Agresif Posterior Prematüre Retinopatisinde İntravitreal Bevacizumab Monoterapisinin Uzun Dönem Etkinliğinin Değerlendirilmesi

Long-Term Efficacy of Intravitreal Bevacizumab Monotherapy in Aggressive Posterior Premature Retinopathy

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ÖZ

Amaç: Agresif posterior prematüre retinopatisi (AP-ROP) tanısı ile tek doz intravitreal bevacizumab (İVB) uygulanan infantlarda tedavi sonrası retinal vaskülarizasyonu değerlendirmek

Gereç ve Yöntemler: Bu çalışmada 2015-2017 yılları arasında AP-ROP tanısı ile tedavi ettiğimiz olgular retrospektif olarak değerlendirildi. Olguların doğum haftaları, doğum ağırlıkları, post-gestasyonel tedavi haftaları, retinal vaskülarizasyon süreleri, rekürrens ve ek tedavi ihtiyaçları incelendi.

Bulgular: Çalışma kapsamında 11 infantın 21 gözü değerlendirildi. Altı olgunun 12 gözüne (0,625 mg/0,025 ml) ve 5 olgunun 9 gözüne (0,312 mg/0,012 ml) İVB enjeksiyonu yapıldı. Olguların ortalama doğum haftaları 27,6±2,0 (24-30), doğum ağırlıkları 1108±377 (680-1880) gr ve tedavinin yapıldığı ortalama post-gestasyonel haftaları 35,2±2,0 (33-39) idi. Tedavi sonrası tüm olgularda ROP bulguları regresyon gösterdi ve plus hastalık geriledi (%100). İki olgunun dört gözüne ek lazer fotokoagulasyon tedavisi yapıldı. Bu olguların takip sürecinde 5 olgunun 9 gözünde tam retinal vaskülarizasyon sağlandı. Ortalama tam retinal vaskülarizasyon haftası 59,4±12,7 (52-82) idi.

Sonuç: AP-ROP olgularında IVB monoterapisi ile yüksek oranda regresyon elde edilirken, ileri dönem takiplerde tam retinal vaskülarizasyon sağlanabilmektedir.

Anahtar Kelimeler: Agresif posterior prematüre retinopatisi, intravitreal bevacizumab, retinal vaskülarizasyon.

ABSTRACT

Purpose: To evaluate retinal vascularization after treatment with single dose intravitreal bevacizumab (IVB) in infants with agressive posterior premature retinopathy (AP-ROP)

Material and Methods: In this study, we retrospectively evaluated AP-ROP cases treated with IVB in between 2015 and 2017. The gestational age at birth, birth weight, post-gestational age at treatment, complete retinal vascularization time, recurrence rate and need for additional treatment were analyzed.

Results: Twenty-one eyes of 11 infants were evaluated. IVB injection was performed in 12 eyes of 6 patients (0.625 mg/0.025 mL) and 9 eyes of 5 patients (0.312 mg/0.012 mL). The mean gestational age at birth was 27.6±2.0 weeks (24-30) while mean birth weight was 1108±377 g (680- 1880) and the mean post-gestational age at treatment was 35.2±2.0 weeks (33-39). In all cases, regression was observed in ROP and plus disease signs after treatment (100%). Additional laser photocoagulation therapy was performed to 4 eyes of 2 infants due to reactivation signs. Complete retinal vascularization was achieved in 9 eyes of 5 patients in the follow-up period of these cases. The mean time to complete retinal vascularization was 59.4±12.7 weeks (52-82).

Conclusion: High regression rate can be achieved with intravitreal bevacizumab monotherapy in AP-ROP cases. Furthermore, complete retinal vascularization can be obtained with long-term follow-up.

Key Words: Aggressive posterior premature retinopathy, intravitreal bevacizumab, retinal vascularization.

