Subthreshold micropulse yellow 577 nm laser therapy of diabetic macular oedema in rural and urban patients of south-eastern Poland

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Abstract

Objective. To evaluate the efficacy of subthreshold micropulse yellow (577 nm) laser photocoagulation in diffuse macular edema (DME) in rural and urban patients of south-eastern Poland.

Materials and method. Seventy-five eyes of 75 patients with diffuse DME were treated with subthreshold micropulse yellow laser photocoagulation with a 5% duty cycle at an energy level. The laser exposure time was 20 ms and the spot diameter was 100 µm. Best corrected visual acuity (BCVA), reading vision (Snellen) and optical coherence tomography-determined central retinal thickness (CRT) were estimated before and 2, 4 and 6 months after laser treatment. There were no statistically important differences in: the advancement of DME, HbA1c (glycated hemoglobin) level, duration of diabetes mellitus (DM), the degree of vision damage between rural and urban patients.

Results. The follow-up was 6 months later. The baseline BCVA was 0.20 and remained stable- 0.3 after 6 months. The Snellen at baseline was 1.0 and improved to 0.5 finally (p=0.0004). The CRT at baseline was 500 µm and changed to 346 µm (p=0.00000) at the final follow-up. Finally, no retinal damage was observed.

Conclusions. Place of residence had no statistically significant effect on the demographics data, baseline visual acuity, reading visual acuity and central retinal thickness. Subthreshold micropulse yellow laser showed a highly significant efficiency in the treatment of DME. The effects of the treatment were more significant in rural patients than in urban ones.

Key words
diabetic maculopathy, macular edema, laser treatment, micropulse laser, diabetic retinopathy

INTRODUCTION

Diabetes mellitus (DM) is a main cause of blindness in the working-age population worldwide [1]. Proliferative diabetic retinopathy (PDR) most often leads to severe deterioration of vision or visual loss in patients with diabetes mellitus type 1, because of complications of retinal neovascularizations due to hypoxia, such as vitreous hemorrhage and tractional retinal detachment [2]. Diabetic Macular Edema (DME) is the most common cause of visual loss in person under 50 years of age [2, 3]. DME is often found in the course of diagnosis of DM type 2 [4]. It is associated with damage to the blood-retina barrier and accumulation of the fluid in extracellular space of the outer and inner nuclear layer of the retina [5]. According to the Early Treatment Diabetic Retinopathy Study (ETDRS) a gold standard of the clinically significant macular edema (CDSME) treatment is laser photocoagulation for the retina, which would prevent a significant loss of vision by approximately 50% at three-year follow-up [6]. Unfortunately, this method had numerous disadvantages in the long-term, such as field sensitivity deterioration, impaired colour vision and sense of contrast, and a decrease in visual acuity as a result of the spread of scars or subretinal fibrosis [7]. Laser treatment does not allow for the improvement of visual acuity. However, the conventional laser photocoagulation remains the gold standard for the treatment of DME located outside the fovea.

Intravitreal steroid injections, in spite of their effectiveness in reducing edema, had an adverse effect on intraocular pressure and the development of cataract [8]. A revolution in the treatment of DME became the anti-VEGF agents (VEGF-vascular endothelial growth factor) initially used in the treatment of wet Age-related Macular Degeneration (AMD). The Diabetic Retinopathy Clinical Research Network Study showed a beneficial effect on visual acuity of ranibizumab in DME [9]. Several studies have shown that the effect of anti-VEGF agents can improve baseline visual acuity in patients with DME [9–15]. Nevertheless, the costs of that treatment and the lack of procedures for intravitreal injections in DME under the National Health Fund cause poorer availability of the therapy in relation to the needs.

Advances in laser technology have allowed for selective photocoagulation for the retinal pigment epithelium (RPE) layer via the subthreshold micropulse laser photocoagulation system. This reduces thermal effect on the sensory retina and choroid. Recent understanding of the modification of gene expression mediated by the healing response of the RPE to thermal injury, suggests that useful therapeutic cellular cascade is activated, not by laser-killed RPE cells, but by the still-viable RPE cells surrounding the burned areas that are reached by the heat diffusion at sublethal thermal elevation [16]. According to Vujosevic and Lavinsky, micropulse laser photocoagulation treatment was effective in stabilizing visual acuity and reducing macular edema, [17, 18].
OBJECTIVES

The objective of the study was to evaluate the efficacy of subthreshold micropulse yellow (577 nm) laser photocoagulation in the treatment of DME in rural and urban patients in south-eastern Poland.

