·Clinical Research·

Effect of focal laser photocoagulation in eyes with mild to moderate non-proliferative diabetic retinopathy

Seong Hun Jeong, Jung Il Han, Sung Won Cho, Dong Won Lee, Chul Gu Kim, Tae Gon Lee, Jong Woo Kim

Department of Ophthalmology, Kim's Eye Hospital, Myung-Gok Eye Research Institute, Konyang University College of Medicine, Seoul 07301, Korea

Correspondence to: Jung Il Han. Department of Ophthalmology, Kim's Eye Hospital, Myung-Gok Eye Research Institute, Konyang University College of Medicine, Seoul 07301, Korea. han66139@kimeye.com

Received: 2016-03-16 Accepted: 2016-04-19

Abstract

• AIM: To report the effect of focal laser photocoagulation on both the severity of hard exudates (HEs) and the rate of disease progression in eyes with mild to moderate non-proliferative diabetic retinopathy (NPDR).

• METHODS: We retrospectively reviewed the medical records of 33 patients (60 eyes) who had been diagnosed with mild to moderate NPDR between January 2006 and December 2012. The patients were divided into 2 groups: Group A (38 eyes in 20 patients treated using focal laser photocoagulation) and Group B (treated without laser photocoagulation). We also reviewed the best corrected visual acuity measurements, and the fundus photographs taken at both baseline and follow-up visits.

• RESULTS: In Group A, HE severity grade had decreased significantly from baseline to the final visit ($P<0.05$), but this was not the case in Group B ($P=0.662$). The cumulative probabilities of retinopathy progression at 5y were 26% in Group A and 30% in Group B. Kaplan-Meier survival curves showed no significant difference between the groups with regard to retinopathy progression ($P=0.805$).

• CONCLUSION: Focal laser photocoagulation reduced the levels of HEs in eyes with mild to moderate NPDR. However, the treatment was not able to decelerate the progression of DR.

• KEYWORDS: focal laser; diabetic retinopathy; retina; non-proliferative diabetic retinopathy

DOI:10.18240/ijo.2016.10.12

Jeong SH, Han JI, Cho SW, Lee DW, Kim CG, Lee TG, Kim JW. Effect of focal laser photocoagulation in eyes with mild to moderate non-proliferative diabetic retinopathy. *Int J Ophthalmol* 2016;9(10): 1439-1443

INTRODUCTION

Diabetic retinopathy (DR) is a serious cause of visual impairment in developed countries. The prevalence of DR increases with the elapsed duration of diabetes, and nearly all persons with type 1 diabetes, and more than 60% of those with type 2 diabetes, have some level of retinopathy after 20y[1].

The earliest signs of DR are damage to the microvasculature, and the formation of lesions such as hard exudates (HEs), which are lipid leaks from the blood vessels[2]. Apperance of HEs in macular area can be clue of the presence or previous existence of diabetic maculopathy [3]. Furthermore, large HE deposits are known to increase the risk of subretinal fibrosis[4] and Chew *et al* [5] showed that size of HE were correlated with later decreased of visual acuity over 5y.

Focal laser photocoagulation is an effective treatment in cases involving HEs; possibly because it leads to the closure of microaneurysms and subsequent cessation of leakage into the retinal space [6]. According to the result of the Early Treatment Diabetic Retinopathy Study (ETDRS) for diabetic macula edema (DME), focal laser photocoagulation is commonly used to treat DME with guide of fluorescein angiography (FA) [7]. Characterization of diabetic microaneurysms can be visualized using spectral-domain optical coherence tomography (OCT)[8]. On the other hand, a study by Lovestam-Adrian and Agardh [9] found that when HEs are present, photocoagulation leads to a higher risk of both subretinal fibrosis and atrophic creep of the pigment epithelium than when HEs are not present. This is particularly true when the HEs are subfoveally located.

