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Nondamaging retinal laser therapy in recurrent diabetic macular edema after anti-VEGF injections

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Background/aim: Subthreshold yellow nondamaging retinal laser therapy (NRT) could provide a greater safety profile when compared to conventional laser methods. NRT may also improve diabetic macular edema (DME). This study aims to assess whether the severity of DME affects the efficacy of subthreshold yellow NRT.

Materials and methods: The study included 70 eyes that had previously been treated with ranibizumab for DME and then developed recurrent macular edema, which was treated with NRT once. The central foveal thickness (CFT) and best-corrected visual acuity (BCVA) were evaluated retrospectively 2 months following the NRT. The eyes in the study were divided into 4 different groups according to the baseline CFT values. The initial CFT was 250–300 µm in Group 1 (n = 26), 301–400 µm in Group 2 (n = 24), and >401 µm in Group 3 (n = 20). Group 4 (n = 20) included control subjects with 250–300 µm CFT, diagnosed with DME, and not previously treated. The alterations in the BCVA and CFT were measured.

Results: In the study, it was determined that 45 right eyes and 45 left eyes were involved. Statistically significant decrements (42.84 µm reduction) in CFT were detected only in the Group 1 (p = 0.01). There was no significant improvement in CFT within Group 2, 3 and 4 (p = 0.29, p = 0.73, p = 0.22, respectively). Solely Group 1 had statistically significant improvement (from 0.54 to 0.39 LogMAR) in BCVA (p = 0.01), while groups 2, 3 and 4 had no improvement at all (p = 0.74, p = 0.96, p = 0.66 respectively).

Conclusions: Based on the results, NRT provided an improvement in BCVA and CFT in eyes with CFT less than 300 µm at the short-term follow-up. However, CFT and BCVA outcomes after NRT were inferior to those achieved after previous ranibizumab treatment. No positive effect of NRT was not observed in patients with moderate and severe macular edema in DME treatment.

Key words: Central foveal thickness, diabetic macular edema, subthreshold laser, nondamaging retinal laser

1. Introduction

Numerous pathobiological alterations are leading to the decreased visual acuity of patients with diabetic retinopathy. The most important cause is diabetic macular edema (DME) [1]. Many therapeutic options have been used to manage DME, including laser photocoagulation/pharmacologic therapy like intravitreal steroids and anti-vascular endothelial growth factor (anti-VEGF) drugs [2]. However, the cost of steroid and anti-VEGF treatments has been quite high. Currently, the conventional laser is not a treatment option for DME.

The use of subthreshold retinal laser was first initiated using a near-infrared (810 nm) diode laser in the late 1990s [3]. The nondamaging retinal laser therapy (NRT) was recently defined. The nondamaging hyperthermia was demonstrated in mice by observing the expression of heat shock protein [4]. Based on those reported results, the titration protocol has been developed by adjusting laser power and duration. This protocol is called endpoint management (EpM) and is related to the minimal tissue effects in a visible titration [5]. The EpM laser therapy uses an Arrhenius integral algorithm to control laser power and pulse duration, optimizing the therapeutic effect of the laser at subvisible levels [5].

The laser power is titrated to create a barely visible lesion at a pulse duration of 15 or 20 ms, and EpM using 15 ms is called NRT [5,6]. The yellow laser (577 nm) is suitable for macular disease. Because it is well absorbed by melanin and hemoglobin and minimally absorbed by macular xanthophylls. For this reason, it could be used for the treatment over the fovea [7,8].

This study aims to assess the impact of DME severity or central macular thickness on short-term NRT efficacy and whether it can be used as a substitute for costly intravitreal treatments.

2. Material and methods

This clinical study was conducted from January 2016 to December 2017. Local ethical committee approval was obtained by the local ethical committee of the Ankara Numune Education and Research Hospital. The study was conducted following the tenets of the Declarations of Helsinki on medical research involving human subjects. Informed consent was obtained from each participant.

