Treatment of the Subretinal Hemorrhage by the Use of Deep Periocular Injection of Bevacizumab ---- A Safer Method

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Abstract:

Purpose: To evaluate the visual outcome of patients with subretinal hemorrhage after deep periocular injection of bevacizumab.**Methods**: Three patients having subretinal hemorrhage with poor vision were treated with at least one deep periocular injection of bevacizumab (0.3 ml). Patients underwent a complete evaluation at the baseline and follow-up visits. This evaluation included the Snellen best-corrected visual acuity, fundus biomicroscopy and ocular coherence tomography.**Results:** The follow-up point ranged between 3 and 6 months. Improvement of vision was observed, and they all had better visual acuity. The subretinal hemorrhage cleared in all eyes and no complications were noted.**Conclusion**: Deep periocular injection of bevacizumab was safer and effective in the treatment of subretinal hemorrhage. It can induce effective regression of retinal neovascularization and rapid clearance of the subretinal hemorrhage It may enhance the absorption of hemorrhage with subsequent deferral from surgery. [Chih-Yaun Yang, Kuang-Jen Chien, Tsung-Hsung Chang, Ren-Jy Ben, Jen-Hsiel Lin, Chi-Ting Horng. **Treatment of the Subretinal Hemorrhage by the Use of Deep Periocular Injection of Bevacizumab ---- A Safer Method**. Life Science Journal. 2012;9(4):1237 -1241] (ISSN:1097-8135). http://www.lifesciencesite.com.

Keyword: periocular injection, bevacizumab, subretinal hemorrhage

1. Introduction

Bevacizumab (Avastin, Genentech) is the first Food and Drug Administration(FDA) approved therapy applied intravenously as an adjunct for the treatment of metastatic colorectal cancer〔1〕. It also improves progression-free survival rates in patients with previously untreated metastatic breast cancer. Bevacizumab is a monoclonal antibody that binds all isoforms of vascular endothelial growth factor A (VEGF-A). It is a potent inhibitor of angiogenesis, and has also been used effectively in the treatment of neovascular ARMD (age-related macular degeneration)〔2〕. Intravitreal injection of anti-VEGF agents has been reported effective in inducing the regression of new vessels in proliferative diabetic retinopathy (PDR)〔3〕, and neovascular glaucoma (NVG)〔4〕.

Intravitreal injection of anti-VEGF drugs may be considered a new therapeutic option for patients with submacular hemorrhage. The clearing effect has been attributed to bevacizumab〔5〕. Subretinal hemorrhage is a complication of various ocular pathologies such as ARMD, trauma, myopia and retinal artery macroaneurysm. It may cause a sudden loss of vision〔6〕. The rate of spontaneous resorption is low, and the overall visual prognosis of untreated subretinal hemorrhage is poor with patients losing on average 3.5 lines of visual acuity after 3 years. Removing the subretinal blood clearly with treatment of the underlying cause might allow for better visual recovery. However, as clearing of the media might take some time, we decided to evaluate the outcome of the patients with subretinal hemorrhage by means of deep periocular injection of bevaciuzumab.

2. Material and Methods

Material

From January 2012 to August 2012, consecutive cases with subretinal hemorrhage were treated with deep periocular injection of bevacizumab. Patients with a history of preoperative and postoperative anticoagulant therapy, or with a history of blood diseases associated with abnormal coagulation were excluded. The study was approved by the institutional research board of Kaohsiung Armed Forces General Hospital. The procedures were performed after informed consent for the patients was obtained.

After proper disinfection using 5% povidone-idodine and deep periocular injection of bevacizumab (0.3 ml) was carried out under topical anesthesia.

After treatment, patients were followed at regular intervals. The Snellen best-corrected visual acuity measurement, intraocular pressure, slit-lamp examination and ocular coherence tomography. were performed at each follow-up visit. Data including the extent of the subretinal hemorrhage and the cleaning of the subretinal hemorrhage were recorded.

