Therapeutic Effect of Macular Grid Photocoagulation in Treatment of Nonexudative Age-Related Macular Degeneration

Mehdi Nili-Ahmadabadi MD*, Ladan Espandar MD*, Mohammad-Reza Mansoori MD*, Reza Karkhane MD*, Mohammad Riazi MD* Ehsanollah Ardestani MD*

Background: To investigate the effect of prophylactic subthreshold laser macular grid photocoagulation on drusen area and to evaluate the visual outcome and incidence of choroidal neovascularization in patients with soft drusen maculopathy.

Methods: In a nonrandomized nonmasked clinical trial, 18 patients (36 eyes) with bilateral soft drusen maculopathy were studied. For each patient, one eye was treated with 48 subthreshold (invisible end-point) applications of 532-nm KTP-laser in a macular grid pattern and the fellow eye was observed. Soft drusen areas were calculated and compared between the two groups at baseline and follow-up visits at 3, 6, 12, and 30 months of therapy. Best corrected visual acuity was also compared in observed and laser-treated eyes. Reduction of drusen area, change in visual acuity, and rate of CNV were assessed in both groups.

Results: At baseline, there was no significant difference in the mean drusen surface area between the two groups (P = 0.90). The mean surface area of soft drusen in treated eyes was 6.51 mm² after 30 months and 7.58 mm² (P = 0.50) in the control eyes. There was a trend towards reduction in the mean soft drusen area after 30 months from baseline in laser-treated eyes (6.51 vs. 6.97 mm²). In treated eyes, there was no statistically significant difference between the mean best corrected visual acuity at the baseline (0.28 logMAR) and after 30 months (0.32 logMAR) (P = 0.40).

Conclusion: Subthreshold macular grid photocoagulation with 532-nm KTP-laser did not seem to reduce drusen surface area significantly and did not improve best corrected visual acuity after 30 months. No exudative lesion developed in laser-treated eyes.

Introduction

Results of several clinical and histologic studies have suggested that multiple large confluent drusen and focal hyperpigmentation are correlated with a high risk of progression to exudative age-related macular degeneration (AMD).¹² For patients with bilateral drusen, the 3-year risk of developing choroidal neovascularization (CNV) is estimated to be 13% overall and 18% for those aged 65 years or older.³ Therefore, prophylactic treatment in patients with high-risk characteristic drusen has potential benefit. Many investigators have studied prophylactic treatments with different treatment techniques.⁴¹¹² Pilot studies in the United States and other countries have suggested that additional benefits of laser treatment may also include improvement and/or stabilization of visual acuity, as well as delaying and/or reducing the incidence of CNV in eyes with nonexudative AMD and large soft drusen.¹³ It is clear that several laser treatment modalities in eyes with large drusen can induce reduction in drusen. However, the characteristics of drusen reduction after treatment are variable, even with the same treatment technique used.⁴¹¹²

In this study, to evaluate the extent of disappearance of drusen areas with minimal side-effects, we performed subthreshold prophylactic laser treatment in patients with high-risk characteristic soft drusen, while aiming to deliver a minimum amount of energy to the retina, retinal
pigment epithelium (RPE), and choroid. We also monitored the influence of treatment on the appearance of fundus to determine if the results of other studies could be reproduced in our population.

Patients and Methods

Patients

From February 2003 through January 2004, eighteen patients (36 eyes) older than 50 years with bilateral soft drusen maculopathy and a best corrected visual acuity (BCVA) of 20/60 or better on Snellen’s chart or 0.5 BCVA ≤ 0.5 in logMAR were enrolled in this study. The eye with better BCVA was considered as the control eye; the fellow eye was treated. When BCVA was equal between the two eyes, the eye with less acuity was chosen subjectively. Patients diagnosed as AMD with at least 5 large (≥ 63 microns) soft drusen within 2250 µm of the center of the foveal avascular zone (FAZ) were included (Figure 1). Patients with exudative macular degeneration in either eye, macular or retinal diseases that would interfere with vision such as central serous choroidopathy, optic atrophy, macular pucker, macular hole, retinal vascular disease such as diabetic retinopathy and retinal vein occlusion, active uveitis, other sight-threatening retinopathies, or other retinal degeneration in either eye were excluded. Patients with media or lens opacity or any other disease that could complicate the evaluation of AMD were not included in the study.

Examination

All patients completed eye examination, including manifest refraction using the Snellen chart, slit-lamp examination, indirect ophthalmoscopy, fundus photography, and fluorescein angiography (Retinal Camera, Topcon, TRC-50XS, Topcon Inc., Japan). Oral and written informed consent, approved by the Ethics Committee of Tehran University of Medical Sciences, were obtained.

