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Original Article

Combined diode laser cyclophotocoagulation and intravitreal bevacizumab (Avastin) in neovascular glaucoma

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Abstract

Background: Intravitreal injection of bevacizumab (Avastin) in eyes with neovascular glaucoma (NVG) has recently been shown to induce rapid regression of anterior segment neovascularization and has promise as adjunct treatment to diode laser cyclophotocoagulation (CPC) to control intraocular pressure (IOP). This study presents the outcome of concomitant treatment with CPC and intravitreal bevacizumab in painful poor visual potential eyes in a case series of consecutively diagnosed NVG.

Methods: Twelve patients (14 eyes) were treated with CPC and concurrent intravitreal bevacizumab 0.05 mL (1.25 mg) and study end-points were IOP lowering, regression of anterior segment neovascularization and resolution of pain.

Results: The mean preoperative IOP was 42.1 ± 11.4 and was lowered to 16.6 ± 7.1 mmHg at 1-month postoperatively. Anterior segment neovascularization regressed dramatically within 1 week of intravitreal bevacizumab in 12 eyes. Thirteen eyes reported persistent relief of ocular pain at 6 months following treatment.

Conclusions: Combined intravitreal bevacizumab and CPC treatment for NVG provides rapid control of anterior segment neovascularization and may lead to improved symptomatic relief and IOP control.

Key words: bevacizumab (Avastin), diode laser cyclophotocoagulation, intraocular pressure, neovascular glaucoma.

Introduction

Neovascular glaucoma (NVG) resulting from anterior segment neovascularization is a severe consequence of ischaemic retinal diseases and proliferative diabetic retinopathy. Treatment for NVG aims to achieve both regression of anterior segment neovascularization and intraocular pressure (IOP) lowering.[1,2] Retinal ischemia stimulates production of vascular endothelial growth factor (VEGF), which has been shown to play a key role in neovascularization.[3–5] Panretinal photocoagulation (PRP), has been the treatment of choice for ischaemic retinal pathologies and reduces the ischaemic drive that stimulates VEGF production.[6–8] However, PRP can take several weeks to bring about regression of neovascularization and it is often difficult to perform in patients with media opacities, including corneal oedema, cataract, anterior chamber or vitreous haemorrhage and poor pupillary dilation.[2,9] Several recent case series have reported dramatic regression of iris neovascularization following intravitreal bevacizumab (Avastin), a recombinant antibody against VEGF, for the treatment of NVG.[10–17]

Management of elevated IOP in NVG can be challenging as there is often a limited response to topical and systemic ocular hypotensive agents.[18] Furthermore, glaucoma filtration or drainage device surgery

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in the presence of active anterior segment neovascularization has low long-term success.[2,19,20] Diode laser cyclophotocoagulation (CPC) induces effective IOP lowering in many eyes with NVG, but on its own does not lead to regression of anterior segment neovascularization.[20] We thus sought to investigate the efficacy of combining CPC with intravitreal bevacizumab in eyes with NVG to achieve both effective IOP lowering and regression of neovascularization. Here we report the preliminary outcome of CPC administered concomitantly with intravitreal bevacizumab and in eyes with NVG.

Materials and methods

Study design and participants

Our department initially considered intravitreal bevacizumab as adjunctive treatment for NVG in 2006 and given the favourable outcomes following internal auditing, combination treatment with intravitreal bevacizumab and CPC was implemented as standard protocol for all such patients. In this case series, NVG patients receiving combined intravitreal bevacizumab and CPC from June 2006 to January 2008 were followed up for a minimum of 6 months. Patients were treated at the Glaucoma Investigation and Research Unit at the Royal Victorian Eye and Ear Hospital (Melbourne, Australia). The inclusion criteria were eyes with NVG with uncontrolled IOP on maximum tolerated medical therapy and/or ocular pain. All 14 eyes included in the study did not have any major media opacities and underwent PRP before CPC/intravitreal bevacizumab treatment. Patients with previous CPC were excluded from the study.

