Combined Modified Grid and Panretinal Photocoagulation for Diffuse Diabetic Macular Edema and Proliferative Diabetic Retinopathy

Carol M. Lee, MD; R. Joseph Olk, MD; Levent Akduman, MD

■ PURPOSE: To determine the effectiveness of combined macular modified grid and peripheral panretinal photocoagulation in diabetic eyes with both macular edema and proliferative retinopathy.

■ MATERIAL AND METHODS: We evaluated 52 eyes with diffuse diabetic macular edema and proliferative diabetic retinopathy. Treatment was performed in two sessions consisting of initial modified grid to the macula and panretinal photocoagulation to the inferior half of the peripheral retina, followed 2 to 4 weeks later by panretinal photocoagulation to the superior half.

■ RESULTS: At one year, visual acuity was improved in 8%, stable in 79%, and worse in 13%. At two years, visual acuity was improved in 4%, stable in 72%, and worse in 24%. Macular edema resolved in 43 of 46 eyes (93%), and proliferative retinopathy was reduced in 25 of 29 eyes (86%) at last examination.

■ CONCLUSION: Combined macular modified grid and peripheral panretinal photocoagulation is an effective treatment approach in diabetic eyes with both macular edema and proliferative retinopathy. Laser photocoagulation in those diabetic eyes with diffuse diabetic macular edema and proliferative diabetic retinopathy can be completed in less number of treatment sessions with this method, compared to conventional treatment techniques.


INTRODUCTION

Peripheral panretinal photocoagulation for proliferative diabetic retinopathy has been associated with visual loss after treatment, especially in eyes with pre-existing macular edema.1-7 This visual loss, although usually transient, has been attributed in part to exacerbation of the macular edema. It has been suggested that if focal and/or grid treatment to diabetic macular edema is initiated prior to peripheral panretinal photocoagulation (for instance when retinopathy is less than high risk),1,2 this may reduce this adverse macular effect of peripheral panretinal photocoagulation.

Retinopathy risk factors were determined by the Diabetic Retinopathy Study8,9 and are defined by the presence, location, and severity of neovascularization, and the association with preretinal or vitreous hemorrhage; this terminology is used throughout this report.

The efficacy of panretinal photocoagulation in the management of high-risk diabetic retinopathy is well established.8,9 The efficacy of macular treatment emphasizing the use of "focal" treatment10-12 as
described by the Early Treatment Diabetic Retinopathy Study and the use of “modified grid”
treatment as described by Olk and coworkers,18-21 or
“grid treatment”18-21 have also been well established.

MATERIALS AND METHODS

All patients enrolled in this study were initially examined and treated by the same surgeon, (Olk).
Inclusion criteria included a known diagnosis of type 1 or type 2 diabetes mellitus, diffuse diabetic macular edema (DDME) with or without cystoid macular edema, and proliferative retinopathy. Risk factors were graded according to the established guidelines of the Diabetic Retinopathy Study4,9 and all eyes with high-risk retinopathy (three or four retinopathy risk factors) and those eyes with two retinopathy risk factors that were believed to warrant photocoadulation were included. This latter situation included monocular patients, patients with severe retinopathy in the fellow eye, and history of either poor compliance or inadequate follow-up. Eyes with a prior history of macular treatment at least 12 months prior to entry without previous panretinal photocoadulation were eligible.

The macular edema and proliferative retinopathy were diagnosed on clinical examination, and the macular edema was confirmed by stereo fundus photography and 10% sodium fluorescein angiography. DDME was defined as retinal thickening of two or more disc areas and involving some portion of the foveal avascular zone. Only eyes with both DDME and proliferative retinopathy were enrolled into this study. Eyes with less than two disc areas of retinal thickening, retinal thickening not involving the foveal avascular zone, nonproliferative retinopathy, or proliferative retinopathy with only one retinopathy risk factor were excluded.

Other entry criteria included glycosylated hemoglobin equal to or less than 10.0%, diastolic blood pressure less than 100 mm Hg, and best corrected visual acuity of 20/200-3 or better as measured by an independent examiner using the Early Treatment Diabetic Retinopathy Study visual acuity chart at 4 meters. Eyes were required to have media clear enough to allow for good laser photocoadulation burns. Exclusion criteria included patients with chronic renal failure undergoing renal dialysis, diastolic blood pressure greater than 100 mm Hg, or patients with glycosylated hemoglobin greater than 10.0%.

