

Intravitreal Injection of Bevacizumab as Adjunctive Treatment for Proliferative Vitreoretinopathy

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Abstract

Objectives: To evaluate the midterm anatomical and functional outcomes of intravitreal injection bevacizumab in silicone oil-filled eyes as an adjunctive treatment for proliferative vitreoretinopathy.

Material/patients and Method: The study included all 16 patients who underwent pars plana vitrectomy for treatment of proliferative vitreoretinopathy grade C or D, who received pars plana vitrectomy combined with silicone oil tamponade and intravitreal injection of 1.25mg bevacizumab at the end of surgery, and who were operated on by the same surgeon.

Results: In all, 16 eyes from 16 patients were included in this study. Mean follow up time was 6.70 (SD = 2.07) months (range 3.0-10.0 months). The mean best-corrected visual acuity was 1.99 ± 0.327 log MAR at baseline, which improved to 0.82 ± 0.48 log MAR at the last visit ($P < 0.001$). Best-corrected visual acuity increased in 15 (93.7%) eyes and decreased in 1 (6.3%) eye at last visit compared with baseline. 93.7 % of eyes had attached retina after SO removal in the end of study .

Conclusions: This pilot study suggests that intravitreal injection of 1.25 mg bevacizumab as an adjunct to vitrectomy and silicone oil tamponade in treating proliferative vitreoretinopathy (grade C or D) appears to be effective and safe.

Keywords: Proliferative Vitreoretinopathy; Intravitreal Injection Bevacizumab; Rhegmatogenous Retinal Detachment Vascular Endothelial Growth Factor; Parsplana Vitrectomy; Silicone oil

Abbreviations: (PVR): Proliferative Vitreoretinopathy; (IVB): Intravitreal Injection Bevacizumab; (RRD): Rhegmatogenous Retinal Detachment; (VEGF): Vascular Endothelial Growth Factor; (PPV): Parsplana Vitrectomy; (SO): Silicone oil;

Introduction

Proliferative vitreoretinopathy (PVR) is most commonly observed after surgery for Rhegmatogenous retinal detachment (RRD). It is estimated to occur in 5 to 11% of such cases making it the most common cause of failed repair of a primary RRD [1]. This occurs because traction induced by the membranes creates new breaks in the retina or reopens previously treated ones. It is also important to note that PVR can happen in cases of RRD without any previous surgical intervention. A large number of risk factors for developing PVR have been identified, some more consistently than others. Giant retinal tears, retinal detachments larger than two quadrants, vitreous hemorrhage, intraocular inflammation and preoperative choroidal detachment have all been associated with an increased risk of developing PVR [2]. The prior retinal detachment repair is the most common factor predisposing an eye to PVR [3].

In human eye disease, vascular endothelial growth factor (VEGF) has been attributed an important role in ocular angiogenesis, such as in diabetic retinopathy, retinopathy of prematurity, and wet age-related macular degeneration [4]. Surprisingly, it has also been demonstrated in nonangiogenic ocular diseases. The association of VEGF with the pathogenesis of proliferative vitreoretinopathy (PVR), a proliferative disorder that is characterized by the formation of avascular epiretinal membranes and subretinal membranes, has been

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investigated by several groups. Vascular endothelial growth factor levels were found to be higher in PVR subretinal fluid and vitreous fluid samples compared with uncomplicated Rhegmatogenous retinal detachment (RRD) controls [5,6].

Contradictory results have been reported for the association between VEGF levels and the duration of retinal detachment. Whereas no correlations were demonstrated between VEGF and the extent of retinal detachment [5,7,8]. Retinal pigmented epithelial cells and retinal glia, which constitute the major components of PVR membranes and membranes in ischemic retinopathies, each produce VEGF [9-11]. Interestingly, epiretinal membranes in ischemic retinopathies, such as proliferative diabetic retinopathy, are vascularized, while those associated with PVR are mainly avascular. This finding raises the question why PVR membranes lack blood vessels if VEGF is present.

