญผิดปกติอย่างรุนแรง โดยตรวจด้วยเครื่องมือ Indirect ophthalmoscope ซึ่งได้รับการรักษาด้วยวิธีเลเซอร์จอตาในบริเวณจอตาที่ไม่มีหลอดเลือดเจริญออกไปร่วมกับการฉีดยา anti-VEGF ในน้ำวุ้นตา และมีการถ่ายรูปจอตาของผู้ป่วยทารกทั้งก่อนและหลังผ่าตัดด้วยเครื่องมือถ่ายภาพจอตา (RetCam)*

ผลการศึกษา: *พบว่าผู้ป่วยที่หลังได้รับการรักษาด้วยวิธีเลเซอร์จอตาร่วมกับการฉีดยา bevacizumab ในน้ำวุ้นตาจำนวน 23 ตา จะมีหลอดเลือดจอตาเจริญปกติไม่มีจอประสาทตาหลุดลอก มี 2 ตา ที่พบว่ามีพังผืดที่จอตาแต่จุดรับภาพชัดปกติ และไม่พบผู้ป่วยที่เกิดผลข้างเคียงในลูกตา และอวัยวะส่วนอื่น ๆ จากการใช้ยา bevacizumab ฉีดเข้าในน้ำวุ้นตา*

สรุป: *ในการศึกษานี้พบว่าการรักษาด้วยวิธีเลเซอร์จอตาร่วมกับการฉีดยา bevacizumab ในน้ำวุ้นตาในกลุ่มผู้ป่วยทารกคลอดก่อนกำหนดที่มีเส้นเลือดจอตาเจริญผิดปกติอย่างรุนแรง ได้ผลที่น่าพอใจทุกราย ซึ่งทางคณะผู้นิพนธ์หวังว่าการรักษาด้วยวิธีนี้น่าจะช่วยป้องกันความพิการทางสายตาและทำให้ผู้ป่วยกลุ่มนี้ มีการมองเห็นที่ดีในอนาคต*