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Comparison of Intravitreal Bevacizumab and Laser Photocoagulation in the Treatment of Retinopathy of Prematurity

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Purpose: To compare the outcomes of patients with type I retinopathy of prematurity (ROP) treated with either intravitreal bevacizumab (IVB) or retinal laser photocoagulation (RLP).

Design: Retrospective case series.

Participants: Infants treated for type I ROP with IVB or RLP.

Methods: Patients who were born between January 2011 and December 2014 and were treated in Farabi Eye Hospital were included. The outcomes were stratified and analyzed, based on the treatment type and ROP zone.

Main Outcome Measures: Need for retreatment, time to regression, refractive errors, retinal adverse anatomic outcomes, and rate of complications.

Results: Five hundred twenty-three patients were treated for type 1 ROP, of whom 493 (986 eyes) met inclusion criteria. Seven hundred twenty-four eyes (73.4%) received IVB, and 262 eyes (26.5%) received RLP. Retreatment (because of recurrent or persistent retinopathy) occurred in 14.4% (106/724) of eyes initially treated with IVB and in 8.8% (23/262) eyes initially treated with RLP ($P = 0.065$). Re-treatment was not significantly different between the 2 groups for patients with zone I disease ($P = 0.978$). Re-treatment rate was considerably higher in patients with zone II disease treated with IVB (69/558 [12.3%]) compared with those treated with RLP (20/251 [7.9%]; $P = 0.017$). In the IVB group, 82.8% and 53.4% of eyes showed an avascular area in zone III (despite ROP regression) at 1 and 2 years after treatment, respectively. The spherical power and the spherical equivalent were significantly higher in eyes treated with RLP (-1.31 ± 2.83 diopters [D] and -2.84 ± 2.77 D, respectively) than eyes treated with IVB (0.19 ± 3.21 D and -1.26 ± 3.19 D, respectively; $P = 0.016$ and $P = 0.007$, respectively). Differences in astigmatic power were not significant.

Conclusions: Both IVB and RLP are effective treatments for type 1 ROP. Longer follow-up time is necessary for infants treated with IVB. More patients with zone II disease treated with RLP achieved disease regression after a single treatment than those who received IVB, although outcomes after re-treatment were comparable except for a greater refractive error in patients treated with RLP. *Ophthalmology Retina 2018;■:1–7 © 2018 by the American Academy of Ophthalmology*

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Retinopathy of prematurity (ROP) continues to be a leading cause of visual morbidity worldwide.[1] Although its incidence has declined in developed countries, increases in premature births, improvements in keeping premature children alive, and lack of ROP screening programs have resulted in high disease prevalence in the developing world. Although the pathogenesis of ROP is incompletely understood, the 2 main established risk factors are low gestational age and low birth weight.[2] Retinopathy of prematurity is a biphasic disorder consisting of an initial phase of oxygen-induced vascular obliteration followed by a period of hypoxia-induced vessel proliferation. Vascular endothelial growth factor (VEGF) dysregulation has been implicated as an important factor.[3]

Peripheral retinal ablation with cryotherapy and, now more commonly, retinal laser photocoagulation (RLP) reduce proangiogenic factors by destroying ischemic tissue; however, these treatments are associated with negative sequela including visual field loss and the risk of high myopia developing.[4,5] Moreover, RLP requires sedation or general anesthesia and requires a high level of expertise. As a result, less destructive and simpler methods to treat ROP long have been sought.[4,6,7] The off-label use of anti-VEGF, most commonly intravitreal bevacizumab (IVB), increasingly has

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been studied in the treatment of ROP. Although the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (Beat-ROP) demonstrated a significant benefit of IVB compared with conventional laser treatment in infants with zone I stage 3 plus ROP, confirmatory studies are lacking.[8] Most subsequent studies have been single armed and limited by small sample size. It should be noted that IVB-treated eyes need intense follow up schedule.[8–10] Here we present a large, retrospective case series comparing the clinical outcomes of patients with type 1 ROP treated with IVB and RLP.

Methods

The institutional review board/ethics committee of the Tehran University of Medical Science approved this retrospective cohort study. All research adhered to the tenets of the Declaration of Helsinki and all infant's parents or legal guardians provided informed consent. A chart review of infants who underwent treatment for type 1 ROP was conducted to compare effectiveness and safety of IVB (Avastin; Genentech, Inc., South San Francisco, CA) with RLP. The medical records of preterm infants born between January 2011 and December 2014 who were examined and treated for type I ROP with either IVB or RLP at Farabi Eye Hospital (a tertiary referral hospital in Tehran, Iran) were reviewed. Preterm infants with a gestational age less than 34 weeks or birth weight less than 2000 g were screened for ROP with indirect ophthalmoscopy at 4 weeks' chronological age or 31 weeks' postmenstrual age (whichever was later).[11,12] Patients with less than 12 months of follow-up, presence of stage 4 or 5 ROP before treatment, or other ocular diseases (such as congenital cataract or glaucoma) were excluded. Type 1 ROP was defined by the criteria outlined in the Early Treatment for Retinopathy of Prematurity study: zone I with any stage with plus disease, zone I with stage 3 without plus disease, or zone II with stage 2 or 3 with plus disease.

