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Evaluation of the long-term efficacy of intravitreal bevacizumab in retinopathy of prematurity

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ABSTRACT

Aims: To evaluate retinal vascularization following intravitreal bevacizumab (IVB) treatment in infants diagnosed with retinopathy of prematurity (ROP).

Methods: The study retrospectively evaluated patients diagnosed with type 1 ROP and aggressive ROP (A-ROP) who received treatment between 2021 and 2024. The analysis included gestational age at birth, birth weight, weeks of post-gestational treatment, timing of retinal vascularization, recurrence of ROP, and the need for additional treatments.

Results: In total, 30 infants were included in the study, with a total of 58 eyes evaluated. Intravitreal bevacizumab injection at a dose of 0.625 mg (0.025 ml) was administered to all 58 eyes. The average birth weight of the preterm infants was 1178±509 grams (ranging from 500-2790) and their average gestational age was 28.2±2.7 weeks (ranging from 23-34 weeks). The average gestational age of the preterm infants at the time of receiving intravitreal bevacizumab treatment was 36.6±2.1 weeks (range: 32-39), while the average duration of follow-up post-treatment was 29.5±4.3 weeks (range: 21-37) after treatment. After treatment, ROP findings showed significant regression, and plus disease regressed in 93.3% of the cases. Additional laser photocoagulation was done in four eyes of two cases. The mean week for complete retinal vascularization was 61.9±3.5 (range 55-67) weeks.

Conclusion: Intravitreal bevacizumab monotherapy achieves high rates of regression in cases of type 1 ROP and aggressive ROP (A-ROP). Furthermore, complete retinal vascularization can be attained during the follow-up period.

Keywords: Retinopathy of prematurity, aggressive retinopathy of prematurity, type 1 retinopathy of prematurity, intravitreal bevacizumab, retinal vascularization, laser photocoagulation

INTRODUCTION

Retinopathy of prematurity (ROP) condition is considered among the top three causes of childhood blindness which can be prevented in many countries.[1] The incidence of ROP has, however, worsened in the past decade because of the advancements in managing and supporting the survival of preterm infants.[2] This condition's development is predominantly influenced by low birth weight and advanced prematurity.[3] In ROP, visual sequelae, including total loss of vision, can develop if adequate follow-up and treatment processes are not implemented. To aid in the assessment of ROP and in directing any necessary follow-up or treatment actions, a system of classification has been introduced.[4] ROP is, therefore, classified in the light of three zones demarcating retinal involvement, clock hours bearing extent, and five stages indicating severity. Also employed are expressions like plus disease (which involves venous dilation and increased tortuosity of arteries), pre-threshold stage, and threshold stage for patients who need treatment urgently. As an uncommon yet the most destructive subtype, aggressive retinopathy of prematurity (A-ROP) does not adhere to the classical developmental stages.[5] In the early stages of A-ROP, all of the posterior pole vessels predominantly exhibit significant dilatation and tortuosity. It typically presents in posterior zones (Zone I and posterior Zone II) and can cause blindness if left untreated.[6]

The treatment of ROP is guided by the criteria established by the early treatment for retinopathy of prematurity (ET-ROP) study group. Treatment is permitted only for type 1 ROP cases, which include: ROP at any stage in zone 1 including when plus disease is present; in zone 1 without plus disease, at stage 3 ROP; and in zone 2 with plus disease, at stages 2 and 3 ROP. Based on the ET-ROP data, laser photocoagulation (LP) continues to be the gold standard for ROP treatment.[7] However, despite achieving anatomical success with LP, visual outcomes can be particularly limited in cases of ROP that involve the posterior region.[8,9] According to the Bevacizumab eliminates the angiogenic threat of ROP (BEAT-ROP) study, intravitreal bevacizumab (IVB) (0.625

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mg/0.025 ml) is more effective than laser photocoagulation for cases of zone 1 retinopathy of prematurity.[10] In the current study, the records of ROP cases treated in our clinic with IVB injection (0.625 mg/0.025 ml) were retrospectively examined to investigate treatment effectiveness and retinal vascularization completion times.

METHODS

This study involved 58 eyes from 30 preterm infants with retinopathy of prematurity who were followed up at a Training and Research Hospital in Samsun from 2021 to 2024, in whom type 1 ROP and A-ROP were observed, and intravitreal bevacizumab injection was applied. Approval from the Ondokuz Mayıs University Clinical Researches Ethics Committee was obtained (Date: 26.09.2024, Decision No: OMÜ KAEK 2024/381). The principles of the Declaration of Helsinki were considered when carrying out this research.

