

ANGIOGRAPHIC ESTIMATION OF THE EFFECT OF PANRETINAL LASER PHOTOCOAGULATION ON EVOLUTION OF NEOVASCULARIZATION AT PROLIFERATIVE DIABETIC RETINOPATHY

Nenad T. Petrović and Sunčica B. Srećković

Center of Ophthalmology, Clinical Center Kragujevac, Kragujevac, Serbia and Montenegro

ANGIOGRAFSKA PROCENA EFEKTA PANRETINALNE LASER FOTOKOAGULACIJE NA EVOLUCIJU NEOVASKULARIZACIJE KOD PROLIFERATIVNE DIJABETSKE RETINOPATIJE

Nenad T. Petrović i Sunčica B. Srećković

Centar za oftalmologiju, Klinički centar Kragujevac, Kragujevac

Received/Primljen: 28. 06. 2005. Accepted/Prihvaćen: 03. 02. 2006.

SAŽETAK

Uvod: Najbitnija karakteristika proliferativne dijabetske retinopatije (PDR) je pojava novih krvnih sudova na disku tj. papili optičkog nerva ili duž glavnih vaskularnih arkada retine.

Cilj rada: Izvršiti angiografsku analizu efekata panretinalne laserfotokoagulacije na sprečavanje daljeg razvoja i regresiju već stvorenih neovaskularnih sudova retine, a takođe i utvrditi angiografsko ponašanje rezidualnih neovaskularnih krvnih sudova.

Materijal i metode: Kod 124 oka sa proliferativnom dijabetskom retinopatijom izvršena je angiografska analiza prepapilarnih i preretinalnih neovaskularnih sudova pre započinjanja panretinalne laser fotokoagulacije i nakon njenog završetka. Laser intervencija je izvršena upotrebom argon lasera Visulas 532 firme Zeiss upotrebom monohromatskog zelenog zračenja talasne dužine 532 nm. Prosečan period praćenja lečenih očiju je iznosio 37 ± 9 meseci.

Rezultati: Potpuna regresija novoformiranih krvnih sudova je postignuta kod 20.6% prepapilarnih i 26.5% preretinalnih neovaskularnih formacija. Dodatna angiografska stabilnost preostalih neovaskularnih struktura postignuta je kod 31.9% očiju sa prepapilarnom i kod 28.4% očiju sa preretinalnom neovaskularizacijom. Sumarni rezultati anatomskog i angiografskog poboljšanja nalaza na očnom dnu u ovoj studiji su zabeleženi kod 52.6% lečenih očiju sa prepapilarnom i kod 54.9% lečenih očiju sa preretinalnom neovaskularizacijom.

Zaključak: Iako panretinalna laserfotokoagulacija dovodi do kompletne regresije neovaskularizacije tek u oko ¼ lečenih očiju, ovaj način lečenja znatno smanjuje okularni morbiditet za vi{e od 50% i u slu~ajevima gde perzistiraju rezidue neovaskularnih krvnih sudova.

Cljučne reči: proliferativna dijabetska retinopatija (PDR), fluoresceinska angiografija, panretinalna fotokoagulacija (PRP)

Skraćenice: ETDRS, Early Treatment Diabetic Retinopathy Study; NVD, new vessels at disk; NVE, new vessels elsewhere; NVP, prepapillar neovascularization; NVR, preretinal neovascularization; PDR, proliferative diabetic retinopathy; PEDF, pigment endothelium derived factor; PPDR, preproliferative diabetic retinopathy; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor.

ABSTRACT

Introduction: The most significant hallmark of proliferative diabetic retinopathy (PDR) is development of new blood vessels at the optic nerve disc i.e. papilla, or along the course of the major vascular arcades of the retina.

Aim: Conducting angiographic estimation of the effect of panretinal laser photocoagulation (PRP) on the prevention of further development and regression of already existing retinal new blood vessels, as well as qualification of the angiographic condition of residual neovascularization.

Material and methods: The angiographic analysis of new blood vessels of the optic disc and retina has been carried out on 124 eyes with proliferative diabetic retinopathy, before and after panretinal laser photocoagulation. Laser intervention was performed using the Zeiss apparatus VISULAS 532 with the application of monochromatic argon green radiation with a wave length of 532 nm. The average follow-up period of treated eyes was 37 ± 9 months.

