

Combination of laser photocoagulation and intravitreal bevacizumab (Avastin®) for aggressive zone I retinopathy of prematurity

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Abstract

Background This report describes the use of combined laser photocoagulation and intravitreal bevacizumab administration for aggressive zone I retinopathy of prematurity (ROP). **Methods** A male patient, born at 25 weeks gestation with a birth weight of 884 g, received indirect laser photocoagulation and a 0.75 mg intravitreal bevacizumab injection to each eye for aggressive stage 3 zone I ROP. Structural outcomes were evaluated 3 months after treatment. **Results** At 3-month follow-up, treatment had resulted in ROP regression, prompt resolution of plus signs and neovascular proliferation in both eyes, and no signs of systemic or ocular adverse events. **Conclusions** The combination of indirect laser photocoagulation and intravitreal bevacizumab injection was well tolerated and induced prompt regression of aggressive zone I ROP.

Keywords Retinopathy of prematurity · Indirect laser photocoagulation · Intravitreal bevacizumab injection

Introduction

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness [1]. Zone I disease is known to have a worse prognosis even after cryotherapy or laser photocoagulation compared to zone II or III disease [2–7].

Vascular endothelial growth factor (VEGF) has been known as one of the major factors in ROP development and mediates the formation of new blood vessels in various retinal neovascular diseases [8–11]. Serum VEGF levels are reported to be higher in infants with stage 3 and threshold ROP than in those with less severe disease [12].

Bevacizumab is an anti-VEGF monoclonal antibody. Intravitreal bevacizumab injections have recently gained popularity as a potential treatment for several intraocular neovascular diseases without known serious ocular systemic adverse events [13, 14]. However, most of the reports on use and safety of intravitreal bevacizumab are data from treatment of adult patients, not children and especially not premature newborns with their specific situation, risks and needs.

The present report describes the use of intravitreal bevacizumab combined with indirect laser photocoagulation to treat aggressive zone I ROP in a premature (25-weeks gestation) male newborn.

Materials and methods

The male patient was born at 25 weeks gestation with a birth weight of 884 g. His first screening examination at 8 weeks of age showed bilateral stage 3 zone I ROP with severe plus disease and extensive epiretinal vascular proliferation (Fig. 1). The patient was, hence, scheduled for a combined treatment of intravitreal bevacizumab and

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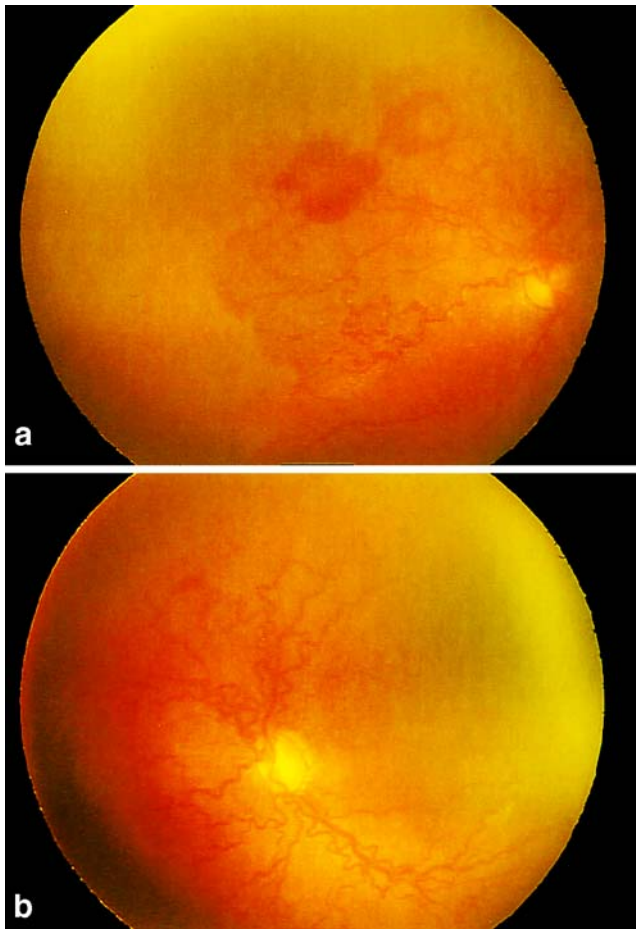