Previous studies proved that the risk of development of proliferative diabetic retinopathy (PDR) can be reduced by glycemic control [10]. Moreover, panretinal photocoagulation (PRP) in eyes with high-risk PDR can reduce the risk of severe visual loss compared with that of untreated eyes [11]. However, PRP is a destructive treatment procedure and it can cause adverse effects including complications of misdirected or excessive burns and despite of appropriate treatment, visual loss can progress in nearly 5% of individuals.

The purpose of the current study was to report the effects of focal laser photocoagulation on both HE severity and the rate of disease progression in eyes with mild to moderate non-proliferative diabetic retinopathy (NPDR).

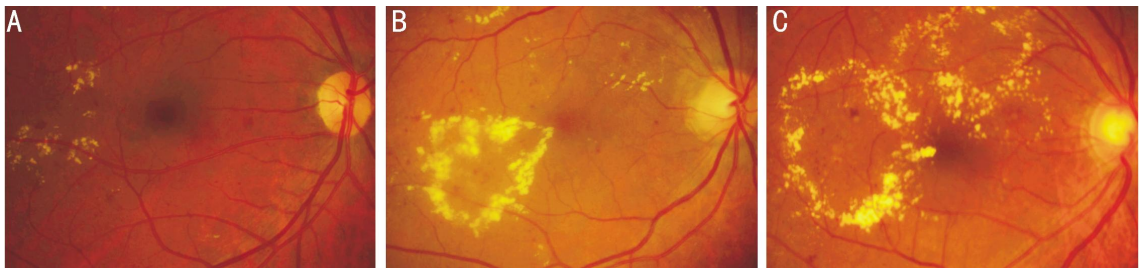

Figure 1 Standard photograph for grading hard exudates (HEs) Grade 1 (A): Total HE area less than 1/4 disc area; Grade 2 (B): Total HE area more than 1/4 disc area, but less than 1 disc area; Grade 3 (C): Total HE area more than 1 disc area.

SUBJECTS AND METHODS

From January 2006 to December 2012, 60 eyes of 33 patients with mild to modereate NPDR were included in the study. The study was approved by the Medical Ethics Committee of Kim's eye Hospital of Konyang University and adhered to the provisions of the Declaration of Helsinki for research involving human subjects. All the patients involved in the study gave written informed consent after thorough discussion on the potential benefits and risks of focal laser photocoagulation.

One or both of the participants' eyes had to meet the following criteria to qualify for enrolment in this study: 1) best-corrected Snellen visual acuity ≥0.8, 2) no definitive retinal thickening at the macular center upon clinical examination, 3) presence of HEs at the posterior pole, and 4) mild to moderate NPDR.

The patients were divided into 2 groups: Group A included patients who had been treated using focal laser photocoagulation, Group B included patients who had been treated without laser photocoagulation. We reviewed both the best corrected visual acuity measurements and the fundus photographs of the central 30°, which were taken at the baseline and follow-up visits. Furthermore, OCT measurements were reviewed when macular edema had developed or was suspected. Photographs were evaluated in a masked fashion independently by two authors.

We excluded patients with a history of eye injury, previous vitreoretinal surgery, glaucoma, or uveitis. Additionally, we excluded eyes that were administered any intravitreal steroid or anti-vascular endothelial growth factor (VEGF) injections in either the 6-month period before laser photocoagulation or during the follow-up period. In such cases, we also excluded the contralateral eyes.

HEs were graded using standard photographs (Figure 1) as follows: 1) Grade 1: total area less than 1/4 disc area (Figure 1A); 2) Grade 2: total area more than 1/4 disc area, but less than 1 disc area (Figure 1B); 3) Grade 3: total area more than 1 disc area (Figure 1C).

Laser photocoagulation was performed using the following parameters: spot size, 100-130 μm; duration, 100ms; and power, 70-150 mW. The laser burn intensity was adjusted to achieve a gray-white burn that was less intense than PRP burns and which directly treated leaking microaneurysms.

