Macular Grid Photocoagulation After Intravitreal Triamcinolone Acetonide for Diffuse Diabetic Macular Edema

Se Woong Kang, MD; Ho-Seok Sa, MD; Hee Yoon Cho, MD; Jong In Kim, MD

Objective: To evaluate the clinical outcomes of macular laser photocoagulation after the intravitreal injection of 4 mg of triamcinolone acetonide (IVTA) for diffuse diabetic macular edema (DME).

Methods: Eighty-six eyes of 74 patients with diffuse DME were randomized into 2 groups. The laser group eyes (n=48) were subjected to a macular grid laser photocoagulation 3 weeks after IVTA. The control group eyes (n=38) underwent only IVTA. Both groups were compared with regard to the changes in visual acuity and central macular thickness at 3 weeks, 3 months, and 6 months after IVTA.

Results: The mean central macular thickness before, 3 weeks after, and 3 and 6 months after IVTA were 538, 250, 295, and 301 µm in the laser group vs 510, 227, 302, and 437 µm in the control group, respectively. The logMAR visual acuities were not significantly different between the 2 groups at baseline and at 3 weeks after IVTA but were significantly better in the laser group at 3 (P=0.02) and 6 months (P<0.001) after IVTA.

Conclusions: Macular laser coagulation effectively maintains improved visual acuity after IVTA for diffuse DME and is believed to reduce recurrent DME after IVTA.

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Macular edema affects approximately 29% of diabetic patients with a disease duration of 20 years or more and constitutes the primary cause of visual impairment in this population. The Early Treatment Diabetic Retinopathy Study reported that focal laser photocoagulation alleviated moderate visual loss in eyes with clinically significant macular edema by 50%. However, 12% of treated eyes still exhibited a loss of 15 or more letters (on the Early Treatment Diabetic Retinopathy Study chart) at the 3-year follow-up interval. Some reports have asserted that diffuse diabetic macular edema (DME) is refractory to macular photocoagulation. The limited efficacy of laser photocoagulation on diffuse DME has drawn attention to alternative treatments.

Intravitreal triamcinolone acetonide (IVTA) is reported to generate favorable results in the treatment of diffuse macular edema. However, the chief limitation of IVTA is the recurrence of DME, which develops after a relatively short duration of action. Massin et al also reported that the difference between the central macular thickness of injected and control eyes was no longer significant after 6 months because of the recurrence of macular edema in the injected eyes. Although repeated administration of IVTA might be an option, the effectiveness of this approach has not yet been evaluated. Furthermore, repeated IVTA may potentiate toxicity due to intraocular corticoids, characterized as the elevation of intraocular pressure, cataractogenesis, injection-related endophthalmitis, and toxicity to ocular structures, including photoreceptors and retinal pigment epithelial cells.

Although IVTA has recently been popularized for the treatment of diffuse macular edema refractory to grid photocoagulation, few reports on the effects of macular laser treatment performed after IVTA are currently available. In this study, we attempted to determine whether macular grid laser photocoagulation after IVTA might be helpful in the maintenance of improved vision after IVTA.

METHODS

This study included 86 eyes from 74 diabetic individuals, all of whom had been diagnosed with diffuse DME between September 2003 and August 2004. Individuals included in this study met biomicroscopic, angiographic, and tomographic criteria of diffuse DME. Diffuse DME was defined by a zone, or zones, of retinal thickening...
ing, 1 disc area or larger at any part within 1 disc diameter of the center of the macula on biomicroscopy, and diffuse fluorescein leakage involving the center of the macula on fluorescein angiography. Another criterion involved significant reduction in the reflectivity of the outer layer and/or subfoveal fluid collection on optical coherence tomography (OCT). Also, the central macular thickness had to be greater than 250 µm. None of the eyes studied had a history of either ocular hypertension or glaucoma. Eyes that underwent macular laser photocoagulation within the previous 6 months or intraocular surgery other than cataract extraction were also excluded from this study.