Ophthalmologic exclusion criteria included the following: history of previous panretinal photocoadulation; preretinal or vitreous hemorrhage severe enough to preclude adequate visualization of the retina; history of retinal detachment or retinoschisis; significant cataract; iris neovascularization; previous retinal or other intraocular surgery that would interfere with adequate treatment or follow-up; cataract extraction or lens implantation within the previous 12 months; and a history of glaucoma or other ocular disease that could affect treatment, follow-up, or interpretation of the treatment results.

Baseline examination included a best-corrected visual acuity, slit-lamp and contact lens examination, direct and indirect ophthalmoscopy, fundus photography, and intravenous 10% sodium fluorescein angiography. Fluorescein angiograms and color fundus photographs were reviewed independently by at least two authors to determine the presence of preoperative cystoid macular edema and the extent of macular edema and ischemia. Eyes with angiographic evidence of more than six clock hours of capillary nonperfusion at the foveal avascular zone (ie, more than six clock hours of irregular foveal avascular zone), focal leakage only, or retinal thickening either less than two disc areas or not involving the foveal avascular zone were excluded. Postoperative angiograms were reviewed in masked fashion by at least two authors independently without knowledge of the visual outcome to evaluate the resolution of the DDME and cystoid macular edema if present.

Patients received argon green (514 nm), krypton red (647 nm), or diode (810 nm) consistently throughout the course of treatment. If either supplemental modified grid or panretinal photocoadulation was required, eyes received the same wavelength as the initial treatment.

Supplemental macular treatments were performed a minimum of three months after initial treatment only if residual macular thickening was present in an area involving the foveal avascular zone, as noted on stereo biomicroscopic examination and fluorescein angiography. Eyes were considered stable if the central macula involving the foveal avascular zone was no longer thickened. If islands of residual thickening were present away from and not directly involving the foveal avascular zone, the eye was considered stable without need for supplemental modified grid treatment.

Supplemental panretinal photocoadulation was performed no earlier than three months after the ini-
tial panretinal treatment. The decision to perform supplemental panretinal photocoagulation was based solely on the clinical examination, and, in general, supplemental panretinal treatments were performed until retinopathy was noted to have regressed to less than high-risk without further recurrence or progression of the risk factors.

Follow-up examinations were performed every 3 to 4 months with visual acuity measured by an independent examiner using the same Early Treatment Diabetic Retinopathy Study visual acuity chart at 4 meters in the same lane as originally examined. Each follow-up visit included a complete ophthalmologic examination with fundus photography. Fluorescein angiography was performed for the purpose of this study at each visit until the eye was believed to be stable and not requiring any further macular treatments. Patients were examined at four-month intervals in their first year, and then semiannually if stability of their retinopathy was noted. Follow-up visits are reported here at four-month intervals in the first year, at the 18-month follow-up, and then at the annual visits up to the third follow-up year. Patients were followed for up to eight years, but follow-up data was statistically analyzed only up to the third year. These data were analyzed for each visit with respect to visual outcome, regression of retinopathy, and resolution of macular edema. All P values are reported for the appropriate Chi-Square test unless indicated otherwise.

Treatment Technique

All patients were treated as outpatients. Retrobulbar anesthesia of a 50:50 mixture of 0.75% bupivicaine and 2% lidocaine with hyaluronidase was used in most cases, although a few selected cases received topical anesthesia. A recent fluorescein angiogram was projected on a Topcon® viewer to guide the surgeon (Olk) in each of the macular treatments.

Argon green (514 nm), krypton red (647 nm) or diode (810 nm) was used in all cases. Combined treatment was performed as follows: eyes were treated in two sessions with the modified grid treatment to the macula combined with panretinal photocoagulation to the inferior half of the retina initially (Figure 1A), and then followed 2 to 4 weeks later by the completion of the panretinal treatment to the superior half of the retina (Figure 1B).

