Effects of Initial Intravitreal Bevacizumab (Avastin) Prior to Laser Photocoagulation in Threshold ROP

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ABSTRACT

Purpose: Threshold zone 1 and 2 ROP is a progressive disease with vision threatening complications. In this cohort, we could achieve retinal stabilization when 0.625mg/ 0.05 ml injection was performed 3-4 days prior to retinal ablation.

Material and Methods: Fourteen eyes received intravitreal bevacizumab. Inclusion criteria was zone 1,2 disease, stage 3, or 4 disease with plus disease. Four days later, laser PRP was given in a scatter pattern to the retinal periphery. Mean gestational age was 30 weeks, mean birth weight was 1279 gms, mean incubation period was 36 days and oxygen delivery for 15 days.

Results: 11 eyes achieved retinal stabilization. Three eyes progressed to progressive tractional retinal detachment. One eye was successfully reposited by lens-sparing vitrectomy, one eye failed surgery and one eye was not operated. No systemic toxicity was observed from bevacizumab injection.

Conclusions: Bevacizumab 0.625 mg / 0.05 ml is a useful adjunct in posterior zone 1,2 ROP when followed by scatter laser photocoagulation.

Key Words: Intravitreal bevacizumab, laser photokoagulasyon, retinopathy of prematurity.

INTRODUCTION

In the past decade, infant mortality rate in Egypt has declined from 40% live births during the period from 1994-1998 to 25% live births in the period from 2004-2008.[1] The estimated number of premature birth in Egypt in 2008 was 123,131. Survival of premature infants in Egypt has increased in the past few years due to the advances in care taken in the NICUs, and therefore the possibility of retinopathy of prematurity among other diseases of premature neonates is expected to increase.[1]

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the developing retina that continues to be a major cause of blindness of children in the developed and developing world.[2] ROP in general is a two-phase process, namely oxygen-induced vascular obliteration (phase I) followed by a hypoxia-induced over-production of vasoactive cytokines (phase II), such as vascular endothelial growth factor (VEGF).[3] It has been proposed that angiogenesis is driven by VEGF, and one of the important factors that increases VEGF expression is hypoxia.[4-5] This process is responsible for development of ROP. VEGF protein concentration is elevated in the vitreous of ROP, and was found to reach 3500 pg/ml vitreous in vascularly active ROP eyes (phase II), and blockage of VEGF receptors was found to effectively abolish retinal angiogenesis.[6] Bevacizumab (Avastin; Genentech Inc, South San Francisco, California, USA), a full anti-VEGF antibody of 149 kD approved for use in the treatment of colorectal cancer and is used off-label for the treatment of many ocular conditions among which is severe ROP.[7-15]

Classic management of zone I and aggressive posterior ROP cases, often have unfavorable outcomes.[16-21] The Cryotherapy for Retinopathy of Prematurity Cooperative Study reported a 77.8% unfavorable outcome rate using cryotherapy,[17] and the Early Treatment for Retinopathy of Prematurity Cooperative Group reported a 55.2% unfavorable outcome rate using laser photocoagulation in zone I disease.[18]

In this paper, we explore the use of 0.625 mg/0.05 ml injection of bevacizumab in severe zone 1-2 ROP followed by laser photocoagulation and vitrectomy when indicated in management of aggressive ROP

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Geliş Tarihi - Received: 13.01.2014
Kabul Tarihi - Accepted: 14.01.2014
Ret-Vit 2014;22:93-98

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MATERIALS AND METHODS

This study is a prospective evaluation of 14 eyes of 9 babies with vascularly active ROP considered at high risk for progression or development of tractional retinal detachment including acute stage 3 ROP in zone I or posterior zone II with threshold and plus disease and stage 4 ROP.

Vascular activity was defined as an eye with plus disease manifesting as dilatation and tortuosity of the posterior pole retinal vessels in at least 2 quadrants, neovascularization growing onto the vitreous at the ridge or onto the localized tractional detachment area. Stage 5 disease was excluded from the study or cases where predominant fibrosis was noted in the fibrovascular component of the disease.

Our management strategy included intravitreal injection of bevacizumab (Avastin®) 0.625 mg (0.05 ml) as the initial treatment in the operating room under standard aseptic precautions. The anesthesia involved the intravenous injection of fentanyl to sedate the infant before the intravitreal injection. Vital signs were monitored throughout the entire procedure. The eye was prepped in a standard fashion using 5% povidone iodine and topical anesthesia was applied.