Before laser, patients underwent a complete ophthalmic examination, including assessment of best corrected visual acuity by Snellen acuity charts, slit lamp biomicroscopy, Goldman applanation tonometry, gonioscopy and fundoscopy. The primary outcome measures included: change in IOP, relief of ocular pain (pain was assessed upon questioning by the treating physician and noted accordingly), regression of anterior segment neovascularization and visual acuity at last follow up (minimum 6 months). A minimum of 30% reduction of IOP before the treatment was considered as IOP control in this series.

Signed informed consent was obtained before intervention and study approval was obtained from the Human Ethics Committee of the Royal Victorian Eye and Ear Hospital.

Intraoperative procedure

Cyclophotocoagulation treatment was performed under peribulbar anaesthesia (2% lignocaine) using the OcuLight SLX semiconductor diode 810 nm laser (Iris Medical Instruments Inc, Mountain View, CA, USA) and the contact G-probe. Treatment was delivered through a 600-μm quartz fibre protruding 0.7 mm from the G-probe contact surface to indent the conjunctiva and sclera. Transillumination was used to identify the ciliary body and 20–30 laser 'shots' were applied, 10 in each quadrant of the ciliary body sparing the 3- and 9-o'clock positions. The laser parameters used were 2000 mW for 2000 ms. A 180°C or 270°C circumferential treatment was given at the discretion of the treating physician.

Intravitreal injection of bevacizumab was performed as a sterile procedure. Following paracentesis, commercially available bevacizumab (Avastin; 100 mg/4 mL; (Genentech, South San Francisco, CA) was administered to the vitreous cavity (0.05 mL [1.25 mg]) via the pars plana route, in the superotemporal quadrant, 3.5–4 mm posterior to the limbus. Patients were commenced on topical prednisolone acetate 1% with phenylephrine 0.12% and chloramphenicol 0.5% for a minimum period of 1 month after treatment. Topical anti-glaucoma medications were continued after the procedure.

Postoperative follow up

Patients were followed up within the first week, 1 and 3 months then at 3-monthly intervals after receiving combined CPC/intravitreal bevacizumab. At each follow up, patients underwent a routine ophthalmic examination including measurement of IOP and visual acuity, assessment of reported ocular pain and regression of anterior segment neovascularization. Any additional procedures that the patients required during the follow up were recorded.

Statistical analysis

Statistical analysis was performed with the Graphpad Prism software for Windows. Statistical significance (defined as $P < 0.05$) was detected with the Student's *t*-test.

Results

Demographic profile and pretreatment characteristics

A total of 12 patients (14 eyes) were treated with combined CPC and intravitreal bevacizumab with a mean follow up of 9.3 ± 3 (range 6–12) months. The patient demographics and baseline characteristics are presented in Table 1. In all eyes included in this study, PRP was initiated before CPC/bevacizumab treatment. One eye had previous failed tube filtration

Table 1. Baseline characteristics and patient demographics

Parameter	CPC and IVB ($n = 14$)
Gender (male/female)	8/6
Age (years)	
Mean ± SD	64.4 ± 15.53
Range	34–87
Visual acuity (Snellen Chart)	HM – CF 3 m: 11 >CF 3 – 6/60:3
NVG diagnosis, *n* (%)	
PDR	8 (57)
CRVO	4 (29)
OIS	2 (14)
Previous treatment, *n* (%)	
PPV	3 (21)
Tube filtration surgery	1 (7)

CF, Counting Fingers; CPC, cyclophotocoagulation; CRVO, central retinal vein occlusion; HM, Hand movements; IVB, intravitreal bevacizumab; m, meters; NVG, neovascular glaucoma; OIS, ocular ischaemic syndrome; PAS, peripheral anterior synechiae; PDR, proliferative diabetic retinopathy; PPV, pars plana vitrectomy.

