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Diffuse Diabetic Macular Edema – 18 Months Observation of the 577 nm Subthreshold Micropulse Laser Treatment Results

Rozlany cukrzycowy obrzęk plamki – 18 miesięczne obserwacje wyników leczenia podprogowym laserem mikropulsowym 577 nm

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Abstract: Purpose: To evaluate the efficacy of subthreshold micropulse laser treatment in diabetic macular edema at 18 months of follow-up.
Material and Methods: 112 eyes of 112 patients with diabetic macular edema were treated with subthreshold micropulse yellow laser and followed up every 3 months. If the edema was present, the treatment was repeated. The mean age of patients was 65.64±8.75 years. The mean duration of diabetes was 14.4±8.75 years. The glycated hemoglobin level was ≤ 7mg% only in 18 patients. The primary outcomes were the mean change in best-corrected distance and near visual acuity and central macular thickness. Secondary outcomes included variables correlation with glycated hemoglobin level.
Results: The mean baseline best-corrected distance visual acuity was 0.31±0.2 and improved finally to 0.47±0.2 (p=0.00). The mean baseline best-corrected near visual acuity was 1.08±0.8 and improved finally to 0.56±0.2 (p=0.00). The mean baseline central macular thickness was 449.16±162.5 μm and improved finally to 256.6±118.2 μm (p=0.01). The laser treatment was performed in 7 patients one time, in 16 - two times, in 73 - three times, and in 16 - four times. There was no significant correlation between glycated hemoglobin level and disease duration, baseline and final best-corrected distance and near visual acuity and central macular thickness. There was significant negative correlation between glycated hemoglobin level and patients' age.
Conclusions: Subthreshold micropulse yellow laser showed long-term efficacy in diabetic macular edema treatment. The level of glycated hemoglobin was not important for initial distance and near best-corrected visual acuity and central macular thickness.

Key words: diabetes mellitus, diabetic macular edema, micropulse laser.

Abstrakt: Cel pracy: Ocena efektywności laseroterapii mikropulsowej w cukrzycowym obrzęku plamki po 18 miesiącach obserwacji.
Materiał i Metody: 112 oczu u 112 pacjentów z cukrzycowym obrzękiem plamki leczono podprogowo żółtym laserem mikropulsowym i kontrolowano co trzy miesiące. Jeśli na wizycie kontrolnej nadal był obrzęk, leczenie powtarzano. Średni wiek pacjentów wynosił 65,64±8,75 lat. Średni czas trwania cukrzycy wyniósł 14,4±8,75 lat. Poziom hemoglobiny glikowanej ≤ 7mg% miało tylko 18 pacjentów. Podstawowe cele pracy zawierały ocenę zmiany średniej ostrości wzroku do dali i bliży na tablicach Snellena z najlepszą korekcją oraz centralnej grubości plamki. Wtórne cele obejmowały korelację badanych zmiennych z poziomem hemoglobiny glikowanej.
Wyniki: Średnia ostrość wzroku do dali z najlepszą korekcją wynosiła pierwotnie 0,31±0,2 i poprawiła się ostatecznie do 0,47±0,2 (p=0.00). Średnia wyjściowa ostrość wzroku do bliży z najlepszą korekcją wynosiła 1,08±0,8 i poprawiła się ostatecznie do 0,56±0,2 (p=0.00). Średnia wyjściowa grubość siatkówki w plamce wynosiła 449,16±162,5 μm i poprawiła się ostatecznie do 256,6±118,2 μm (p=0.01). Leczenie laserowe przeprowadzono 1 raz u 7 pacjentów, 2 razy u 16, 3 razy u 73, a 4 razy u 16 chorych. Nie wykazano istotnej korelacji poziomu hemoglobiny glikowanej z czasem trwania choroby, z wyjściową oraz ostateczną ostrością wzroku do dali i do bliży oraz grubością siatkówki w plamce. Poziom hemoglobiny glikowanej istotnie statystycznie ujemnie korelował z wiekiem chorych.
Wnioski: Podprogowa laseroterapia mikropulsowa wykazała długoterminową skuteczność w leczeniu cukrzycowego obrzęku plamki. Poziom hemoglobiny glikowanej nie był istotny dla początkowej i ostatecznej ostrości wzroku do dali i do bliży oraz centralnej grubości siatkówki.

Słowa kluczowe: cukrzyca, cukrzycowy obrzęk plamki, laser mikropulsowy.

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Introduction

Diabetic macular edema (DME) is a leading cause of blindness in patients with diabetes mellitus (DM) (1). DME is often found in the course of DM type 2 diagnosis (2). It is associated with damage to the blood-retina barrier and accumulation of fluid in extracellular space of outer and inner nuclear layer of

the retina (3). The standard treatment of DME is the anti-VEGF (Vascular Endothelial Growth Factor) therapy, initially used in the treatment of wet age-related macular degeneration (wet AMD). The Diabetic Retinopathy Clinical Research Network Study showed a beneficial effect on visual acuity of ranimizumab in DME (4). Several studies have shown that the effect of anti-VEGF agents can improve baseline visual acuity in patients with DME (4-9). But the costs of that treatment and the lack of programme for intravitreal injections in DME under the National Health Fund, cause poorer availability of the therapy in relation to needs. Intravitreal steroid injections, although their effectiveness in reducing edema, had an adverse effect on intraocular pressure and cataract development (10).