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INTRODUCTION

Premature retinopathy (ROP) is a retinal vascularization disorder affecting preterm infants.[1-3] A classification system was published to define severity and to inform treatment and/or follow-up in premature retinopathy.[4-5] In this system, the ROP is categorized according to localization of retinal involvement by 3 zones, extent of retinal involvement by clock hour and severity by 5 stages. In addition, terms including plus disease accompanied by venous dilatation and tortuosity of arteries, pre-threshold disease and threshold disease are also being used. Aggressive posterior premature retinopathy (AP-ROP) is an uncommon and severe form with rapid progression beyond classical stages of ROP.[5] In AP-ROP, severe dilatation and increased tortuosity are seen in all posterior pole vessels at early phases of disease development. It commonly shows posterior localization (zone I and II) and may result in blindness if not treated.[6]

Currently, the ROP treatment relies on ET-ROP Work Group criteria and cases with type 1 ROP (zone 1, any stage with plus; zone 1, stage 3 without plus; zone 2 stage 2-3 with plus) are treated[7] According to ET-ROP data, laser photocoagulation (LFC) remains to be gold standard in the treatment of ROP.[7] However, LFC may have limited visual success despite its anatomical effectiveness, particularly in ROP with posterior involvement.[8-9] In particular, in the BEAT-ROP study, it was shown that intravitreal bevacizumab (İVB) (0.625 mg/0.025 ml) therapy is more beneficial than LFC in zone 1 ROP cases. [10] In this manuscript, we aimed to investigate treatment effectiveness of two different IVD doses (0.625 mg/0.025 ml and 0.312 mg/0.012 ml) and time to complete retinal vascularization by retrospectively reviewing AP-ROP cases treated IVB.

MATERIALS AND METHODS

The study included 21 eyes of 11 infants who were diagnosed as ROP and treated with IVB injection due to development of AP-ROP at Samsun Training and Research Hospital between 2015 and 2017. The study was approved by Institutional Ethics Committee and conducted in accordance to Declaration of Helsinki. All parents/legal guardians gave written informed consent.

In our facility, ROP screening is routinely performed in all infants with birth weight <1500 g and/or gestational age at birth<32 weeks. In addition, all high-risk cases (birth weight>1500 g and gestational age at birth>32 weeks) underwent cardiopulmonary support therapy and referred to our clinic are also screened routinely. These infants are managed according to recommendations in American Academy of Pediatrics (AAP) guidelines on retinopathy of prematurity published in 2013[11] and Turkish Neonatology and Ophthalmology Societies consensus guidelines on retinopathy of prematurity[12]

The International Committee for the Classification of the Retinopathy of Prematurity (ICROP)[5] criteria were used in the diagnosis of AP-ROP. Based on these criteria, AP-ROP id defined as disease that frequently involves zone 1 and less frequently zone 2 with unusual disease course and is accompanied by plus disease. Venous dilatation and arterial tortuosity is not only observed in peripheral retina but also diffusely in retina. In addition, there may be diffuse neovascularization, arteriovenous shunt vessels, blurring in vitreous and vitreous hemorrhage, and pupillary rigidity.

Data regarding gestational age at birth, time of AP-ROP on set, time at treatment, post-natal time to first treatment, dose of IVB injection, time from treatment to complete retinal vascularization, fundus findings, probable complications and need for additional laser therapy were extracted from patient files. In all cases, baseline and control examinations were performed by binocular indirect ophthalmoscopy.

IVB injection was performed in 12 eyes of 6 infants at a dose of 0.625 mg/0.025 ml and 9 eyes of 5 infants at a dose of 0.312 mg/0.012 ml (Avastin, Genentech Inc., San Francisco, California, USA). All injections were performed in operating theatre. After placing patient to operating table, ocular anesthesia was achieved by topical anesthetic eye drop under supervision of pediatric anesthesiologist. Eyelids and eyelashes were prepared by 10% povidone-iodine solution and covered by sterile clothing. After inserting eyelid speculum, 5% povidone-iodine was applied to conjunctiva and awaited over 3 minutes for sterilization. Intravitreal injection was performed at 1 mm posterior to superior-temporal limbus by 30 G insulin injector. After injection, topical antibiotic (0.5% moxifloxacin five times daily; Vigamox®, Alcon, Turkey) was applied over a week.

Follow-up

On days 1, 3 and 7 after injection, control examination was performed to monitor AP-ROP and potential complications. Following acute period, control visits were scheduled every two weeks for 3 months and every 3 or 4 weeks thereafter until complete retinal vascularization. Regression was defined as decline in plus findings and ROP stage while reactivation was defined as recurrence of plus findings and observation of classical ROP stages. The reactivation was treated with LFC. Complete retinal vascularization was defined as extension of retinal vessels to ora serrata. All ocular examinations were performed by binocular indirect ophthalmoscopy with 360° scleral indentation. No fundus angiography was performed in serial follow-up.