Modified grid photocoagulation was performed first as described in previous publications.13-17 Two to three rows of 100 or 125 μm spots were applied to all areas of juxtafoveal retinal thickening up to and including the edge of the foveal avascular zone; these initial spots were placed 100 microns apart. Then, 150 to 200 μm spots were placed approximately 200 microns apart to the remaining areas of retinal thickening and capillary nonperfusion. Focal leakage was treated directly with 100 or 125 micron spots. Average initial macular treatment consisted of 250 spots at 100 to 200 mw for argon green, 254 spots at 100 to 300 mw for krypton red, and 242 spots at 200 to 600 mw for diode. Supplemental macular treatments for all wavelengths averaged 205 spots per session.

Modified grid photocoagulation is applied only to areas of retinal thickening and/or capillary nonperfusion as seen on clinical examination. The fluorescein angiogram is used to delineate the foveal avascular
zone and demonstrate areas of capillary nonperfusion. If the area of DDME measuring at least two disc areas is located temporally, treatment is applied to this temporal zone in grid fashion. If there are obvious focal areas of leakage either within or located outside this temporal zone, focal treatment is directly applied to those leaks. Supplemental modified grid treatment is applied until the central macular region involving the foveal avascular zone is biomicroscopically flat; once the central foveal avascular zone shows resolution of edema, no further macular treatments are necessary. The end point of each laser burn is a light intensity burn just barely visible at the level of the outer retina or retinal pigment epithelium. (Figures 2A-F)

Panretinal photocoagulation is applied with a panfunduspic endoscopic lens. Average settings are 400-500 μm at 0.1 second durations with a power of 300-400 mw for argon green, 400-500 mw for krypton red, and 200-600 mw for diode laser. Laser spots are spaced between one-half to one spot width apart. The scatter pattern is placed outside the temporal arcades, two disc diameters from the center of the macula temporally and usually one disc diameter from the edge of the optic disc. Treatment could usually be extended beyond the equatorial region using the panfunduspic lens. Areas of surface neovascularization elsewhere are treated with confluent focal ablation to the underlying retina. For the patients in this study, an average of 810 spots in the first session to the inferior half of the retina was given in combination with modified grid photocoagulation. An average of 948 spots was given in the second session to the superior half of the retina to complete the panretinal photocoagulation.

Supplemental panretinal photocoagulation was given if there was either no regression in the retinopathy risk factors or if there was progression of proliferative retinopathy. On average, 800 laser photocoagulation spots were added at each supplemental panretinal session attempting to apply treatment to areas not previously treated.

RESULTS

Fifty-two eyes of 46 patients were included in this study and followed from 4 to 9 years; analysis of the 4-month (follow-up visit 1), 8-month (follow-up visit 2), 12-month (follow-up visit 3), 18-month (follow-up visit 4), 24-month (follow-up visit 5), and 36-month (follow-up visit 6), and last follow-up visits are reported.

Twenty-two patients were female and 24 were male. Age range at entry was from 21 to 76 years with a median of 58.5 years and a mean of 54.8 years. Of 46 patients, 33 (72%) had type I diabetes and 13 (28%) had type II diabetes controlled. The duration of diabetes ranged from 1 to 46 years with a median and mean of 15 years. Twenty-seven (59%) of 46 patients had a history of hypertension controlled by oral antihypertensives, and 18 patients (39%) had a history of systemic vascular disease defined here as a history of cerebrovascular accident, transient ischemic attack, carotid disease, intermittent claudication, peripheral vascular bypass surgery, limb or digit amputation, myocardial infarction, or coronary artery bypass surgery.

Twenty eyes (38%) had a distant history (greater than one year prior to treatment) of previous macular treatment. Thirty-nine eyes (75%) had three or four retinopathy risk factors, and 13 (25%) had two retinopathy risk factors on entry into our study. All 52 eyes had DDME of which 17 eyes (33%) had evidence of cystoid macular edema as determined on preoperative stereo fundus photography and fluorescein angiography.