MATERIALS AND METHOD

The examined group consisted of 46 females and 29 males, aged 26–83 years (mean age 67±8.0). Patients with renal failure or uncontrolled hypertension were excluded from the study. Patients were qualified for laser photocoagulation if they did not agree to start or continue anti-VEGF treatment. Seventy five eyes of 75 patients (37 urban inhabitants, 38 rural inhabitants) were treated with subthreshold micropulse yellow laser photocoagulation (Iridex OcuLight IQ 577 nm) with a 5% duty cycle at an energy level. The laser exposure time was 20 ms and the spot diameter was 100 µm. Best corrected visual acuity (BCVA) using a decimal chart, reading visual acuity (Snellen) and optical coherence tomography-determined central retinal thickness (CRT) were examined before laser treatment and in 2, 4 and 6 months follow-up. Median duration of DM in the treated group was 15±10 years (range 1–39), median glycated hemoglobin - HbA1c level was 7.3±0.96 (range 6.1–9.78%). Laser treatment was performed using micropulse laser Iridex OcuLight IQ 577 nm with an Area-Centralis lens (Volk Optical). The micropulse laser power was derived from a test burn. The test burn was performed in the continuous-wave mode using a 100 µm spot diameter and a 20 ms duration outside the vascular arcade with the power titrated from 50 mW upward until a burn became barely visible. To perform laser treatment, the laser was switched from continuous-wave emission mode into micropulse emission mode at 5% duty cycles and double the laser power. The number of spots varied according to the extension of DME. If needed, re-treatment was performed according to the same protocol after 2 months if DME persisted on SD-OCT images. Spectral optical coherence tomography was performed in all patients by Zeiss Cirrus HD-OCT imaging system, using macular cube 512x128 protocol or SOCT Copernicus HR.

Statistical analysis. Statistica 12,5 PL software was used for statistical analysis. Distribution of variables were checked with Kolmogorov Smirnov test with Lilliefors adjustment. Due to not-Gaussian distribution, nonparametric tests were used for further analysis. Anova-Friedman test and post hoc tests were used for analysis of repeated measurements. U Mann-Whitney test was used for comparison between two groups. Spearman’s rank correlation was used to measure statistical dependence between two variables. Differences were considered as significant at p<0.05. Results are shown as median value followed by quartile range.

RESULTS

The demographic characteristics and treatment modalities of the patients are presented in Table 1. No statistically important differences were found in demographic characteristics and baseline values between urban and rural patients. Rural patients were a bit older than urban patients (68±8.0 vs. 67±6.0), had better HbA1c level (7.0±1.05 vs. 7.5±1.04) but worse CRT (532±242 µm vs. 457±158 µm) (Tab. 1). The differences were not statistically significant. The follow-up was 6 months later. The baseline median BCVA was 0.20±0.27 and remained stable: 0.30±0.37 after 6 months (p=0.0019). The improvement was more significant in rural patients (p=0.038) vs. urban patients (p=0.051) (Tab. 2). Median Snellen improved from 1.0±1.0 at baseline to 0.5±1.2 at final follow-up (p=0.00042), in rural patients more significantly than in urban patients (p=0.0031 vs. p=0.039) (Tab. 2).

Table 1. Demographic characteristic of urban and rural groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Urban</th>
<th>Rural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67±6</td>
<td>68±8</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td>11.5±10</td>
<td>15±12</td>
</tr>
<tr>
<td>HbA1C</td>
<td>7.5±1.04</td>
<td>7±1.05</td>
</tr>
</tbody>
</table>

Table 2. Parameters of treated patients before laser treatment and at final follow-up

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Urban</th>
<th>Rural</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA before laser</td>
<td>0.2±0.32</td>
<td>0.2±0.27</td>
<td>0.2±0.27</td>
</tr>
<tr>
<td>BCVA after 6 months</td>
<td>0.25±0.41</td>
<td>0.35±0.3</td>
<td>0.30±0.37</td>
</tr>
<tr>
<td>Significance level</td>
<td>p=0.051</td>
<td>p=0.038</td>
<td>p=0.0019</td>
</tr>
<tr>
<td>Snellen before laser</td>
<td>1.0±1.25</td>
<td>1.0±1.0</td>
<td>1.0±1.0</td>
</tr>
<tr>
<td>Snellen after 6 months</td>
<td>0.5±0.75</td>
<td>0.5±0.25</td>
<td>0.5±1.2</td>
</tr>
<tr>
<td>Significance level</td>
<td>p=0.039</td>
<td>p=0.0031</td>
<td>p=0.00042</td>
</tr>
<tr>
<td>CRT before laser</td>
<td>457 µm ± 158</td>
<td>325.5 µm ± 242.5</td>
<td>500 µm ± 205</td>
</tr>
<tr>
<td>CRT after 6 months</td>
<td>325 µm ± 150</td>
<td>348.5 µm ± 173</td>
<td>346 µm ± 153</td>
</tr>
<tr>
<td>Significance level</td>
<td>p=0.00003</td>
<td>p=0.00000</td>
<td>p=0.00000</td>
</tr>
</tbody>
</table>

The median CRT at baseline was 500±205 µm and decreased significantly to 346±153 µm (p=0.00000) at the final follow-up. Again, the improvement was more significant in the rural population (p=0.00000 vs p=0.00003) (Tab. 2). The level of HbA1c ≤ 7% was found to be significantly associated with improved Snellen and reduced CRT. Finally, no retinal damage was observed.