BULGULAR

Of the cases included, 6 (54.5%) were boys and 5 (45.5%) were girls.

IVB injection was performed in 12 eyes of 6 infants at a dose of 0.625 mg/0.025 ml and 9 eyes of 5 infants at a dose of 0.312 mg/0.012 ml. The mean birth weight was 1108±377 g (680-1880) while mean gestational age at birth was 27.6±2.0 weeks (24-30). Mean post-gestational age at time of intravitreal bevacizumab injection was 35.2±2.0 weeks (33-39) while time from birth to treatment was 7.6±3.6 weeks (Table 1).

In all cases, regression was observed in ROP signs and plus disease after treatment (100%). During follow-up, complete retinal vascularization was detected in 9 eyes of 5 infants (42.8%). One infant was referred to our clinic after laser therapy in left eye performed in another facility; thus, only right eye was included to the study (case 8). In 4 eyes of two infants (case 6 and 11), additional laser therapy was given as reactivation in plus disease signs although retinal vascularization reached up to zone 3. One infant (case 4) died due to intra-ventricular hemorrhage upon week 28; thus, excluded. In remaining 6 eyes of 3 infants, follow-up without additional treatment was maintained as vascularization extended up to zone 3 without reactivation. There was no significant difference in birth weight and gestational age at birth between cases with reactivation and vascularized cases followed without treatment (p>0.05).

Mean follow-up was 32.4±17.0 weeks (15-66). The cases were classified into 2 groups according to IVB injection dose given. The group 1 included 6 infants received ½ dose (0.625 mg) while group 2 included 5 infants received ¼ dose (0.312 mg). Mean time to complete retinal vascularization was 59.4±12.7 weeks in 9 eyes of 5 cases including 3 infants from group 1 and 2 infants from group 2. There was no significant difference in time to retinal vascularization between groups (p=0.374). Six eyes of 3 infants has been followed for retinal vascularization for mean 21.3±9.2 weeks (15-32).

Table1: *Data of infants followed with AP-ROP*

Sex *(m/f))*	6/5
Infant/Eye	11/21
Birth weight *(g, mean*±SD*)* *(min-max)*	1108±377 (680-1880)
Gestational age at birth *(mean*±SD*)* *(min-max)*	27.6±2.0 (24-30)
Gestational age at treatment *(mean*±SD*)* *(min-max)*	35.2±2.0 (33-39)
Post-natal time to treatment *(week, mean*±SD*)*	7.6±3.6 (4-14)
Time to complete vascularization *(week, mean*±SD*)*	59.4±12.7*
Regression rate	100%
Proportion of cases with reactivation and additional therapy	19%

AP-ROP: Aggressive posterior retinopathy of prematurity
**Cases with complete vascularization*

Table 2 presents data and follow-up findings in all patients.

No IVB injection-related complication was detected in infants included. Figure 1 and 4 show pre-treatment and post-treatment pictures.

DISCUSSION

In our study, we assessed retinal vascularization with single dose IVB in association with demographic data of patients who were diagnosed as AP-ROP. Considering results, regression was observed with single dose IVB therapy in all patients with AP-ROP. Lacking of poor anatomical outcome and 100% regression rate suggest that single dose IVB therapy is an effective treatment option in AP-ROP.

In studies investigation effectiveness of IVB in cases with AP-ROP, complete regression was achieved by single dose IVB (0.625 mg) in 91.9% of 62 eyes in the study by Yetik et al.[13] and in 85.2% of 34 eyes in the study by Nicoara et al.[14]. In the study by Yetik et al., additional therapy with same dose of IVB was given and 100% regression was achieved in AP-ROP cases. In a case series including 3 patients, Travassos et al. observed regression within 24 hours after 0.75 mg IVB injection in all 3 cases without need for additional therapy.[15] In another study, Dorta et al. achieved regression without need for additional treatment in 6 eyes of 3 cases with AP-ROP by 0.625 mg IVB monotherapy.[16] On contrary, Lorenz et al. observed 25% regression in cases with AP-ROP vs. 100% regression in acute ROP cases involving zone 2 posterior by 0.312 mg IVB.[17] We think that the low regression rate may be due to limited number of cases and difference across study populations. In that study, mean birth weight was 581 g and mean gestational age at birth was 23.5 weeks while they were 1108 g and 27.6 weeks in our study, respectively.

