Original Article

The safety and effectiveness of 0.16 mg bevacizumab plus or minus additional laser photocoagulation in the treatment of retinopathy of prematurity

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Purpose: Retinopathy of prematurity (ROP) is the leading cause of preventable blindness in premature infants. Antivascular endothelial growth factor (anti-VEGF) therapy has been used increasingly in treatment as a pharmacological alternative to laser therapy. In this study, we evaluate the results of low-dose anti-VEGF treatments. **Methods:** Design: Retrospective--observational study. Infants who had been evaluated for ROP disease between February 2016 and February 2017 were assessed. We retrospectively reviewed the ROP stages, treatment results, and complications. Laser photocoagulation (LPC) and intravitreal bevacizumab (0.16 mg IVB) were used for treatment and fundus fluorescein angiography (FFA) was also performed in some of the cases. **Results:** IVB was applied to 43 infants. A macular hole was seen in one infant's eye after IVB. LPC was applied to avascular areas in 21 infants. In three patients, persistence of the disease was observed after administration of a low dose of IVB. Additional LFK was performed in these patients. None of the infants who received LPC had any complications. **Conclusion:** IVB is increasingly becoming the first-line treatment for ROP. For severe ROP, 0.16 mg IVB is effective. Using LPC to treat avascular areas after 70 weeks' gestational age (GA) may decrease the risk of late recurrence and appears to be a safe treatment to use.

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Retinopathy of prematurity (ROP) is the leading cause of preventable blindness in premature infants, and it is a growing problem in low- and middle-income countries.[1,2] In order to prevent ROP complications, effective screening and treatment programs are essential. ROP screening programs differ from county to county. Timely diagnosis and treatment are essential for the prevention of undesirable results.[3-7]

In ROP treatment, ablative therapy is preferred. This treatment first began in the 1980s and used cryotherapy to treat the outer surface of the sclera.[8] Later, in the 1990s, laser photocoagulation (LPC) was introduced.[9,10] However, since the definition of the role of vascular endothelial growth factor (VEGF) in the etiopathogenesis of ROP, the intravitreal injection of anti-VEGF drugs has also become a treatment option.[11] As such, anti-VEGF therapy has been used increasingly as a pharmacological alternative to laser therapy.[7,12,13] The side effects of anti-VEGF drugs and the most effective dosages for ROP treatment among premature infants are still unknown, especially where retinal angiogenesis and avascular regions are concerned.[12,14] The dosage of bevacizumab used as off-label generally accepted is half of the adult dose (0.625 mg). Today, intravitreal bevacizumab (IVB, 0.25--0.625 mg) is being used increasingly to treat Type 1 ROP, but there remain concerns about systemic toxicity. It has been shown that a dosage of bevacizumab as low as 0.031 mg can be effective in ROP treatment, and further investigation into the optimal dosage is required, as are new assessments of the effectiveness and systemic safety of the treatment.[15] IVB monotheraphy might be a feasible option for the achievement of ROP regression with good anatomical outcomes. However, several cases of delayed reactivation have been reported with this method—sometimes as long as 3 years post-IVB treatment. The primary purpose of this study was to evaluate the results of anti-VEGF treatments with low doses (0.16 mg) of bevacizumab.

Methods

Premature infants (GA: 34 weeks or younger) either born at our hospital or at an external centre and examined at our facility for treatment/follow-up due to known ROP disease between February 2016 and February 2017 were included in the study. The subjects were evaluated retrospectively, with the stage of ROP, the follow-up time, the treatment requirements and/or results, and any treatment complications being assessed.

This study was approved by ethics committee for the Bursa Yuksek Ihtisas Training and Research Hospital Health Science

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University in Bursa, Turkey. The principles of the Declaration of Helsinki were followed.

The infants were examined by scanning the fundus under a 28-dioptre lens following the dilatation of the pupils using three consecutive single drops of 2.5% phenylephrine (Mydfrin, Alcon, USA) and 0.5% tropicamide (Tropamid, Bilim Ilac, Turkey) at 10-min intervals.

All the examinations were carried out using indirect ophthalmoscopy (Omega 500, Heine, Germany), with scleral indentation being performed by the same two ophthalmologists (Dr M.A. and Dr G.C.).