DME was defined as hard exudate and/or retinal thickening involving the central macula and fovea with central foveal thickness (CFT) \geq 250 µm on OCT. The cases were selected from patients who had previously received

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3 or 4 consecutive monthly doses of ranibizumab for DME, followed monthly, regressed macular edema and the injection treatment was terminated. Among these patients, those with recurrent macular edema during their follow-up were included in the study. The patients were treated with NRT laser for one session. The period between the last ranibizumab treatment and NRT was more than 2 months. The cases were examined 2 months after the laser treatment. The CFT and best-corrected visual acuity (BCVA) was assessed retrospectively 2 months after the NRT. Intravitreal ranibizumab injection was administered again to patients whose BCVA decreased and CFT increased in the 2nd month follow-up.

Patients with previous conventional laser administration, intravitreal or subtenon steroid injections, and patients with proliferative diabetic retinopathy were excluded from the study. Patients with a follow-up period of fewer than 6 months after laser and patients with ischemic maculopathy were also excluded from the study. Besides, patients with other retinal and ocular diseases that affect BCVA were excluded from the study.

All of the patients underwent routine ophthalmologic examination. The spectral-domain optical coherence tomography (Spectralis HRA+OCT, Heidelberg, Germany) was performed before NRT and 2 months after NRT to analyze CFT. Retinal thickness in the ETDRS subfields was analyzed. For fundus autofluorescence images, 488 nm wavelength was used and images were obtained. As adverse effects of laser; scotoma declaration, the retinal scar on clinical examination, retinal tissue damage on fundus autofluorescence, and damage on optical coherence tomography were recorded.

To evaluate the effect of NRT, eyes in the study were divided into 4 different groups and the initial CFT values were based on the grouping. The initial CFT was 250–300 µm in Group 1, 301–400 µm in Group 2, and >401 µm in Group 3. Group 4 included control patients, who had been diagnosed with DME, had 250–300 µm CFT, had visual acuity in the range of 20/40 to 20/20, had never been treated and macular edemas were present in the OCT. There was no atrophy and ellipsoid zone defect in the initial and follow-up OCT. The change in CFT and BCVA was evaluated before and after treatment.

The patients were treated with NRT once. The laser was administrated with an Area-Centralis lens (Volk Optical, USA). The NRT protocol was applied with yellow light having a spectrum of 577 nm (Topcon Laser Systems, USA) with the following parameters: 200 µm spot size, 15 ms, 0.50 spacing, 30% EpM, off landmark. The power of

the laser used in NRT for each eye was determined by test burn. All eyes were treated by the same person according to the OCT-based thickness map around the macula. Laser applied to areas 500 microns away from the fovea center. The test burn was performed outside the vascular arcade with the power titrated from 100 mW upward until a burn became barely visible. The maximum power was 150 mW. Once the clinical threshold is determined, NRT was applied by reducing this power level to 30%.

Data analysis was performed using IBM SPSS v. 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was applied to test the normality assumption. Since the distribution of the test was determined as normal, the parametric test was applied. The paired t-test was used to compare changes in CFT and BCVA in each group at baseline and after 2 months. One-way ANOVA was used to evaluate differences in CFT and BCVA among groups. Bonferroni test was used as post hoc test after one-way ANOVA. The alterations in CFT and BCVA between the control group and Groups 1, 2, and 3 were compared using independent sample t-tests. At the beginning of this study, the intraclass correlation test was performed because two eyes were included in the study. The value was determined as 0.2. It was defined that there was no problem with including two eyes in the study. The p-value of less than 0.05 was considered statistically significant.

3. Results

The study included 70 eyes with an average age of 59.15 ± 8.03 years (41–75 years). In the study, it was determined that 45 right eyes and 45 left eyes were involved. There were 26 eyes in Group 1, 24 eyes in Group 2, 20 eyes in Group 3, and 20 eyes in Group 4. There was no statistically significant difference in age and gender assessment between the groups (p = 0.83 and p = 0.88). The demographic characteristics of the patients are depicted in Table 1.

The mean preoperative CFT was 319.93 ± 73.47 µm. In the 2nd month of follow-up, the CFT value in Group 1 decreased by 42.84 µm to 229.64 µm, (p = 0.01) (Figures 1a-b). Scar and atrophic lesions caused by NRT lasers were not recorded in the patient (Figures 1c-d). There was no significant improvement in CFT values in Group 2, 3, and 4 (p = 0.29, p = 0.73, p = 0.22 respectively) (Figure 2A-B). Table 2 shows the mean CFT values for the baseline and 2nd months of follow-up. Scar and atrophic lesions caused by NRT lasers were also not recorded in patients in these groups (Figure 2c-d).