Case Reports

Case 1 :

A 70-year-old female patient presented with decreased vision in the left eye over a two-week peroid. The best-corrected visual acuity(BCVA) in the left eye was 0.05. The fundus of the eye showed massive subretinal hemorrhage(Fig 1A). Optical coherent tomography (OCT) suggested a large pigmentary epithelial detachment (Fig 2A). The patient was treated with a deep periocular injection of avastin (0.3 cc) three times every month. Three months later, no inflammatory cells were present in the vitreous and the BCVA returned to 0.5. The color fundus and OCT also revealed the normal images (Fig 1B, Fig 2B).

Case 2 :

An 80-year-old female presented with sudden diminution of vision in the right eye which she had been experiencing for one month. The right eye was 0.1. The fundus revealed a subretinal hemorrhage near the macula (Fig 3A). She received a deep periocular injection of avastin (0.3 cc) two times every month and the vision returned to 0.7 after four months. At the same time, no apparent complications were found. The subretinal hemorrhage had also disappeared after the 4-month follow-up. (Fig 3B)

Case 3 :

A 70-year-old female patient presented with decreased vision in the left eye over 1 week. Her vision was limited to seeing only a counting finger. We found a mild vitreous hemorrhage and a subretinal hemorrhage in the posterior segment (Fig 4A). Then the patient was received with 0.3 cc avastin by the deep periocular injection three times every month. After regular follow-up for three months, the VA had increased to 0.8 with normal anterior and posterior segment findings (Fig 4B).

3. Discussion

Bevacizumab (Avastin, Genentech Inc. San Francisco, CA), is a full length humanized monoclonal antibody to VEGF; it was approved by the Food and Drug Administration for the treatment of colorectal cancer. It can inhibit both types of VEGF receptors: VEGFR-1 and VEGFR-2〔7〕. It has recently shown to enhance the clearance of vitreous hemorrhage and to induce the involution of retinal neovascularization with no reported complication. It has also been tried in the treatment of macular edema caused by the central retinal vein occlusion〔8〕. Anti-VEGF substances have to be injected intravitreally repeatedly and at relatively short intervals of 4 to 6 weeks.

Vascular endothelial growth factor (VEGF) plays an important role in many diseases of the posterior pole that are characterized by macular edema and/or intraocular neovascularization. Such diseases include proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), neonascular glaucoma, retinopathy of prematurity, choroidal neovascularization (CNV) and retinal vein occulusions. For example, bevacizumab resulted in the marked regression of neovascularization and rapid resolution of vitreous hemorrhage within several months〔3〕. Bevacizumab may also offer a therapeutic benefit including antipermeability and antiproliferative effects. However, as with all antiangiogenic compounds, intravitreal injections have to be repeated frequently for as long as the disease process is active, leading to high rates of repeat injections〔9〕.

To our knowledge, subretinal hemorrhages may occur from a variety of etiologies, including age-related macular degeneration (ARMD), trauma, intraocular tumors, sickle cell disease, retinal tear in primary rhegmatogenous retinal detachments and complications of scleral buckling procedures〔10〕. It may damage the sensory retinal tissue by means of the limitation of the passage of nutrition to the retina〔11〕, shrinkage of the outer retinal layers owing to clot formation, and the release of toxic substances such as fibrin, iron, and hemosiderin〔12,13〕. Toxic effects of subretinal blood can be evidenced 24 hours after the occurrence. The literature included a few reports describing subretinal hemorrhage management by surgery. Wade et al demonstrated the subretinal blood clots were treated with pars plana vitrectomy combined with internal drainage〔14〕. Unfortunately, poor visual outcome was found. Subretinal injection of recombinant tissue plasminogen (tPA) during pars plana vitrectomy followed by an intravitreal gas tamponade was proposed by Haupert et al〔15〕. Until now, Chawla er al. proposed that the intravitreal tPA and perfluoropropane gas infusion for the treatment for submacular hemorrhage. The tPA would enzymatically liquefy the blood, which would then be pneumatically displaced inferior in the subretinal space without vitrectomy〔16〕.

Characterization of the molecular and cellular processes involved in vascular growth and cellular and hypermeability has led to the recognition that the angiogenic growth factor and vascular permeability factor VEGF play pivotal role in the retinal microvascular complications of subretinal hemorrhage. Thus, VEGF represents an important target for therapeutic intervention in this condition. Recently reports attested to the benefit of bevacizumab were used in the treatment of subretinal hemorrhage.

