Role of Adjunctive Use of Intravitreal Bevacizumab for Severe Proliferative Diabetic Retinopathy before Vitrectomy

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Abstract

Purpose: To evaluate the safety and efficacy of intravitreal injection of bevacizumab advanced to vitrectomy for severe proliferative diabetic retinopathy.

Methods: This is a prospective study in which, Ten eyes of ten patients with an average age 54.1 ±6.5 years (45-64 years old) complaining of severe proliferative diabetic retinopathy were investigated. An intravitreal injection of 1.25mg bevacizumab was performed 3-10 days prior to planned vitrectomy. A written informed consent was obtained from all patients. All of them were completely evaluated in the outpatient department. Fluorescein angiography was advised to every patient.

Results: All cases showed minimum bleeding during surgical dissection of fibro-vascular membrane and less post-operative complications were observed. Two eyes receiving bevacizumab 3-10 days before the surgery showed strong fibrosis and adhesion of fibro-vascular membrane, resulted in some surgical complications. The cases having intravitreal bevacizumab for shorter time before vitrectomy did not show extensive fibrosis.

Conclusion: Intravitreal bevacizumab was safe and effective in pre treatment of proliferative diabetic retinopathy prior to vitrectomy. It can induce effective regression of retinal neovascularization and rapid clearance of vitreous hemorrhage.

Key Words: Bevacizumab – Vitrectomy – Proliferative diabetic retinopathy.

Introduction

PROLIFERATIVE diabetic retinopathy (PDR) is one of the most prevalent but severe ocular disorders and it remains the leading cause of new blindness in young adults. Without treatment, 50% of those with proliferative disease will be blind within 5 years [1]. Hyperglycemia induces retinal hypoxia that up regulates a range of vasoactive factors which may lead to macular edema and/or angiogenesis and hence potentially sight threatening retinopathy [2].

A generally accepted explanation of the fibro-vascular proliferations found in proliferative diabetic retinopathy (PDR) is that widespread retinal ischemia leads to release of vasoproliferative factors such as vascular endothelial growth factor (VEGF) which diffuses through out the vitreous as well as the anterior segment inducing neovascularization [3]. Vitreous levels of VEGF were elevated by approximately 3-fold in patients with advanced proliferative retinopathy [2]. Intraocular injection of VEGF causes micro vascular abnormalities and retinal ischemia [4,5].

To date, vitrectomy and Argon laser are predominant treatments for proliferative diabetic retinopathy [6], while the risk of complication is of special concern due to the bleeding from fibro-vascular membrane (FVM).

Bevacizumab (Avastin Genetech Inc, South San Francisco, California, USA) is a humanized vascular endothelial growth factor (VEGF) antibody used for metastatic colorectal carcinoma [7].

Recent reports have described the application of Bevacizumab to treat ocular neovascular disorder including proliferative diabetic retinopathy [8]. Because of its almost immediate effect on the perfusion of ocular neovascularizations, it might have the potential to decrease the blood flow in neovascular tissues [9]. Adjunctive use of intravitreal Bevacizumab for severe proliferative diabetic retinopathy before vitrectomy has also been reported. However the preferable timing from the intravitreal injection to surgery has not been determined [10].

Patients and Methods

This prospective study included ten patients with ten eyes complaining of PDR. All the patients underwent complete ophthalmological examination...
including record of visual acuity, IOP, slit-lamp bimicroscopic examination, indirect ophthalmoscopy and complete medical evaluation in the outpatient department. Fluorescein angiography was carried out in every patient before intravitreal Avastin injection to rule out macular ischaemia. Dose of Avastin was 1.25mg/0.05ml. Intravitreal injection was given 3 days to 10 days before vitrectomy.