Fig. 1 Zone I ROP with severe plus disease and extensive epiretinal vascular proliferation. (a) Right eye, (b) left eye

indirect laser photocoagulation. The off-label use of bevacizumab and the potential risks were discussed with the parents of the patient. We explained potential drug-related adverse events such as systemic thromboembolic events, blood pressure increase, intraocular inflammation and a possible negative effect on normal retinal vasculogenesis and neurogenesis, as well as potential injection-related adverse events including lens injury, endophthalmitis, retinal detachment and vitreous hemorrhage. We also explained that although preliminary short-term data suggested intravitreal drug use was safe, there were no published data regarding safety in premature newborns. After a thorough discussion regarding the possible consequences of treatment, the parents agreed to proceed with the combination therapy.

Under general anesthesia, both eyes received a near confluent pattern of indirect diode laser photocoagulation to the avascular retina, immediately anterior to the border of the vascular zone extending to the ora serrata for 360°. After photocoagulation, 0.75 mg (0.03 cc) bevacizumab was injected intravitreally using a 30-gauge needle placed 1 mm behind the limbus in each eye. The perfusion of

optic nerve heads was then confirmed using indirect ophthalmoscope.

The systemic condition of the patient was closely monitored during the perioperative and postoperative periods in the neonatal intensive care unit, including continuous monitoring of blood pressure, oxygen saturation and heart rate.

Results

The surgery was uneventful, and the general status of the patient during the operation and perioperative period was stable without any serious ocular or systemic events associated with drug or surgical procedures. A substantial decrease in vascular engorgement and tortuosity was noticeable from postoperative day 1, and neovascular proliferation regression was obvious in both eyes by postoperative 1 week. At 3 months follow-up, a fundus examination revealed clear media with well-regressed ROP in both eyes (Fig. 2).

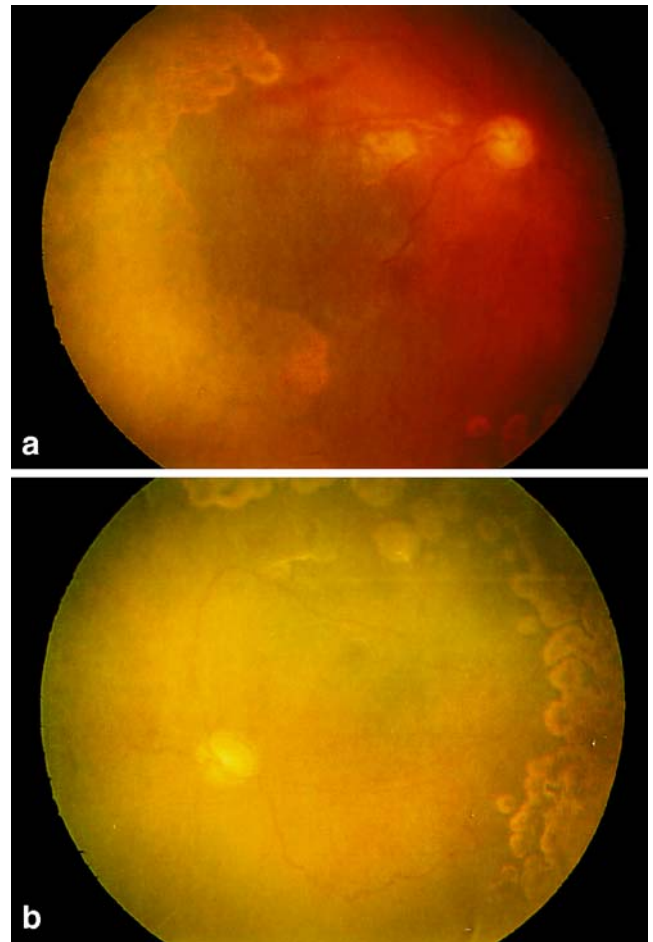


Fig. 2 Fundus findings at 3 months post-treatment. (a) Right eye, (b) left eye. Note ROP regression and resolution of vascular proliferation and plus disease

Discussion

Zone I ROP is an uncommon disease, occurring in approximately 10% of all premature infants with retinopathy that requires treatment. Even after conventional treatment, patients with zone I disease often progress to unfavorable outcomes, such as a posterior fold, retinal detachment involving the posterior pole or a retrolental mass obstructing the view of the retina. The Cryotherapy for Retinopathy of Prematurity Cooperative Study reported a 77.8% unfavorable outcome rate, using cryotherapy, and the Early Treatment for Retinopathy of Prematurity Cooperative Group reported a 55.2% unfavorable outcome rate, using laser photocoagulation in zone I disease [2–4]. Other studies using diode laser photocoagulation for ROP showed unfavorable outcome rates, ranging from 40–77.8% [5–7]. One study showed a 100% unfavorable outcome rate following use of laser photocoagulation for posterior zone I ROP [7].