A 0.625 mg (0.05 ml) of bevacizumab was injected intravitreally via the pars plica, 1.5 mm from the limbus after transillumination was performed to localize the pars plicata. The needle was injected in a 45˚ angulation to the sclera. After the injection, intraocular pressure was checked, and patients received topical antibiotic for 3 days.

Follow up was done next day to check on the possibility of inflammatory reaction or infection. Three days later, indirect laser ablation to the ischemic retina was performed under general anesthesia using diode laser. The child was transferred to a NICU in an equipped ambulance under pediatrician surveillance and was put under observation in the NICU for 24-48 hours at the discretion of the pediatrician.

Topical steroid four times a day and cycloplegic drops twice a day were prescribed for a week. Wide angle digital fundus photography using RetCam 2 (Clarity Medical Systems, Inc., Pleasanton, CA) was performed before and after injection and following laser photocoagulation and on follow up. Repeat examinations were performed at day 3, week 1 postoperative and 1,3,6 and 12 months.

The response to treatment was observed in the form of degree of dilatation of pupil and regression or progression of ROP following the treatment, complete blood picture, general examination of the child by a pediatrician, focusing on chest, and heart condition was performed before injection and on follow up.

Informed consent from the parents was obtained and institutional review board approval was also obtained. Each patient's parent or legal guardian signed a consent form before the administration of bevacizumab. On disease progression, when the retinal detachment progressed threatening or involving the retina, a 23 G pars plicata vitrectomy with or without lensectomy was performed under general anesthesia.

Intravitreal triamcinolone was used to identify the vitreous gel and posterior hyaloids. The primary goal of surgery was to isolate the traction bands without creating a break in the retina. Once achieved, surgery was terminated. Closure of sclerotomies was done using 8/0 vicryl sutures if they were leaky. Postoperative steroid/antibiotics combination along with cycloplegics were given for a month. Repeat fundus examination was performed at 1 week, one month, 3, 6 and 12 months post-operatively.

RESULTS

14 eyes received bevacizumab 0.625 mg (0.05 ml). The mean gestational age was 30 weeks (range 26-35 weeks), and the mean birth weight was 1279 gms (range: 980-1700 gms). Mean incubation period was 36 days (range 22-57 days) with an average oxygen delivery period of 15 days (range 10-30 days). Mean follow up was 29 months (range 14-36 months).

In this cohort, there were 11 cases with stage 3 ROP, with 6 cases in zone 1, and 5 cases in posterior zone 2. Stage 4 eyes with a traction fold were found in 3 cases with a single case in zone 1, and 2 cases in zone 2. The mean injection time was 36.4+/-1.4 weeks postmenstrual age for eyes with stage 3 ROP.

Retinal stabilization was achieved in 11 of the 14 eyes following bevacizumab injection and laser photocoagulation. All 5 cases of zone 2 ROP achieved retinal stabilization without any further intervention. For zone 1 ROP, there were 6 eyes. Three cases stabilized following bevacizumab and laser with no further intervention (figure 1), and one year later a single case of these developed buphthalmos (Table 2).

Three eyes progressed to tractional retinal detachment. One eye with a zone 1 stage 3 ROP developed progressive traction and foveal dragging that was successfully reposited by lens sparing vitrectomy (Figure 2).

Another case with stage 3 zone 1 ROP progressed to tractional retinal detachment with failed lensectomy/vitrectomy to reposit the retina. A third case was lost to follow up for a month and presented with an unusual form of tractional retinal detachment with tangential traction on the retina and falciform folds to the retinal periphery.

