Intravitreal Bevacizumab and Panretinal Photocoagulation as Combined Treatment in Proliferative Diabetic Retinopathy

Proliferatif Diabetik Retinopatide Kombine Tedavi Olarak İntravitreal Bevacizumab ve Panretinal Fotokoagülasyon

Emiliano FULDA[1], Enrique ARIZA[1], Antonio LOPEZ[1], Federico GRAUE[1]

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ABSTRACT

Objective: To document proliferative control of fluorescein angiography in diabetic retinopathy after intravitreal bevacizumab and hemiretinal photocoagulation, compared to a complete panretinal photocoagulation in the contralateral eye.

Material and Methods: Patients with bilateral and symmetrical proliferative diabetic retinopathy without history of previous treatment were included. The right eye received intravitreal bevacizumab and a single session of 800 scattered laser spots. The left eye underwent a full 1,600 laser panretinal photocoagulation. Angiography was performed monthly for 6 months to document inactivity of the diabetic retinopathy. Statistical significance in between eyes of persistent angiographic activity, time of reapplication and also number of retreatments with panretinal photocoagulation were analyzed using T-tests set as $p<0.05$.

Results: 109 patients were enrolled. In the first month, 16.6% of right eyes presented activity, compared to 34% of left eyes ($p<0.05$); the difference was statistically significant up to the 4th month. In the 5th and 6th months, the activity in both eyes was not statistically significant. The median time of reapplying laser in the right eyes was 112 days, compared to 65 days in the left. In the first four months, the left eye was retreated 3 times more than the right eye.

Conclusions: Applying bevacizumab with half panretinal photocoagulation is more effective in inactivating the proliferative diabetic retinopathy, compared to a full panretinal photocoagulation up to the 4th month. Adding bevacizumab accelerates the time of inactivity in the angiography, avoids up to twice the time for reapplying laser and is 3 times less likely to be retreated.

Key Words: Avastin, PRP, diabetic retinopathy.

ÖZ

Amaç: Diabetik retinopatide intravitreal bevacizumab ve hemiretinal fotokoagülasyon tedavisinin, diğer gözde uygulanan tam panretinal fotokoagülasyona göre floresein anjiografide proliferatif kontrolünün ortaya konulmasıdır.

Gereç ve Yöntem: Daha önce herhangi bir tedavi hikayesi olmayan, bilateral ve simetrik proliferatif diabetik retinopatili olgular çalışmaya dahil edildi. Sağ göze intravitreal bevacizumab ve tek seansta 800 atım lazer uygulandı. Sol göze ise 1600 atım tam panretinal fotokoagülasyon uygulandı. 6 ay boyunca her ay diabetik retinopatinin inaktivasyonunun gösterilmesi için anjiografi yapıldı. Dirençli anjiografik aktivite, tekrar uygulama zamanı ve ayrıca panretinal fotokoagülasyon tedavi sayıları açısından gözler arasındaki farklar, istatistiksel anlamlılık ölçütü $p<0.05$ alınarak T-testi ile analiz edildi.

Bulgular: 109 hasta çalışmaya dahil edildi. İlk ayda, sağ gözlerin %16.6'sında, sol gözlerin %34'ünde aktivite vardı ($p<0.05$); bu fark 4. aya kadar istatistiksel olarak anlamlıydı. 5. ve 6. aylarda her iki gözde aktivite istatistiksel olarak anlamlı değildi. Sağ gözlerde ortalama tekrar lazer uygulama zamanı 112 günken; sol gözlerde 65 gündü. İlk dört ayda sol göz, sağ göze göre 3 kat daha fazla tedavi edildi.

Sonuç: İlk 4 aya kadar, proliferatif diabetik retinopatinin inaktifleştirilmesinde, yarım panretinal koagülasyon ile beraber bevacizumab uygulaması, tam panretinal koagülasyon uygulamasına göre daha etkilidir. Bevacizumabın eklenmesi, anjiografide inaktivite oluşumunu hızlandırmakta, tekrar lazer uygulama zamanını iki kata kadar uzatmakta ve 3 kat daha az yeniden tedavi gerekmektedir.

