ERYTHROPOIETIN CONCENTRATIONS IN THE VITREOUS BODY FROM PATIENTS WITH PROLIFERATIVE DIABETIC RETINOPATHY

CONCENTRACIÓN DE ERITROPOYETINA EN EL VÍTREO DE PACIENTES CON RETINOPATÍA DIABÉTICA PROLIFERANTE

ASENSIO-SÁNCHEZ VM¹, GÓMEZ-RAMÍREZ V², MORALES-GÓMEZ I²

ABSTRACT

Objective: To measure erythropoietin (Epo) levels in the vitreous body from patients with proliferative diabetic retinopathy (PDR).

Patients and methods: Undiluted vitreous samples were obtained from 44 patients who had not undergone prior vitreous or intraocular surgery. Patients were divided into two groups: A (n= 24) patients with PDR and B (n= 20) patients with retinal detachment, preretinal macular membranes and macular holes.

Epo was determined using radioimmunoassay.

Results: Epo vitreous concentration in group A was 512 mU/mL (range 120-880) and in group B was 25.1 mU/mL (range 5.2-201) (p< 0.001).

Conclusions: These results show that the concentration of Epo in the vitreous body was significantly higher in patients with PDR than in the control group (Arch Soc Esp Oftalmol 2008; 83: 169-172).

Key words: Diabetes, hypoxia, neuroprotection, angiogenesis, erythropoietin, proliferative diabetic retinopathy.

RESUMEN

Objetivo: Determinar los niveles de eritropoyetina (Epo) en el vítreo de pacientes con retinopatía diabética proliferante (RDP).

Material y método: Mediante vitrectomía vía pars plana, se recogieron muestras no diluidas de vítreo de 44 pacientes sin antecedentes de cirugía vítreo o intraocular previa, que fueron divididos en dos grupos: A (n=24) pacientes con RDP y B (n=20) pacientes con desprendimiento de retina, membrana premacular y agujero macular.

La concentración de Epo se determinó mediante radioinmunoensayo.

Resultados: La concentración vítreo de Epo en el grupo A fue 512 mU/mL (rango 120-880) y en el grupo B fue 25,1 mU/ml (rango 5,2-201) (p< 0,001).

Conclusiones: Estos resultados demuestran que la concentración vítreo de Epo está más elevada en los pacientes con RDP en comparación con el grupo control.

Palabras clave: Diabetes, hipoxia, neuroprotección, angiogénesis, eritropoyetina, retinopatía diabética proliferante.
INTRODUCTION

In 1989, the vasculo-endothelial growth factor (VEGF) was discovered and cloned. This was a key factor in the development of retinal neovascularization (1). Studies have proved a correlation between the VEGF levels and the severity of proliferative diabetic retinopathy (PDR) as well as a reduction of said levels after successful PDR treatment (2). The inhibition of VEGF is not associated to total regression of retinal neovascularization secondary to PDR, which means that other angiogenic factors are released in diabetic patients (3,4). Recently, erythropoietin (Epo) has been related to ischemic retinal diseases such as PDR (5,6). The object of this work is to determine the vitreous levels of Epo in patients with PDR in comparison with non-diabetic patients.

SUBJECTS, MATERIAL AND METHODS

This study was approved by the Research and Teaching Committee of our hospital. The patients were recruited in the retina consulting room. Forty-four eyes of 44 patients were studied, classifying them in two groups: group A with PDR (n= 24) and group B with non-diabetic vitreous-retinal pathology (n= 20) (tables I and II).

The inclusion criteria for group A patients were:
— To accept participation in the study, with signature of informed consent.
— Diabetes mellitus treated by primary health care physician, internist or endocrinologist.
— Diagnosis of PDR, classified as active (greater vascular component) or quiescent (greater fibrous component) (2,3).
— The ability to access their medical records.
— The inclusion criteria for group B patients were:
— To accept participation in the study, with signature of informed consent.
— No diabetes mellitus diagnostic, with normal glycemia curve.
— The ability to access their medical records.

The exclusion criteria were patients with previous vitrectomy, glaucoma and other vascular processes. The samples with bleeding were also discarded.

After performing 3 sclerectomies and placing the infusion cannula, the vitreotome was inserted in the central vitreous body, obtaining an undiluted sample between 0.3-0.5 mL in a syringe, subsequently proceeding to open the infusion and perform a 20G or 25G vitrectomy. The samples were sent to the biochemistry lab where they were frozen at–80ºC up to analysis. The determination of Epo levels was made with radioimmunoessay.

Statistical study: the individual data were studied according to the global Kruskal-Wallis analysis and when the values were statistically significant (p<0.05) an individual comparative study was made with the non-parametric Mann-Whitney test. All data were statistically processed with the software SPSS 10.0 (SPSS for Windows, SPSS Inc, Chicago, USA).

RESULTS

The mean Epo in vitreous of Group A patients was of 512 mU/mL (range between 120 and 880) and in group B patients of 25.1 mU/mL (range between 5.2 and 201) (p<0.001). The group A patients with active PDR had vitreous levels of 462 mU/mL (range between 350 and 880) and the levels of group A patients with quiescent PDR were of 248 mU/mL (range between 120 and 260) (p<0.001).

DISCUSSION

The function of tissues depends on an adequate supply of oxygen by vessels. Hypoxia induces local and systemic adaptation mechanisms which
are controlled by hypoxia-inducible factors such as VEGF and Epo, among others (6). Epo is a multifunctional glucoprotein whose concentration in tissues is regulated by hypoxia (8-10) and stimulates the formation of red blood cells, increasing their proliferation and differentiation, avoiding apoptosis of erythrocyte precursors (10,11). The main stimulus which regulates the production of erythropoietin is hypoxia (12,13). The brain and the retina have a para-endocrine system for producing Epo and its receptors. This suggests that Epo protects neurons from apoptosis due to ischemic damage (9-13).

Epo also shows angiogenic activity, stimulating the proliferation and migration of endothelial cells (14). The Epo increase in hypoxia is due to a cellular mechanism which is identical to that of VEGF, including the inducible hypoxia factor (15,16). This paper studied erythropoietin in the vitreous of patients with and without proliferative diabetic retinopathy and found that Epo levels in the vitreous were significantly higher in patients with PDR than in non-diabetic ones. In addition, Epo values in patients with active PDR were significantly higher than in those with quiescent PDR (3).

By means of multiple regression, Watanabe et al (3) determined that Epo was an angiogenic factor independent of VEGF in patients with PDR and that its action is more closely associated to PDR than to VEGF. However, they failed to find a significant correlation between erythropoietin levels in the vitreous and in plasma. In a study with 12 PDR patients, Hernández et al (17) found Epo concentrations in the vitreous 30 times higher than in serum. Therefore, it seems clear that Epo is produced locally in the retina. Epo is a power retinal angiogenic factor independent of VEGF which is capable of stimulating retinal angiogenesis in proliferative diabetic retinopathy (3). Additional evidence support the role of Epo in PDR. In the vitreous of patients with PDR, Epo stimulates the proliferation of retinal endothelial cells in a dosage-dependent manner (18,19). The blockage of Epo inhibits cellular growth as efficiently as VEGF, which suggests that Epo has an angiogenic power equivalent to that of VEGF in patients with PDR. Even though VEGF is the main mediator of retinal angiogenesis, in certain patients its blockage is not enough to prevent neovascularization (3,4). For this reason, other angiogenic factors such as Epo must be considered in the physiopathology of PDR.

REFERENCES

sed in the human retina and it is highly elevated in the vitreous fluid of patients with diabetic macular edema. Diabetes Care 2006; 29: 2028-2033.