Treatment

Eyes were treated with a slit-lamp integrated classic G KTP-laser using 532-nm wavelength (ARC Laser GmbH, Germany). Forty-eight laser lesions of 100 – 125 were applied in four concentric circles outside the FAZ in a grid pattern between 750 – 2250 µm from the center of the FAZ (Figure 2).

All treatments were performed under topical anesthesia using Centralis Direct Laser Lens (Ocular Instrument™, WA, USA). Only one session of laser treatment was applied to each eye throughout the study.

Test spot laser lesions were applied to the retina nasal to the optic disc using a 200-ms duration, and the power was increased to produce a mild gray lesion (visible burn). Then, by keeping the laser power setting constant, the duration of the laser pulse was decreased to 100 ms. Laser spots were placed with reasonable accuracy by dividing the target area into four quadrants and then placing 12 lesions in each section of the treatment annulus.

Fundus photographs at baseline and follow-up visits were scanned at 300 dpi using a scanner (Genius HR7, X-Slim, China). Each image was stored with the resolution of 72 DPI and size of 640 × 480 pixels in bitmap format using Adobe Photoshop CS2. The areas of soft drusen and laser-induced RPE change after laser treatment were

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Figure 1. Soft drusen within 2250 microns of the center of the FAZ were outlined manually.

Figure 2. The placement of 48 laser lesions in a grid pattern of 4 concentric circles, 750 to 2250 microns from the center of the FAZ.
calculated with an image processing program in Retcam (Class I, Retcam 120 Ophthalmic Wide Field Imaging System). Soft drusen areas at baseline and follow-ups were compared between the treatment and control groups.

We used logMAR (MAR = reciprocal of Snellen’s fraction) for scoring and analyzed the BCVA at baseline and follow-ups in each group.

Follow-up examinations were performed at 3, 6, 12, and 30 months after therapy.

**Results**

A total of 36 eyes of 18 patients were enrolled in this study (10 males and 8 females). The mean age of patients was 69.7 (range: 52 – 81) years. Laser-treated eyes included 10 right eyes and 8 left eyes, the mean laser power-intensity was 218 (range: 100 – 330) mW.

**Visual acuity**

BCVA was measured using a Snellen’s chart but is reported and analyzed in logMAR. Before treatment, BCVA of 18 patients was 0.04 – 0.52 (logMAR) or 0.3 – 0.9 (Snellen’s chart). The mean ± SD BCVA at baseline in the control group was 0.23 ± 0.12 logMAR; in the laser-treated group it was 0.28 ± 0.13 logMAR ($P = 0.30$).

The change of mean BCVA through follow-up is shown in Table 1.

In the treatment group, BCVA improved in three eyes (in one eye, it improved by two lines and in the other two eyes, it improved by one line). BCVA deteriorated in three eyes (in two eyes by two lines as a consequence of chorioretinal atrophy and in one eye by one line) (Figure 3). In the control group, the mean BCVA did not change significantly after 30 months. In one eye, BCVA deteriorated by two lines as a result of chorioretinal atrophy; in others no change in BCVA was observed.

**Surface drusen area**

At baseline, there was no significant difference in the mean surface drusen area between the treatment and control groups ($P = 0.90$). The change in the mean surface drusen area over the time is shown in Table 2.

Despite the reduction in the mean surface drusen area in treated eyes over the time, and the increase of mean surface drusen area in the control eyes, these findings were not statistically significant (Figure 4).

**Complication**

No patients in the treatment or in the control groups suffered from new exudative lesions. One eye in the control group developed chorioretinal atrophy after six months of observation and had a visual loss of two lines after one year.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean ± SD BCVA (logMAR)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated eyes</td>
<td>Control eyes</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.28 ± 0.13</td>
<td>0.23 ± 0.12</td>
</tr>
<tr>
<td>3 months</td>
<td>0.29 ± 0.21</td>
<td>0.22 ± 0.17</td>
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<tr>
<td>6 months</td>
<td>0.31 ± 0.21</td>
<td>0.23 ± 0.13</td>
</tr>
<tr>
<td>12 months</td>
<td>0.30 ± 0.18</td>
<td>0.22 ± 0.13</td>
</tr>
<tr>
<td>30 months</td>
<td>0.32 ± 0.14</td>
<td>0.21 ± 0.22</td>
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</table>

**Figure 3.** Color fundus photographs of a 74-year-old male patient before (A) and after laser treatment (B). Note the chorioretinal atrophy in treated area.
**Discussion**

AMD is the leading cause of visual loss in people older than 65 years in the United States and in many European countries. Ninety percent of the severe visual loss from AMD results from CNV. However, only 5% to 15% of patients with late AMD have lesions eligible for treatment, and only half of the eligible patients may receive benefit from laser treatment, since the high recurrence rate after laser treatment causes further deterioration of vision. Because large drusen is a known risk factor for the development of late complications of AMD (geographic atrophy and CNV) and subsequent central visual loss, a variety of prophylactic laser treatments for patients with high-risk drusen have been evaluated.