Bevacizumab is well known for its anti neovascular properties [12]. However, recent studies have shown its advantages as a potent antifibrotic agent to limit ocular scar tissue formation [13].

The PVR is an intraocular fibroglial proliferation and is associated with some devastating complicated retinal detachment repair. Therefore, it is plausible that bevacizumab could be used as a medical prophylaxis for PVR and exuberant fibrovascular proliferation in complicated RRD. In this prospective study, we evaluated the effect of intravitreal bevacizumab in Patients with proliferative Vitreoretinopathy grade C or D received pars plana vitrectomy combined with silicone oil tamponade.

Methods

Patients

Bevacizumab is well known for its anti neovascular properties [12]. However, recent studies have shown its advantages as a potent antifibrotic agent to limit ocular scar tissue formation [13].

This study was designed as a prospective uncontrolled clinical trial study and was performed from December 2012 to January 2013 in the Nikokari Eye Hospital in Tabriz, Iran.

Informed consent was taken from all of the patients, and the study was approved by the ethical committee of Tabriz University of medical science and conducted accordance with the ethical principle outlined in the declaration of Helsinki.

Technique

All operations were performed under general anesthesia. 23G pars plana vitrectomy was performed. Posterior vitreous cortex and epiretinal membrane were removed and peeled off, respectively. Perfluorodecalin was injected into the vitreous cavity to stabilize the retina. Laser photocoagulation or transscleral cryopexy was performed on the area of retinal tears or peripheral retinal degeneration. After gas–fluid exchange, intravitreal injection of 1.25 mg bevasizumab in 0.05 ml was followed by SO injection.

Silicone Oil Removal

After general anesthesia, emulsified SO in the anterior chamber, if any, was removed by irrigation and aspiration. Three-port pars plana sclerotomies were made as in traditional 20G vitrectomy. The SO was removed passively. Gas–fluid exchange was carried out 3 times and was followed by anterior chamber irrigation and aspiration again. Peripheral retina was examined with scleral indentation, and laser photocoagulation or cryopexy was applied to areas of peripheral retinal degeneration or retinal break. Gas tamponade of 16% C3F8 was carried out after gas–fluid exchange if necessary.

Outcome Measures and Statistical Analysis

The patients were followed-up after surgery. Visual acuity, intraocular pressure (IOP), retinal status, and complications were recorded in each visit. Primary outcome measures were retinal reattachment rate and the best-corrected visual acuity (BCVA). Retinal reattachment was defined as complete reattachment of the retina without any localized detachment. The presence of extensive proliferation in an attached retina also is considered to be successful. Visual acuity was converted to log MAR units for analysis. Paired t-test was used to compare the BCVA before and after surgery. Visual acuity increase or decrease was defined as difference of log MAR 0.3 or more after

surgery compared with baseline. Secondary outcome measures included IOP and complications. SPSS version 16.0 was used to conduct the statistical analysis.

Results

In all, 16 eyes of 16 patients were included in this study (Tables 1 and 2). The mean age was 51.25 ± 15.75 years (range, 19–74 years). There were 10 men and 6 women. The PVR was secondary to RRD in all eyes. After vitrectomy with SO tamponade and IVB, the patients were followed-up for a mean period of 5.40 ± 1.36 months (range, 4–9 months) before SO removal.