Twenty-two eyes received an average of 1.5 supplemental grid sessions, and 14 eyes received an average of 1.6 supplemental panretinal sessions. The first supplemental grid treatment occurred at a median of 5.0 months after the initial grid treatment; the second supplemental grid treatment occurred at a median of 5.9 months after the first supplemental grid treatment. The first supplemental panretinal treatment occurred at a median of 7.5 months after completion of the combined treatment; the second supplemental panretinal treatment occurred at a median of 5.5 months after the first supplemental panretinal treatment.

Of the 22 eyes that received supplemental modified grid treatments, 13 eyes received one additional treatment, 7 received two additional treatments, and one each received 3 and 4 additional treatments. Of the 14 eyes that received supplemental panretinal photocoagulation, 8 received one supplemental treatment, 4 received two supplemental treatments, and one each received 3 and 4 supplemental treatments. Seven of these supplemental modified grid and panretinal treatments were given in combination during one supplemental treatment session.

A change of vision was defined as three or more lines of change on the Early Treatment Diabetic Retinopathy Study visual acuity chart (either halving or doubling of the visual angle).
Figure 2. This 42-year-old woman presented with high-risk retinopathy with extensive neovascularization on the disc, neovascularization elsewhere, and diffuse diabetic macular edema (A, B, C). She received combined treatment of modified grid to the macula and panretinal photocoagulation to the inferior one-half of the retina; in addition, focal ablation was applied to the retina underlying surface neovascularization elsewhere, located just inside the superotemporal arcade (D, E). Note that the modified grid is placed in the areas of macular thickening mainly temporal to the fovea, and focal leaks treated directly with focal photocoagulation. This was followed three weeks later by panretinal photocoagulation to the superior one-half retina (F).

Follow-up data are reported at intervals of four months in the first year, semi-annually in the second year, and annually at the third year. At the first follow-up visit, 49 eyes were examined; one patient died prior to his first return visit. Another patient missed his first follow-up visit, and another patient never returned for follow-up. By follow-up visit 5, 29 of a possible maximum of 33 eyes were examined. (Table 1)

Individual follow-up visits are shown in Table 2. At one year, 3 eyes (8%) had improved, 30 (79%) had
Table 1. Follow-up Examinations

<table>
<thead>
<tr>
<th>Follow-up Visits</th>
<th>#1 (4 mos)</th>
<th>#2 (8 mos)</th>
<th>#3 (12 mos)</th>
<th>#4 (18 mos)</th>
<th>#5 (24 mos)</th>
<th>#6 (36 mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Eyes with Follow-up</td>
<td>29 (56%)</td>
<td>49 (94%)</td>
<td>41 (79%)</td>
<td>36 (73%)</td>
<td>30 (58%)</td>
<td>19 (37%)</td>
</tr>
<tr>
<td>Lost due to death</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Missed visit*</td>
<td>1 (2%)</td>
<td>6 (11%)</td>
<td>0</td>
<td>5 (10%)</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1 (2%)</td>
<td>0</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
<td>3 (6%)</td>
<td>9 (17%)</td>
</tr>
<tr>
<td>No follow-up†</td>
<td>0</td>
<td>4 (8%)</td>
<td>10 (19%)</td>
<td>15 (28%)</td>
<td>19 (36%)</td>
<td>23 (44%)</td>
</tr>
</tbody>
</table>

*Missed visits are eyes that did not return for follow-up at one or more visits but who did return for a later follow-up visit.
† No follow-up possible because of entry date. Eyes that could not attain a follow-up visit because of the continuing enrollment of eyes during the last year, for example, an eye enrolled in the last year could not have follow-up visits 4, 5, or 6.

the same, and 5 eyes (13%) had worse visual acuity. At two years, 1 eye (4%) had improved, 21 eyes (72%) had the same, and 7 (24%) had worse visual acuity. By three years, 1 eye (5%) had improved, 13 eyes (69%) had the same, and 5 (26%) had worse visual acuity (Figure 3). At each follow-up visit, the causes of worse visual acuity were not because of exacerbation of macular edema but rather to sequelae of proliferative disease, including vitreous hemorrhage, traction retinal detachment, macular ischemia or subretinal scarring, or worsening cataract. (Figure 3)