Over the last decades, the use of intravitreous injection (IVT) has gained increasing acceptance in the therapeutic management of many intraocular diseases, affecting the posterior segment. For example, we can use the intravitreous injection of antiviral agents in treating the cytomegalovirus (CMV) retinitis. In addition, IVT injection of various gases (SF_6 or C_3F_8) has been used for the management of retinal detachment in the setting of pneumatic retinopexy. Recently IVT triamcinolone acetonide (Kenolog) injection is under investigation for a number of disorders, including macular edema and retinal edema and retinal neovacularization 〔17〕.

The potential advantages of IVT injection have been become more widely appreciated and the number of possible applications has been grown. With over 15,000 annual IVT injections worldwide, bevacizumab is rapidly becoming one of the popular methods in the treatment of many diseases. However, questions have arisen regarding risks associated with the route of administration. Several potential complications of IVT can be vision-threatening and even life-threatening. Surprisingly, systemic adverse events were reported. Anti-VEGF agents gain access to the systemic circulation following an intravitreal injection. Systemic blockade can give rise to various complications. These may include acute elevation of systemic blood pressure, epistaxis, hemoptysis, proteinuria, delayed wound healing after surgery, and impaired reproductive function 〔17,18〕. Other severe problems included the cerebrovascular accidents, myocardial infarctions, iliac artery aneurysms, toe amputations and deaths 〔19〕. In addition, as many as 5% of all patients using systemic bevacizumab in combination with chemotherapy may have an increased risk of developing a serious or fatal thromboembolic event.

Ocular complications included increased intraocular pressure, cataract, bacterial endophthalimitis, tractional retinal detachment, uveitis, rhegmatogenous retinal detachment and vitreous hemorrhage〔20〕. Some of these problems may be solved by lowering intraocular pressure agents, topical steroids and even further surgery. However, the possibilities of vision loss may be threatening to the patients. For example, bacterial endophthalmitis is an expected and dreaded complication of any intravitreal injection. The rate varies from 0.04% to 0.33% Sterile technique and antisepsis with instillation of topical povidone iodine 5% into the conjunctival fornix prior to an intravitreal injection may reduce the risk of endophthalmitis 〔21〕. We also cannot ensure the safety of IVT injection. Another troubling complication is tractional retinal detachment. After the IVT injection, the neovacularization may regress. We found that the resulting fibrous scar tissue led to the development or progression of tractional retinal detachment. This disease needed further complicated surgeries and the outcome was always bad.

Risk assessment of IVT injection is complex. Studies reporting risks for IVT cross a number of indications and underlying pathologic conditions. Moreover, the occurrence of complications directly related to the toxicity of administration compounds confounds estimations of the prevalence of complications related to the IVT injection procedure itself.

Another issue that has been addressed is the legal problem resulting from complications occurring with off-label therapy. Bevacizumab is not legally approved for intraocular use in Taiwan. Intraocular inflammation has been reported with intravitreal injection of bevacizumab. The possibility of myocardial infarction, stroke and even mortality may impact the relationship between patients and ophthalmologist. The doctors may be bothered by the annoying medical disputes.

In our reports, the use of deep peri-ocular and sub-tenon's injection was a safer approach. No ophthalmological and systemic complications were found. The pharmacokinetic characteristics of compounds of peri-ocular injection remained unknown and deserved further study. However, the technique may be another alternative.

4. Conclusion

Deep periocular injection of bevacizumab was effective in the treatment of subretinal hemorrhage without safety concerns. It can induce the effective regression of retinal neovascularization and rapid clearance of the hemorrhage. It can be used as an adjunctive with laser photocoagulation and to enhance the absorption of subretinal hemorrhage with subsequent deferral operation. This method was shown to be safer than intravitreal injection. Deep periocular injection may be another safe procedure.

Fig.1A：Fundus of the left eye showed massive subfoveal subretinal hemorrhage.

