

# VITRECTOMY AFTER INTRAVITREAL BEVACIZUMAB (AVASTIN) FOR RETINAL DETACHMENT IN RETINOPATHY OF PREMATURITY

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**Purpose:** The purpose of this study was to evaluate the feasibility of performing vitrectomies after using bevacizumab (Avastin, Genentech, South San Francisco, CA) for the management of retinal detachments in retinopathy of prematurity.

**Methods:** Eleven eyes of 8 children with retinopathy of prematurity retinal detachment that developed despite peripheral ablation with indirect diode laser were injected with 0.625 mg bevacizumab. Injections were given through the pars plicata, and the status of the central retinal artery was checked with indirect ophthalmoscopy. A vitreoretinal surgery was scheduled for 1 week after the bevacizumab injection. All eyes underwent surgery using 25- or 23-gauge instrumentation. Demographic data, neovascular activity, and the anatomic status of the retina were evaluated. Systemic and local perioperative complications were recorded.

**Results:** The average gestational birth weight was 950 g, and the average gestational age at birth was 25.7 weeks. Although 9 eyes had stage 4A, 2 had stage 4B retinal detachments. Six eyes had zone II and five eyes had zone I disease. Bevacizumab was injected at an average postgestational age of 38 weeks. A notable reduction in the vascular activity could be observed 1 week later when vitrectomy was performed. With a mean follow-up of 8.5 months (range, 2–13 months), a favorable outcome could be observed in all eyes. Only one eye with persistent vitreous hemorrhage required reoperation. No complications attributable to the bevacizumab injections were noted.

**Conclusion:** These data show that vitrectomy after intravitreal bevacizumab can be effective in selected cases. The regression of the vascular activity induced by this drug might contribute to better results in some of these cases. There were no apparent short-term safety concerns for intravitreal bevacizumab injections in these babies. However, additional studies are needed to define the role of bevacizumab as a possible adjuvant in the management of retinopathy of prematurity retinal detachments.

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Retinopathy of prematurity (ROP) is a leading cause of childhood blindness in many countries in the world. Retinopathy of prematurity is now affecting emerging economies and middle-income countries where the rates of disease requiring treatment also tend to be higher.<sup>1,2</sup> In the majority of the cases, laser photoco-

agulation has proven to be very effective in the treatment of the vision-threatening forms of ROP.<sup>3–6</sup>

Despite our better understanding of the disease,<sup>7</sup> and the introduction of the Early Treatment for Retinopathy of Prematurity Randomized Trial for a more timely intervention with laser ablation of the avascular retina, retinal detachment does continue to occur in some patients.<sup>8</sup> Good anatomic and functional outcomes can be obtained in cases of ROP-related retinal detachments with the use of vitreoretinal surgery.<sup>9–12</sup>

The role of vascular endothelial growth factor in the pathogenesis of ROP has long been known.<sup>13</sup> Recent evidence suggests that antivascular endothelial growth factor drugs injected in the vitreous cavity might contribute to the management of ROP.<sup>14–18</sup>

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Table 1. Summary of the Data of the Study Group

Patient No.	Sex	Birth Weight (g)	Gestational Age (Weeks)	Eye	ROP Zone	Laser Treatment/Age (Weeks)	ROP Stage at Presentation	Age at Avastin Injection (Weeks)	Surgery	Age at Surgery (Weeks)
1	M	1,500	30	OD	II	Yes/unknown	4B	41	23-gauge V-L	42
				OS	II	Yes/unknown	4B	41	23-gauge V-L	42
2	M	—	23	OD*	—	—	—	—	—	—
				OS	I	Yes/31	4A	38	23-gauge V-L	39
3	M	980	27	OD†	—	—	—	—	—	—
				OS	II	Yes/unknown	4A	41	23-gauge V-L	42
4	M	894	24	OD	I	Yes/34	4A	36	23-gauge V-L	37
				OS*	—	—	—	—	—	—
5	F	1,200	29	OD	I	Yes/35	4A	36	23-gauge V-L	38
				OS‡	—	—	—	—	—	—
6	F	866	24	OD	II	Yes/unknown	4A	36	25-gauge LSV	37
				OS	II	Yes/unknown	4A	36	25-gauge LSV	37
7	M	760	24	OD	I	Yes/37	4A	37	25-gauge LSV	38
				OS	I	Yes/37	4A	37	25-gauge LSV	38
8	M	810	25	OD	II	Yes/unknown	4A	38	25-gauge LSV	39
				OS†	—	—	—	—	—	—
Mean	—	950	25.75	—	—	—	—	37.9	—	39

\*Not part of the series; did not require vitrectomy because of bevacizumab-induced regression.