No statistical difference in visual outcome was noted for any of the following factors: systemic hypertension, peripheral vascular disease, cystoid macular edema, and better initial visual acuity (entry visual acuity (20/63) versus worse initial visual acuity (entry visual acuity (20/80)) at any follow-up visit. In comparing eyes with two versus three or four preoperative retinopathy risk factors, no statistically significant difference in visual outcome was noted (Fisher's exact test, P=0.4). During follow-up, 5 eyes experienced an occurrence of at least one episode of visual loss equal to or less than 5/200. All 5 had high-risk retinopathy preoperatively. Three of the five had worse vision attributed to vitreous hemorrhage; the other 2 eyes developed severe macular ischemia and subretinal scarring. Three of the five underwent surgical treatment after which one had improved visual acuity of greater than three lines.

Of the 46 postoperative fluorescein angiograms and color fundus photographs reviewed, 43 eyes (93%) showed resolution of central edema, defined as complete resolution of retinal thickening involving any portion of the foveal avascular zone. Three eyes (7%) showed persistence of central macular edema. Fifteen of the 17 eyes with preoperative cystoid macular edema had postoperative fluorescein angiograms and fundus photographs available for review. Only one eye (7%) had persistence of its cystoid component; 14 eyes (93%) showed resolution of the cystoid macular edema at last follow-up.

When analyzing the treatment trends, having 3 or 4 versus 2 retinopathy risk factors, on average, both groups had the same number of supplemental sessions. This mean number of panretinal treatments in eyes that experienced regression of proliferative disease was 1.4; eyes that had persistent proliferative disease without regression had 2.0 treatments; this was not statistically significant (P = .08). The mean number of modified grid treatments in eyes that experienced res-

Table 2. Visual Results at Each Follow-up Examinations

<table>
<thead>
<tr>
<th>Follow-up Visits</th>
<th>#1 (4 mos)</th>
<th>#2 (8 mos)</th>
<th>#3 (12 mos)</th>
<th>#4 (18 mos)</th>
<th>#5 (24 mos)</th>
<th>#6 (36 mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>2 (4%)</td>
<td>3 (7%)</td>
<td>3 (8%)</td>
<td>3 (10%)</td>
<td>1 (4%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Same</td>
<td>42 (86%)</td>
<td>34 (83%)</td>
<td>30 (79%)</td>
<td>24 (80%)</td>
<td>21 (72%)</td>
<td>13 (69%)</td>
</tr>
<tr>
<td>Worse</td>
<td>5 (10%)</td>
<td>4 (10%)</td>
<td>5 (13%)</td>
<td>3 (10%)</td>
<td>7 (24%)</td>
<td>5 (26%)</td>
</tr>
</tbody>
</table>
The efficacy of laser photocoagulation in the management of proliferative diabetic retinopathy is well established. Similarly, the efficacy of laser photocoagulation in the management of diabetic macular edema using a modified grid, focal, or grid pattern is well established. It has been noted that macular edema may increase after panretinal photocoagulation with either a transient or sustained loss of vision. The presence of both proliferative retinopathy and significant macular edema can be approached by any of several different ways. The macular edema can be treated first if the proliferative retinopathy is not yet high-risk, followed by panretinal photocoagulation when indicated. However, if the proliferative retinopathy is either at or approaching the high-risk level, it must be treated expeditiously. The proliferative retinopathy may be treated first followed by the treatment of macular edema; this can be accompanied by the known side effect of panretinal photocoagulation exacerbating preexisting macular edema. Or a combined treatment approach as we describe in this report can be used to treat both the proliferative disease and macular edema at the same time without experiencing this side effect.

Our visual results in this study including eyes with proliferative disease are comparable to previous studies of eyes with DDME alone. In a recent report of long-term follow-up, 14% of eyes had improved visual acuity, 70% had the same, and 16% had worse visual acuity at two years; at three years, 14% had improved visual acuity, 61% had the same, and 25% had worse visual acuity after modified grid photocoagulation for diffuse diabetic macular edema. In the present study, at two years, 1 of 29 eyes (4%) had improved, 21 of 29 eyes (72%) had the same, and 7 of 29 eyes (24%) had worse visual acuity; at three years, 1 of 19 eyes (5%) had improved visual acuity, 13 of 19 eyes (69%) had the same, and 5 of 19 eyes (26%) had worse visual acuity. The small difference in improved versus same visual acuity is most likely due to small sample size and is probably insignificant. As follow-up increases, the proportion of eyes with worse vision increases until the two-year visit and then stabilizes at the three-year visit. Of the 14 eyes with greater than three years of follow-up in this present study, 9 eyes (64%) remained the same, 4 eyes (29%) worsened, and 1 eye (7%) improved throughout the follow-up.