Anahtar Kelimeler: Avastin, PRP, diabetik retinopati

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1- Department of Retina and Vitreous Instituto de Oftalmologia Conde de Valenciana, M.D.

1- M.D.Instituto de Oftalmologia Conde de Valenciana, Retina and Vitreus, Mexico City, MEXICO,
FULDA E., drfulda@gmail.com
ARİZA E., eariza@yahoo.com.mx
LOPEZ A., alopez@yahoo.com.mx
GRAUE F., fedgraue@hotmail.com

Correspondence: M.D., Emiliano FULDA
Department of Retina and Vitreous Instituto de Oftalmologia Conde de Valenciana, Chimalpopoca 14 Col. Obrera Del. Cuauhtemoc, 06800 MEXICO DF

INTRODUCTION

Vascular endothelial growth factor (VEGF) plays key role in retinal hypoxia, stimulating the growth of neovessels of the retina in proliferative diabetic retinopathy (PDR)[1-5]. For more than a decade, the use of laser in proliferative diabetic retinopathy (PDR) has been the golden standard treatment, reducing up to 50% the possibility of severe visual loss, especially in patients at high risk of PDR. The internationally accepted parameters of treatment include the use of 1,200 to 1,600 scattered laser spots divided in 2 or more sessions[3]. Even though highly effective, panretinal photocoagulation (PRP) is not exempt of side effects as loss of 1 or 2 lines of visual acuity, night vision and contrast, as well as visual field lost.[6,7]

Nowadays, the use of intravitreal antiVEGF agents is not only restricted to choroidal neovascularitation[8-11], but also in diabetic macular edema[12-15], neovascular glaucoma[16,17], retinal angiomatous proliferation[18], vascular vena occlusion[19] and even retrolental vascularization.[20] The potential uses of antiVEGF in PDR are the neovascularization of iris[21,22], persistence of neovessels despite PRP[23], vitreous hemorrhage after PRP[24], macular edema[12-15] and prior to vitrectomy to reduce possible bleeding.[25]

The added effect of antiVEGF to PRP in patients with RDP is unknown, for which a comparative, experimental and interventional study was performed. A complete PRP was compared to half a PRP in the contra lateral eye with the single use of intravitreal bevacizumab.

MATERIAL AND METHODS

Patients that were older than 18 years of age with bilateral and symmetrical PDR were included, from November of 2006, to November of 2007 that accepted written enrollment. Exclusion criteria were described in *table 1*. Patients were eliminated if stage III neovascular glaucoma was detected, tractional retinal detachment, lack of follow-up, or any opacity that made treatment or follow-up impossible. Every patient underwent a complete ophthalmological examination that included best corrected visual acuity, intraocular tension, gonioscopy and funduscopy, as well as an initial fluorescein angiography and initial glucose levels.

Table: Exclusion criteria.

EXCLUSİON CRİTERİA
Asymmetrical DR
Imposibility of fundus visualization
History of PRP or intravitreal antiangiogenic
Patients with one eye
Tractional or regmatogenic retinal detachment
History of vitrectomy
Less than 6 month heart attack
Uncontrolled or untreated high blood pressure
Pregnancy

The rigth eye (OD) was arbitrarily determined to be the experimental eye undergoing at day zero a single intravitreal via pars plana injection of bevacizumab *(Avastin® Genentech Inc.)* at 1.25 mg/dl at 0.05 ml, prior antiseptic with Povidone-iodine at 5% in the cul-de-sac. Prophylactic gatifloxacin was given every 6 hours for 4 days as well as a 24 hours eye patch. At day 3, a single half PRP (800 scattered laser spots) was given with a diode *(Zeiss Corp. VISULAS 532®)* using a contact lens *(Volk. Intrum. QuadrAspheric®)*. The left eye became the control, having undergone a complete PRP (1,600 scattered laser spots) divided in two sessions, 2 weeks apart. A complete ophthalmological examination was done monthly with a fluorescein angiography up to 6 months. Reapplying laser was performed in all patients that presented fluorescein leakage during the montly angiography due to persistence of neovessels in the retina with a scattered mid-equator panretinal photocoagulation.