### Results

The patients included 7 males and 3 females with an average age 54.1 ±6.5 years (range between 45 and 64 years). All patients had type 2 diabetes. The injection was given 3-10 days ahead of surgery in four eyes. While in six eyes, injection was given in less than seven days before surgery. All patients showed remarkable regression of new vessels in fibrovascular membranes. Which necessitated minimum intra-operative haemostasis and achieved complete resolution of retinal tractions. Extensive fibrosis of fibrovascular membrane accompanied with strong adhesion to the retina was found in two of the four eyes, which received intravitreal Bevacizumab more than 7 days ahead of the surgery and the other two eyes receiving injection in the range of 3-10 days bleeds more during the surgery. Where as the six eyes having shorter administration time of Bevacizumab (less than 7 days) prior to vitrectomy did not show firm adhesion of the fibro-vascular membrane to the retina and peeling of pre-retinal membrane was not difficult during vitrectomy Table (1).

<table>
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<tr>
<th>No.</th>
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### Discussion

Retinal neovascularization and macular edema are central features of diabetic retinopathy, a major cause of blindness in working age adults. The currently established treatment for diabetic retinopathy targets the vascular pathology by laser photocoagulation [11]. According to diabetic retinopathy study [12-13], Pan retinal laser photocoagulation (PRP) reduced the risk of severe vision loss by more than 50%. This approach is associated with significant adverse effects due the destruction of neural tissue and is not always effective.

Characterization of the molecular and cellular processes involved in vascular growth and hyper permeability has led to the recognition that the angiogenic growth factor and vascular permeability factor VEGF plays a pivotal role in the retinal microvascular complications of diabetes. Thus, VEGF represents an important target for therapeutic intervention in diabetic retinopathy. Agents that directly inhibit the actions of VEGF and its receptors show considerable promise [11]. Pegaptanib (Macugen) has been reported to cause involution of retinal neovascularization [14].

Bevacizumab is a recombinant humanised monoclonal antivascular endothelial growth factor antibody used to induce regression of neovascularisation and reduce permeability [15]. It has increasingly been used to treat choroidal neovascularisation and diabetic macular oedema [16]. It has also proven to be effective for the treatment of severe PDR [17]. Results of fluorescein angiography revealed a reduction in leakage from the foci of neovascularisation and regression of the neovascular component of fibro-vascular tissue in eyes with PDR within 1 week after intravitreal Bevacizumab injection (IVB).

Chen 2006 [10] first reported that preoperative IVB was helpful in facilitating vitrectomy in severe PDR. It has been observed that during vitrectomy of proliferative diabetic retinopathy (PDR) there is severe bleeding which obscures the surgical field and prolongs the surgical time, resulting in an increased number of complications and difficulty in handling the situation [10].

In the present study eight eyes of ten patients with PDR were successfully treated with combination of vitrectomy and Bevacizumab intravitreal injection. Our cases showed less bleeding in surgical excision of fibrovascular membrane especially in subjects operated in less than seven days after administration of intravitreal Avastin.

Consistently Avery et al. [8] have demonstrated the efficacy of Bevacizumab for the treatment of PDR, which remarkably attenuates the activity of fibro-vascular membrane at one week post-administration. Therefore, it provided good visibility to surgeon and reduced the risks of surgical complications.
However the generation of strong adhesion between fibro-vascular membrane and retina was observed, in those eyes in which Bevacizumab was administered 1-2 weeks before surgery. In these cases peeling of proliferative retinal membrane from retina was very difficult, and sometimes it was impossible to separate posterior hyphoid [8].

Since the cases that received intravitreal Bevacizumab in shorter period (3-5) before surgery did not show extensive fibrosis of fibrovascular membrane and less bleeding during surgical excision of fibro-vascular membrane, shorter administration period of Bevacizumab (less than 7 days) may be preferable [18]. Further studies are required on this subject to determine the appropriate timings of vitrectomy after intravitreal Bevacizumab injection.

In conclusion an appropriate use of intravitreal Bevacizumab is effective as an adjunctive therapy prior to vitrectomy for severe proliferative diabetic retinopathy.

Especially if surgery is performed within 3-7 days after intravitreal injection of Bevacizumab.

References