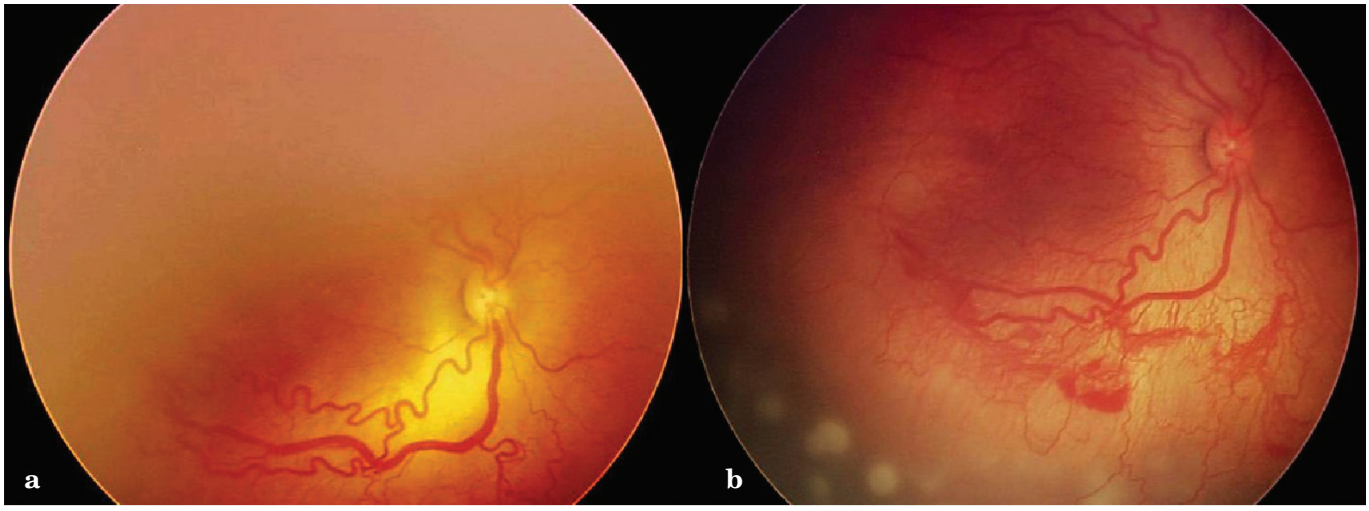

Figure 1a,b: *Retcam fundus picture showing: A: zone 1, plus ROP. B: 3 days post-Bevacizumab with laser photocoagulation (Note: Decongestion of central vessels and regression of neovascularization).*

The patient's family refused further intervention. There were 3 cases of stage 4 ROP. Two cases in zone 2 presented with mild foveal dragging and stabilized with bevacizumab and laser with arrest of the fibrous component and no further surgery was performed, and a third case with zone 1 central tractional component was successfully reposited with lens-sparing vitrectomy.

DISCUSSION

The avascular retina in ROP created by the hypoxic environment is responsible for the upregulation of VEGF and other factors. When hypoxia is triggered, VEGF expression is increased in retinal pigment epithelial cells, retinal endothelial cells, pericytes and Müller cells.[11-14] Pan-vascular endothelial growth factor blockade, using bevacizumab, appears to be effective for down-regulating VEGF, thus treating infants with aggressive retinopathy of prematurity.

While laser photocoagulation remains the standard of care in the treatment of advanced retinopathy of prematurity (ROP), regression is not seen in all cases (especially in zone 1 ROP and aggressive posterior disease) following laser alone.[16-22] Additionally, supplementary laser retreatment is performed in such cases in up to 30% of eyes that might need to extend posterior to the ridge to assure retinal stability. In zone 1 or posterior zone 2 ROP, this might endanger the fovea.[19] Unfavorable outcome was noted to be as much 55.2% following laser photocoagulation of zone 1 ROP.[18] In our series, all zone 2 ROP showed favorable outcome, and for those with zone 1 ROP, 4 out of 6 cases stabilized completely after the intervention, one of which needed vitrectomy to arrest progressive traction. One case with zone 1 ROP failed surgery and another case showed an unusual form of retinal detachment with many retinal folds going to the periphery with a possible explanation of alteration of the tractional forces by the bevacizumab followed by the laser.

Table 1: *Patient demographics.*

Patient	Gestational age (weeks)	Birth weight (grams)	Incubation/O2 /days
Case 1	26	1650	22
Case 2	28	1280	40
Case 3	34	1000	37
Case 4	29	1300	31
Case 5	30	1100	22
Case 6	28	1200	57
Case 7	35	1300	55
Case 8	28	980	32
Case 9	33	1700	34
Mean	30.11	1278.89	36.67