In most studies, green laser (514 nm) has been used with different visible end-points from barely visible to grayish white. The different laser spot sizes, numbers, and patterns have been used in attempts to treat drusen directly or indirectly by avoiding drusen. Some protocols have included retreatment strategies. However, the optimal laser delivery characteristic to induce drusen resorption is still not known and prophylactic laser photocoagulation remains to be fully evaluated for long-term complications, benefit for CNV prevention, and effect on visual function. The mechanisms by which the laser photocoagulation induces drusen disappearance are still not well-understood. Direct laser treatment to the drusen may destroy RPE cells and thereby inhibit drusen formation. Moreover, direct treatment may trigger RPE proliferation and increase the phagocytosis of drusen by macrophages and choroidal pericytes. Indirect treatment may cause thinning of abnormally thick Bruch’s membrane and increase the outflow of drusen material. This may create a barrier, which blocks centripetal flow of drusen from the peripheral posterior retina toward the center of the macula.

In our study, we used subthreshold 532-nm KTP-laser that provides a continuous wave of frequency doubled Nd-YAG laser. We found no significant improvement in the mean BCVA in laser-treated eyes during 30 months after the treatment ($P = 0.40$). This finding was consistent with Frennesson and Nilsson’s study in which no significant change in visual acuity was found, and also with an update finding of choroidal neovascularization prevention trial (CNVPT) that revealed no major difference between treated and observed eyes with respect to the visual acuity.

**Table 2.** The change in mean ± SD drusen surface area.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean ± SD drusen surface area (mm²)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated eyes</td>
<td>Control eyes</td>
</tr>
<tr>
<td>Baseline</td>
<td>6.97 ± 3.3</td>
<td>7.12 ± 4.4</td>
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<tr>
<td>3 months</td>
<td>6.86 ± 3.2</td>
<td>7.13 ± 4.5</td>
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<td>6 months</td>
<td>6.76 ± 3.4</td>
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<td>12 months</td>
<td>6.61 ± 3.5</td>
<td>7.53 ± 4.7</td>
</tr>
<tr>
<td>30 months</td>
<td>6.51 ± 3.3</td>
<td>7.58 ± 4.6</td>
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![Figure 4. Color fundus photographs of a 75-year-old male patient before (A) and after laser treatment (B). Note the reduction in total drusen area.](image)
In our study, the mean soft drusen area was reduced over the time in the treatment group, while in the control group it was increased; nonetheless, we did not find a statistically significant difference.

In some other studies such as Sigelman, Sarks et al., Figueroa et al., Guymer et al., Little et al., Frennesson and Nilsson, the Choroidal Neovascularization Trial Research Group, and Olk et al., the mean drusen area in the treated group was decreased significantly while in the untreated group it was increased significantly. Discrepancy between this study and the above reports might be attributed to the number of patients included or the type of laser used to treat patients. Having symmetrically matched paired eyes with each patient as his or her own control gives greater credit to the results of this study.

In our study, no one developed CNV over the 30-month follow-up period.

According to CNVPT research group, the incidence of CNV in laser-treated eyes and observation eyes are 2.6% and 1.3%, respectively. They showed that prophylactic application of visible green laser at higher intensities though associated with a greater risk of development of CNV, associated with a more extensive drusen reduction. Furthermore, they showed that drusen areas closer to the treatment burns resolved more quickly.

In the pilot study by Olk and his colleagues, the incidence of CNV in subthreshold laser-, threshold laser-treated, and control eyes were 0%, 9.4%, and 4.4%, respectively. The rarity of this complication in our study may have been a result of very low energy setting and the short duration of the laser treatment, which minimized damage and avoided rupture of Bruch’s membrane.

Results of a recent multicenter study demonstrated that subthreshold laser treatment of multiple large drusen in a patient whose fellow eye has already developed a CNV places the treated eye at a higher risk for developing CNV. Although they advised against prophylactic laser treatment, their study population included patients who have already developed CNV and thus might be considered to be susceptible to CNV formation. On the other hand, we recruited patients without CNV in either eye and, therefore, theoretically eliminated the susceptibility issue. Based on our findings, we propose conduction of a large randomized clinical trial to further study the effectiveness of sub-threshold laser photocoagulation in reducing the drusen surface area and CNV formation.

Acknowledgments

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References