In our group of patients, the preoperative presence of systemic hypertension, peripheral vascular disease, cystoid macular edema, initial better visual acuity (visual acuity ≥ 20/63) versus worse visual acuity (visual acuity ≤ 20/80) did not significantly affect visual outcome (P > .05). Comparable to studies of DDME alone where approximately 91% had resolution of central macular edema at the two-year follow-up, 93% of eyes showed resolution of the central edema and 93% showed resolution of the cystoid macular edema at last examination in this study.

Proliferative retinopathy was graded according to the established guidelines of the Diabetic Retinopathy Study. An eye was considered to have regressed if it had a decrease in risk factors by one or more. At the one- and two-year follow-up visits, 33 of 38 eyes (87%) and 25 of 29 eyes (86%), respectively had regression of retinopathy. Complete regression at one-year occurred in 30 of 38 eyes (79%); at two-years, 24 of 29 eyes (83%); whereas 5 of 38 eyes (13%) and 4 of 29 eyes (14%), respectively showed no regression of retinopathy. Five eyes throughout the course of our study had at least one visit with visual acuity equal to or less than 5/200. A total of 4 eyes (8%) had a final visual acuity of less than 5/200, all of which had preoperative high-risk retinopathy.

In eyes with both high-risk retinopathy and diffuse diabetic macular edema, we believe that prompt treatment in a combined fashion addresses both processes expediently without the known side effect of
exacerbation of macular edema. In our earlier follow-up visits at four and eight months, the proportion of eyes with worse visual acuity is low (10% at each visit). In the Diabetic Retinopathy Study, 26% of eyes with high-risk retinopathy and macular edema present at baseline demonstrated a visual loss of two or more lines when treated with panretinal argon laser photocoagulation alone. In another study, 28% of eyes followed for less than one year after panretinal photocoagulation experienced a loss of two or more lines of vision.

The ninth report of the Early Treatment Diabetic Retinopathy Study \(^2\) examined a treatment strategy for eyes with macular edema and more severe retinopathy (defined as severe nonproliferative or early nonhigh-risk proliferative disease). One of the arms of that study examined the effect of immediate focal macular treatment and immediate mild or full scatter treatment and the effect of immediate mild or full scatter with deferral of focal treatment. They found an early increase in moderate visual loss (doubling of the visual angle) in all strategies of early treatment up to the first year of follow-up and then a reduced risk of moderate visual loss compared to deferral of treatment. The four-month, one-year, two-year, and three-year rates of occurrence of doubling of the initial visual angle were 12.2%, 16.2%, 21.1%, and 23.6%, respectively. In comparing the Early Treatment Diabetic Retinopathy Study report to ours we have included both eyes with high-risk and nonhigh-risk characteristics. Our findings of 10.5%, 13.2%, 24.9%, and 26% worsening of vision at the four-month, one-, two-, and three-year follow-up visits reflect closely the reduction of the early side effect of exacerbation of macular edema at one year with combined treatment and then the adverse effects of duration on the severity of proliferative retinopathy seen with longer follow-up.

We are not aware of a reported treatment strategy for the management of high-risk proliferative disease with significant macular edema. The Diabetic Retinopathy Study \(^2\) suggests that focal treatment with nasal scatter treatment may be followed by additional scatter treatment to the temporal quadrants, but no specific treatment protocol is addressed.

We recognize that this report is without adequate controls for statistical comparison. Side effects of our treatment were not evaluated. We also recognize that modified grid laser photocoagulation is only one treatment modality for macular edema. Nevertheless, we believe that combined modified grid and panretinal photocoagulation as outlined in this study is an effective treatment approach in the management of diabetic eyes with both macular edema and proliferative retinopathy.

REFERENCES


11. The Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study