Results: The complete regression of newly formed blood vessels was achieved in 20.6% optic discs, and in 26.5% retinal neovascular formations. The additional angiographic stability of residual neovascular formations was achieved in 31.9% eyes with the optic disc and in 26.4% eyes with retinal neovascularization. The summary results of the anatomic and angiographic fundus condition improvements, in this study, were recorded on 52.6% treated eyes with the optic disc and on 54.9% treated eyes with retinal neovascularization.

Conclusion: Although panretinal laser photocoagulation hardly brings to the complete elimination of neovascularization in approximately ¼ of treated eyes, this treatment significantly reduces the ocular morbidity by more than 50%, even in cases where residual neovascularization exists.

Key words: proliferative diabetic retinopathy (PDR), fluorescein angiography, panretinal photocoagulation (PRP)

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; NVD, new vessels at disk; NVE, new vessels elsewhere; NVP, prepapillar neovascularization; NVR, preretinal neovascularization; PDR, proliferative diabetic retinopathy; PEDF, pigment endothelium derived factor; PPDR, preproliferative diabetic retinopathy; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor.

INTRODUCTION

The most prominent characteristic of proliferative diabetic retinopathy (PDR) is development of new blood vessels in the region of optic disc (NVD-new vessels at disk i.e. NVP-pre-papillar neovascularization), or along the course of the major vascular arcades of the retina (NVE-new vessels elsewhere i.e. NVR-pre-retinal neovascularization). Neovascularization typically occurs in retinas with extensive zones of vascular occlusion, which indicates a direct connection between retinal ischemia

and neovascularization. At present it is known that there is a whole family of angiogenic factors synthesized by ischemic retina which stimulate this process of retinal neoangiogenesis. One quarter of the retina should be non-perfused, for the papillar neovascularization to develop. An important characteristic of proliferative diabetic retinopathy is its bilaterality; about 90% of diabetic patients with proliferative retinopathy in one eye have the similar pathological manifestations in the other. The major causes of the loss of sight in case of

eyes with neovascularization are sudden occurrence of pre-retinal or intravitreal bleeding due to their bursting during partial detachment of vitreous or occurrence of traction detachment of retina due to fibrovascular contraction of these structures (1-3).

Blindness is 25 times more frequent with diabetic patients than with population in general. The incidence of proliferative diabetic retinopathy is particularly high in diabetes type 1 patients: it develops in 25–40% of patients 15 years after the onset of the illness and in 60–72% of patients 30 years after onset of diabetes. (4) The only therapeutic procedure that has been proven as efficient in treatment of proliferative diabetic retinopathy is panretinal laser photocoagulation (PRP) of fundus, provided that satisfactory metabolic control of diabetes had been achieved. Early laser photocoagulation in due time, can reduce the risk of blindness by 73% (5). Panretinal photocoagulation actually means controlled destruction of 15–50% of the retina surface and involves application of laser spots upon the retina surface at the periphery of major vascular arcades of blood vessels. The study group ETDRS (Early Treatment Diabetic Retinopathy Study) has defined 3 criteria of „High risk proliferative retinopathy” necessitating an urgent panretinal photocoagulation (6):

- 1) papillar neovascularization (NVP) of the surface exceeding $\frac{1}{4}$ of the papillar diameter, or peripapillar neovascularization within the range of one papillar diameter of the surface exceeding $\frac{1}{4}$ of optic disc.
- 2) papillar neovascularization (NVP) of the surface smaller than $\frac{1}{4}$ of papillar diameter but which is accompanied by vitreous or preretinal haemorrhage.
- 3) pre-retinal neovascularization (NVR) of the surface larger than $\frac{1}{2}$ of papillar diameter associated with vitreous or pre-retinal haemorrhage.

Fluorescein angiography is a useful addition to ophthalmological examination of diabetic fundus, pointing to indication for laser photocoagulation treatment. In angiography the newly formed blood vessels are recognized by intensive early leakage of the contrast and it can also identify surfaces of retinal non-perfusion to be laser treated by priority.

The aim of this work was to make angiographic analysis of the effects of panretinal laser photocoagulation upon prevention of further development and regression of already formed neovascular vessels of the retina and also to determine angiographic behaviour of residual neovascular blood vessels.

PATIENTS AND METHODS

This retrospective examination was carried out in the Cabinet for Argon laser photocoagulation and fluorescein angiography, Ophthalmology Center-Clinical Center Kragujevac in the period from 1.01 2000. to 31. 12 2004. The basic criterion for choosing the patients for this testing was the diagnosis of proliferative diabetic retinopathy of high or moderate risk necessitating panretinal laser photocoagulation.