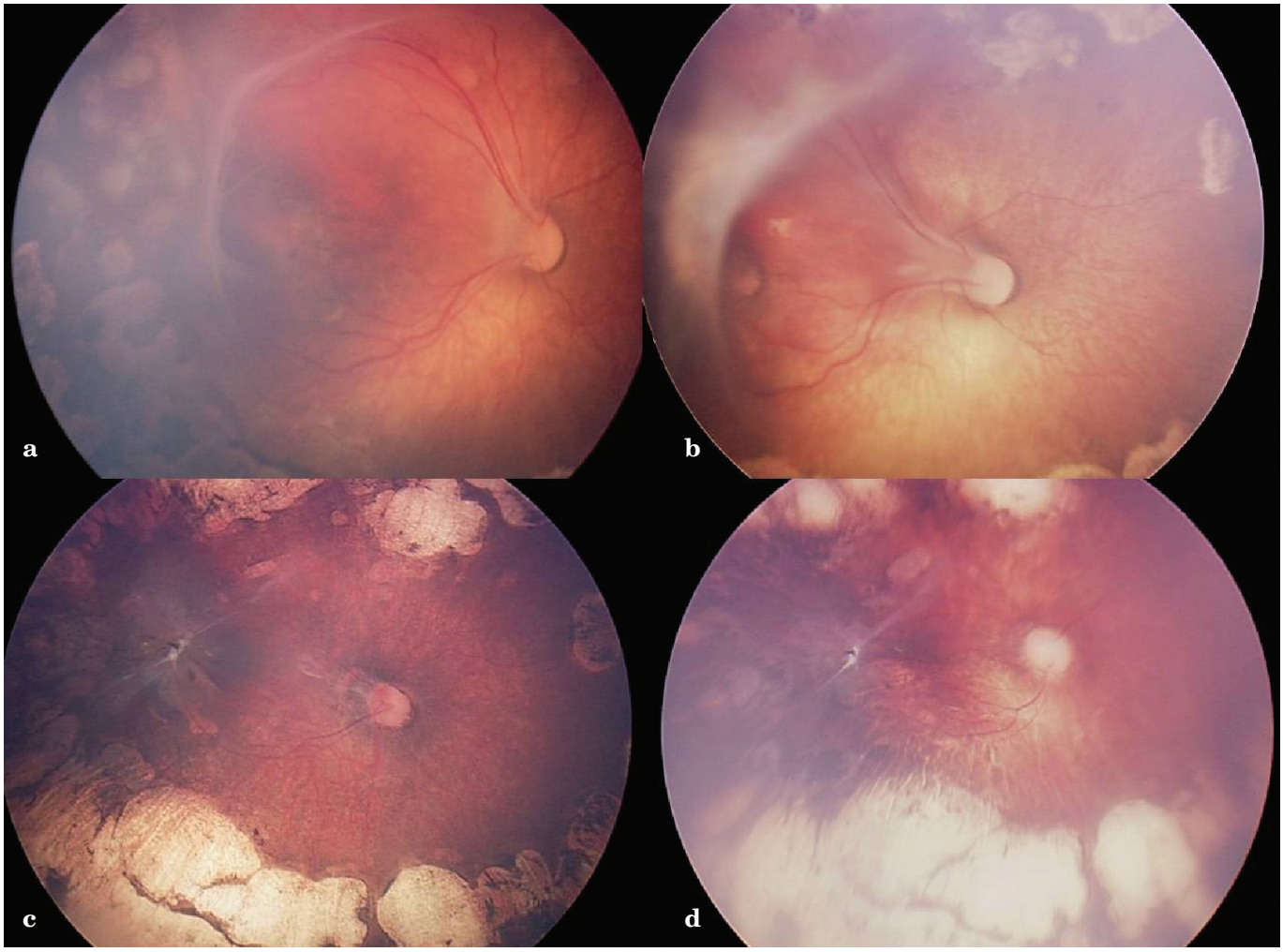

Figure 2a-d: *Retcam fundus picture OD: A: temporal traction fold post-Avastinand laser with gradual foveal dragging. C / D one and 6 months postvitrectomy.*

During the time of laser application, the vascular component of the neovascular frond was regressed to a degree sufficient to safely perform laser safely till the demarcation line between vascular and avascular retina. Proper pupillary dilatation allowed us to properly ablate the peripheral retina and there was no retreatment needed for those cases. Infants with aggressive ROP using the drug, showed significant decrease in vascular activity 24 hours following the injection. Notable decrease in venous dilatation with shrinkage of neovascular frond activity was noted in all cases (Figure 1) with no apparent systemic or local complications.

It was found that bevacizumab suppresses endothelial cell proliferation in an ROP mouse model, without increase in apoptotic cell death. At a concentration of 1.25 mg and 0.625 mg, there were no observed mitochondrial dysmorphology in the mouse model.[23] The appropriate dosing of bevacizumab injection in eyes with posterior ROP is yet to be determined. The largest reported ROP-associated vitreal VEGF concentration was 3500 pg/ml vitreous or about 0.23 pmol of VEGF in vascularly active ROP eyes.

