

Role of Systemic Control Prior to Laser Photocoagulation in Diabetic Macular Edema

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ABSTRACT

Background and purpose: Poor systemic control results in recalcitrant macular edema despite laser photocoagulation in patients with clinically significant macular edema (CSME). The present study aims to determine the effect of control of systemic factors prior to focal/grid laser photocoagulation in CSME in patients with type 2 diabetes.

Materials and methods: 101 patients (129 eyes) with type 2 diabetes mellitus and CSME were prospectively randomized into two groups prior to laser photocoagulation: 51 patients in group I (65 eyes) did not undergo enforced metabolic control, while 50 patients in group II (64 eyes) were subjected to an enforced control of systemic factors including blood glucose, blood pressure, serum lipids for 6 weeks before undergoing focal laser photocoagulation. The outcome measures studied at 3 months were change in retinal thickness on OCT, grade of hard exudates on fundus photography and visual acuity.

Results: The central foveal thickness at presentation was $277.28 \pm 96.93 \mu\text{m}$ in group I and 254.95 ± 118.42 in group II and 283.66 ± 94.71 and $313.77 \pm 128.47 \mu\text{m}$ respectively at final follow-up (not significant). There was a significant reduction in the hard exudates in group II both at 6 and 12 weeks with 36 eyes (56%) in group II showing reduction in the grade of hard exudates compared with 20 eyes (30.7%) in group I at the final follow-up. There was a trend toward visual improvement in systemically controlled group with nine eyes (14%) in group II showing improvement of ≥ 10 ETDRS letters from baseline compared with six eyes (9%) in group I.

Conclusion: Enforced control of systemic factors especially lipids may be beneficial in patients of CSME undergoing laser photocoagulation.

Keywords: Diabetic macular edema, Diabetes, Laser, Clinically significant macular edema.

INTRODUCTION

Diabetic macular edema (DME) is the most common cause of moderate visual loss in patients with diabetes.¹ Laser photocoagulation (focal or grid) leads to a 50 to 70% decrease in the visual loss (doubling of the visual angle) in eyes with clinically significant macular edema² and is currently considered the standard of care in such patients.

Diabetic macular edema is multifactorial in etiology and its incidence increases with an increase in the duration of the disease,³ higher glycosylated hemoglobin levels in blood,³⁻⁶ proteinuria,³⁻⁶ anemia,⁷⁻¹⁰ higher blood pressure¹¹ and hyperlipidemia.¹²⁻¹⁵ Though these reports indicate a strong correlation between these systemic risk factors and the development of macular edema, there are only few anecdotal reports of the effect of control of these risk factors prior to laser therapy.¹⁶⁻¹⁸ In a pilot study of thirty patients with type 2 diabetes with CSME, oral HMG CoA reductase inhibitor, Atorvastatin, was reported to be an important adjunct in the management of CSME that helped in reducing the incidence of subfoveal lipid migration after laser photocoagulation.¹⁶ In another pilot study,¹⁷ 14 patients with nonproliferative diabetic

retinopathy and CSME underwent multifactorial interventions for systemic control prior to laser photocoagulation and showed decrease in retinal thickness on optical coherence tomography. More recently, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study¹⁹ found that the long-term lipid-lowering therapy with fenofibrate (200 mg/day) could reduce the progression of retinopathy and the need for laser treatment. However, the question that still remains unanswered is, whether the systemic control of the metabolic factors prior to laser photocoagulation is justified. The present study was designed to study the effect of control of systemic factors before focal/grid laser photocoagulation on the retinal thickness, grade of hard exudates and visual acuity in 101 patients with CSME.