After examination of the fundus by means of indirect binocular biomicroscopy, each patient has been subjected to standard procedure of fluorescein angiography with injection of 5–10 cm³ of 10% Na-fluorescein into cubital vein. The retinal camera of the firm Topcon model TIC-F was used for testing. The analysis of the angiograms served for assessing the type, size and maturation of neovascular blood vessels, angiographic appearance of the macula and detection of the zone of retinal perfusion.

Based on biomicroscopic and angiographic examination, the size of pre-papillar neovascularization-NVP has been graded from 1–3 as follows: 1) up to $\frac{1}{4}$ of the papilla ($<500\mu\text{m}^2$) 2) from $\frac{1}{4}$ to 1 papillar diameter ($500\mu\text{m}^2$ – $2000\mu\text{m}^2$) 3) greater than 1 papillar diameter, that is, stretches over to peri-papillar zone too ($>2000\mu\text{m}^2$). The cumulative size of the surfaces of preretinal neovascularization -NVR has also been graded from 1–3 as follows: 1) up to $\frac{1}{2}$ of the surface of papillar diameter ($<1000\mu\text{m}^2$) 2) from $\frac{1}{2}$ to 3 papillar diameters ($1000\mu\text{m}^2$ – $6000\mu\text{m}^2$) 3) over 3 papillar diameters ($>6000\mu\text{m}^2$).

Then the protocol of panretinal laser photocoagulation (PRP) started consisting of a number of laser treatments conducted using Argon laser of the firm Zeiss (Visulas 532) with the application of monochromatic green radiation of the wave-length of 532 nm. The laser treatment was conducted by different lenses with anti-reflexive layers (panfundoscopic lens or Goldman lens with three mirrors), depending upon the region of the retina the laser spots are being applied to. If at the beginning of the treatment there has been a pre-existing macular oedema it has first been treated by focal or grid photocoagulation. The panfundoscopic lens has mainly been used for photocoagulation of the retina zones around major vascular arcades and medium retinal periphery, whereas the size of the spot selected was 200–300 μm , exposure time 0.1 sec and the intensity was individually applied to obtain slightly greyish retinal burning. For photocoagulation of more peripheral zones of the retina Goldman lens with 3 mirrors was used, where the size of the spot selected was 300–500 μm with identical above given parameters of exposure time and laser intensity. Non-confluent PRP was mainly conducted with slightly detached individual laser spots, while for the zones around pre-retinal neovascularization confluent photocoagulation with attached edges of laser burns was applied. The initial laser burning was carried out along the temporal arc at the distance of 2 papillar diameters from the centre of the macula, and then, in the subsequent sessions the treatment included the following by this order: bottom hemi retina, nasal retina, upper hemi retina and at the very end, temporal retina. The number of laser spots per individual session has never exceeded 500. The number of sessions and that of applied laser spots for complete realization of panretinal laser photocoagulation treatment have been individually determined in each particular case.

Upon completion of the treatment, all the patients have been followed-up in four-month intervals and, when necessary, at each check-up photocoagulation was supple-

mented by application of new spots mainly in the space between the previously made laser burns. During the follow-up period each treated eye has been at least once subjected to control fluorescein angiography in order to assess the effects of the therapy. The average follow-up period of treated eyes was 37 ± 9 months.

We have defined 2 criteria for the successful treatment: 1) complete regression of neovascularization and 2) partial regression or unchanged size of newly formed blood vessels, but with improved angiographic characteristics in terms of reduction of intensity of leakage of the contrast. We have also defined 2 criteria for the failure of the treatment: 1) increase of neovascularization with frequent repetitive intra-vitreous haemorrhage 2) partial regression or unchanged size of newly-formed blood vessels, but without any improvement of their angiographic characteristics in terms of reduction of the intensity of leakage of the contrast.

In the statistical analysis, methods of descriptive statistics were used (frequencies, percents, mean, std. deviation).

RESULTS

This study included 124 eyes of 75 diabetic patients (46 male and 29 female). The youngest patient was 18 and the oldest 69 years old (the average age of the patients was 53 ± 15.69). Type 1 diabetes was the diagnosis with 31 (41.3%) patients, while 44 (58.7%) patients had type 2 diabetes. In 39 (52%) patients, the diabetes has been treated only by insulin, a combination of insulin and oral hypoglycaemics has been used in case of 11 (14.7%) patients, while 25 (33.3%) patients have been taking only oral hypoglycaemics. The average duration of the diabetes was 16.5 ± 5.49 years.