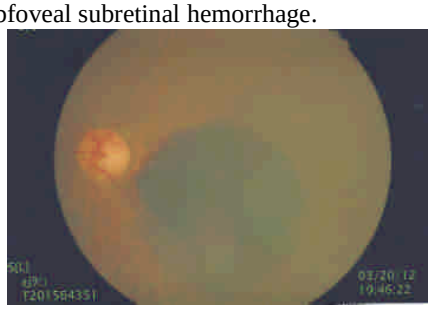


Fig.1B：The subretinal hemorrhage had disappeared dramatically after deep pericular injection of avastin for three months.

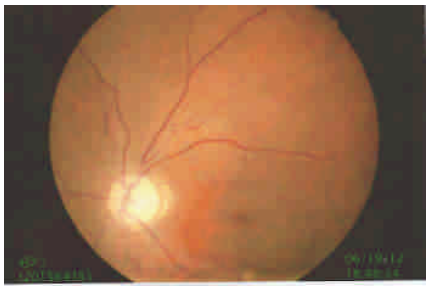


Fig.2A ： Optical coherence tomography showing variable reflectivity of the retinal pigmentary epithelium suggestive of choroidal neovascular membrane with subretinal blood and large pigmentary epithelial detachment

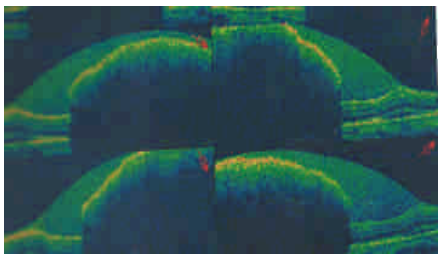


Fig.2B：Optical coherence tomography showing the relatively normal macular region after 3-month follow up.

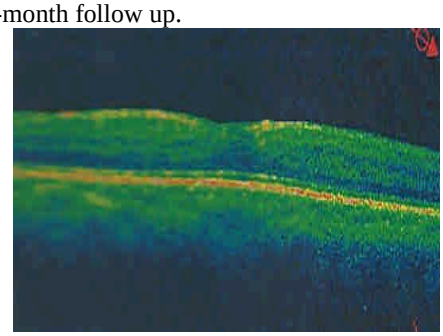


Fig.3A. ： Red free image of right eye showing submacular hemorrhage along with pigmentary epithelial detachment.

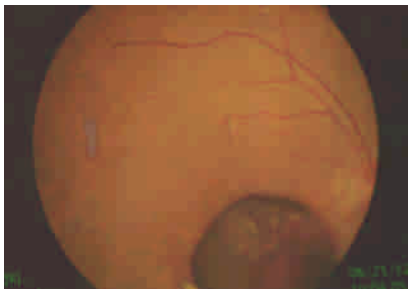


Fig.3B. ： Color fundus showed normal appearance after four months.

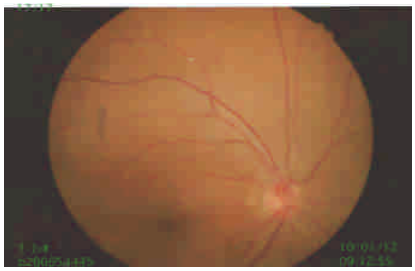


Fig.4A. ：Red free image of left eye showing vitreous hemorrhage combined with subretinal hemorrhage.

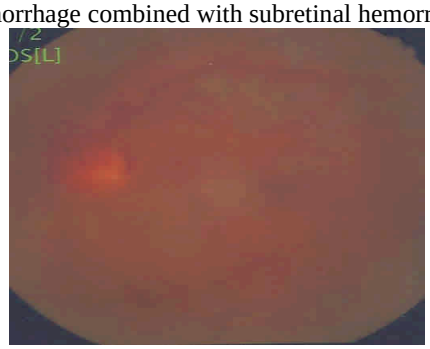
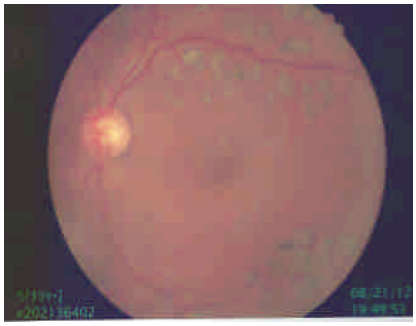


Fig.4B. ：The color fundus revealed that the vitreous hemorrhage and subretinal hemorrhage had absorbed after three months.



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