Based on modification of a hierarchical DR progression algorithm proposed by Bressler *et al*[12], the progression of DR was defined as including any of the following: 1) cases that had progressed from NPDR to PDR wherein no PDR had been identified at baseline on the basis of fundus photographs, 2) additional cases of DR that had been treated using PRP during follow-up period, and which were not defined under criterion 1) above, and 3) additional cases wherein vitreous hemorrhage had occurred during follow-up period, and which were not defined under either criterion 1) or 2) above.

Clinically significant macular edema (CSME) was defined when any of following criteria were met: 1) retinal thickening at or within either 500 μm or 1/3 disc diameter of the macular center, 2) HEs at or within 500 μm of the macular center, combined with adjacent retinal thickening, 3) a thickened retinal area at least 1 disc area in size, any part of which was located within 1 disc area of the foveal center.

Statistical Analysis The demographics and clinical characteristics of the patients [age, duration of diabetes, and logarithm of the minimum angle of resolution (logMAR) visual acuity] were analyzed using the independent *t*-test. Significance of sex and systemic hypertension were evaluated using Fisher's exact test. Changes in HE severity were analyzed using the Wilcoxon signed-rank test. Cumulative probabilities of DR progression at each biannual visit up to 60mo were analyzed in each treatment group using Kaplan-Meier methods. Statistical analyses were performed using the commercially available software package SPSS ver. 22.0 for Windows (SPSS Sciences, Chicago, IL, USA). A *P*-value of <0.05 was considered statistically significant.

RESULTS

A total 60 eyes of 33 patients were included in the analysis assigned to groups based on whether they had received laser therapy (Group A, *n*=38) or not (Group B, *n*=22). Of these patients, 17 were men (51.5%) and 16 were women (48.5%). Their mean age was 62.1y (range: 44-76y). The average follow-up period was 51.4mo. The clinical and demographic characteristics of both groups at baseline and at 5y are summarized in Table 1.

Table 1 Demographic and clinical characteristics of the patients in Groups A and B

Parameters	Group A	Group B	*P*
No. of eyes	38	22	
Age (a)	61.5±7.96	63.0±6.77	0.580
Sex			0.481
M	9	8	
F	11	5	
Systemic hypertension	4	6	0.139
Duration of diabetes (a)	5.14±9.65	7.4±13.9	0.059
Visual acuity (logMAR, baseline)	0.05±0.08	0.05±0.05	0.841
Visual acuity (logMAR, at 5-year follow up)	0.14±0.21	0.04±0.08	0.078

Group A: Treated with focal laser photocoagulation: Group B: Treated without laser photocoagulation.

In Group A, HE severity had decreased significantly between the baseline and final visits (P<0.05), but this was not the cases in Group B (P=0.662; Figure 2). The mean changes in HE severity between baseline and 5y were -0.39 in Group A *vs* 0.05 in Group B (P<0.05).

Progression of retinopathy was partitioned into a stepwise hierarchy of criteria in order to meet the outcome definition or treatment of each criterion (Table 2). Nine of 38 eyes in Group A and 6 of 22 eyes in Group B progressed to PDR. The need for PRP was the most common evidence of progression to PDR in both groups.

Throughout the 5-year follow-up period, the cumulative probabilities of DR progression in Group A were 12% up to 3y, 18% up to 4y, and 26% up to 5y. The corresponding values in Group B were 9%, 19%, and 30%, respectively. However, the Kaplan-Meier survival curves showed no significant difference between the groups with regard to in DR progression (P=0.805; Figure 3).

Two of the 38 eyes in Group A and 1 of the 22 eyes in Group B developed CSME. This did not constitute a statistical difference (P=0.698).