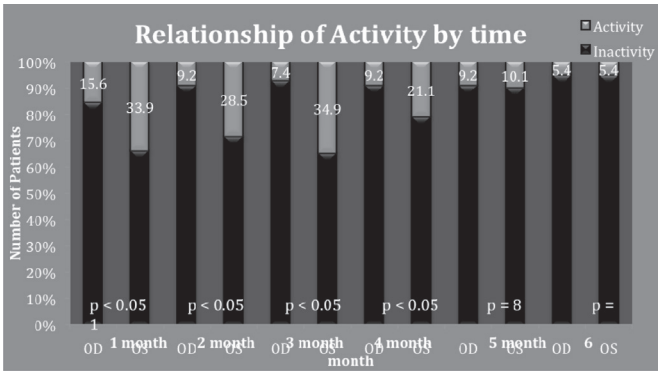
The statistical significance of the changes in between eyes inactivity of PDR, time of reapplication as well as number of retreatments by scattered PRP was analyzed using T-test to compare continuous variables with the significance level set as 0.05.

RESULTS

One hundred and nine patients (67 females) with a median age of 60 years (range 40-85) were enrolled. Medial time of diabetic diagnosis was 12.5 years and had an average glucose level of 184μgr/dl at the initial evaluation.

The difference between the right and left eye and its proliferative activity after initial treatment is showed in *Graph*. The rigth eye was statistically significant ($p<0.05$) compared to the left eye, in eyes that presented proliferative activity in the fluorescein angiography despite complete PRP. This statistically significant difference remained up to the fourth month. In the fifth and sixth month, the difference between activity/inactivity in both eyes was not significant ($p=0.8$) and ($p=1$).

The medial time for reapplying laser in the right eyes was 112 days (range 30 to 180 days) compared to 65



Graphic: Relationship of activity vs. inactivity by time in both eyes.

days (range 30 to 120 days) in the left eye. In the first four months, 45 patients had retreatment in both eyes. One patient only had it in the right eye and 82 patients in the left eye. At the 5th and 6th months, 13 patients underwent bilateral retreatment, one patient only in the right eye and 2 patients in the left one.

There were 2 cases of elevated intraocular pressure, after intravitreal application of bevacizumab that required topical treatment for a week. During intravitreal injection, 38 eyes presented reflux of the bevacizumab and 55 patients had subconjuntival hemorrhage. There were no cases of tractional retinal detachment, cataract, central arterial occlusion or endophthalmitis.

CONCLUSIONS

Applying bevacizumab with half panretinal photocoagulation is equally effective in inactivating the proliferative diabetic retinopathy, compared to a full panretinal photocoagulation up to the 4th month. When added to a panretinal photocoagulation bevacizumab accelerates the time of inactivity in the angiography avoids up to twice the time for reapplying laser and is 3 times less likely to be retreated**.**

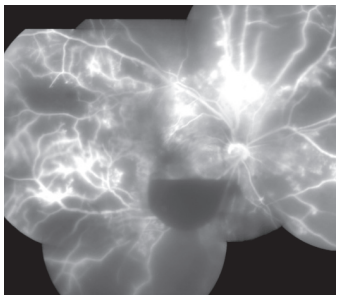
DISCUSSION

Taking the left eye as the control eye and the right eye as our experimental eye, gave the hypothetical benefit of having the same hyperglycemia affect the same individual, permitting both eyes to be comparable. Special attention was taken in selecting bilateral and almost symmetrical proliferative diabetic retinopathy patients. It has been proven that antiVEGF delivered intravitreally has a systemic absorption and possible effect in the contralateral eye[26]. These contralateral effects would then benefit by itself the eye that received only PRP or the control group, making the already significance difference in between eyes even greater. *Figure 1a and 1b* represents a typical patient enrolled with bilateral and symmetrical PDR.

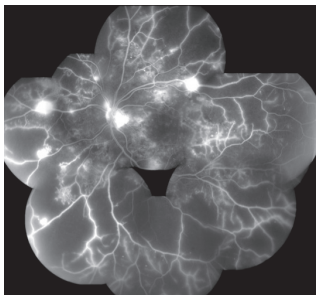
The statistic significance found in between eyes could had been a result of the fast and temporal effect of the antiVEGF, giving time for the partial PRP to make a more lasting antiVEGF effect in the hypoxic retina. After the fifth month, the antiVEGF effect of the complete PRP was comparable to the bevacizumab and half PRP, emphasizing that there is no substitution of laser treatment in PDR in the long term. Never the less, at five months, the right eye had only received half the laser spots, giving the patient in the future more space for PRP and avoiding the side effects of laser. *Figure 2a and 2b* represents patient's follow-up at 5 months. It was not the purpose of the study, but the use of bevacizumab could also avoid macular edema after PRP.