The infants with ROP were classified into four groups, according to the international classification of retinopathy of prematurity's (ICROP) scale of the prevalence and severity of retinal proliferation, as follows: group 1: zone 1--2, stage 0--1 ROP; group 2: zone 1--2, stage 1--2 ROP; group 3: zone 1--2, stage 2--3 ROP; group 4: aggressive posterior ROP (APROP), which has the following characteristics: (1) a more posterior location, (2) rapid progression, rather than progression through the five typical stages, and (3) a poor prognosis, despite early treatment.[16,17] The infants with zone 1, stage 1--3+ disease and zone 2, stage 2--3+ disease were treated, as were those with APROP and zone 1--3 without plus infants. IVB (first treatment) and LPC (if needed) were utilized. The IVB dose administered was 0.16 mg (Altuzan®, Roche, Switzerland) for all the infants. The dose was administered to all the infants under topical anesthesia, using 0.5% propacaine hydrochloride drops (Alcaine®, Alcon, USA), application of povidone--iodine to the conjunctival sac, and after periocular skin is prepared with chlorhexidine gluconate 2%, a periocular drape and speculum applied given in the operating room at 1 mm posterior to the limbus and utilizing a 32-gauge needle.

Each of the infants receiving IVB was re-examined on day 1 and then at 1 week and 2 weeks post-administration. If the disease did not regress after 1 week, it was considered to be persistent. It was evaluated as the regression criterion at least 1 stage and plus disease regression. If there were no regression criteria, the disease was considered as persistent. The frequency of the examination was determined according to the disease and vascularization status.

Panretinal photocoagulation was performed on all avascular sites using an 810 nm diode laser (Iridex, Oculight SL, USA) by leaving a half-shoot space (150--200 mW of power for 0.2 s) in the theatre. LPC was performed on avascular sites or vascular leakage areas after 70 weeks' gestational age (GA) (if the avascular areas were observed to be of more than two discs' diameter with indirect ophthalmoscopy or RetCam 3) and in cases of recurrence or persistence post-IVB treatment. LPC was not used as the first treatment. In all cases, LPC was performed under general anesthesia or sedation.

Fundus fluorescein angiography (FFA) was undertaken using RetCam 3 (Clarity Medical Systems, Pleasanton, CA, USA) on patients whose parents had approved the procedure. FFA was carried out in an operating room under intravenous sedation. The FFA examinations used a bolus of 10% fluorescein solution (Alcon Pharma GmbH, Freiburg, Germany), which was administered intravenously at a dose of 0.1 mL/kg body weight. Photographs were recorded during the early, middle, and late phases. OCT measurements were taken using a spectral domain OCT device (Heidelberg, Germany), with the help of an experienced nurse.

SPSS version 21.0 software for Windows (Statistical Package for the Social Sciences, IBM, Chicago, IL, USA) was used for the data analyses. The Mann--Whitney U test was utilized to compare variables. Descriptive statistics are expressed as frequencies and percentages for qualitative data, and as means ± standard deviation or medians (range) for quantitative data (with and without normal distribution, respectively). A P value of < 0.05 was considered statistically significant.

Results

Various stages of ROP were observed in 118 infants (51 [43.4%] girls and 67 [56.8%)] boys). The infants were followed for an average of 50 (range: 42--73) weeks. Group 1 contained 42 (35.6%) patients, group 2 contained 38 (32.2%) patients, group 3 consisted of 16 (13.6%) patients, and group 4 included 22 (18.8%) patients. The clinical characteristics and treatment options for the groups are shown in Table 1.

All the infants in group 1 showed regression without treatment. Twelve (12/38) of the patients in group 2 were administered IVB. Two (2/12) of these infants also underwent LPC due to recurrence of the disease, while a further four (4/12) underwent LPC to treat avascular zones. In group 3, nine (9/16) infants were administered IVB, among whom four (4/9) underwent additional LPC to treat avascular zones. In group 4, all the infants (22) were administered IVB, and 11 (11/22) underwent additional LPC due to avascular zones. LPC was performed on a further six (6/22) patients to treat disease recurrence. In three (3/22) of the APROP patients, LPC was performed due to the persistence of disease. All the recurrences were observed to be examples of classic ROP disease.