Baseline						After Vitrectomy				After Oil Removal		
ID	Sex	Age (years)	Previous surgery	BCVA (logMAR)	IOP (mmHg)	FU	BCVA (logMAR)	IOP (mmHg)	Retina	FU	BCVA (logMAR)	IOP (mmHg)
1	M	19	Yes	2.3	9	6	2.3	7.1	Detached	4	2.3	4.9
2	F	63	No	1.5	11	5.5	1.2	15.2	Attached	8	1.0	14.1
3	M	62	No	2.0	5.1	6	1.4	7.7	Attached	9	0.8	10
4	M	63	No	2.3	7.6	7	1.1	8	Attached	10	0.7	16
5	F	53	No	2.3	6.7	4	1.9	14.5	Attached	8	0.8	7.9
6	M	35	No	2.0	16.9	6	1.1	18	Attached	8	0.2	21.5
7	M	23	No	1.7	20.6	4	1.1	10.8	Attached	9	0.9	13.3
8	F	60	Yes	1.9	8.9	9	1.2	14	Attached	5	1.0	9
9	F	34	No	2.3	8.5	5	1.9	13	Attached	6	1.2	11.4
10	F	57	No	1.7	7	4	1.1	15	Attached	5	0.3	14
11	M	61	No	1.9	16	4	1.2	19	Attached	7	0.9	16
12	M	60	No	2.3	8	6	0.7	10	Attached	7	0.3	16
13	M	52	Yes	2.3	6.5	6	1.9	19	Attached	8	0.4	14
14	F	60	No	1.8	17	5	1.1	14	Attached	3	0.9	13
15	M	74	No	1.3	9	4	1.2	13	Attached	6	0.8	17
16	M	44	No	2.3	8	6	1.9	15	Attached	4	0.7	10

Table 1: Patients' Demographic and Clinical Characteristics.

M: Male; F: Female; FU: Follow-up (months).

Retina remained attached in 15 (93.7%) patients at the last visit. There was redetachment in 1 (6.3%) eye because of recurrence of PVR. The mean best-corrected visual acuity was 1.99 ± 0.327 log MAR at baseline, which improved to 0.82 ± 0.48 log MAR at the last visit after vitrectomy (P < 0.001).

Of the six remaining phakic eyes after vitrectomy, five remained cataract free while one had recurrent PVR and RD with total lens opacity. Silicone oil emulsification was noted in two eyes. All patients received SO removal after a mean follow-up period of 5.40 months.

During the oil removal surgery, combined laser photocoagulation or cryopexy and C3F8 tamponade was carried out in four eyes, laser photocoagulation alone was applied in one eye.

After SO removal, the patients were followed-up for 6.67 ± 2.06 months (range, 4-10 months). One case developed retinal redetachment because of peripheral retinal break 3 days after SO removal and was repaired by cryopexy and C3F8 tamponade. The retina of 15 eyes remained reattached at the last visit. The difference in BCVA at the final visit and baseline is statistically significant (P < 0.001). When the BCVA at last visit after SO removal was compared with the vision at baseline, it was increased in 15 (93.7%) eyes and decreased in 1 (6.3%) eye (Table 3). There was only 1 case whose IOP was > 21 mmHg at the final visit. There were some cases of mild to moderate peri-SO proliferation and macular pucker, and all of them were removed during the SO removal surgery.

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Characteristics	
Number of patients	16
Mean age (years)	51.25
Gender (male/female)	10/6
Baseline BCVA (logMAR)	1.99 ± 0.32

Table 2: Baseline Demographics and Clinical.

Baseline BCVA (logMAR)	1.99 ± 0.327
Final BCVA (logMAR)	0.82 ± 0.48
Improvement in BCVA	15 (93.7%)
Decrease in BCVA	1 (6.3%)
Retinal reattachment	15 (93.7%)

Table 3: Primary Outcome Measures.

Discussion

As far as the authors know, this is the first report to assess the intravitreal injection bevacizumab in silicone oil-filled eyes as an adjunctive treatment for proliferative vitreoretinopathy.

Various studies have investigated whether VEGF played a role in the pathogenesis of PVR. The VEGF was found to be up regulated in vitreous or subretinal fluid samples of patients with PVR [5,6]. Furthermore, VEGF staining was prominent in all or almost all PVR membranes investigated [14,15]. The role of an imbalance between VEGF and pigment epithelium-derived factor in the pathogenesis of PVR has not been elucidated yet. Ogata, *et al.* found increased VEGF concentrations and decreased pigment epithelium-derived factor concentrations in vitreous of PVR eyes [6], similar to the inversion found in the vascularized form of fibrosis, that is, Proliferative diabetic retinopathy [16].