This study was approved by the institutional review board, and all patients included in the study provided written informed consent with regard to the experimental character of the treatment. All patients received a complete ocular examination, including best-corrected visual acuity on a Snellen chart; applanation tonometry; slitlamp examination; and dilated fundus examination using biomicroscopy, fundus fluorescein angiography, and OCT (Stratus OCT version A 3.0; Carl-Zeiss Meditec, Dublin, Calif). The central macular thickness was automatically measured via OCT.

The enrolled eyes were divided into 2 groups, the laser group and the control group. The determination of the group for the individual patient was dependent on the last digit of the hospital ID number. If it was an odd number, the patient was allocated into the control group. If it was an even number, the patient was allocated into the laser group.

The eyes of the laser group patients underwent IVTA and macular grid photocoagulation 3 weeks afterward. The eyes of the control group patients were treated only with IVTA.

All members of both laser and control groups received IVTA. Topical anesthesia was administered with 0.5% proparacaine hydrochloride eye drops, followed by 2 drops of 0.5% levofloxacin and preparation with 5% povidone iodine. Triamcinolone acetonide was then injected into the vitreous through the inferior pars plana with a 30-gauge needle at a dose of 4 mg in 0.1 mL suspension. Paralimbal paracentesis of anterior chamber was then performed to normalize intraocular pressure. All patients were examined 1 week after the injection with regard to intraocular pressure and other injection-related complications.

The modified macular grid laser coagulation 3 weeks after undergoing IVTA was applied only in the laser group eyes. All treatments were performed under topical anesthesia with a fundus contact lens (TransEquator lens; Volk Optical Inc, Mentor, Ohio). Test laser spots were applied to the retina near a vascular arcade with argon green wavelength (Novus Omni; Coherent Inc, Palo Alto, Calif), a duration of 100 milliseconds, a diameter of 100 µm, and the power increased from 75 mW to produce a mild gray burn. Based on the findings of fluorescein angiography and OCT prior to IVTA, we performed the grid pattern of the macular photocoagulation on all areas of capillary nonperfusion and retinal thickening. About 50 laser spots were applied to the parfoveal region up to the edge of the foveal avascular zone. Direct photocoagulation was applied only to areas in which locally leaking microaneurysms were observed.

The responses to treatment in both groups were monitored with respect to corrected visual acuity and central macular thickness on OCT examination by masked independent observers at 3 weeks (immediately before grid laser treatment with the laser group), 3 months, and 6 months after IVTA. To assess the incidence of complication, biomicroscopic examinations and intraocular pressure monitoring were also performed on each follow-up visit.

The corrected visual acuities were transformed to a logarithmic scale (logMAR) for statistical analysis. The null hypothesis was rejected for P values less than .05.

### RESULTS

The laser and control groups included 48 eyes from 43 patients and 38 eyes from 31 patients, respectively. Two of the laser group patients and 2 of the control group patients failed to attend the examinations scheduled for 6 months after the IVTA, and all others completed the 6-month follow-up examination. The baseline features such as visual acuity, central macular thickness, stage of retinopathy, mean duration of diabetes, lens status, and the number of prior macular photocoagulation procedures were not different between the 2 groups (Table 1).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Laser Group (n = 48)</th>
<th>Control Group (n = 38)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y (range)</td>
<td>61.1 ± 9.3 (35-79)</td>
<td>57.4 ± 10.6 (42-77)</td>
<td>.09‡</td>
</tr>
<tr>
<td>Sex, No.</td>
<td>Male 24</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female 19</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Duration of diabetes, mean ± SD, y (range)</td>
<td>13.9 ± 6.0 (4-30)</td>
<td>14.3 ± 8.4 (1-30)</td>
<td>.53*</td>
</tr>
<tr>
<td>Lens, No.</td>
<td>Phakic 42</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pseudophakic 6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Prior macular laser treatments, mean, No. (range)</td>
<td>0.33 (0-2)</td>
<td>0.42 (0-2)</td>
<td>.57†</td>
</tr>
<tr>
<td>Retinopathy, No.</td>
<td>NPDR 22</td>
<td>15</td>
<td>.55†</td>
</tr>
<tr>
<td></td>
<td>PDR 26</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Visual acuity, mean ± SD, logMAR</td>
<td>0.90 ± 0.36</td>
<td>0.97 ± 0.41</td>
<td>.25‡</td>
</tr>
<tr>
<td>Central macular thickness, mean ± SD, µm</td>
<td>538 ± 156</td>
<td>510 ± 168</td>
<td>.44‡</td>
</tr>
</tbody>
</table>