Both eyes have been analyzed in 49 patients, while in 26 patients only one eye has been taken into consideration (15 eyes of these patients were in the state of pre-proliferative diabetic retinopathy, with 9 eyes there was thick intravitreal haemorrhage which made examination of the fundus and laser treatment impossible, and in 2 eyes traction detachment of retina was found which necessitated vitreal operation).

After biomicroscopic and angiographic examination in 75 (60.5%) eyes was found proliferative diabetic retinopathy with associated pre-papillary and pre-retinal neovascularization, in 22 (17.7%) eyes there was only pre-papillary, and in 27 (21.8%) eyes there was only pre-retinal neovascularization.

On the basis of the previously determined criteria, presence of pre-papillary neovascularization (NVP) was determined in 97 eyes: 28 (28.9%) of these eyes of them had NVP surfaces smaller than $1/4$ of papillary diameter, 47 (48.4%) had NVP surfaces from $1/4$ to 1 papillary diameter, and 22 (22.7%) eyes had NVP exceeding the papillary borders.

Pre-retinal neovascularization (NVR) was determined in 102 eyes: 21 (20.6%) of them had NVR with size of up to $1/2$ of papillary diameter, in 62 (60.8%) eyes NVR was from $1/2$ to 3 papillary diameters, while in 19

(18.6%) eyes there was NVR of cumulative size over 3 papillary diameters.

Figure 1 shows the fundus with proliferative diabetic retinopathy of high risk: a) papillary neovascularization-NVP b) retinal neovascularization-NVR, while figure 2 shows an angiographic recording which identifies: a) intensive early leakage of the contrast from neovascular vessels and b) spacious zones of retinal non-perfusion.

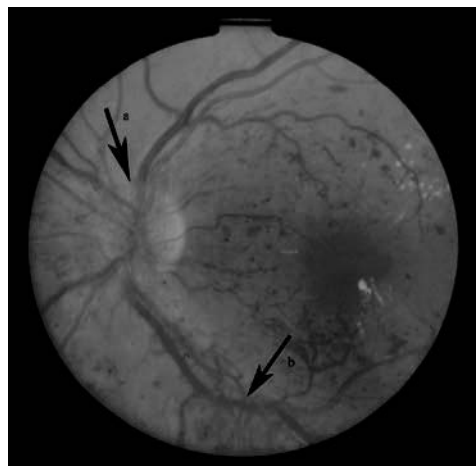


Figure 1. High risk PDR: a) papillary neovascularization-NVP b) retinal neovascularization-NVR.

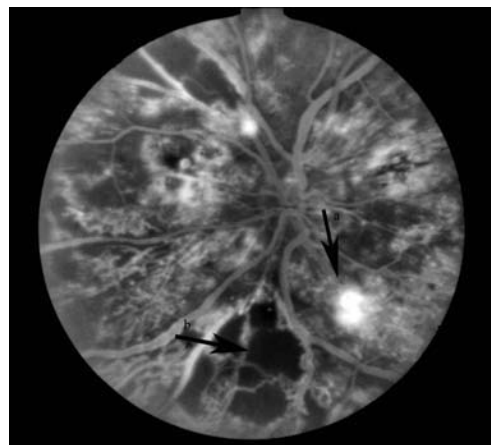


Figure 2. Angiographic photo of an eye with PDR: a) intensive early leakage of the contrast b) non-perfused zones of the retina.

With the eyes having NVP of the size up to $1/4$ of diameter, PRP was 2110 laser spots on average ($SD=177$); with the eyes having NVP of the size from $1/4$ to 1 papillary diameter the average number of applied spots during PRP was 3085 ($SD=414$), while with the eyes with extensive NVP exceeding the papillary borders the average number of laser spots was 4840 ($SD=674$). In case of eyes with isolated existence of NVR, the average number of applied spots at the end of the treatment was 1112 ($SD=203$). Figure 3 shows the appearance of slightly pigmented scars at the locations of applied laser spots, while figure 4 shows angiographic appearance of chorioretinal scars after confluent photocoagulation of preretinal neovascularization in the region of vascular arcades. Figure 5 shows angiographic photo of an eye with retinal neovascularization-NVR, there is early leakage of the contrast from newly formed retinal blood vessels. Figure 6 shows control angiographic photo of the same eye 3 months after photocoagulation; there

is chorioretinal atrophy at the locations of applied laser spots and noticeable reduction of leakage of the contrast from newly formed blood vessels.