CONCLUSIONS

Place of residence had no statistically significant effect on the demographics data, baseline visual acuity, reading visual acuity and central retinal thickness. Subthreshold micropulse yellow laser showed a highly significant efficiency in the treatment of DME. The effects of the treatment were more significant in rural patients than in urban ones. Subthreshold micropulse yellow laser showed short-term efficacy in the treatment of DME. No retinal damage was observed after laser treatment.

DISCUSSION

About 360 mln people suffer from Diabetes Mellitus (DM) worldwide [15]. It is estimated that by 2030 the disease will develop in a half billion population [15]. The Diabetic...
Retinopathy (DR) now affects nearly 93 million people worldwide, of which 17 million have Proliferative Diabetic Retinopathy (PDR) and 21 million have Diabetic Macular Edema (DME) [19]. In the USA, DME occurs twice as often as PDR [15]. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) revealed that DME develops after 10 years of the disease in 14% of the patients with DM type 2 [17]. In patients with DM type 1, DME occurs in 27% after 9 years of the disease, and in DM type 2 relates to 30% after 30 years [20]. DME is revealed in 5% of the patients with DM type 2 at the time of diagnosis [20]. In the presented study, only one patient was treated on DM type 1 and DME had developed after 19 years of disease duration. In other patients, DME appeared after 1 – 39 years after diagnosis of DM. In the current study, duration of disease was not associated significantly with BCVA, Snellen, CRT or HbA1c. It is known that untreated DME leads to a reduction in visual acuity of 15 letters in 25–30% of patients after 3 years [21]. Risk factors for the development of DME include the duration of the disease, proteinuria, gender, blood glucose, HbA1C increased, hypertension, diuretics and hyperlipidemia [19, 20]. Intensive control of glucose, blood pressure and hyperlipidemia is designed to reduce the risk of developing complications of DR in DM [22]. The risk factors found in the patients in the current study were a long course of the disease and HbA1c level >7%. Median duration of DM in the treated group was 15±10 years (range 1–39), median HbA1c level was 7.3±0.96 (range 5.5–9.78%). Rural patients had lower HbA1c level and longer DM duration than urban patients, but the difference was not significant (HbA1c: 7.0 vs. 7.5; DM duration: 15 years vs. 11.5 years). According to the American Diabetes Association HbA1c should be kept within the limits of 6.5–7% [19]. In the presented study, the median HbA1c level was not very high (median HbA1c=7.3±0.96), but ranged from 5.5 – 9.78%. It is interesting that rural patients had a better HbA1c level, despite a longer duration of the disease and, on the other hand, better HbA1c level did not correlate with the lower CRT. It is possible that blood lipid levels also affected the retinal edema. In many cases of long-term macular edema, hard exudates we observed we observed that corresponded with the accumulation of lipids in the retina. This require further research in the future. No similar studies on the rural and urban populations have been performed previously, rendering any reference to other results impossible.

CONCLUSION

This study shows that micropulse yellow subthreshold laser photocoagulation improved BCVA and Snellen statistically significantly in patients with DME (BCVA p= 0.00191; Sn p=0.00042). Previous studies have also reported the improvement of visual acuity after yellow micropulse laser therapy [17, 23]. Another advantage of the micropulse laser is the lack of scars, which minimizes the risk of vision loss over time [16, 22, 24]. In patients in the current study, no damage to the retina was found. Additionally, it was found that better basal visual acuity allowed for obtaining better outcomes at the final point. The presented results correlate with observations of the ETDRS study which showed that the output of better visual acuity determined the better final visual acuity [6]. In addition, it was found that the HbA1c level ≤ 7% significantly affected the improvement in reading visual acuity and central retinal thickness. This confirms the importance of glycemic control.

According to Central Statistical Office data, diabetes was the third leading cause of death in Poland in 2013 [25]. Simultaneously, the study shows that knowledge regarding diabetes mellitus type 2 was on an unsatisfactory level, independent of gender, age and education of the respondents [26]. Therefore, education of the public is very important, as well as early detection and cure the disease. The most modern drugs used in patients with DME do not fulfill their role if there is lack of cooperation from the patient. It is necessary to tighten glycemic control, hypertension and lipid profile. Only a comprehensive approach to the patient with diabetes and an agreement with the diabetologist / GP (general practitioner) will allow the protection patients prior to permanent loss of vision.

Micropulse laser 577 nm system seems to be a new treatment option, which can provide a chance to maintain and even improve visual acuity in patients with diffuse DME.

REFERENCES