Abbreviations: NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

*Wilcoxon 2-sample test.
†Pearson χ² test.
‡2-Tailed t test.
VISUAL OUTCOME

The mean ± SD logMAR visual acuity measurements before and at 3 weeks, 3 months, and 6 months after IVTA were 0.90±0.36, 0.70±0.33, 0.70±0.39, and 0.71±0.41 in the laser group vs 0.97±0.41, 0.77±0.40, 0.93±0.48, and 1.06±0.45 in the control group, respectively (Figure 1). The differences in vision between the 2 groups were not significant at baseline (P=.40 using 2-tailed t test) and 3 weeks after IVTA (P=.39) but were significant at 3 months (P=.02) and 6 months (P<.001) after IVTA (Table 2).

The differences between baseline logMAR visual acuity and the values obtained in the follow-up examinations in the laser group eyes were found to be significant at 3 weeks (P<.001 using an analysis of variance test with a Bonferroni correction), at 3 months (P<.001), and at 6 months (P<.001). The corresponding values in the control group eyes were found to be significant at 3 weeks (P<.001) but were no longer significant at 3 months (P=1.00) or 6 months (P=.63).

CENTRAL MACULAR THICKNESS

The mean±SD central macular thicknesses prior to IVTA, and at 3 weeks, 3 months, and 6 months afterwards, are shown in Figure 2. On the 6-month follow up, 31 of 48 eyes in the laser group and 21 of 38 eyes in the control group completed OCT examinations. The differences between the central macular thickness of the laser group eyes at the baseline and follow-up examinations were found to be significant at 3 weeks (P<.001) but were no longer significant at 3 months (P=1.00) or 6 months (P=.63).

COMPLICATIONS

During the study period, intraocular pressure was found to be higher than 21 mm Hg in 19 (39.6%) of 48 laser group eyes and in 15 (39.3%) of 38 control group eyes. In most eyes, intraocular pressure was normalized by topical antiglaucoma medication, and glaucomatous damage to the optic nerve was not observed. One eye in the laser group exhibited an intractable elevation in intraocular pressure, which was normalized after trabeculectomy.

Cataract progression was noted in 2 eyes in the laser group and in 1 eye in the control group. Cataract extraction was not contemplated because we noted only mild posterior capsular opacity in those cases. No injection-related complications, including infectious endophthalmitis, vitreous hemorrhage, and retinal detachment, were encountered in any of the study eyes.

In this study, we found that the visual benefit of macular grid laser photocoagulation subsequent to IVTA for diffuse DME became apparent 3 and 6 months afterwards. In contrast to IVTA only, this combination therapy appears to maintain reduced central macular thickness, at least until a 6-month follow-up. Central macular thickness was minimal at the examination performed 3 weeks after IVTA, and gradual increases in thickness were noted in both of the groups afterward (Figure 2). However, the mean increment since 3 months after IVTA was only 6 µm in the laser group but was 135 µm in the control group. Thus, the macular rethickening in the laser group apparently had reached its plateau since 3 months after IVTA, unlike in the control group, in which progressive rethickening had occurred. Although further study is required to determine the long-term effectiveness, our results strongly indicate that macular grid laser photocoagulation maintains the functional and anatomical improvements achieved by IVTA in eyes with diffuse DME.

Table 2. Comparisons of logMAR Visual Acuity Between the 2 Groups

<table>
<thead>
<tr>
<th>Time of logMAR Score</th>
<th>Laser Group</th>
<th>Control Group</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before IVTA</td>
<td>0.90 ± 0.36 (n = 48)</td>
<td>0.97 ± 0.41 (n = 38)</td>
<td>.40</td>
</tr>
<tr>
<td>3 wk after IVTA</td>
<td>0.70 ± 0.33 (n = 48)</td>
<td>0.77 ± 0.40 (n = 38)</td>
<td>.39</td>
</tr>
<tr>
<td>3 mo after IVTA</td>
<td>0.70 ± 0.39 (n = 48)</td>
<td>0.93 ± 0.48 (n = 38)</td>
<td>.02</td>
</tr>
<tr>
<td>6 mo after IVTA</td>
<td>0.71 ± 0.41 (n = 46)</td>
<td>1.06 ± 0.45 (n = 36)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: IVTA, intravitreal triamcinolone acetonide.