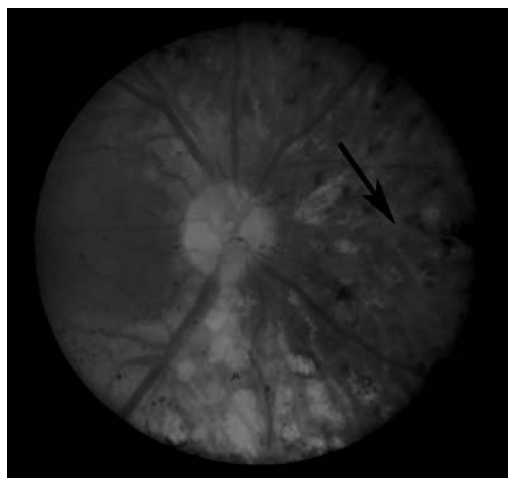


Figure 3. Slightly pigmented scars at the locations of applied laser spots.

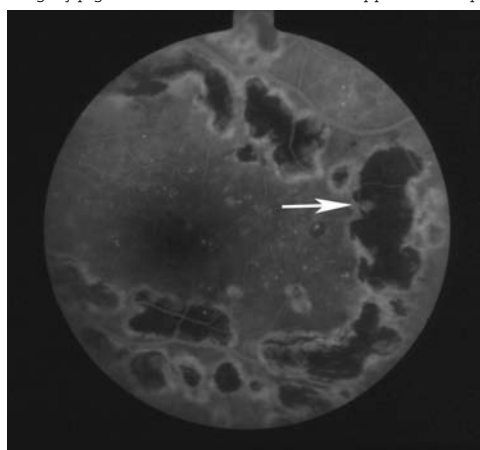


Figure 4. Angiographic photo of intensive pigmented spots after confluent photocoagulation of retinal neovascularization.

Table 1 gives the results of panretinal laser photocoagulation upon evolution of pre-papillary neovascularization, depending on its initial size. With the initial NVP of the surface up to 1/4 of papillary diameter, its complete regression was achieved in 9 (32.1%) eyes, and additional angiographic stabilization in case of 10 (35.7%) treated eyes in addition. Eleven (48.4%) eyes with initial NVP

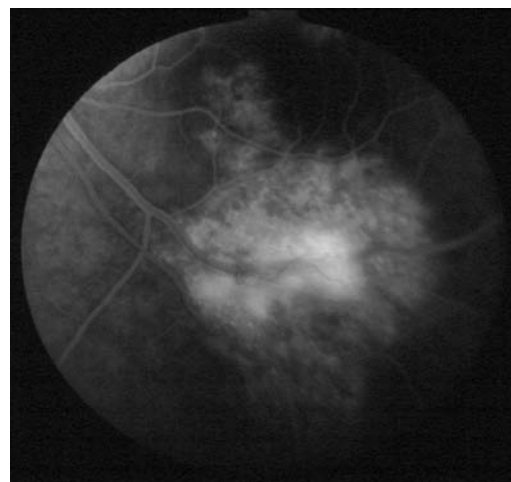


Figure 5. Angiographic photo of an eye with retinal neovascularization-NVR; notice intensive early leakage of the contrast from newly formed retinal blood vessels.

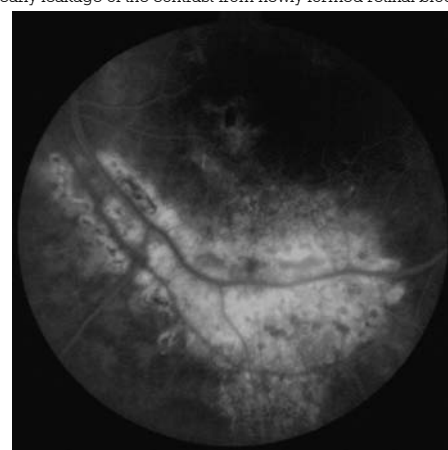


Figure 6. Control angiographic photo of the same eye 3 months after photocoagulation; reduction of leakage of the contrast from newly formed blood vessels.

of the size from 1/4 to 1 papillary diameter have shown complete regression of newly formed blood vessels, and additional angiographic stability 15 (31.9%) of treated eyes in addition. Complete regression of neovascularization of the size over 1 papillary diameter was not observed in any single case, while its angiographic stability was achieved in 6 (27.2%) of treated eyes.

Table 1. Results of panretinal laser photocoagulation upon evolution of pre-papillary neovascularization (NVP), depending on its initial size.