Screening and treatment were carried out by 4 experienced pediatric vitreoretinal surgeons (R.R., A.K., A.D.F., M.I.). Type of treatment was selected based on surgeons' preferences. The need for treatment or re-treatment and type of treatments required the agreement of at least 2 experts. RetCam photographs (Clarity Medical Systems, Pleasanton, CA) were obtained before treatment. All procedures were performed within 2 days of diagnosis. After the initial treatment, each infant was examined every 1 to 2 weeks based on the severity of ROP until complete regression was achieved. In IVB-treated patients, examinations continued until retinal vessels extended into zone III, after which infants were examined less frequently in a staged fashion starting with monthly examinations that then were extended to every 3 to 6 months. In the RLP group, follow-up visits were continued monthly until 90 weeks after regression and then tapered to every 3 to 6 months.

All IVB injections were performed in the operating room with a dose of 0.625 mg/0.025 ml under topical anesthesia (tetracaine 0.5%). Injections were in the most convenient quadrants, 1.5 to 2 mm from the limbus through pars plicata, aiming the needle directly toward the optic nerve. In bilateral cases, both eyes were injected on the same day with different injection sets, medication vials, and set-ups. Patients received sulfacetamide 10% eye drops every 6 hours for 3 days after injection.

Patients receiving laser photocoagulation underwent indirect laser ablation (wavelength, 810 nm) or transscleral diode laser treatment to the peripheral avascular retina under general anesthesia or topical anesthesia with sedation. For indirect transpupillary or transscleral laser photocoagulation, the entire avascular retina was treated in the standard method: applying laser spots to the avascular area separated by one-half burn width.

Demographic and clinical data were recorded for each patient including estimated gestational age, birth weight, gender, oxygen therapy duration, intubation duration, any history of transfusion or phototherapy, ROP zone, ROP stage, presence of plus disease, treatment type, time to regression, regression type, other comorbidities (including sepsis, respiratory distress syndrome, and intraventricular hemorrhage), mean age at the treatment, and follow-up period. All data were reviewed by 2 separate investigators (R.R. and J.H.). The status of the retina at the time of last dilated fundus examination was noted for each patient. The status was classified as regression, vascularization, partial or total retinal detachment (stage 4 or 5 ROP), and other (with specification). The last cycloplegic refractive error during the first 3 years of life, including spherical power, cylindrical power, axis, and age at the examination, were recorded.

The primary outcome was the rate of initial need for re-treatment because of treatment failure, which was defined as either ROP persistence or recurrence. Persistence of ROP was defined as the absence of the regression of either neovascularization or plus disease 3 weeks after the treatment. Recurrence of ROP was defined as new extraretinal neovascularization with the arrest of normal retinal vascularization during the follow-up period after initial disease regression. Persistent vascular tortuosity, especially after IVB injection without other signs of ROP activity, was not considered a sign of treatment failure. All the eyes in which treatment failed were retreated based on the following protocol: if the initial failed treatment was RLP, retreatment consisted of additional laser treatment between the previous laser scars or IVB injection (treatment switch) and if the initial failed treatment was IVB, retreatment was IVB reinjection. Secondary outcomes were time to regression (disappearance of all active neovascularization and perfused shunts),[4,6] refractive error, retinal anatomic outcome, and rate of secondary sequel based on treatment type and ROP zone.

Statistical Methods

The Kolmogorov-Smirnov test and Q-Q plot were used to assess normal distribution of data. To evaluate the patient-specific parameters between the groups, we used the t test, Mann–Whitney U test, chi-square test, and Fisher exact test as appropriate. To assess the eye parameters when considering the correlation between 2 eyes in a single patient, the generalized estimating equation was used. The time to regression was evaluated by Cox regression. In the last step, all of the variables for which the P value was less than 0.1 in comparison with the treatment were considered in multiple generalized estimating equation and Cox regression analyses to avoid possible confounders. All statistical analyses were performed with IBM SPSS Statistics for Windows software version 22.0 (IBM Corp., Armonk, NY). Statistical significance was set at $P < 0.05$.

Results

Of 523 patients who were treated for type 1 ROP during the study period, a total of 986 eyes of 493 patients met inclusion criteria. Seven hundred twenty-four eyes (73.4%) were treated with IVB, and 262 eyes (26.5%) were treated with RLP. Clinical and demographic data are presented in Table 1 (available at www.ophthalmologyretina.org). Systemic comorbidities, including sepsis, respiratory distress syndrome, intraventricular hemorrhage, the need for intubation or transfusion, and duration of oxygen therapy, were similar between 2 treatment groups.

Of the 724 eyes treated with IVB, 166 (22.5%) demonstrated zone I ROP and 558 (75.5%) demonstrated zone II ROP. Zone I