The IVB injection has gained popularity in ROP cases after BEAT-ROP study.[8] However, the hypothesis that anti-VGEF agents can affect development of rapidly growing organs in premature infants by decreasing systemic VGEF levels hasn't been clarified.[18,19] Angiogenesis plays an important role in maturation of many organs and neural tissues. It was shown that anti-VGEF agents given via intravitreal route decreases systemic VGEF levels over weeks or months.[18] Thus, lowest IVB dose that may be effective with minimal decrease in systemic VGEF level should be administered

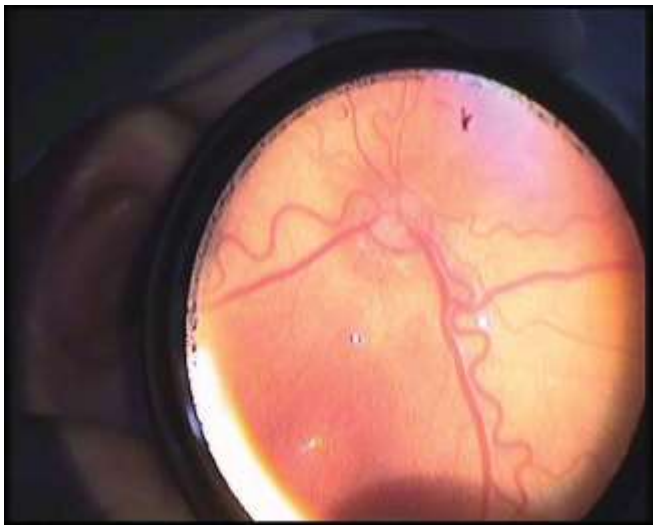
Table 2: *Data regarding demographics, comorbidity, time of IVB injection and post-treatment follow-up in infants included*

Case	Gender	BW	GE	Timing	Comorbidity	Right fundus follow-	Left fundus Vascularization	Mean Complete Up	Dose Add. therapy		
1	Female	29	1480	33	HMD,ASD	Avascular upon zone 2 posterior	Avascular upon zone 2 posterior	32	At follow-up period	1/2	-
2	Male	30	1880	34	HMD	Vascularized	Vascularized	45	56	1/2	-
3	Female	26	680	33	HMD,PDA,ASD	Vascularized	Vascularized	66	82	1/2	-
4	Male	26	790	36	HMD, IVH,VSD Hydrocephaly	The patient died during follow-up				1/4	-
5	Female	25	700	39	HMD Hydrocephaly	Avascular upon zone 2 posterior	Avascular upon zone 2 posterior	15	At follow-up period	1/2	-
6	Female	30	1400	35	HMD	Avascular upon zone 2 posterior, peripheral laser spots	vascularized upon zone 2 posterior peripheral laser spots	54	At follow-up period	1/2	LFC
7	Male	29	1020	34	HMD, PDA	Vascularized	Vascularized	23	52	1/2	-
8	Male	29	1140	34	HMD, PDA	Vascularized	Avascular upon zone 2 posterior laser spots in peripheral retina	23	52	1/4	-
9	Male	28	1000	35	HMD Inguinal Hernia	Vascularized	Vascularized	27	55	1/4	-
10	Male	28	1300	37	HMD, PDA	Avascular upon zone 2 posterior	Avascular upon zone 2 posterior	17	At follow-up period	1/4	-
11	Female	24	800	38	HMD ,ASD, PDA	Vascularized upon zone 2 posterior peripheral laser spots	Vascularized upon zone 2 posterior peripheral laser spots	22	At follow-up period	1/4	LFC

BW: Birth weight, GE: Gestational age at birth, IVB: Intravitreal *bevacizumab, LFC: Laser photocoagulation, HMD: Hyaline membrane disease*, IVH: Intraventricular hemorrhage,, *ASD:atrial septal defect, VSD: Ventricular septal defect, PDA: Patent ductus arteriosus.*

In the literature, half of adult dose (0.625 mg) for IVB was in infants in majority of the studies.[17] Ongoing debate on systemic side effects has driven researchers to design studies aiming to establish lowest effective dose of bevacizumab in order to minimize systemic risk. In a study, 0.625 mg/0.025 ml bevacizumab was given to one eye while 0.25 mg/0.01 ml bevacizumab to other eye and it was shown that there was no significant difference in anatomical recovery. [20] However, there are ongoing studies on lower doses.