MATERIALS AND METHODS

The study included 101 patients with type 2 diabetes mellitus and CSME (as defined by the ETDRS) with nonproliferative diabetic retinopathy, attending the retina clinic of a tertiary care referral institute. An informed consent was taken from all the patients and the study was approved by the Institute of Ethics Committee. The following were the exclusion criteria:

Proliferative diabetic retinopathy, hazy ocular media that would preclude a good clinical examination, fundus photography and OCT imaging, any history of focal laser or pan retinal photocoagulation in the past 3 months of enrollment, history of previous vitreous surgery in the study eye, debilitating systemic illnesses like renal failure, cardiac failure or other diseases that would not allow regular clinical follow-up, associated vascular occlusion, macular ischemia or cystoid macular edema. All patients had a detailed history recorded and underwent complete ocular examination including best corrected visual acuity using the ETDRS chart, slit lamp biomicroscopy and fundus examination with +90D lens, fundus photography, fundus fluorescein angiography and retinal thickness measurement of the central 6 mm of the macula on Zeiss STRATUS OCT (model 3000, Carl Zeiss Meditec, Humphrey Systems, USA). All patients underwent the baseline laboratory investigations including hemoglobin, glycosylated hemoglobin, supine blood pressure, blood urea, serum creatinine, total lipid profile (serum cholesterol, triglycerides, LDL, VLDL and HDL), 24-hour urinary protein, fasting and postprandial blood glucose.

The patients were then prospectively randomized using Tippet's random number tables into two subgroups as follows:

- *Group 1:* Patients in this group received focal laser photocoagulation without undergoing any further control of systemic factors. They, however, continued to receive the systemic treatment they were already receiving.
- *Group 2:* Patients in this subgroup were subjected to control of systemic factors from an endocrinologist for 6 weeks. At the end of 6 weeks, these patients underwent a repeat fundus photograph and OCT for assessing any change in the retinal thickness/hard exudates. All the patients received focal laser photocoagulation at the end of 6 weeks, irrespective of the metabolic control achieved.

Focal laser was done using 532 nm green laser by applying light grey burns 100 μ m in size to all leaking microaneurysms beyond 500 μ m from the center of the macula by projecting the arteriovenous phase of the angiogram and inverting the image. Retreatment was done after 3 months by repeating the FFA and applying focal to all leaking microaneurysms within 300 to 500 μ m from the center of the macula.

At 6 and 12 weeks following focal laser photocoagulation in both the groups, the following investigations were done: Best corrected visual acuity on the ETDRS charts, dilated fundus exam using a +90D lens, fundus photograph and OCT. Additionally, fundus fluorescein angiography and all baseline laboratory investigations were repeated at 12 weeks follow-up.

The best corrected visual acuity at 12 weeks following laser photocoagulation was compared with the baseline visual acuity. The visual acuity was said to be improved, if there was an improvement of ≥ 10 letters from the baseline. Worsening was indicated by the deterioration of ≥ 10 letters from the baseline, whereas visual acuity was said to be stabilized, if it remained unchanged or showed a change of less than 10 letters from the baseline.

Grading of hard exudates was done using a color fundus photograph of the central 50 degrees of the retina using the standard photographs 3, 5 and 4 of the modified Airlie house classification²⁰ of diabetic retinopathy for comparison as follows: Grade 0: No evidence of hard exudates, grade 1: questionable hard exudates, grade 2: Hard exudates less than standard photo 3, grade 3: More than in standard photo 3, less than standard photo 5, grade 4: More than in photo 5, less than photo 4, grade 5: Hard exudates more than or equal to photo 4. The hard exudates were graded at the baseline and at the follow-up visits by two experienced retina specialists (VG and AG) and changes in the grades were noted. The effect of instituting control on systemic parameters as mentioned earlier was seen by comparison between the profile of investigations between as well as within the two groups at baseline and final follow-up.

STATISTICAL METHODS

All the patients were observed for change in macular thickness, visual acuity and biochemical parameters during the course of the study. The baseline demographic characteristics between the two groups namely age, duration of diabetes mellitus, height, weight and body mass index were compared using the independent samples t-test. The gender distribution was compared using the Chi-square test.

The difference between the two groups in terms of the drug treatments namely insulin, oral hypoglycemics, antihypertensives and lipid lowering drugs was compared by the Pearsons two-sided Chi-square test at the start and end of the study. The difference in the biochemical parameters namely hemoglobin, glycosylated hemoglobin, fasting blood glucose, postprandial blood glucose, blood urea, serum creatinine, total serum cholesterol, serum HDL, LDL, VLDL, TGs, 24 hour urine protein and blood pressure between the two groups were compared at baseline and at the end of the study using the independent samples t-test. The mean values at baseline and final follow-up were also compared within each of the two groups using the paired t-test.