*2-Tailed t test.
Diabetic macular edema is characterized by intraretinal and subretinal accumulations of fluid, resulting principally from retinal vascular leakage.\(^2\) As evidenced by fluorescein angiography of diffuse DME, microvascular obstruction and resultant ischemia induce derangements in the integrity of the inner blood-retinal barrier. In contrast, outer blood-retinal barrier damage at the level of the retinal pigment epithelium has also been suggested as a mechanism to explain the development of diffuse edema.\(^3,15,17,18\)

Previous studies have demonstrated that direct argon laser photocoagulation applied to focally leaking microaneurysms and/or grid treatment applied to areas of diffuse macular edema results in a substantial reduction of the risk of visual loss in eyes with DME.\(^2,4,19,20\) Although the exact mechanism underlying grid photocoagulation remains a matter of some controversy, it may be attributable to the effects on both endothelial cells of the retinal blood vessels and the retinal pigment epithelial cells. Some authors have suggested that grid photocoagulation enhances the debridement of disordered retinal pigment epithelial cells and fosters their replacement by a healthy population of cells.\(^3\) Laser-induced changes in the retinal pigment epithelium may also stimulate the repair of endothelial cells in the inner blood-retinal barrier with subsequent resolution of the macular edema.\(^21\)

Grid laser photocoagulation may also work simply by destroying a certain population of photoreceptors; eliminating high oxygen consumers may result in an increase in the level of inner retinal oxygen and a reduction in tissue vascular endothelial growth factor, which has been implicated in the development of DME.\(^22\) It is possible that pigment epithelium-derived factor may also be involved in the effects associated with the macular grid laser.\(^23,24\) In diffuse DME, however, profound foveal thickening, retinal opacification, and fluid accumulation, predominantly in the retinal outer layers, interfere with the transmission of laser energy into the retinal pigment epithelium. Furthermore, the laser effects on the retinal vascular endothelium and photoreceptors are hard to expect under such circumstance. In addition, diffuse DME originates from a more generalized breakdown of the blood-retinal barrier, representing an advanced stage of diabetic retinopathy. For these reasons, diffuse DME is associated with poor prognoses despite grid laser photocoagulation.\(^2-4\) Lee and Olk\(^4\) demonstrated that visual acuity decreased by 3 lines or more in 24.6% of eyes after grid-pattern laser photocoagulation for diffuse DME. In this regard, guarded visual prognosis would be anticipated in the eyes of our study, if they were treated by macular grid laser photocoagulation only. These results have spurred exploration into new treatment strategies such as IVTA.

Previous reports have demonstrated improvements in the visual acuity and the alleviation of diffuse macular edema after IVTA.\(^5,6\) Although the mechanism of action of corticosteroids in the treatment of macular edema has yet to be well defined, their action may rely on their ability to inhibit the arachidonic acid pathway and down-regulate the production of vascular endothelial growth factor.\(^3\) These phenomena result, collectively, in the reduction of overall vascular permeability.\(^25,26\) Although IVTA has been reserved for DME refractory to laser photocoagulation, IVTA as a primary treatment for diffuse DME has recently been advocated because of its favorable results.\(^27,28\) However, because the beneficial effect on vision and central macular thickness did not persist 6 months after IVTA in our control group, DME relapse represents a major drawback of IVTA.\(^6\) According to one prospective study, no significant improvement in visual acuity and no significant reduction of macular thickness could be observed 3 months after intravitreal injection of 4 mg triamcinolone.\(^29\) This early disappearance of the effect of IVTA might be consistent with the results reported by Beer et al.\(^30\) who calculated that measurable concentrations of triamcinolone could be expected to last no more than 3 months in nonvitrectomized eyes. Although the incidence of relapse may justify repeated applications of IVTA,\(^6\) neither its long-term effectiveness nor its possible toxicity have been adequately assessed.