In a phase I study including type 1 ROP cases exclusively, gradually decreased doses of IVB were compared and IVB effectiveness was shown doses as low as 0.031 mg.[21] However, in the literature, there is no study comparing low doses of IVB in AP-ROP. In our study, no significant difference was detected between patients received 0.312 mg IVB and those received 0.625 mg IVB regarding both regression and complete vascularization.



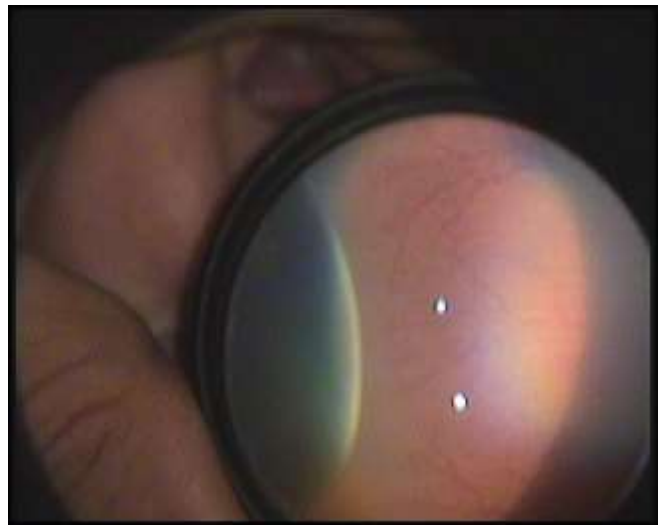
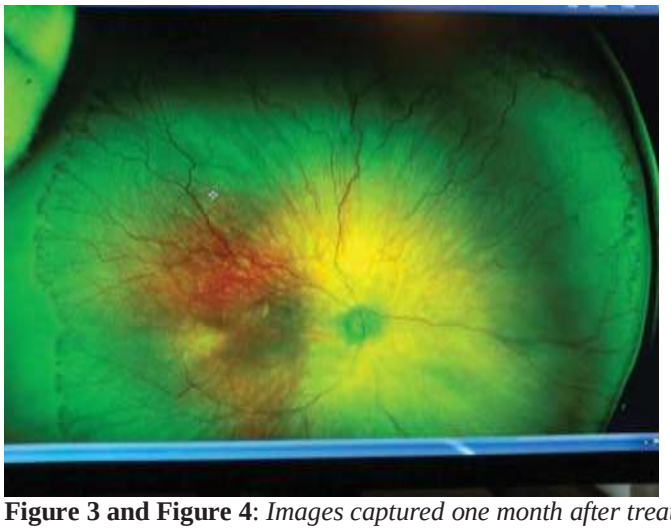


Figure 1 and Figure 2: *Pretreatment images captured by bincoular indirect ophthalmoscopy in a case (case 3) diagnosed as aggressive posterior retinopathy of prematurity (AP-ROP)*



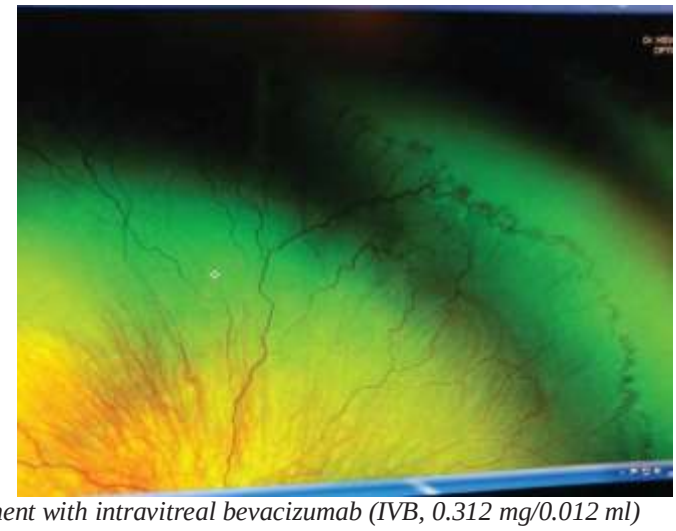


Figure 3 and Figure 4: *Images captured one month after treatment with intravitreal bevacizumab (IVB, 0.312 mg/0.012 ml) in a case (case 9) diagnosed as aggressive posterior retinopathy of prematurity (images were captured by Optus ®)*