Pre-papillary neovascularization NVP	Complete regression of NVP	Partial regression of NVP		Unchanged size of NVP		Increased size of NVP	Total stabilization
Up to 1/4 of papillary diameter 28 (28.9%)	9 (32.1%)	11 (39.3%)		5 (17.9%)		3 (10.7%)	19 (67.8%)
		+ FA stabilization	- FA stabilization	+ FA stabilization	- FA stabilization		
		8 (28.6%)	3 (10.7%)	2 (7.1%)	3 (10.8%)		
from 1/4 to 1 papillary diameter 47 (48.4%)	11 (23.5%)	15 (31.9%)		12 (25.5%)		9 (19.1%)	26 (55.4%)
		+ FA stabilization	- FA stabilization	+ FA stabilization	- FA stabilization		
		11 (23.4%)	4 (8.5%)	4 (8.5%)	8 (17.0%)		
over 1 papillary diameter 22 (22.7%)	0 (0%)	6 (27.3%)		10 (45.4%)		6 (27.3%)	6 (27.3%)
		+ FA stabilization	- FA stabilization	+ FA stabilization	- FA stabilization		
		3 (13.65%)	3 (13.65%)	3 (13.6%)	7 (31.8%)		
97 (100%)	20 (20.6%)	32 (33.1%)		27 (27.7%)		18 (18.5%)	

Table 2 shows the results of panretinal laser photocoagulation upon evolution of pre-retinal neovascularization depending on its initial size. With the initial NVR of the size up to 1/2 of papillar diameter its full regression was achieved in 11 (52.5%) eyes, and additional angiographic stabilization in another 5 (23.8%) treated eyes; 16 (25.9%) eyes with initial NVR of the size from 1/2

to 3 papillar diameter have shown complete regression of newly formed blood vessels, and additional angiographic stability another 18 (28.9%) treated eyes. The complete regression of NVR larger than 3 papillar diameters has not been observed in any of the cases, while its angiographic stability has been achieved in 6 (31.6%) treated eyes.

Table 2. Results of panretinal laser photocoagulation upon evolution of pre-retinal neovascularization (NVR), depending upon its initial size.

Pre-retinal neovascularization NVR	Complete regression of NVR	Partial regression of NVR		Unchanged size of NVR		Increased size of NVR	Total stabilization
Up to 1/2 of papillar diameter 21 (20.6%)	11 (52.5%)	4 (19%)		4 (19%)		2 (9.5%)	16 (76.3%)
		+ FA stabilization	- FA stabilization	+ FA stabilization	- FA stabilization		
		3 (14.3%)	1 (4.7%)	2 (9.5%)	2 (9.5%)		
from 1/2 to 3 papillar diameter 62 (60.8%)	16 (25.9%)	19 (30.6%)		20 (32.2%)		7 (11.3)	34 (54.8%)
		+ FA stabilization	- FA stabilization	+ FA stabilization	- FA stabilization		
		12 (19.3%)	7 (11.3%)	6 (9.6%)	14 (22.6%)		
over 3 papillar diameter 19 (18.6%)	0 (0%)	5 (26.3%)		8 (42.1%)		6 (31.6%)	6 (31.6%)
		+ FA stabilization	- FA stabilization	+ FA stabilization	- FA stabilization		
		3 (15.8%)	2 (10.5%)	3 (15.8%)	5 (26.3%)		
102 (100%)	27 (26.5%)	28 (27.5%)		32 (31.3%)		15 (14.7%)	

DISCUSSION

The process of angiogenesis is inherent to proliferative diabetic retinopathy and occurs as a result of synthesis of numerous mediators, that is, growth factor (EDGF-eye derived growth factors) by ischemic retina. The most frequently quoted stimulators of neovascularization are: (VEGF-vascular endothelial growth factor), EGF-epidermal growth factor, IGF-insulin like growth factor, PDGF-platelet derived growth factor, FGF-fibroblast growth factor, TGF-transformation growth factors, etc. (7). Fresh neovascular blood vessels are characterized by thick wall, narrow lumen and numerous endothelial extensions. Their basal membrane exhibit numerous localized ruptures. Mature neovascular blood vessels have thinner wall and wide lumen. Their basal membrane is of normal appearance. The extreme permeability of neovascular formations which is well-known in angiography is most likely associated with abnormally formed basal membrane or inter-endothelial connections while fenestrations on endothelial cells occur in only 30% of neovascular membranes.