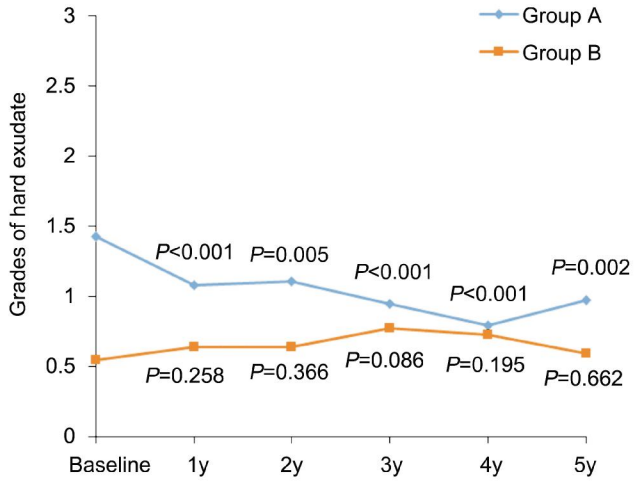

Figure 2 Changes in HE severity during a 5-year follow-up.

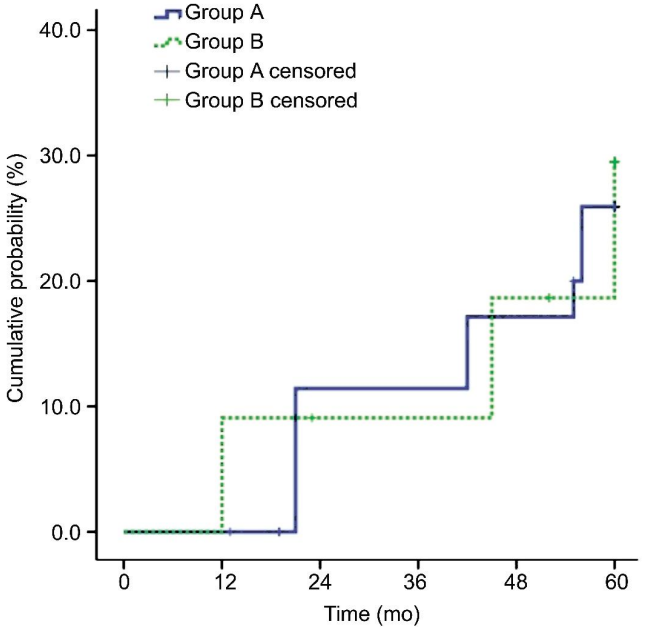

Figure 3 Cumulative probability of DR progression by treatment group defined as change from NPDR to PDR, treatment using PRP, or occurrence of vitreous hemorrhage.

DISCUSSION

Macular HEs in cases of DR have previously been shown to increase the risk of visual impairment and developing of subretinal fibrosis[5,13].

Previous study involving HE patients have shown that laser photocoagulation can decrease the retinal area covered by HEs during the first 6mo, but HE increases again between 6 and 12mo [14]. Therefore, a follow-up period of 12mo is not sufficient to draw any conclusions regarding the long-term efficacy of laser photocoagulation. In the present study, we found that HEs decreased significantly in severity between 12mo and 5y in patients with mild to moderate NPDR (P< 0.05).

Many factors can influence the severity of HEs such as, anemia, higher blood pressure, proteinuria, glycated hemoglobin (HbA1c), intravenous insulin use, and peripheral vascular disease [15]. Moreover, medical treatment can also decrease the level of HEs, and a previous study have reported strict control of serum cholesterol levels can reduce the degree of HEs[16].

The positive effect of laser photocoagulation has been well known for many decades in eyes with macular edema, and it

Table 2 Participants progressing to proliferative diabetic retinopathy by treatment group up to 5y

Progression category	1-year		2-year		3-year		4-year		5-year	
	Group A (*n*=38)	Group B (*n*=22)	Group A (*n*=38)	Group B (*n*=22)	Group A (*n*=38)	Group B (*n*=22)	Group A (*n*=38)	Group B (*n*=22)	Group A (*n*=38)	Group B (*n*=22)
Total cases that progressed from NPDR to PDR[1]	0	0	2	0	0	0	0	2	0	0
Received PRP laser (not counted in row above)	0	2	2	0	0	0	2	0	1	1
Reported vitreous hemorrhage (not counted in 2 rows above)	0	0	0	0	0	0	0	0	2	1
Total with progression to PDR	0	2	4	0	0	0	2	2	3	2

Data shown are total/additional numbers of patients (not counted in preceding rows). NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; PRP: Panretinal photocoagulation. [1]Documented on fundus photographs.

still remains as a widely used modality for exudative DME [7]. However, it is not without limitations and controversy, as one clinical study showed that during the three-year follow-up, the 10 letter decline of visual acuity was observed in 12% of the eyes [17]. In this study, focal laser photocoagulation for the treatment of HE was not effective in the prevention of macular edema in eyes with mild to moderate NPDR (P=0.698) during the 5-year follow up period.