However, Dieudonne SC., *et al.* could not confirm this inversion, because the balance between VEGF and pigment epithelium derived factor was found to be similar between PVR and controls [17].

It was shown that retinal pigmented epithelial cells in situ and retinal pigmented epithelial cells in epiretinal membranes and in culture, express VEGF receptors. In many epiretinal membranes, VEGF and its receptors were colocalized, suggesting that an autocrine and/or paracrine mechanism may exist [14].

The studies identified VEGF receptors on other nonendothelial cells in the eye such as on adult photoreceptor cells and Muller cells [18]. The study concluded that endogenous VEGF is implicated in the maintenance of the adult neural retina by supporting cell survival of these retinal cells. Interestingly, VEGF has also been shown to induce monocyte activation manifested by the induction of tissue factor and monocyte chemotaxis [19].

The influx of a high number of macrophages in most PVR subjects in the first stage of the disease compared with PVR- negative RRD patients underlines their importance in the pathogenesis of PVR, as was shown by Martin, *et al.* [20].

Thus, VEGF probably exerts pleiotropic effects on diverse cell types such as retinal pigmented epithelial cells and monocytes, which are assumed to play major roles in the development of PVR.

Ricker, *et al.* found that total VEGF levels to be significantly elevated in PVR group of patients as compared with patients without PVR [21].

Neovascularization is a key step in fibrovascular proliferation, and higher levels of vascular endothelial growth factor have been related to PVR by some investigators [6]. Thus, in theory, bevacizumab may be useful in preventing tractional fibrovascular and/or fibrocellular membranes. In addition, it decreases the vascular permeability [22,23], which may subsequently reduce intraocular inflammation (and its sequels such as macular edema) in response to tissue injury [24,25].

We have shown in this prospective study that intravitreal injection of 1.25 mg of bevasizumab as an adjunct to vitrectomy and SO tamponade in treating PVR (grade C or D) is effective and safe.

Furthermore, removal of SO was performed in all study eyes (100%), and a high retinal reattachment rate (93.75%) was achieved.

The prospective study Design is one of the strengths of this study. The limitations in our study include the lack of a control group, small sample size, lack of full data on the lens and posterior capsule status, and extent of PVR in terms of clock hours. Additionally, the all of eyes in this study were primary PVR. None of the 16 eyes that had primary RRD had received surgical treatment procedures previously. This is significantly lower than the 56.3% to 84.2%, reported in the literature by other studies [25-27]. The eyes with primary PVR may have better outcomes than those that have multiple earlier vitreoretinal procedures. This may be part of the reason explaining better results in this study comparing with reports in the literature. In berker study in patients with RRD and PVR after PPV and SO removal, 82% Of eyes had reattached retina [28]. In lam study the succses rate of PPV for RRD with PVR were 82 % [29]. That is lower to our study. Chen., *et al.* received to 97 % succses rate with injection of 2 mg triamcinolone into SO [30]. Chen results are better than our results.

In conclusion, this study shows that intravitreal injection of bevacizumab at the time of surgical repair as an adjunct to vitrectomy and SO tamponade in treating PVR (grade C or D) appears to be effective and safe and may decreased the degree of intraocular fibrocellular proliferation and the resultant tractional forces on the retina. We suppose that these effects are resulted from a reduction in vascular permeability and associated decreases in cytokines and growth factors, decreasing intraocular inflammation, wound healing modification of the drug. Therefore, it may decrease the development of tractional RD and improves the final visual outcome .But more researchs with controls groups is needed to establish the role of intravitreal bevacizumab injection in prevention of PVR reformation and redetachment of retina after primary vitrectomy and SO tamponade.

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