About 1/4 of the retina must be non-perfused for the papillar neovascularization to be formed. Absence of internal limiting membrane over the head of optic nerve may account for the frequent incidence of neovascularization at this site. The optic nerve is also inclined to development of neovascularization because it represents an inter-surface between retinal and choroidal circulation. Neovascular vessels on the papilla develop from superficial papillar blood vessels, and in the beginning they are located on the surface of the disc or within the region of physiological excavation. Later, collateral circulation with retinal vascular arcades may be established. In extreme cases, spreading centrifugally, above vascular arcades and sometimes above the macula, this NVP may comprise the surface of 3–4 papillar diameters. During angiography these neovascular blood vessels allow for

abundant diffusion of the contrast and hyper fluorescence becomes prominent even during the first minute after injection of the contrast and then fills the vitreous cavity abundantly. NVP impregnated by the contrast before retinal blood vessels indicates that it is associated with ciliary blood vessels. On the contrary, NVP impregnated by the contrast in the late retinal laminar time indicates that it is associated with venous retinal circulation (8). This NVP with late fluorescence reacts faster and more regularly on panretinal laser photocoagulation than NVP with early fluorescence. Actually, there is an important correlation between NVP and rubeosis of the iris. In the eyes with NVP, the zones of capillary non-perfusion are more spacious and numerous than with eyes with NVR. It has been estimated that 1/2 of the retina must be ischemic for the rubeosis of the iris to occur. NVP is found in 93% of the eyes with rubeosis of the iris. The NVP associated with ciliary circulation on the papilla of optical nerve could divert a part of blood intended for anterior eye segment, which deepens the ciliary hypoxia and favours occurrence of rubeosis of the iris and neovascular glaucoma (9).

While NVP mainly develops in the eyes where intraocular stimulus of neovascularization is intensive, NVR develops in the eyes where non-perfusion is relatively limited. If in these eyes non-perfusion increase, pre-papillar vessels are likely to develop at the same time, and these may or may not be in connection with pre-retinal blood vessels. This leads to the conclusion that pre-retinal neovascular proliferation occurs when retinal non-perfusion is more or less stabilized. NVR usually develops from large retinal venous arcades after the first venous bifurcation. It can develop also on the posterior pole in macular or para macular region while its localization in the region of equator or more anterior is rare, and more frequently occurs with patients suffering from some other system disease, such as hypertension, hemoglobi-

nopathies etc. Ninety-four percent of these preretinal neovascularizations are localized within the circle of 6 papillar diameters from the papilla of optical nerve. NVR almost always starts from the zones of the perfused retina located around the zones of capillary non-perfusion.

Panretinal laser photocoagulation (PRP) is a type of controlled destruction of 15–50% of the surface of the retina by laser burning. Generally, it takes at least 1500–2000 laser burns to stop further development of neovascularization, and in extreme cases even 11 000 laser coagulations are necessary to achieve this goal (10). The study group ETDRS has given recommendations for urgent PRP of proliferative retinopathy of high risk. According to the recommendations of the above study group, if these criteria are not met, the laser treatment is not to be carried out, or if it has already started, it is to be stopped and the patients are to be followed up in three-month intervals. It seems, however, that the recommendations of French laser-therapeutics for early start of PRP are more acceptable and reasonable; the treatment should start already in the stadium of medium-risk proliferative retinopathy, and even in the stadium of pre-proliferative retinopathy. Namely, in the eyes with pre-proliferative retinopathy presence of over 5 soft „cotton wool“ exudates indicates a high risk of developing neovascularization in the period of ≤ 2 years (5). Favourable effect of photocoagulation is archived mainly by destroying ischemic and hypoxic areas of the retina, thus reducing production of mediators of angiogenesis, too. Successful panretinal photocoagulation has been found to reduce intraocular VEGF levels by 75% in patients treated for ocular neovascularization (3). On the other hand, laser photocoagulation by destruction of external retinal layers makes possible for larger quantity of oxygen, not used by destroyed photoreceptors, to diffuse from chorio-capillaries to internal layers of the retina, which is manifested by increased concentration of oxygen towards physiological values. Partial oxygen pressure in pre-retinal vitreous rises after laser photocoagulation as a result of either increased transport through pigment epithelium in the region of laser spots and/or decreased consumption of oxygen in the external layers of the retina, since the number of photoreceptors has been reduced by the laser treatment (2). Improved oxygenation would then have a favourable hemodynamic effect too, which is manifested by upgrading of auto regulation of passive permeability as therapeutically favourable effects of the laser treatment. By destroying the changed cells of pigment epithelium, laser photocoagulation could stimulate re-proliferation of new pigment cells, thus resulting in restoration of the external blood-retinal barrier. The retinal blood vessels

located in the region of laser spots exhibit particular endothelial proliferation; it is possible that coagulation necrosis of the pigment epithelium causes release of diffusible factor (pigment endothelium-derived factor PEDF) which stimulate endothelial repair thus restoring the inner blood-retinal barrier (11).