Table 1. Demographic data of patients in different groups.

| | | Group 1 n = 26 (eyes) | Group 2 n = 24 (eyes) | Group 3 n = 20 (eyes) | Group 4 n = 20 (eyes) | P value |
|-------------|------------|--------------------------|--------------------------|--------------------------|--------------------------|---------|
| Age (years) | Mean range | 58.94 (49–74) | 57.43 (42–75) | 60.82 (45–72) | 59.86 (41–68) | 0.83 |
| Gender | Female | 14 | 12 | 10 | 12 | 0.88 |
| | Male | 12 | 12 | 10 | 8 | |

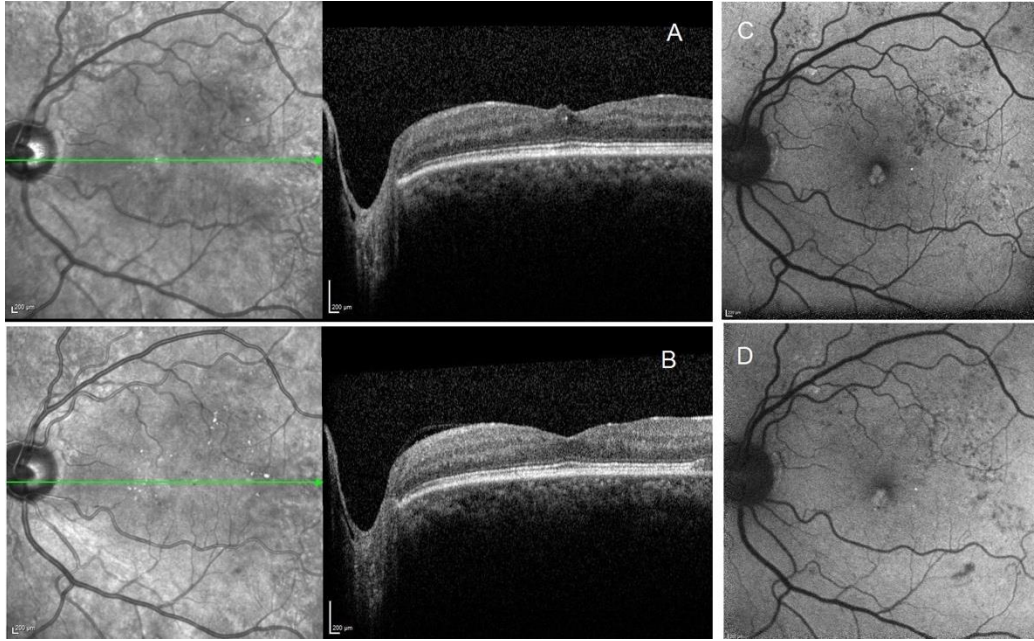


Figure 1. Optical coherence tomography and fundus autofluorescence image of a patient who underwent nondamaging retinal laser therapy. The central foveal thickness decreased from 271 μm (A) to 231 μm (B) and the best-corrected visual acuity increased from 20/40 to 20/32. Fundus autofluorescence imaging demonstrated hyperautofluorescence spots in the fovea (C). After treatment, hyperautofluorescence appearance decreased and autofluorescence alteration due to laser-related scar was not detected (D).