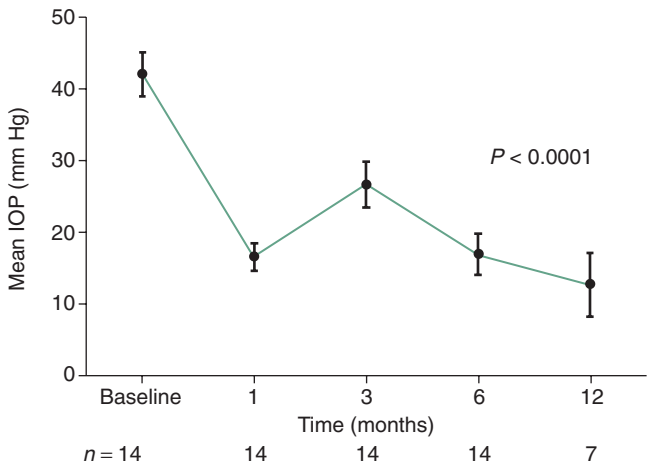

Figure 1. Intraocular pressure (IOP) profile before and after intravitreal bevacizumab and diode laser cyclophotocoagulation treatment.

surgery and three eyes had previous vitrectomy for proliferative diabetic retinopathy. All eyes had extensive peripheral anterior synechiae (angle closure) on gonioscopy at baseline.

IOP profile and anti-glaucoma medications

The IOP profile before and after treatment with CPC/bevacizumab is presented in Figure 1. Mean IOP decreased from 42.1 ± 11.4 mmHg at baseline to 16.6 ± 7.1 mmHg at 1 month postoperatively. Six months postoperatively mean IOP was 17.1 ± 3.6 mmHg. A 30% reduction of IOP was achieved in 9 eyes at 6 months.

Before CPC/bevacizumab treatment, five patients were receiving oral acetazolamide. At 6 months, however, all patients were able to stop acetazolamide for IOP control and 11 patients were able to reduce their use of topical medications.

Pain

Early symptomatic relief was observed in all patients after treatment with CPC/bevacizumab and at 6 months, 13 out of 14 patients were symptom-free.

Visual acuity

Preoperatively 11 eyes had visual acuity of counting fingers or less and at 1 month postoperatively, an improvement in visual acuity of at least one Snellen line, was observed in four eyes. At last follow up, visual acuity deteriorated in three eyes, improved in three eyes and was unchanged in the remaining eight eyes.

Anterior segment neovascularization

A dramatic regression of iris and angle neovascularization was observed in 12 eyes (86%) receiving CPC/bevacizumab within the first week postoperatively (Fig. 2). Recurrence of iris neovascularization was seen in 2 eyes at 3 months and 2 eyes at 10 months.

Adverse events and additional procedures

Recurrent neovascularization in two patients was controlled with additional CPC/bevacizumab 3 months after initial treatment. One patient underwent trabeculectomy surgery to control a persistently elevated IOP 3 months after initial treatment.

Discussion

Neovascular glaucoma is a refractory glaucoma that generally caries a poor visual prognosis. The recent introduction of intravitreal bevacizumab has provided a novel method to pharmacologically target intraocular neovascularization by inhibiting VEGF, a key factor in angiogenesis. Several case series have indicated that over the short-to-medium term, intravitreal bevacizumab brings a rapid regression of neovascularization and IOP lowering when used as an adjunct to PRP.[10–17,21] However, in most patients with NVG and complete angle closure, PRP or