Only one infant in group 4 had Stage 4B ROP (anti-VEGF and LPC for persistence), and PPV surgery was performed; no other patient had a higher stage of ROP. In total, 19 (44.1%) patients received additional LPC to treat avascular areas (of which four were examined with RetCam 3 and 17 were examined via indirect ophthalmoscopy). A macular hole developed after IVB administration in one eye of an infant with APROP (+) referred from another centre [Fig. 1], although the infant's other eye showed regression in both ROP stage and activity with the same dose. Vitreoretinal surgery (PPV) was performed at another centre to repair the macular hole. FFA was performed on five patients; a peripheral avascular area and leakage were seen in four of these patients [Figs. 2-4], while

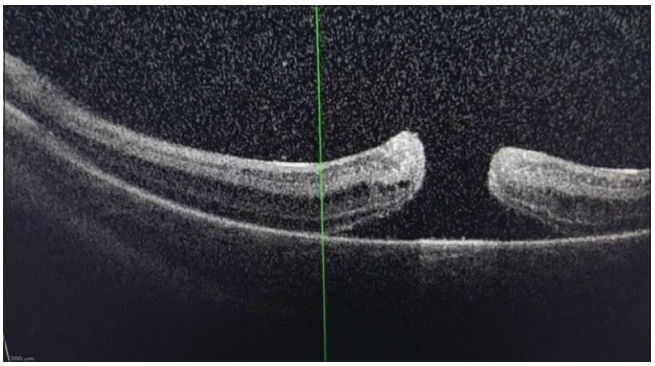

Figure 1: Preoperative macular hole on OCT image

Table 1: Groups, clinical characteristics and treatment options for patients with ROP

Group GA (w) Stage	Number (%100-118)	Clinical characteristics	IVB (%)	LPC for persistence/recurrence (%)	IVB + additional laser (%)	Surgery (%)
Group 1 30±2.5(w) Stage 0--1	42 (35.6%)	Shallow, thin demarcation line pre-plus +/-	----	----	----	----
Group 2 30.5±2.5(w) Stage 1--2	38 (32.2%)	Marked demarcation line pre-plus +/-	12 (10.1%)	2--2 (1.6--1.6%)	4 (3.3%)	----
Group 3 30.5±3.2(w) Stage 2 and higher	16 (13.6%)	Marked, bulging extraretinal vascular growth and effusion/ retinal detachment pre plus +/-	9 (7.6%)	2--2 (1.6--1.6%)	4 (3.3%)	---
Group 4 27±2.5(w) APROP	22 (18.6%)	Severe vascular alterations at the posterior pole plus +	22 (18.6%)	4--7 (3--6%)	11 (9.3%)	2 (1.6%) Macular holeretinal detachment

IVB: intravitreal bevacizumab; LPC: laser photocoagulation; APROP: aggressive posterior retinopathy of prematurity; ROP: retinopathy of prematurity; GA: gestational age