The results of PRP may be assessed already 6–8 weeks upon its termination; in eyes with good effects of laser treatment within the first 3 months upon completion of the treatment the favourable effects are maintained for almost 4 years (12). A well conducted PRP may ensure good anatomic and functional stability for the period of 10 years and more (13). Nevertheless, it is necessary to keep following all the patients treated, since neovascularization is likely to occur again even in 50% of the cases with initial favourable effects.

Although the effect of PRP on the reduction of the risk of sight loss is without any doubt, the complete regression of neovascularization is achieved only in 21% of the eyes treated. In our material, the complete regression of newly formed blood vessels was achieved in 20.6% of pre-papillar and 26.5% of pre-retinal neovascular formations. An explanation for incomplete resolution of neovascularization may be insufficient number of applied laser spots necessary for the complete regression, but also the so-called „laser-resistance“ where the desired therapeutic effect can not be achieved even with a very high number of laser spots (6000–11000). In spite of rare complete regression of neovascular formations, favourable effect of the laser treatment could be noticed also in terms of certain maturation of newly formed blood vessels and stabilization of blood-retinal barrier. An additional angiographic stability of residual neovascular structures with our patients was achieved in 31.9% of the eyes with pre-papillar and 28.4% of the eyes with pre-retinal neovascularization. The summary results of anatomic and angiographic improvement of the findings on the fundus in this study were recorded in 52.6% of treated eyes with pre-papillar and 54.9% eyes with pre-retinal neovascularization.

It may be concluded that although panretinal photocoagulation results in complete regression of neovascularization only in about $\frac{1}{4}$ of treated eyes, this treatment significantly reduces the ocular morbidity by about 50%, even in cases where residual neovascular blood vessels persist. Fluorescein angiography is very useful in assessing the state of blood-retinal barrier, identifying the zones of retinal non-perfusion and estimating maturity of neovascular blood vessels before starting panretinal laser photocoagulation and during the efficiency evaluation of the treatment as well.

REFERENCES

1. Stanford MR. The pathogenesis of diabetic retinopathy. *Br J Ophthalmol* 2004; 88: 444–5.
2. Robert N, Frank MD. Diabetic retinopathy. *N Engl J Med* 2004; 350: 48–58.
3. Thomas A, Armando G, Bernard Z. Diabetic retinopathy and diabetic macular edema. *Diabetes Care* 2003; 26: 2653–64.
4. Klein R, Klein BEK, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy: prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol* 1984; 102: 527.
5. Cunha-Vaz JG. Natural history of diabetic retinopathy. Focus on Diabetic Retinopathy 1995; 2: 48–55.
6. Early Treatment Diabetic Retinopathy Study Research Group. Early Photocoagulation for Diabetic Retinopathy. ETDRS report number 9. *Ophthalmology* 1991; 98: 766–85.

7. Paques M, Massin P, Gaudric A. Growth factors and diabetic retinopathy. *Diabetes Metab* 1997; 23: 125–30.
 8. Sdobnikova SV, Mazurina NK. The origin of papillary neovascularization in patients with proliferative diabetic retinopathy. *Vestn Oftalmol* 2004; 120: 7–11.
 9. Bonnet M. Neovaisseaux papillaires dans la retinopathie diabétique. In: *Symposium International sur la retinopathie diabétique*. Rev Chibret *Ophthalmol* 1985; 105: 281–85.
 10. Hendrikse E. New concepts in the treatment of diabetic retinopathy. *Focus on Diabetic Retinopathy* 1994; 1: 5–8.
 11. Funatsu H, Hori S, Yamashita H, Kitano S. Effective mechanisms of laser photocoagulation for neovascularization in diabetic retinopathy. *Nippon Ganka Gakkai Zasshi* 1996; 100: 339–49.
 12. Vander JE, Duker JS, Benson WE. Long term stability and visual outcome after favorable initial response of proliferative diabetic retinopathy to panretinal photocoagulation. *Ophthalmology* 1991; 98: 1575–79.
 13. Bek T, Kjaergaard J. The prognostic value of post-treatment retinopathy after panretinal photocoagulation for proliferative diabetic retinopathy in type 1 diabetes. *Eur J Ophthalmol* 2004; 14: 538–42.
-