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Early Refractive Outcome After Intravitreous Bevacizumab for Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a neovascular retinal disease that has usually been treated by peripheral argon laser coagulation. Retinal laser coagulation has disadvantages and adverse effects such as the need for general anesthesia, scarring of the peripheral retina and choroid, and presumably induction of myopization.[1,2] Based on the role of vascular endothelial growth factor in retinal neovascularization, recent studies have shown the therapeutic effect of intravitreous bevacizumab as a vascular endothelial growth factor inhibitor for the therapy of ROP.[3,4] Besides the short-term effects of this anti–vascular endothelial growth factor therapy in terms of a regression of retinal neovascularization, effects of the therapy on the development of myopia have not yet been examined. We therefore assessed the refractive error of children who had received intravitreous bevacizumab for therapy of ROP.

Methods. The prospective study included all children who had been treated with an intravitreous injection of bevacizumab (0.375 mg; Avastin) for ROP threshold disease in posterior zone 2 or zone 1 or for prethreshold ROP in zone 1. Diagnosis was based on the guidelines of the International Committee for the Classification of Retinopathy of Prematurity.[5] The study group was compared with a control group that had previously undergone retinal argon laser therapy of ROP in the same center and was matched with the study group for birth weight, gestational age, and length of follow-up. The follow-up examination included sciascopy and automated refractometry (Retinomax 3; Nikon) under cycloplegic conditions and examination of the anterior and posterior segments of the eye.

Results. The study group consisted of 12 eyes of 6 children with a mean (SD) birth weight of 627 (116) g and a mean (SD) age of 24.8 (1.2) weeks. The follow-up examination was performed at a mean (SD) corrected age of 10.5 (2.7) months (**Table**). The control group included 20 eyes of 10 children (Table). The mean refractive errors for the right eyes and left eyes were significantly less myopic in the study group than in the control group ($P = .03$ for the right eyes; $P = .02$ for the left eyes) (Table). Refractive astigmatism did not differ significantly between the groups. An additional child received an intravitreous injection of bevacizumab in her left eye in which an excessive tunica vasculosa lentis prevented retinal laser therapy, and she received retinal argon laser coagulation in her right eye. At a corrected age of 29 months, the refractive error was –8.00 diopters (D) OS and –10.25 D OD. The right eye after laser therapy showed macular ectopia, while the posterior pole of the left eye was unremarkable.

Table. Demographic Data and Examination Results for Children With Retinopathy of Prematurity Threshold Disease

Characteristic	Study Group[a]	Control Group[a]	*P* Value
Eyes, No.	12	20	
Patients, No.	6	10	
Male/female, No.	4/2	4/6	
Birth weight, g			
Mean (SD)	627 (116)	732 (226)	.24
Median (range)	595 (480 to 810)	665 (440 to 1090)	
Age, wk			
Mean (SD)	24.8 (1.2)	25.1 (1.9)	.42
Median (range)	25.1 (23 to 27)	24.6 (23 to 28)	
Follow-up time, mo			
Mean (SD)	10.5 (2.7)	11.5 (1.0)	.72
Median	10.8	11.3	
Right eye, D			
Refractive error			
Mean (SD)	–0.27 (4.09)	–6.25 (5.31)	.03
Median (range)	–0.50 (–7.00 to 4.25)	–8.25 (–12.00 to 3.50)	
Astigmatism			
Mean (SD)	1.13 (0.54)	1.80 (1.49)	.22
Median (range)	1.00 (1.00 to 2.00)	1.25 (0.00 to 5.00)	
Left eye, D			
Refractive error			
Mean (SD)	1.54 (2.19)	–4.20 (5.92)	.02
Median (range)	0.75 (–0.75 to 4.63)	–5.00 (–14.00 to 4.38)	
Astigmatism			
Mean (SD)	0.92 (0.52)	1.58 (0.88)	.09
Median (range)	1.00 (0.00 to 2.00)	1.00 (1.00 to 3.00)	

Abbreviation: D, diopters.
[a]The study group received intravitreous bevacizumab; the control group had previously undergone retinal laser therapy.