The previous studies also have reported the effectiveness of intravitreal triamcinolone (IVTA) for the reduction of the HE and DME. Larsson *et al* [18] showed that a single 4-mg injection of IVTA reduced HE deposition and improved visual acuity within 3mo. IVTA can induce regression of macular edema by reducing breakdown of the blood-retina barrier in patients with diabetes[19]. Additionally, it was more effective to treat the HE and DME with the concomitant treatment of laser photocoagulation following IVTA, than IVTA or laser photocoagulation alone[17,20].

Slowing the progression of NDPR to PDR can be managed with many well established modalities. As demonstrated in the ETDRS, PRP is one of the early application in eyes with severe NPDR [11]. However, its destructive nature makes its application to be carefully planned in eyes with severe NPDR or PDR. Treatment with triamcinolone also leads to the reductions in DR progression[12]. It also carries unwanted adverse effect such as risks for the development of cataracts and glaucoma. Furthermore, anti-VEGF therapy with ranibizumab reduces the risk of DR progression, and in some cases, regression of DR pathology can be achieved [21]. The purpose of this study was to evaluate the effectiveness of focal laser photocoagulation therapy in slowing the DR progression. Our results showed that the cumulative probabilities of DR progression were not significantly different between the group treated with focal laser photocoagulation and the group without the treatment during the 5-year follow-up period, indicating that the focal laser photocoagulation alone was not sufficient in reducing the rate of the DR progression.

The limitations of the study are as followed. First, this study was non-randomized, retrospective study design. Second, the irregular follow-up intervals and treatment decision depending on the physician's discretion rather than on a given protocol may have resulted in the final outcome. Another limitation of this study was that HE severities were assessed using estimated values based on disc area, and the changes of HE area could not be calculated with the objective measurements.

In summary, focal laser photocoagulation reduced HE severity in eyes with mild to moderate NPDR. However, the same focal laser photocoagulation was not able to prevent DME or slow DR progression. Therefore, we suggest that focal laser photocoagulation can be an option for HE.

ACKNOWLEDGEMENTS

Conflicts of Interest: Jeong SH, None; **Han JI,** None; **Cho SW,** None; **Lee DW,** None; **Kim CG,** None; **Lee TG,** None; **Kim JW,** None.

REFERENCES

1 Klein R, Klein BE, Moss SE, Cruickshanks KJ; The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. *Ophthalmology* 1998;105(10):1801-1815.

2 Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD, Ferris FL 3rd, Klein R, American Diabetes Association. Diabetic retinopathy. *Diabetes Care* 2003;26 Suppl 1:S99-S102.

3 Sasaki M, Kawasaki R, Noonan JE, Wong TY, Lamoureux E, Wang JJ. Quantitative measurement of hard exudates in patients with diabetes and their associations with serum lipid levels. *Invest Ophthalmol Vis Sci* 2013; 54(8):5544-5550.

4 Fong DS, Segal PP, Myers F, Ferris FL, Hubbard LD, Davis MD. Early Treatment Diabetic Retinopathy Study Research Group. Subretinal fibrosis in diabetic macular edema. ETDRS report 23. *Arch Ophthalmol* 1997;115 (7):873-877.

5 Chew EY, Klein ML, Ferris FL 3rd, Remaley NA, Murphy RP, Chantry K, Hoogwerf BJ, Miller D. Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) report 22. *Arch Ophthalmol* 1996;114 (9): 1079-1084.