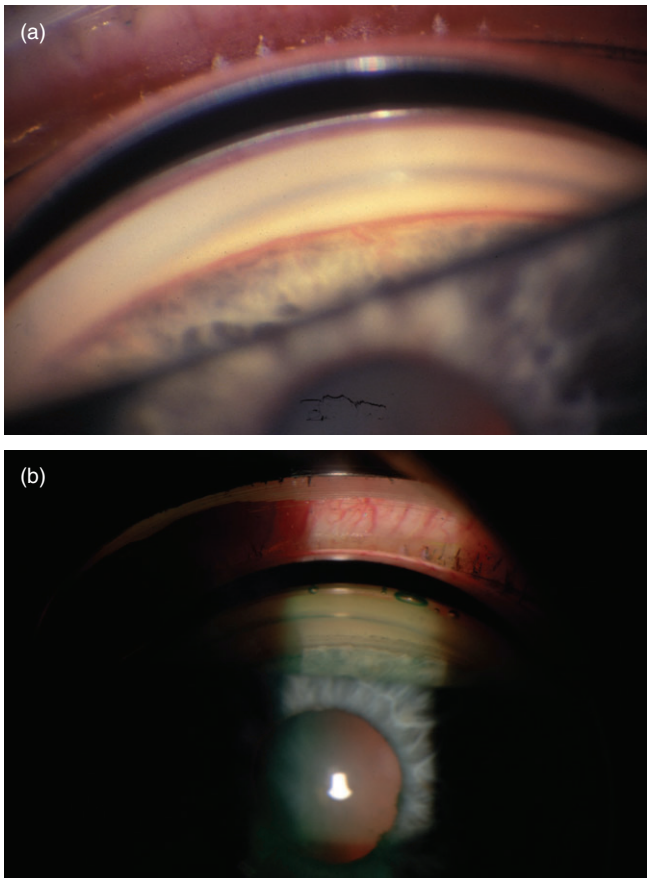

Figure 2. Angle neovascularization before and after combined intravitreal bevacizumab and diode laser cyclophotocoagulation. (a) Pretreatment Goniosocopy showing active inferior angle neovascularization and (b) regression of angle neovascularization at one month.

bevacizumab alone is insufficient to control IOP and a surgical approach is usually indicated.[16] CPC has been shown to be effective for pain relief and IOP control in advanced NVG.[6,22–24] Combining CPC with intravitreal bevacizumab therefore, provides a method to simultaneously combat neovascularization and symptomatic IOP elevation in eyes with advanced NVG. We report favourable outcomes including reduction of IOP, resolution of pain and resorption of anterior segment neovascularization following combined CPC and intravitreal bevacizumab over a long-term follow up.

In the majority of our patients, we observed rapid regression of anterior segment neovascularization within the first week following intravitreal bevacizumab, which is consistent with previous reports that have used bevacizumab alone.[1,10–12,16,21,25] Four eyes out of 14 in our study had recurrent neovascularization following intravitreal bevacizumab. This is similar to a previous report that found recurrence of neovascularization in 2 out of 11 eyes treated with concomitant bevacizumab and PRP.[21] Wakabayashi *et al.* reported recurrence of NVI (Neovascularization of the Iris) in 71% of eyes at 6 months post-bevacizumab; however, only 59% of their patients had complete PRP before bevacizumab.[16] In our four patients with recurrence of neovascularization, two patients underwent additional CPC/bevacizumab treatment, one underwent treatment with bevacizumab alone and the last one had to undergo trabeculectomy due to persistent uncontrolled IOP. Although regression of neovascularization was not achieved in three eyes, the new vessels of the iris and angle appeared stable with no overt progression over the follow-up period.

Over the long term, we observed effective IOP lowering in this group of patients. This outcome is similar to a large retrospective study by Murphy *et al.*, who found 87% of NVG eyes treated with CPC and continued on maximally tolerated medical therapy achieved IOP lowering of 30% or more at a mean final follow up of 17 months.[6] We also found successful symptom relief in our patients, which may be a more clinically relevant end-point in painful NVG eyes with poor visual potential.

This case series suggests a promising role for combination CPC/bevacizumab treatment in NVG to achieve rapid regression of angle neovascularization, sustained IOP lowering and pain relief. Further longer-term prospective randomized studies are recommended to thoroughly evaluate the utility of combination CPC/bevacizumab treatment in NVG.

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