The necessity of reapplying PRP in eyes that received laser and bevacizumab was almost double in time compared to only PRP. Therefore antiVEGF accelerates by 2 the inactivity of the PDR in the fluorescein angiography. In the first 4 months, eyes that only had laser underwent reapplication of PRP more often to inactivate the PDR. There were several cases that had bilateral activity despite the treatment, maybe as a result of an uncontrolled glucose level.

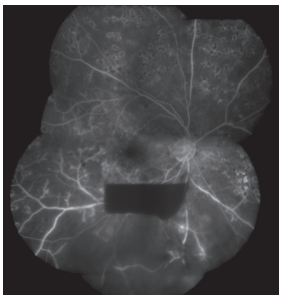
There have been several articles regarding the treatment of PDR with only antiVEGF in one eye[27] compared with the contralateral eye that undergoes PRP.[28,29]



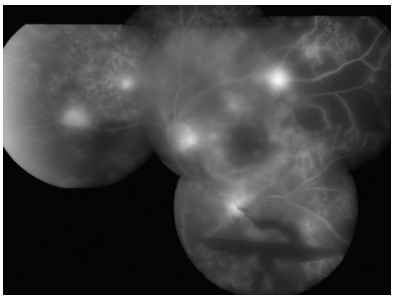
Picture 1a: Fluorescein angiography of OD.



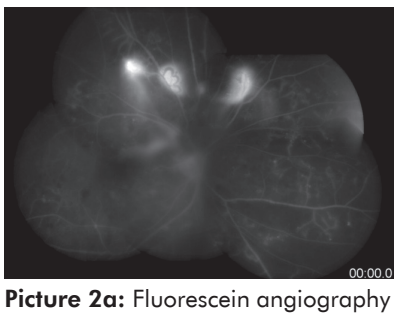
Picture 1b: Fluorescein angiography of OS.



Picture 1c: Fluorescein angiography of OD.

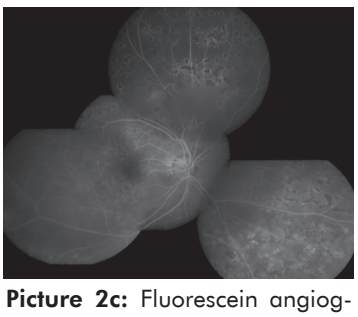


Picture 1d: Fluorescein angiography of OD.

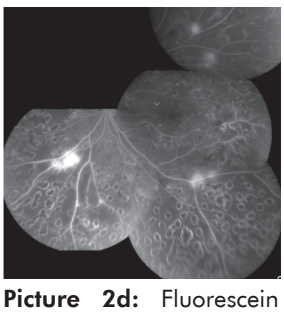


Picture 2a: Fluorescein angiography of OD.

Picture 2b: Fluorescein angiography of OS.



Picture 2c: Fluorescein angiography of OD.



Picture 2d: Fluorescein angiography of OS.

In our opinion, if PRP is not given, it is a matter of time and/or stopping the delivery of antiVEGF when the PDR becomes active again.

The single use of antiVEGF can regress neovessels in the retina in patients with proliferative diabetic retinopathy[30,31], even though its effect is only temporary; it often allows a window of opportunity for a more prolonged treatment. Adding bevacizumab to a PRP can accelerate the reduction of VEGF stimuli while giving time for the permanent antiVEGF effect of laser in the retina.

CONCLUSIONS

Applying bevacizumab with half panretinal photocoagulation is equally effective in inactivating the proliferative diabetic retinopathy, compared to a full panretinal photocoagulation up to the 4th month. When added to a panretinal photocoagulation bevacizumab accelerates the time of inactivity in the angiography avoids up to twice the time for reapplying laser and is 3 times less likely to be retreated.

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