6 Lee SN, Chhablani J, Chan CK, Wang H, Barteselli G, El-Emam S, Gomez ML, Kozak I, Cheng L, Freeman WR. Characterization of microaneurysm closure after focal laser photocoagulation in diabetic macular edema. *Am J Ophthalmol* 2013;155(5):905-912.

7 Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic

Retinopathy Study report number 1. *Arch Ophthalmol* 1985;103 (12): 1796-1806.

8 Wang H, Chhablani J, Freeman WR, Chan CK, Kozak I, Bartsch DU, Cheng L. Characterization of diabetic microaneurysms by simultaneous fluorescein angiography and spectral-domain optical coherence tomography. *Am J Ophthalmol* 2012;153(5):861-867.e1.

9 Lövestam-Adrian M, Agardh E. Photocoagulation of diabetic macular oedema--complications and visual outcome. *Acta Ophthalmol Scand* 2000;78(6):667-671.

10 The Diabetes Control and Complications Trial. The effect of intensive diabetes treatment on the progression of diabetic retinopathy in insulin-dependent diabetes mellitus. *Arch Ophthalmol* 1995;113(1):36-51.

11 Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. *Ophthalmology* 1991;98(5 Suppl):766-785.

12 Bressler NM, Edwards AR, Beck RW, *et al* Exploratory analysis of diabetic retinopathy progression through 3 years in a randomized clinical trial that compares intravitreal triamcinolone acetonide with focal/grid photocoagulation. *Arch Ophthalmol* 2009;127(12):1566-1571.

13 Sigurdsson R, Begg IS. Organised macular plaques in exudative diabetic maculopathy. *Br J Ophthalmol* 1980;64(6):392-397.

14 Møller F, Bek T. The relation between visual acuity, fixation stability, and the size and location of foveal hard exudates after photocoagulation for diabetic maculopathy: a 1-year follow-up study. *Graefes Arch Clin Exp Ophthalmol* 2003;241(6):458-462.

15 Klein R, Sharrett AR, Klein BE, Moss SE, Folsom AR, Wong TY, Brancati FL, Hubbard LD, Couper D, ARIC Group. The association of atherosclerosis, vascular risk factors, and retinopathy in adults with diabetes: the atherosclerosis risk in communities study. *Ophthalmology* 2002;109(7):1225-1234.

16 Cusick M, Chew EY, Chan CC, Kruth HS, Murphy RP, Ferris FL 3rd. Histopathology and regression of retinal hard exudates in diabetic retinopathy after reduction of elevated serum lipid levels. *Ophthalmology* 2003;110(11):2126-2133.

17 Cho HY, Kang SW, Kim YT, Chung SE, Lee SW. A three-year follow-up of intravitreal triamcinolone acetonide injection and macular laser photocoagulation for diffuse diabetic macular edema. *Korean J Ophthalmol* 2012;26(5):362-368.

18 Larsson J, Kifley A, Zhu M, Wang JJ, Mitchell P, Sutter FK, Gillies MC. Rapid reduction of hard exudates in eyes with diabetic retinopathy after intravitreal triamcinolone: data from a randomized, placebo-controlled, clinical trial. *Acta Ophthalmol* 2009;87(3):275-280.

19 Qi HP, Bi S, Wei SQ, Cui H, Zhao JB. Intravitreal versus subtenon triamcinolone acetonide injection for diabetic macular edema: a systematic review and meta-analysis. *Curr Eye Res* 2012;37(12):1136-1147.

20 Liu XD, Zhou XD, Wang Z, Shen YM. Macular laser photocoagulation with or without intravitreal triamcinolone pretreatment for diabetic macular edema: a result from five randomized controlled trials. *Int J Ophthalmol* 2016;9(1):132-138.

21 Ip MS, Domalpally A, Hopkins JJ, Wong P, Ehrlich JS. Long-term effects of ranibizumab on diabetic retinopathy severity and progression. *Arch Ophthalmol* 2012;130(9):1145-1152.