The average values for the retinal thickness on the OCT, grade of hard exudates on fundus photography, visual acuity on the ETDRS chart were computed. The difference between the two groups was analyzed using the unpaired t-test. The trends within each group from baseline to final were compared using the Friedman one-way ANOVA test.

RESULTS

The study included 129 eyes of 101 patients—51 patients (65 eyes) in group I and 50 patients (64 eyes) in group II. There was no statistically significant difference between the two groups in the distribution of these baseline parameters including the age, sex, duration of diabetes, height, weight and body mass indices (Table 1). On comparing the treatment being received by two groups at the start and end of the study, statistically significant differences were found between the two groups at the end of the study in the use of antihypertensives and lipid-

lowering drugs with higher number of patients in group II receiving these drug therapies (Table 2).

Table 3 details the changes in the laboratory parameters seen at the follow-up visits. Though complete systemic control could not be achieved for all the biochemical parameters in patients of group II, there were trends toward improvement in the glycosylated hemoglobin, blood sugar profile especially postprandial blood sugar and total serum cholesterol levels.

Retinal thickness: The difference in the central foveal thickness on OCT was not significant in the two groups at baseline. There was an increase in the retinal thickness in group II after systemic control and following laser treatment (Table 4). At the end of the study period, the difference of retinal thickness between

the two groups remained statistically insignificant. The temporal change in each group from baseline to final follow-up was also not significant.

Hard exudates: The average grade of hard exudates was 4 (1-5) in both group I and II at baseline with no statistically significant difference between the two groups (Table 5). After 6 weeks of control in group II the average grade of hard exudates was 3.53 (range 1-5). Eighteen of the 64 eyes (28%) in group II showed reduction in the grade of hard exudates from their baseline values, 36 eyes remained unchanged and none of the eyes showed worsening after 6 weeks of systemic control. After 6 weeks of laser treatment, the average grade of hard exudates was 4 ± 1 (range 1-5) in group I and 3 ± 1 (0-5) in group II. The difference between the two groups at this point was significant (Table 5). Eight of the 65 eyes (12%) in group I showed reduction/improvement in the grade of hard exudates from baseline compared with 37 of the 64 eyes (58%) in group II. Five eyes (7%) in group I showed worsening/increase in the grade of hard exudates from baseline compared with 3 eyes (5%) in group II after laser treatment. Fifty-two eyes (80%) in group I and 24 eyes (37%) in group II showed no change in the grade of hard exudates after 6 weeks of laser treatment when compared from baseline. At final follow-up, the average grade of hard exudates was 4 ± 1 (range 0-5) in group I and 3 ± 1 (range 0-5) in group II. The difference between the average values was significant between the two groups at final follow-up (Table 5). Twenty eyes (30.7%) in group I showed

Table 1: Comparison of baseline parameters between the two groups

	Group I (n = 51)	Group II (n = 50)	p-value
Age (years)*	54 ± 7.6 (37-73)	55 ± 7.2 (40-70)	0.37
Sex (M:F)**	32:19	29:21	0.6
Duration of diabetes (years)*	13.09	11.64	0.2
BMI (kg/m ²)*	25.08 ± 3.65 (17.39-39.70)	25.77 ± 3.13 (20.50-38)	0.31

*Values for these parameters given as mean ± SD (range). p-values calculated the independent samples t-test

**p-value calculated using Chi-square test

Table 2: Comparison of treatment profile between the two groups

	Group I (n = 51)	Group II (n = 50)	p-value*
Number of patients on both insulin and OHAs at the time of inclusion in the study	12	8	0.224
Number of patients on both insulin and OHAs at the end of the study	12	15	0.7
Number of patients on antihypertensive at the time of inclusion in the study	30	34	0.339
Number of patients on antihypertensive at end of the study	29	40	0.01
Number of patients on lipid-lowering drugs at the time of inclusion in the study	24	24	0.925
Number of patients on lipid-lowering drugs at the end of the study	23	35	0.01