†Not part of the series; laser-induced regression.

‡Not part of the series; no bevacizumab injected; favorable outcome with vitrectomy for stage 4A.

M, male; F, female; OD, right eye; OS, left eye; V-L, vitrectomy plus lensectomy; LSV, lens sparing vitrectomy.

The potential benefits of these drugs in preventing the development of retinal detachment or in facilitating the surgery to treat them are worth studying. The purpose of our work was to evaluate the feasibility of performing vitrectomies after using bevacizumab (Avastin, Genentech, South San Francisco, CA) for the management of retinal detachments in ROP.

### Methods

A consecutive series of 11 eyes in 8 preterm infants diagnosed with retinal detachment from ROP between December 2007 and May 2008 underwent surgical intervention after an intravitreal injection of bevacizumab. This initial series was composed of a heterogeneous group of babies referred from different parts of the country with retinal detachments from ROP after having received laser treatment. When first seen, all 11 eyes were vascularly active. Because eyes must be vascularly quiet at the time of surgery, they were injected with intravitreal bevacizumab to induce a reduction in the neovascular activity.

The bevacizumab injections were given in an operating room under the care of a pediatric anesthesiologist. Sterile unit doses of bevacizumab were prepared in a compounding pharmacy under aseptic conditions and placed in a tuberculin syringe. A dose of 0.625 was injected 1 mm posterior to the limbus after instillations of 10% povidone-iodine. The central retinal artery was patent after injection.

Vitreoretinal surgery was scheduled for 1 week after the bevacizumab injection. Either 23- or 25-gauge instrumentation was used. A three-port approach was used in all cases. Vitrectomy and membrane peeling were performed with settings of 1,200 cpm to 1,500 cpm and suction of 400 mmHg to 500 mmHg (Accurus, Alcon Surgical, Fort Worth, TX). The aim of the vitrectomy was to dissect the tractional proliferation between the ridge and the lens, the ridge and the nerve, the ridge and the vitreous base, and the circumferential traction along the ridge. Partial fluid-air exchange was used at the end of the procedure in the majority of the cases.

The clinical charts were retrospectively reviewed to collect the following data: date of birth, birth weight, gestational age at birth, sex, clinical characteristics of the ROP before treatment, preoperative anatomic status of the retina, date of surgery, perioperative complications, vascular activity, date of last follow-up visit, and anatomic status at last follow-up visit. A favorable result was considered when complete reattachment of the retina was obtained. The anatomic status was determined by ophthalmoscopy during follow-up visits or under general anesthesia. Table 1 shows a summary of the data of the study group. RetCam images were used to document most of the cases.

### Results

The average gestational birth weight was 950 g, and the average gestational age at birth was 25.7 weeks.



**Fig. 1.** Patient 8 was 810 g and 25 weeks at birth. At 38-weeks postconceptual age, a stage 4A ROP with significant vascular activity was present.

Six patients (75%) were boys and 2 (25%) were girls. Although 9 eyes had stage 4A, 2 had stage 4B retinal detachments. Six eyes had zone II disease, and five eyes had a zone I ROP.

Bevacizumab was injected at an average postconceptual age of 38 weeks and the surgery was performed at 39 weeks. Six eyes underwent a 23-gauge vitrectomy plus lensectomy, and 5 eyes had a 25-gauge lens-sparing vitrectomy.

Patient 8 was 810 g and 25 weeks at birth. Laser was applied for a posterior zone II disease and was referred with stage 4A in the right eye in which bevacizumab was injected at 38-weeks postconceptual age. A 25-gauge lens-sparing vitrectomy was performed in that eye at 39 postconceptual weeks. A very significant reduction in the vascular activity of this eye as well as the other eyes in the series could be observed 1 week later when vitrectomy was performed (Figures 1 and 2).