Comment. Children receiving intravitreous bevacizumab therapy as compared with children undergoing retinal laser coagulation were significantly less myopic at 1 year of follow-up. Although the cause for myopization in children treated for ROP has remained unclear so far, the results of our study are in line with previous investigations in which myopization was more pronounced in children randomized for the more invasive cryotherapy than in those who received the less invasive laser therapy.[6] Intravitreous medical therapy for ROP as compared with laser therapy may thus have the following advantages: (1) the possibility of performing the therapy under local anesthesia instead of general anesthesia; (2) the possibility of not destroying the peripheral retina by coagulation; and (3) potentially a lower degree of myopization. Limitations of our study were the small number of included patients, the design as a comparative case series study instead of a randomized trial, and the fact that refractive error can be better determined at a later age. This series provides another premise for a randomized prospective clinical trial.[4]

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Significant Treatment Failure With Intravitreous Bevacizumab for Retinopathy of Prematurity

The mainstay of treatment for retinopathy of prematurity (ROP) with risk of retinal detachment has been ablation of peripheral avascular retina through cryotherapy or laser.[1,2] Because ablative treatments are destructive and treatment often requires intubation and anesthesia in neonates with comorbid conditions, there has been interest in alternative treatments. Intravitreous bevacizumab injection is an emerging treatment that can be performed with minimal sedation. The BEAT-ROP study[3] demonstrated a significant benefit of bevacizumab over laser in reducing treatment-requiring recurrence by 54 weeks. Given that recurrence in eyes treated with bevacizumab occurred later, at a mean (SD) of 16.0 (4.6) weeks after treatment, than in eyes treated with laser, at a mean (SD) of 6.2 (5.7) weeks after treatment, the time course of recurrence and progression of ROP is likely altered. Thus, late recurrences may not have been detected by the study.[4] Herein, we report a case of significant treatment failure after bevacizumab monotherapy.

Report of a Case. A 560-g neonate, born prematurely at 23 weeks' postmenstrual age, was noted was noted to have stage 3 ROP in zone 1 at postmenstrual age 34 weeks. Following informed consent, off-label intravitreous bevacizumab (0.625 mg) was injected into each eye. The patient was then examined every 1 to 2 weeks. Posterior fibrotic tissue was noted first at 48 weeks, and fine vascularity appeared at 50 weeks. Retinal detachment (stage 4a ROP) in the right eye was present at 52 weeks, and the patient was referred by the original treater to our service for surgical intervention. Unfortunately, the patient did not appear for treatment and state department of family services intervention was required to bring the patient to our service, which occurred at 57 weeks. At that time, both retinas were completely detached (stage 5) with fibrovascular tissue immediately posterior to the lens (**Figure 1** and **Figure 2**).

Comment. Retinopathy of prematurity is a proliferative retinal vascular disorder associated with local ischemia and subsequent extraretinal fibrovascular proliferation and tractional retinal detachment. Current standard treatment involves ablation of avascular retina,[1,2] but recent studies[3,5] have shown intravitreous bevacizumab monotherapy to be an effective treatment for ROP.

Despite promising results with intravitreous bevacizumab monotherapy, we believe this case demonstrates that caution must be taken when using bevacizumab. Clearly the progression of ROP is altered, with initial regression but possible recurrence as the effect declines over time. Unfortunately, the timing and rapidity of onset are not well characterized. Moreover, the location and pattern of recurrence may also be altered. Our patient displayed a posterior rather than anterior recurrence that progressed rapidly to retinal detachment.

Although not strictly medical failure, lapses in parental compliance with an extended burden of follow-up may play an important role in outcome and therefore the treatment choice. It is our belief that laser, despite causing less rapid regression of disease, induces a more permanent response because it destroys the source of vascular endothelial growth factor. Additionally, laser induces some retinal adhesion that may slow the effect of contracting fibrovascular tissue, and the recurrence pattern is more