It was estimated that 0.5 mg bevacizumab injection is 1000-fold excess of what is necessary to neutralize vitreous VEGF in active ROP cases.[24] The excess antibody is presumed to maintain low levels of VEGF in the vitreous over time.

Another potential advantage of half adult dose bevacizumab is the immeasurable serum concentrations as noted by Bakri et al.,[25] perhaps lowering systemic side effects, and the lack of any inflammation or extensive apoptosis on histopathologic examination.[10] In our series, no systemic complications were noted regarding lungs or heart maturation. The observed dramatic response in vascular activity 3-4 days post-injection suggest that 0.625 mg is a sufficient dose to achieve a VEGF-downregulation effect for retinal stability following laser photocoagulation. The Blockade for the Treatment of Retinopathy of Prematurity (BLOCK-ROP) study, might give us results about the best anti-VEGF drug dosing regimen in active ROP.

Bevacizumab is given in many studies as adjuvant salvage therapy and is followed or preceded by laser photocoagulation to the peripheral ischemic retina.[8,11-13]

Table 2: *Ocular clinical staging and management. Post-Bevacizumab 0.625 mg/0.05 ml and laser ablation to the retinal ischemic retina.*

Patient	Eye	ROP stage	ROPzone	Postoperative results and further management	Follow up (months)
Case 1	OD	4A	2	Stable, foveal dragging ++	26
Case 2	OS	3	2	Stable	30
Case 3	OD	3	2	Stable	28
	OS	3	2	Stable	28
Case 4	OD	3	1	Stable	36
	OS	3	1	Stable, PPV, improved	36
Case 5	OS	3	1	RD, PPV, failed repair	14
Case 6	OS	4B	1	RD, central traction, PPV OK , no surgery	18
Case 7	OD	3	1	Stable, insignificant traction	32
	OS	3	1	Stable. Buphthalmos	32
Case 8	OD	3	2	Stable	36
	OS	3	2	Stable	36
Case 9	OD	3	1	Stable	28
	OS	4A	2	Stable	28

PPV: Pars Plicata Vitrectomy. RD: Retinal Detachment.

The rationale is that bevacizumab injection neutralizes the high levels of VEGF already present in the vitreous cavity, and laser ablation of the avascular retina prevents new production of VEGF by destroying VEGF expression in the avascular retina. This seems to be a rational approach to obtain long term stability. With this approach, like others, [28] we also observed retinal vascular maturation occurring over the next few weeks to the retinal periphery among the laser scars. Other reports addressed the use of bevacizumab with an intent to be the sole therapeutic agent in management of type 1 ROP.[7, 15-16,26,27]

In a recent multicenter study published from Taiwan[27], 10% of eyes (4/37 eyes) with zone 1,2 ROP required laser treatment 2-3 weeks following bevacizumab injection. In the 41 eyes studied, 9 eyes had zone 1 ROP and 32 eyes had zone 2 ROP. Additionally 5 eyes had prior laser treatment and received bevacizumab as adjuvant therapy. This would increase the eyes with laser therapy to 9 eyes out of 41 eyes and the percentage of the need or prior laser would be 22%. The study did not mention which zone disease required laser therapy.[27] Mintz-Hittner et al.,[15] used bevacizumab as sole therapy in zone 1 or posterior zone 2 stage 3 ROP. The rapid progression of ROP observed from stage 3 to 4 observed by Kusaka et al.,[14], prompted us to think of bevacizumab as adjunctive therapy to be followed by laser peripheral ablation to achieve and maintain long term stability.

Two of our cases of stage 4 A ROP presented in zone 2. Following bevacizumab injection, and laser photocoagulation, the vascular component of the fibrovascular tractional band regressed with no further progression of the detachment and stabilization of the central retina.

One of the cases developed mild foveal dragging. A case of stage 4B, zone 1 ROP was successfully managed with lens-sparing vitrectomy performed 1week following laser ablation with flattening of the retina (Table 2).

Important issues to be addressed besides the appropriate dosing of bevacizumab, the safety and medicolegal liability of using the drug as sole therapy, the sequence in management when the drug is given in combination with laser photocoagulation whether prior or after or in association, and the clear indications of use in type 1, stage 3, 4 or 5 disease.

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