Through our prior experience with small case series that were not included in this study, we assumed that macular grid laser photocoagulation subsequent to IVTA may result in reductions of the incidence of DME recurrence. An interval of 3 weeks for the separation of macu-
lar grid laser treatment from IVTA was chosen empirically because this is when the therapeutic effects of IVTA were found to reach maximum values in most previous studies.5-9

Although the exact mechanism underlying the maintenance of improved vision and decreased central macular thickness due to grid laser treatment after IVTA was not precisely identified, we speculate that several factors are involved. First, decreased foveal thickness after IVTA may enhance the effects of grid laser photocoagulation. One of the criteria for inclusion in this study was significant fluid accumulation in the foveal outer layer and/or the subfoveal space on OCT examination. Without IVTA, markedly increased foveal thickness, subfoveal fluid, and retinal opacity due to diffuse DME might interfere with adequate laser burning of the retinal pigment epithelium and photoreceptor layers. However, after IVTA, the decreased foveal thickness and restoration of retinal transparency achieved by the treatment would facilitate the delivery of the laser energy selectively to the photoreceptors and retinal pigment epithelia. Second, the possibility exists that steroids might act beneficially in the process of mature laser scar formation. It has been established that 2 or 3 weeks should elapse for the formation of a mature laser scar, and laser treatment itself frequently induces the aggravation of macular edema or inflammation during this period.10,31 The presence of intravitreal steroids might exert certain protective effects against the initial deleterious events that follow grid laser treatment and might also modulate retinal pigment epithelial remodeling after grid laser treatment.

We performed grid photocoagulation 3 weeks after IVTA because we thought that the decreased foveal thickness and restoration of retinal transparency achieved by IVTA might facilitate adequate laser burning of the retinal pigment epithelia and photoreceptors. However, as observed in the cases of exudative age-related maculopathy, IVTA conducted on the same day as photodynamic therapy exerted a synergistic effect.32 It was beyond the scope of our study as to whether grid laser treatment prior to or concurrent with IVTA would result in a similar outcome, and further study regarding this issue appears to be meaningful.

In the combination therapy for diffuse DME, the delivery mode for steroids is an interesting issue. Recently, it was reported that posterior sub-Tenon injection of triamcinolone in conjunction with macular laser photocoagulation improved early visual outcome of diffuse DME.33 Severe vision-threatening complications, such as endophthalmitis, that are inherent to intraocular injection can be avoided by periocular injection.34 However, a more potent protective effect on breakdown in the blood-retinal barrier is expected with IVTA than with posterior sub-Tenon injection of triamcinolone.25

In this study, the elevation of intraocular pressure and the development of lens opacity constituted major complications in both groups. The incidences of complications between the 2 groups were similar, and the rates were consistent with previous IVTA studies.5-10,11 Thus, the complications all appeared to be attributable to intraocular triamcinolone, and macular laser treatment appears not to cause significant additional complications.

Some limitations were inherent in this study. Visual acuity was measured on a Snellen chart, as opposed to the more standardized chart from the Early Treatment Diabetic Retinopathy Study. Although this makes comparisons less meaningful, we used logMAR visual acuity measurements for the comparison.

Despite these limitations, our study is a randomized and prospective one and involved a relatively large number of patients. Further trials with a longer follow-up period, randomized to laser photocoagulation alone, IVTA alone, and combination therapy, may provide more solid grounds for this new strategy for diffuse DME. In conclusion, macular grid laser photocoagulation maintains improved visual acuity and reduces the risk of recurrent macular edema after IVTA. This additional treatment does not appear to increase the risk of complications. Macular laser photocoagulation after IVTA seems a promising therapeutic method for diffuse DME.

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Correspondence: Se Woong Kang, MD, Department of Ophthalmology, Samsung Medical Center, 50 Ilwondong, Kangnam-ku, Seoul 135-710, Korea (swkang@smc.samsung.co.kr).

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