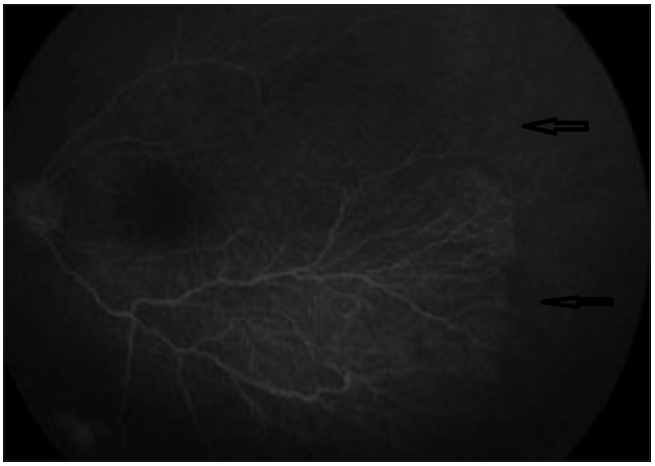

Figure 2: Vascular arrest seen on FFA

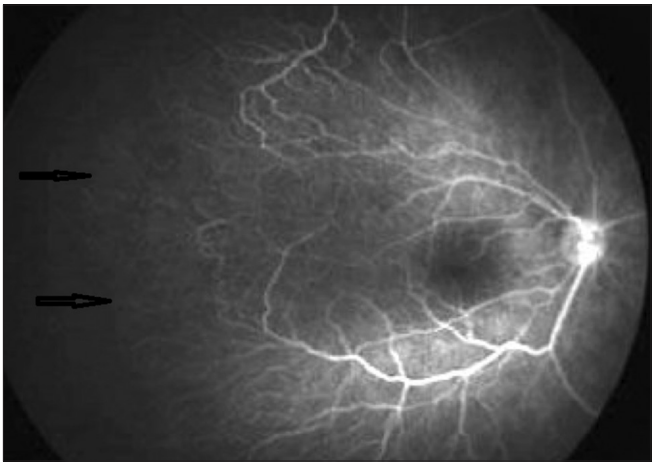

Figure 3: Abnormal arteriovenous communication and vascular arrest seen on FFA

the fifth patient was evaluated as having an abnormal vascular connection [Fig. 5]. Neither cataracts nor endophthalmitis were observed after the LPC and IVB treatments.

Discussion

In recent years, ROP rates have increased in East-Asian, former Eastern-Bloc, and Latin-American countries. Today, the condition is known as the third pandemic to have occurred in developing countries in the 2000s. ROP typically manifests in a severe form in both immature babies and relatively mature babies due to increased life expectancy in premature babies and free oxygen support.[18]

A review was conducted on 118 infants who were screened at our centre due to having various stages of ROP. Forty-three out of 118 (36%) required treatment. In Lorenz *et al*.'s study, 0.312 mg bevacizumab was administered for zone 1 ROP and posterior zone 2 ROP (including APROP disease) to 27 eyes. Acute ROP disease regressed in 19 cases (70%), while in the APROP group, only 25% regression was recorded. In this study, with a dose of 0.125 mg İVB, acute regression was found in 40 (93%) patients (all except 3/22 in the APROP group). In Lorenz *et al*.'s study, the mean weight for the APROP group was 581 ± 113 g. In our APROP group, the mean weight was 627 ± 120 g.[14] Thus, in our study, the babies were heavier, which may have been an important factor in the increased rates of responsiveness to IVB treatment found in our results.

A large retrospective study series by Mintz-Hittner *et al*. reported a 7% risk of ROP recurrence after 0.625 mg bevacizumab monotherapy.[19] In Gonzalez *et al*.'s study, 10 eyes (16%) experienced reactivation of ROP, for which additional treatment was performed with either 0.625 mg or 0.75 mg bevacizumab[20] In this study, the recurrence rate was higher (8/43; 18%). Our bevacizumab dosage was lower than those used by Gonzalez *et al*., which may account for the higher recurrence rate.

Assessment of peripheral avascular areas and FFA leakage is essential after late-phase ROP treatment with IVB.[21] In their study, Tahija *et al*. treated 20 eyes with ROP using IVB