*Pearson's Chi-square test

Table 3: Inter- and intragroup comparisons of the laboratory parameters

	Group I (n = 51)	Group II (n = 50)	p-value*
FBG baseline	131.04 ± 39.17	137.17 ± 45.34	0.47
FBG final	132.44 ± 46.77	129 ± 49.90	0.72
p-value**	p = 0.82	p = 0.21	
PPBG baseline	195.47 ± 66.48	215.98 ± 63.39	0.12
PPBG final	199.41 ± 78.06	188.44 ± 54.62	0.42
p-value**	p = 0.66	p = 0.0003 ^a	
Total cholesterol—baseline	180.42 ± 37.86	184.50 ± 39.99	0.6
Total cholesterol—final	172.73 ± 37.87	173.40 ± 35.92	0.9
p-value**	p = 0.14	p = 0.02 ^a	
TGs—baseline	140.88 ± 58.87	155.74 ± 59.79	0.2
TGs—final	145.77 ± 75.08	144.90 ± 66.71	0.9
p-value**	p = 0.45	p = 0.17	
LDL—baseline	106.72 ± 28.78	103.37 ± 28.49	0.56
LDL—final	99.52 ± 27.74	97.83 ± 33.93	0.82
p-value**	p = 0.08	p = 0.24	

*Intergroup comparison at baseline and final follow-up using independent samples t-test

**Intragroup comparisons at baseline and final follow-up

^aSignificant trend toward improvement of postprandial sugar and total cholesterol with enforced systemic control in group II

Table 4: Changes in the retinal thickness

	Group I (n = 65)	Group II (n = 64)	p-value*
Central foveal baseline (μm)	277.28 \pm 96.93	254.95 \pm 118.42	0.35
Central foveal prelaser (μm)	277.28 \pm 96.93	303.56 \pm 111.88	0.1
Central foveal postlaser (μm)	280.57 \pm 87.21	321.17 \pm 128.27	0.06
Central foveal final (μm)	283.66 \pm 94.71	313.77 \pm 128.47	0.13
p-value**	0.8	0.07	

*t-test (intergroup)

**Friedman one-way ANOVA (intragroup)

Table 5: Change in grade of hard exudates

	Group I (n = 65)	Group II (n = 64)	p-value*
Baseline	4 \pm 1	4 \pm 1	0.71
Postlaser	4 \pm 1	3 \pm 1	0.01
Final	4 \pm 1	3 \pm 1	0.04

*Independent samples t-test

improvement/reduction in the grade of hard exudates from baseline compared with 36 eyes (56%) in group II. Ten eyes (15%) in group I and 4 eyes (6%) in group II showed worsening/increase in the grade of hard exudates from baseline. Thirty-four eyes (52%) in group I and 24 eyes (37%) in group II showed no change in the grade of hard exudates from baseline at final follow-up.

In order to ascertain whether the addition of lipid lowering agents was related to the reduction in the grade of hard exudates, a subset analysis was done in group II. At the end of the study, 35 patients in group II were receiving lipid lowering agents and 15 patients were not. In the group receiving lipid-lowering agents (n = 35), 23 patients showed an improvement in the grade of hard exudates from baseline, 11 remained unchanged and only 1 showed deterioration from baseline. In the group not receiving these agents (n = 15), only three patients showed an improvement in the grade of hard exudates, while nine patients showed no change and three showed a deterioration in the grade of hard exudates from baseline. The difference between these groups was found to be statistically significant using the Pearson's Chi-square test ($p < 0.05$), indicating that the reduction in the grade of hard exudates correlated with the addition of lipid-lowering agents. However, due to the low power of this subset, this inference requires further larger studies for confirmation.