This suggests that AP-ROP could be treated with lower doses. However, lack of significant difference may be due to smaller sample size in our study. We think that larger studies will reveal more relevant outcomes.

In the treatment of ROP with anti-VGEF, one of the major problems is how and when normal retinal vascularization will occur. In this study, we demonstrated that retinal vascularization following AP-ROP cases was slower than physiological vascularization. Clinically, complete retinal vascularization is defined as extension of retinal vessels to ora serrata. In our study, mean time to vascularization was 59.4 weeks. Although time to complete vascularization was shorter in the group received lower dose of bevacizumab, the difference did not reach statistical significance. However, it will more relevant to prove complete vascularization via angiography.

In the BEAT-ROP study, it was seen that mean time from treatment to complete vascularization was 19.5 weeks.[8] In the study by Sukgen et al., it was found that mean time to complete vascularization was 55.9 weeks in ROP cases treated with 0.625 mg IVB.[22] Spandau et al. reported mean time to complete vascularization as 65 weeks. [23] In the literature, there is no study on vascularization time in AP-ROP cases. This is the first study demonstrating mean time to vascularization after IVB therapy in AP-ROP cases in the literature.

Although complete regression was observed in AP-ROP cases treated with İVB, recurrence may be observed during follow-up.

Yetik et al. showed that recurrence after IVB therapy occurred more commonly and earlier in AP-ROP cases when compared to classical ROP cases.[13] Thus, close monitoring is warranted in these cases. In our series, recurrence rate was 19% after IVB monotherapy. Additional LFC therapy was required in the cases with recurrence. Yetik et al. achieved success in 3 of 5 cases (8.1%) with recurrence after first IVB injection while a third injection was performed in remaining 2 cases.[13] Nicoara et al. achieved regression by LFC in 3 of 5 cases (14.7%) with recurrence.[14] LFC is recommended in ROP involving zone 1, ROP with posterior localization and AP-ROP in case of recurrence if vascularization extended to zone 2 while additional anti-VGEF therapy is recommended if vascularization is confined within zone I.[21]

In AP-ROP cases, more effective outcomes have been demonstrated by LFC plus anti-VGEF therapy as first-line treatment when compared to LFC alone so far.[24,25] In a study comparing AP-ROP and non-AP-ROP infants, Ahn et al. suggested that AP-ROP infants requires more intensive LFC therapy and that recurrence is more common in these cases.[26] In addition, Nicoara et al. compared IVB monotherapy with LFC therapy alone in 23 cases with AP-ROP and reported that IVB ensured more effective recovery.[14] In cases with AP-ROP, high recurrence rate has been reported. In a study evaluating effectiveness of LFC therapy, a second laser therapy was required in 31.8% of 22 infants after LFC treatment.[6] In a study on 15 eyes with AP-ROP, Gunn et al. reported this rate as 26.6%.[27] In cases with posterior zone ROP including AP-ROP cases, large retinal ablation areas develops with LFC therapy, resulting in thinning and traction in these areas. It is known that risk for retinal detachment is markedly increased in AP-ROP cases despite sufficient laser LFC therapy at early phase, particularly in those with posterior zone 1 involvement before laser therapy, pre-retinal hemorrhage and those with gestational age at birth<29.5 weeks.[28]

In conclusion, given no requirement to general anesthesia, quick application in outpatient settings, not causing retinal ablation and lack of inhibition in peripheral vascularization, IVB monotherapy seems effective in ROP cases with zone 1 involvement and in those requiring rapid onset of action and at risk for retinal injury with classical LFC in retinal injury. Currently, there is need for larger, multicenter studies which will investigate effectiveness, safety and dose of IVB.

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