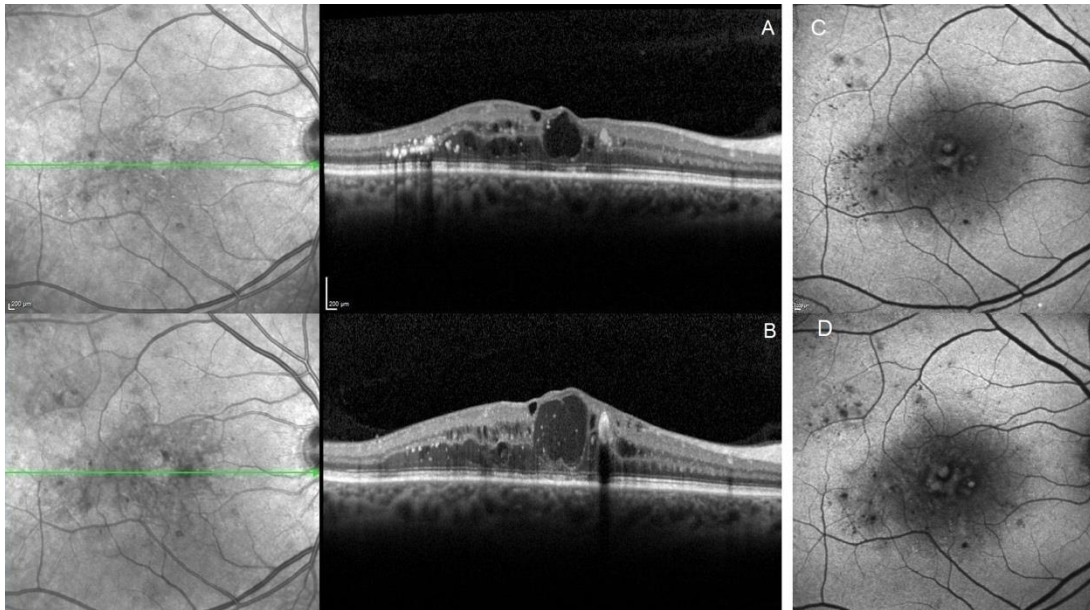


Figure 2. Optical coherence tomography and fundus autofluorescence image of another patient who underwent nondamaging retinal laser therapy. The central foveal thickness increased from 421 μm (A) to 584 μm (B) and best-corrected visual acuity decreased from 20/200 to 20/400. Fundus autofluorescence imaging demonstrated hyperautofluorescence spots in the fovea (C). After treatment, hyperautofluorescence appearance increased, however, autofluorescence alteration due to laser-related scar was not detected (D).

The mean BCVA in Group 1 increased from 0.54 logarithm of the minimum angle of resolution (LogMAR) to 0.39 LogMAR ($p = 0.01$). There was no significant improvement in BCVA in Groups 2, 3, and 4 ($p = 0.74$, $p = 0.96$, $p = 0.66$ respectively). Table 2 also shows the mean BCVA values for the baseline and 2nd months of follow-up.

4. Discussion

The NRT is a treatment based on the adjustment of laser power and pulse duration, concerning the titration settings [9]. EpM algorithm is based upon the modeling of the temperature-dependent rate of protein denaturation [10,11]. In this algorithm, a barely seen lesion is obtained first by laser power using pulses of 15 ms, and this modality is called NRT. Since no tissue damage was detected below 30% of energy on the EpM scale in animal

Table 2. The mean central foveal thickness and best-corrected visual acuity of values at baseline and after nondamaging retinal laser therapy.

| | Central foveal thickness (micron) | | | Visual acuity (The logarithm of the minimum angle of resolution-LogMAR) | | |
|---------|-----------------------------------|--------------------------|---------|---|-------------|---------|
| | Baseline | After laser | P-value | Baseline | After laser | P-value |
| Group 1 | 272.48 ± 39.45 (257–296) | 229.64 ± 38.68 (201–278) | 0.01 | 0.54 ± 0.05 | 0.39 ± 0.06 | 0.01 |
| Group 2 | 311.48 ± 49.75 (303–394) | 317.68 ± 33.95 (295–451) | 0.29 | 0.84 ± 0.14 | 0.87 ± 0.19 | 0.74 |
| Group 3 | 435.02 ± 36.67 (423–546) | 468.76 ± 48.72 (458–603) | 0.73 | 1.30 ± 0.28 | 1.35 ± 0.37 | 0.96 |
| Group 4 | 276.68 ± 41.42 (263–298) | 298.44 ± 39.68 (281–328) | 0.22 | 0.56 ± 0.05 | 0.62 ± 0.06 | 0.66 |

experiments [5], it is set to 30% for clinical applications of NRT. Lavinsky et al. previously indicated that the heat shock protein (HSP) expression in response to thermal energy aids in defining the therapeutic window for NRT [9]. They emphasized that tissue damage was not determined, which allows high-density treatment on fovea [10].