Visual acuity: The average number of letters read at baseline on the ETDRS visual acuity chart was 71 ± 14 (range 27-92) in group I and 68 ± 17 (range 11-90) in group II at baseline. The difference between the two groups was not significant at baseline. The average number of letters read at final follow-up, 12 weeks postlaser on the ETDRS visual acuity chart was 70 ± 15 (range 24-93) in group I and 68 ± 16 (range 22-85) in group II. The difference between the two groups was not significant at final follow-up. Majority of the patients (79% in group I and 76% in group II) showed stabilization of visual acuity at final follow-up. Six eyes in group I (9%) and nine eyes (14%) in group II showed improvement of 10 or more letters from baseline on the ETDRS chart at 12 weeks following laser treatment.

DISCUSSION

Laser photocoagulation is the standard of care for treatment of CSME as proposed by the ETDRS.² Many studies have correlated the onset and progression of macular edema with systemic factors such as glycemic control,³⁻⁶ proteinuria,³⁻⁶ hypertension,¹¹ hyperlipidemia.¹²⁻¹⁵ However, despite the knowledge about these systemic factors in the etiology of diabetic macular edema, incorporation of their control in the management of DME has not become the standard of care as there are no studies addressing this issue. The results of the present study suggest that control of systemic status prior to laser photocoagulation helps in reduction of the retinal hard exudates that is attributable to the lipid-lowering therapy being received by these patients as the reduction of the hard exudates had a significant correlation with the institution of lipid-lowering therapy. This substantiates the observations made in an earlier study that lipid-lowering drugs could be an important adjunct in the management of CSME.¹⁶

As far as the retinal thickness was concerned, there was no beneficial effect of systemic control on the reduction of retinal thickness. In fact the central foveal thickness increased in the group being systemically controlled prior to laser photocoagulation. This could be due to natural progression of the disease as we could not really achieve the optimal control in many patients within 6 weeks. However, based on the previous publications where we have shown that no visual deterioration occurs if we enforce tight systemic control for at least 6 weeks^{17,18} the ethical clearance whereby laser photocoagulation could be delayed only for 6 weeks for granted only for 6 weeks. These patients received laser photocoagulation at 6 weeks, irrespective of the metabolic status. This could have added an element of bias as many of these patients in group II were still uncontrolled when lasered.

Further, there was an increase in the retinal thickness in both the groups following laser photocoagulation. This initial increase in retinal thickness could be in response to an initial inflammation leading to an increased amount of fluid.²¹ Moreover, it has been demonstrated that microaneurysmal closure is a delayed phenomenon and it may take almost 3 months for closure of microaneurysms following laser photocoagulation.²² Persistence of microaneurysms at 6 weeks postlaser may also have contributed to the initial increase in retinal thickness. At the final follow-up after 12 weeks of laser there was a decrease in the retinal thickness compared with the thickness at 6 weeks postlaser. However, there was no significant

difference in the final retinal thickness in the central 1mm when compared from baseline. This could be due to the short period of follow-up in the postlaser period in both the groups. Many of these patients may have untreated microaneurysms causing persistence of retinal thickening and may require another sitting of laser.

Though the final visual acuity did not show any significant difference between the two groups, 14% of the eyes in systemically controlled group showed improvement of 10 or more letters from baseline on the ETDRS chart compared with 9% in the other group. This probably indicates a trend toward better outcome in the systemically controlled group. Also the 6-week period of instituting systemic control and deferring laser therapy did not have any adverse affect on the visual acuity of these patients. A good visual outcome was also observed following enforced systemic control in another study over a 1 year follow-up period.¹⁸

In conclusion, the present study suggests that control of metabolic factors especially lipids is beneficial in reducing the retinal hard exudates, which may be of benefit in patients undergoing laser photocoagulation. The reduction in retinal hard exudates started even prior to laser photocoagulation. We did not find any deleterious effect of postponing laser photocoagulation for 6 weeks. The effect of control on other factors needs to be studied for a longer period in a larger cohort of patients as the present study is limited by a small sample size, low power and a short follow-up duration. However, the increased number of eyes showing reduction in the hard exudates and improvement in visual acuity in systemically controlled group does indicate the beneficial role of good metabolic control that may continue over a long-term follow-up.

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