At our hospital, ROP screening is routinely performed for all preterm infants born with a birth weight below 1500 grams (g) and/or a gestational age of less than 32 weeks. Additionally, all at-risk cases with a birth weight exceeding 1500 grams or a gestational age greater than 32 weeks who were referred to our department, as well as all preterm infants who received cardiopulmonary support therapy, are routinely screened. Diagnosis and follow-up procedures were carried out following the recommendations of the American Academy of Pediatrics published in 2013[11] and the ROP Guidelines of the Turkish Neonatology and Ophthalmology Societies.[12] The criteria established by the International Committee for the Classification of Retinopathy of Prematurity (ICROP)[5] were utilized for the diagnosis of A-ROP. Accordingly, A-ROP typically affects zone I but less commonly zone II, does not follow the classic stages, and is accompanied by plus disease. In addition to peripheral retinal involvement, widespread venous dilatation and arterial tortuosity are observed throughout the retina. Besides, A-ROP may be accompanied by widespread neovascularization, arteriovenous shunt vessels, vitreous haze, and hemorrhage, as well as pupillary rigidity may also be present.

The exclusion criteria included patients who had initially undergone laser treatment, received treatment at another center or had been diagnosed with stage 4A, 4B, or 5 ROP at the first screening. Data were collected from the medical records of the ROP cases included in this study such as birth weeks (BW), birth weights (BWt), time of ROP onset, presence of A-ROP, the start of initial treatment, post-treatment follow-up duration, time to complete retinal vascularization, and the need for additional treatment. All initial and follow-up examinations of the cases were performed using a binocular indirect ophthalmoscope.

IVB injections (0.625 mg/0.025 ml) at a dose of 0.625 mg/0.025 ml (Avastin, produced by Genentech Inc., San Francisco, California, USA) were administered to 58 eyes of 30 preterm infants. All injections were performed in a surgery suite. After positioning the patients on the operating table, ocular anesthesia was applied using topical anesthetic drops under the supervision of a pediatric anesthesiologist. The patients' eyelids and eyelashes were cleansed with 10% povidone-iodine and covered with a sterile drape. Following the insertion of a lid speculum, the conjunctiva was sterilized for 3 minutes with 5% povidone-iodine. Intravitreal injection was performed with a 30-gauge insulin syringe, 1-1.5 mm posterior to the temporal limbus. After injection application, topical moxifloxacin 0.5% (Vigamox®, Alcon, Turkiye) antibiotic treatment was administered five times daily for one week.

Follow-up of the Cases

The cases were monitored at 1, 3, and 7 days post-injection for ROP monitoring and possible complications. Subsequently, until complete retinal vascularization was achieved, the cases were monitored every two weeks during the first three months, followed by check-ups every three to four weeks. Regression was considered as a reduction in plus disease signs and the stages of ROP. Reactivation was considered as the reappearance of plus disease signs and the development of classic ROP stages, and recurrences were managed using LP and IVB. On the other hand, complete retinal vascularization was considered as the extension of retinal vessels reaching the ora serrata. The observations were conducted using binocular indirect ophthalmoscopy with the aid of 360-degree scleral indentation.

RESULTS

Of the preterm infants, 19 (63.3%) were girls, while 11 (36.6%) were boys. Intravitreal bevacizumab (0.625 mg/0.025 ml) injections were administered to 58 eyes of 30 preterm infants. The mean birth weight of the cases was 1178±509 (500-2790) grams, and the mean gestational weeks was 28.2±2.7 (23-34). The average post-gestational weeks when intravitreal bevacizumab treatment was administered was 36.6±2.1 (32-39) weeks with an average post-treatment follow-up period of 29.5±4.3 (21-37) weeks (Table 1).

Table 1. Demographic data of ROP cases treated with IVB

Parameter	Value
Gender (F/M)	19/11
Infant/eye	30/58
Mean birth weight in grams (±SD)	1178±509
(min-max)	(500-2790)
Mean gestational weeks (±SD)	28.2±2.7
(min-max)	(23-34)
Week of treatment initiation (mean±SD)	36.6±2.1
(min-max)	(32-39)
Proportion of cases diagnosed with A-ROP	40%
Follow-up period after treatment (weeks, mean±SD)	29.5±4.3
(min-max)	(21-37)
Time to complete vascularization (weeks, mean±SD)	61.9±3.5*
(min-max)	(55-67)
Proportion of cases requiring reactivation and additional treatment	6.7%

*Cases in which vascularization was completed, ROP: Retinopathy of prematurity, IVB: Intravitreal bevacizumab, SD: Standard deviation, Min: Minimum, Max: Maximum, A-ROP: Aggressive retinopathy of prematurity

A significant proportion of the cases showed regression in ROP symptoms after treatment, and plus disease regressed in 93.3% of the cases. Twelve patients were diagnosed with A-ROP, accounting for 40% of the patients. Only two patients needed further treatment for recurrence, representing 6.7% of the cases. Both of these patients had an initial diagnosis of A-ROP. Additionally, the rate of A-ROP diagnosis was

higher among females compared to males. The average vascularization time was 62.8 weeks for preterm infants diagnosed with A-ROP and 61.3 weeks for those type 1 ROP diagnosis. Among females, the average vascularization time was 62.6 weeks, while for males, it was 60.7 weeks (Table 2) and no statistically significant differences were found (p>0.05). The differences in vascularization times between preterm infants with A-ROP and type 1 ROP diagnosis were not statistically significant (p=0.226). Accordingly, being diagnosed with A-ROP did not lead to a significant difference in vascularization times.