The frequent failure of conventional ablative therapy has been suggested to reflect the different mechanism underlying zone I ROP, involving aberrant vasculogenesis less dependent on VEGF165-mediated angiogenesis [4]. An alternative interpretation could be a second source of VEGF165, such as vitreal macrophages as reported by Naug et al. [15]. Thus, as suggested by other authors, we hypothesized that a combination therapy of conventional laser photocoagulation and intravitreal injection of monoclonal antibodies against VEGF, such as bevacizumab, might be more effective [4]. The drug may not only inhibit tyrosine kinase proteins and attack the process of abnormal vasculogenesis upstream from VEGF165, but may also block secondary sources of intraocular VEGF165 [4]. Bevacizumab was used in the present study as it was the only anti-VEGF drug available at the time at our institute. A more selective VEGF inhibitor, such as pegaptanib (Macugen®), might be a safer option for ROP treatment. Since VEGF is known to play a role in physiological retinal neurogenesis and vasculogenesis, blocking all VEGF isoforms may have negative effects on normal development in premature newborns [16, 17].

The present patient underwent both procedures on the same day as we believed it was safer to perform the injections under general anesthesia in sterile operating room conditions rather than under local anesthesia. Although the optimum intravitreal bevacizumab dose remains to be established as yet, previous reports describe using up to 2.5 mg without serious systemic or ocular adverse events [13, 14]. Animal studies have shown that typical doses of intravitreal bevacizumab did not affect visually evoked potentials and electroretinogram patterns in albino rabbits, nor were they associated with any histological retinal toxicity [18–20]. Considering the smaller vitreous volume in premature newborns, we chose to administer 0.75 mg

bevacizumab rather than the usual adult intravitreal dose of 1.25 mg. Previous case reports also used 0.75 mg in premature newborns with aggressive posterior ROP without any serious complications [21, 22]. Since recent reports suggest that even smaller doses might be sufficient to inhibit intravitreal VEGF and neovascular proliferation, further studies are warranted to establish the optimal doses for premature newborns [23, 24].

In the current case, one combined treatment of drug injection and laser photocoagulation was sufficient to induce ROP regression. Unlike other neovascular diseases, such as choroidal neovascularization associated with age-related macular degeneration and proliferative diabetic retinopathy, ROP is less likely to necessitate repeated injections since the disease is known to undergo spontaneous involution in 90% of patients before 44 weeks of postmenstrual age, and the intravitreal therapeutic drug concentration is maintained for up to 4 weeks [24, 25]. These observations further support the use of intravitreal VEGF inhibitors for ROP since the newborn may not require repeated injections that create a cumulative risk of complications. However, further studies appear essential to determine the timing, interval and drug dose required to provide the optimal intravitreal concentration and to identify the most effective agent with the minimum toxicity.

The present study found that combined intravitreal bevacizumab and laser photocoagulation treatment promptly and strikingly halted the progression of vascular proliferation. Although new vessel regression and the disappearance of plus disease may be achieved by laser photocoagulation alone, the prompt resolution of vascular engorgement and tortuosity from as early as postoperative day 1 suggests a possible adjunct effect of intravitreal bevacizumab. Significantly, we did not observe any serious adverse events attributable to the drug, and there were no signs of any negative effects on normal retinal vessel growth at 3 months postoperatively.

In conclusion, combined laser photocoagulation and intravitreal bevacizumab treatment resulted in prompt resolution of vascular proliferation and a favorable anatomical outcome in a premature newborn with zone I ROP and was not associated with any serious ocular or systemic adverse events. These findings indicate that controlled studies with long-term follow-ups are warranted to determine the potential safety and benefits of VEGF inhibitors for treating zone I ROP.

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