Also, 1 week after the bevacizumab, i.e., when vitrectomy was performed, a remarkable reduction of the subretinal fluid was clinically observed in patient 1 who had a significant exudative component. With a mean follow-up of 8.5 months (range, 2–13 months), a favorable outcome could be observed in all eyes (Figure 3). In patients 2 and 4, although both eyes were injected at stage 4A, 1 eye experienced regression, whereas the other required a vitrectomy.

A change from vascular to fibrous tissue was observed, but there were no rhegmatogenous retinal detachments after the bevacizumab injections. We observed that the bigger the extent of neovascular tissue growing into the vitreous, the more likely for fibrosis development to take place after the bevacizumab.

On some occasions, we experienced better defined surgical planes and easier removal of the membranes



**Fig. 2.** Patient 8, 1 week after bevacizumab injection. A marked reduction in the vascular activity can be observed.

were achieved after bevacizumab. Patient 7 had persistent vitreous hemorrhage for 3 weeks postvitrectomy and was reoperated on with a favorable anatomic outcome. This was the only patient requiring a reoperation.

## Discussion

Retinal detachment may occur in some ROP cases, even in those treated in a timely manner. Visual outcome in eyes with ROP-related retinal detachments is generally poor.<sup>19,20</sup> There is large bibliographic evidence supporting surgical intervention in cases of retinal detachment from ROP,<sup>10–13</sup> but many authors as well have recognized the presence of vascular activity as a potential problem and would prefer to wait before performing vitreous surgery until they find a vascularly quiet eye.<sup>9,10,18,21</sup>



**Fig. 3.** Favorable anatomic outcome after a bevacizumab injection and a 25-gauge lens-sparing vitrectomy were performed in patient 8.

Thus, the fast regression of the vascular activity induced by bevacizumab might contribute to addressing one of the most relevant issues in ROP retinal detachment cases, that is, being able to operate on a vascularly inactive or “quiet eye” rather than on an active one without the drawback of a long wait for naturally induced regression of the neovascular activity. In this series, a very significant reduction in the vascular activity of these eyes could be observed after the bevacizumab injection when vitrectomy was performed. A favorable outcome could be observed in all eyes.

Twenty-three- and 25-gauge instruments were successfully used in these cases. Despite being our first choice, the anatomic configuration of the detachments prevented us from following a lens-sparing approach in some of these cases.

Two clinical observations deserve further attention. The first is that in patient 1, the exudative component of the detachment was significantly decreased after bevacizumab. The other observation is that in patients 2 and 4, 1 eye experienced regression after the bevacizumab injection without the need for a vitrectomy. More clinical studies might contribute to further understanding these observations.

In addition, we noticed that the bigger the extent of neovascular tissue growing into the vitreous, the more likely for fibrosis development to take place after the bevacizumab; in turn, this should be taken into account when timing the vitrectomy. The increase in the tractional forces can induce progression of the tractional detachment or the development of a rhegmatogenous component, the most serious potential bevacizumab-related complication, which did not occur in this series.

The more posterior forms of ROP (aggressive posterior ROP) might produce retinal detachments at an earlier gestational age in which the high levels of vascular endothelial growth factor are present, and thus, the use of bevacizumab might be especially helpful. Despite the major concern about potential side effects with the use of antivascular endothelial growth factor drugs in infants, we have not seen any complications attributable to the bevacizumab injections in any of our patients. Nonetheless, it should be noted that we did not have a systematic way of monitoring for systemic side effects and that subtle developmental defects would not have been detected in this study.

In conclusion, vitrectomy after intravitreal injection of bevacizumab could be performed using current vitreoretinal techniques and can be an effective approach for managing ROP retinal detachments. Not-

withstanding this, additional studies are needed to better define the role of bevacizumab as a possible adjuvant in the management of ROP and specifically in cases of retinal detachments.

**Key words:** Avastin, bevacizumab, retinopathy of prematurity, vitrectomy.

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