Table 2. Vascularization times by A-ROP diagnosis and gender

		Gender		
		Female	Male	Total
Diagnosed with A-ROP	Yes	7	5	12 (62.83)*
	No	12	6	18 (61.33)*
Total		19	11	30
Vascularization time		62.63	60.73	61.96*

*: Time to complete vascularization (weeks), A-ROP: Aggressive retinopathy of prematurity

DISCUSSION

This study evaluated IVB treatment and retinal vascularization in patients diagnosed with type 1 ROP and A-ROP, along with their demographic characteristics. The findings showed regression in 93.3% (n=28) of patients after a single dose of IVB treatment following the diagnosis of ROP. In the two patients who did not show regression, positive outcomes were achieved after additional laser treatment. The absence of negative outcomes in any of the cases and the high rate of regression suggest that IVB treatment works effectively for cases of ROP.

Today, one therapy option is to apply laser to the avascular peripheral retina, an approach whose efficacy has been clinically demonstrated. Although this treatment has proven effective, it also bears serious complications. Laser treatment only works in roughly half of instances, especially when Zone I ROP is present, and even in successful cases, its efficacy is overshadowed by significant visual field losses and myopia.[13-16] In zones I and II, the BEAT-ROP research showed that a 0.625 mg dose of IVB was successful in treating stage 3 ROP.[17] Although the BEAT-ROP study has its limitations, it yields promising outcomes for ophthalmologists regarding the future of ROP treatment.

A big challenge in anti-VEGF treatment for ROP is determining the timing and extent of retinal vascularization completion. Our findings revealed that retinal vascularization slows down compared to physiological vascularization following IVB treatment in ROP cases. Clinically, complete retinal vascularization refers to retinal vessels reaching the temporal ora serrata. The average time to achieve complete vascularization in the current study was 61.9 weeks. However, demonstrating complete vascularization through angiography might have provided more meaningful results. According to the BEAT-ROP research, the average time needed for complete vascularization had been observed to be 19.5 weeks post-treatment.[18] In our study, on the other hand, this time was 25.9 weeks. Sukgen et al.[19] reported that the average time for complete vascularization in ROP cases with IVB treatment of 0.625 mg was 55.9 weeks. Spandau et al.,[20] however, observed an average time of 65 weeks to achieve complete vascularization.

Despite complete regression has been reported in all cases of A-ROP with intravitreal bevacizumab treatment, recurrence can still occur in the following periods. Yetik et al.[21] showed that post-treatment recurrence occurs at an earlier stage and with greater frequency in all patients with A-ROP compared to classic ROP conditions. Therefore, effective follow-up of these cases is essential. In this study, the recurrence rate following IVB monotherapy was found to be 6.7%, with both patients diagnosed with A-ROP. Martinez- Castellanos et al.[22] evaluate 672 ROP cases to which IVB was applied between 2005-2017; they have observed recurrence requiring treatment in 6.8% of cases. In our study, LP was administered as an additional treatment. Yetik et al. achieved success with a second IVB injection in three of the five (8.1%) cases with recurrence, while a third IVB injection was needed for the remaining two cases. Nicoara et al.[23] achieved regression in three of the five (14.7%) cases that developed recurrence by applying LP after IVB. When recurrence is observed in ROP cases involving zone I, posterior ROP, and A-ROP following anti-VEGF monotherapy, LP is recommended as a second treatment if vascularization has progressed to zone II, whereas additional anti-VEGF therapy is suggested if vascularization remains in zone I.[24] In our study, since the vascularization was had reached zone II in both patients, we administered laser photocoagulation therapy to treat the recurrence.

In a comprehensive study Çömez et al.[25] identified recurrence in 38 (14.8%) of 257 eyes. Furthermore, they determined recurrence in 32 (20.8%) of 154 eyes with A-ROP and in 6 (5.8%) of 103 eyes with type 1 ROP, all of which were treated with laser photocoagulation. This treatment resulted in the resolution of ROP and plus disease symptoms in all eyes. However, a second recurrence detected in 6 eyes (2.3%) after LP, necessitating repeated IVB injections, which subsequently resulted in the resolution of ROP findings in all affected eyes.

CONCLUSION

This study demonstrates the effectiveness of IVB treatment in cases of type 1 ROP and A-ROP. Since it does not require general anesthesia, can be applied quickly, does not cause retinal ablation, and does not prevent peripheral vascularization, it is considered the first-line treatment option, particularly in A-ROP cases that require urgent treatment. However, the safety outcomes of IVB treatment for retinopathy of prematurity should be evaluated further in larger clinical research.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ondokuz Mayıs University Clinical Researches Ethics Committee was obtained (Date: 26.09.2024, Decision No: OMÜ KAEK 2024/381).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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