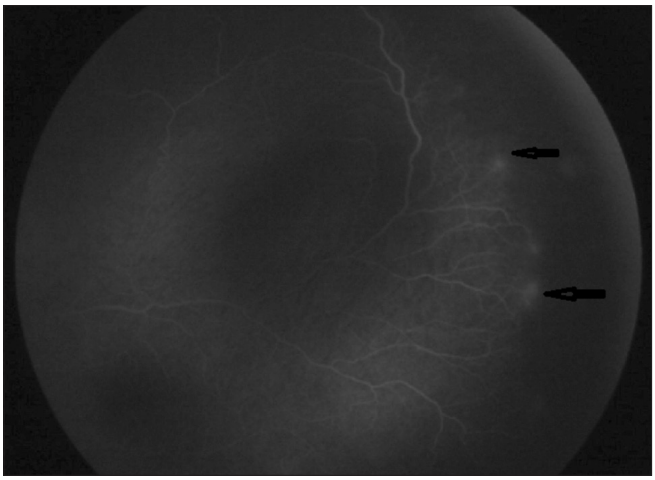

Figure 4: Peripheral avascular area and vascular leakage on FFA image

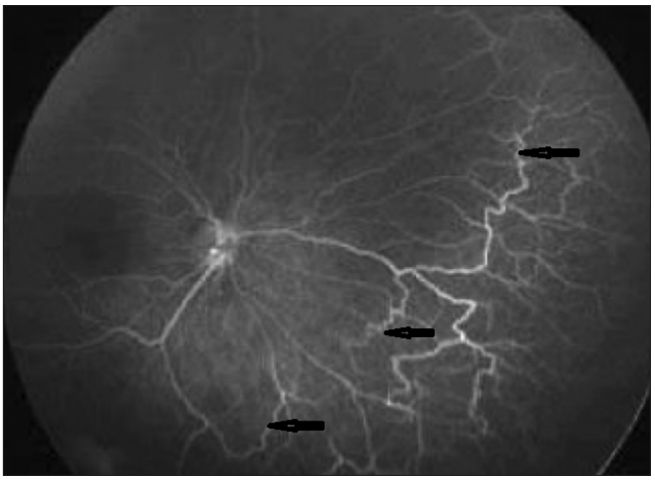

Figure 5: Abnormal vascular connection on FFA image

monotherapy. The results showed that peripheral avascular areas of more than two discs' diameter were present in more than 50% of the eyes ($n = 11$) up to 4 years after treatment.[22] In our study, 19 eyes (44.1%) had peripheral avascular areas, and we performed LPC in each of these cases. It can be assumed that if we had been able to perform FFA on more patients, more leaks and vascular anomalies would have emerged One patient's FFA revealed an abnormal vascular connection (a retina with abnormal vascular connection still functioning).[21] To confirm this result, perimetry may be performed on the patient in the future.

After IVB administration, extremely late reactivations began to appear the reason for which it could be using LPC on avascular retinas, which is essential to the prevention of disease reactivation.[23] In this study, we performed LPC on all avascular retinas after 70 weeks, and we did not observe any side effects due to LPC. In Gonzalez *et al*.'s study, 41/64 eyes examined and injected with bevacizumab received prophylactic laser treatment for an avascular retina after 60 weeks' PMA, leading to the finding that larger areas of nonperfusion and higher proportions of leakage are more likely in APROP patients.[20] In our study, we found similar results, especially where the prevalence of avascular areas in APROP patients was concerned (50% APROP vs. 38% others).

In this study, we used 0.16 mg İVB (low dose) for treatment because of the possibility of systemic side effects.[24] Morin *et al*.'s research compared the use of laser treatment and bevacizumab, observing higher odds of neurodevelopmental disabilities in the group which had received bevacizumab at the end of an 18-month period.[24] Hillier and Sahin *et al*., on the other hand, used low dosages of İVB (0.16 mg and 0.0625 mg), a strategy which led them to find that low-dosage IVB is an effective treatment for severe ROP.[25,26]

A limited number of studies in the literature report severe complications following IVB administration, including the development of macular holes, the occurrence of rhegmatogenous retinal detachment, the development of optical atrophy, and the risk of endophthalmitis.[27] In our series of 43 cases, the only infant who developed a macular hole had APROP. Macular optical coherence tomography studies on ROP have shown that macular edema develops in almost all advanced-stage ROP cases.[28,29] We consider enlargement of the hole to have developed as a result of the rapid regression of acute macular edema due to IVB administration. It should be noted that the widespread use of anti-VEGF therapy has led to an increase in reported complications associated with this treatment method.[24,27]

Retinal detachment is mostly tractional and can develop in exudative and rhegmatogenous forms in infants with ROP.[13] We observed detachment in just one eye in one case: an APROP patient. A Stage 4B retinal detachment was diagnosed and PPV was performed.

We could not perform FFA upon all the patients in our study (due in part to the RetCam being located in a different city). To prevent very late recurrence and the associated difficulties with arranging examinations and follow-ups many years later, we administered LPC to avascular areas. We preferred sedation in anesthesia for avascular areas after a GA of 70 weeks because this is a good approach to decreasing post-anesthesia apnoea to less than 1% risk (determined following a meta-analysis of 8 studies and 225 patients).[30] We did not detect any side effects due to sedation.

Conclusion

Increasingly, intravitreal anti-VEGF therapy is becoming the first treatment option for ROP. Our results demonstrate that 0.16 mg IVB is effective in treating severe ROP. In addition, performing LPC on avascular areas after 70 weeks GA may decrease late recurrence of disease and also appears to be a safe treatment. Although IVB injections are highly effective in treating ROP, rare but very serious complications such as macular holes and neurodevelopmental problems in developing infants should be borne in mind, especially where advanced disease is concerned. However, although low-dose IVB persistence recurrences and rare serious complication risk have been present, the fact is that the LPC areas are less and allowing the LPC to be performed in the more GA infants.

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Conflicts of interest

There are no conflicts of interest.

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