The stimulation of HSP helps to regenerate cellular functions by refolding the damaged proteins. Moreover, HSP-27 and HSP-70 have antiapoptotic functions in degenerative processes [5]. Thus, just after the laser therapy, increased synthesis of HSP and co-chaperones may restore the normal physiology of retinal pigment epithelium [9]. Lavinsky et al. [9] further investigated the EpM protocol to evaluate the clinical effectiveness of NRT in the treatment of chronic central serous chorioretinopathy and macular telangiectasia. They suggested that NRT is an effective and safe treatment option for both diseases. They emphasized that in the treatment of two separate disorders, upregulation of HSE in the retinal pigment epithelium and glial fibrillary acidic protein expression in Muller cells have been accomplished by the activation of endogenous repair pathways. They also proposed that NRT might be effective for the treatment of many retinal diseases including macular edema [9].

For diseases with primary pathology in the retinal pigment epithelium, a yellow (577 nm) wavelength laser is quite proper to use. It is mainly absorbed by melanin and hemoglobin and is only minimally absorbed by macular xanthophylls, which are important for the protection of the fovea [7]. There are many studies reporting improvement of DME after yellow laser treatment [7–9]. In the present study, a yellow laser (577 nm) was used.

Many previous studies investigated the effectiveness of subthreshold photocoagulation in DME [8]. Mansouri et al. [12] investigated the importance of CFT with 810 nm subthreshold micropulse treatment. They reported that treatment responses were better in the patients with CFT less than 400 µm than in patients with CFT greater than 400 µm. In this study, patients with CFT less than 400 µm were divided into 2 groups (250–300 µm and 300–400 µm) for further evaluation. According to the results, after 2 months of NRT, statistically significant CFT reduction and significant BCVA raise are observed in patients with pre-treatment CFT of 300 µm or lower. The cause of

failure associated with CFT increase can be explained by a few theories. First, the distribution of laser energy might change in patients with high CFT values. Secondly, it is thought that NRT stimulates retinal pigment epithelium cells by the release of cytokines. These cytokines restore the pump function of retinal pigment epithelium and cause the absorption of sub-retinal and intra-retinal fluid [13]. A high amount of edema can dilute the concentration of these cytokines. It can be achieved by arranging laser parameters according to CFT values or macular edema might be reduced with pharmacological therapy before the application of NRT.

According to previous studies, half of the reduction in macular edema after subthreshold micro-pulse laser occurs 2–3 months after treatment. In the study of Luttrull et al. [14], most of the patients responded within 2–3 months after the subthreshold laser application. In this study, the duration of the above studies was taken into consideration and 2nd month was chosen as the evaluation time of the effectiveness of the laser to avoid further deterioration of the clinical conditions of the patients. Intravitreal injection was administered to the patients with decreasing BCVA and increasing CFT values in the 2nd month [5,14]. Using anti-VEGF as rescue therapy is an important step in DME cases with a poor or negative response to steroids or lasers [15]. In this study, ranibizumab was used again to avoid further loss in patients with post-laser edema.

There are theoretical additional advantages of EpM compared to subthreshold micropulse photocoagulation. Firstly, EpM has titration protocols that control the power and exposure time of the laser. Secondly, the duration of the pulse with EpM is shorter than the duration of the micropulse. Thirdly, the EpM has the landmark pattern feature, which enables us to treat lesions subvisible, while leaving visible markers for reference and documentation of the treatment region. And EpM can be repeated as often as necessary [16].

The limitations of this study are the small sample size and evaluation after 2 months of follow-up. Also, the history/measurement of confounding factors like duration of diabetes, type of diabetes, hypertension, smoking history, control or un-control of diabetes, lipid profile, and s-creatinine weren't measured. Additionally, both eyes of the subjects were included in the study, and in some cases, there was a difference between the severity of DME levels of the right and left eye of the same patient.

So, the systemic disease may bring a bias for the study. To our knowledge, there is no study comparing the effectiveness of NRT compared to the anatomical severity of DME. From this point of view, the strong side of the study is revealed.

It is reported that by using the landmark pattern feature, the surgeon can choose to leave visible markers for reference and documentation of the treatment region [16]. In that study, the presence of markers or atrophic lesions after NRT therapy was not observed with fundus autofluorescence during the follow-up (Figures 1c-d and 2c-d). In addition to the mechanism of the NRT laser, it can be speculated that bringing the landmark to the off position may have contributed to this situation.

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