Advances in laser technology have allowed to selective photocoagulation for the retinal pigment epithelium (RPE) layer via the subthreshold micropulse laser photocoagulation method. It reduces thermal effect on the sensory retina and choroid. The thermal stress response activates intracelluar factors as PEDF (Pigment Epithelium-Derived Factor), TSP1 (Thrombospondin-1), SDF1 (Stromal Cell-Derived Factor 1) and β-actin (11-13). PEDF and TSP1 are anti-angiogenic factors, while SDF1 and β-actin play role in reparative processes. Another advantage of the mircopulse laser is the lack of scars which minimizes the risk of vision loss over time. Subthreshold micropulse laser treatment (SMPLT) was effective in stabilizing visual acuity and reducing macular edema according to Vujosevic et al. (14).

Purpose: The aim of the study was to evaluate the efficacy and safety of the subthreshold micropulse yellow (577nm) laser treatment in diffuse DME with 18 months follow-up.

Material and Methods: The study included 112 eyes of 112 patients with diffuse diabetic macular edema including the fovea, characterized by the appearance of cysts, who did not agree to treatment with anti-VEGF injections. Inclusion criteria included: diffuse diabetic macular edema and no agreement for anti-VEGF therapy. Exclusion criteria included: cataract surgery in the last 6 months, unstable treated glaucoma, uveitis, foveal damage due to other diseases. Patients were treated with SMPLT and followed-up every 3 months during 18 months. The treated group consisted of 67 women and 45 men, aged 26-83 years (mean age 65.64±8.75). The mean duration of diabetes was 14.4±8.75 years (range 1 to 39 years). At baseline the glycated hemoglobin level (HbA1c) was ≤ 7mg% only in 18 patients, but in 94 patients > 7 mg%. The mean HbA1c was 8,2±1,75 mg% (range 5,31-13). The central macular thickness (CMT) was included in the analysis due to the direct relationship with best-corrected visual acuity (BCVA). The CMT on OCT was measured manually (by one doctor AP) as a distance from internal limiting membrane (ILM) to the complex Bruch's membrane – retinal pigment epithelium in the fovea (Fig. 1).

It ranged from 369 to 875 μm. The primary outcomes were the mean change in distance and near best-corrected visual acuity (BCDVA, BCNVA) and central macular thickness (CMT). Secondary outcomes included correlation of variables with HbA1c, safety and number of laser treatment. At baseline visit and every three months BCDVA and BCNVA were measured on Snellen charts. The CMT was measured using SOCT Copernicus HR software. The subthreshold micropulse yellow laser photocoagulation was performed with a 5% duty cycle at an energy

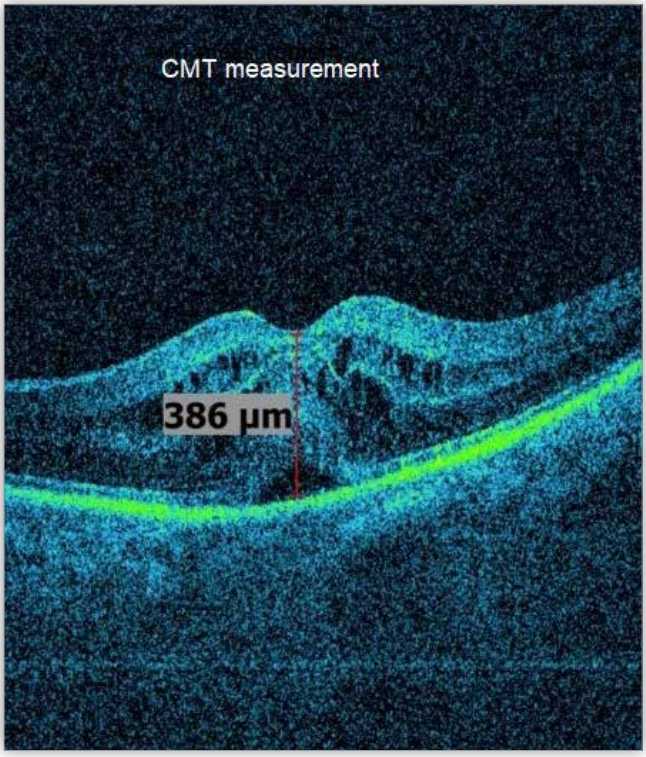

Fig. 1. CMT measurement.
Ryc. 1. Pomiar CMT.

level using Iridex OcuLight IQ 577 nm with an Area-Centralis lens (Volk Optical). The laser exposure time was 20 ms and the spot diameter was 200 μm. The micropulse laser power was derived from a test burn. The test burn was performed in the continuous-wave mode using a 200 μm spot diameter and a 20 ms duration outside the vascular arcade with the power titrated from 50mW upward until a burn became barely visible. To perform laser treatment we switched the laser from the continuous-wave emission mode into micropulse emission mode at 5% duty cycles and quadrupled the laser power. The entire macula was treated. If intraretinal cyst edema persisted in HR-OCT images during the follow-up visit (every 3 months), the treatment was repeated during the same visit according to the described pattern. The aim was to remove the edema and obtain the correct fovea profile.

Statistica 13PL software was used for statistical analysis. Distribution of variables were checked with Kolmogorov Smirnov test with Lillefors adjustment. For the analysis nonparametric tests were used. 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 the statistical dependence between the variables. Differences were considered as significant at $p<0.05$. Results are shown as a mean value followed by a standard deviation (SD).

Results: The mean baseline BCDVA was 0.31±0.2 and improved finally to 0.47±0.2 (p=0.00) (Fig. 2). The mean baseline BCNVA was 1.08±0.8 and improved finally to 0.56±0.2 (p=0.00) (Fig. 3). The mean baseline CMT was 449.16±162.5 μm and improved finally to 256.6±118.2 μm (p=0.01) (Fig. 4). There was statistically significant negative correlation between age and baseline BCDVA (p=0.04). There

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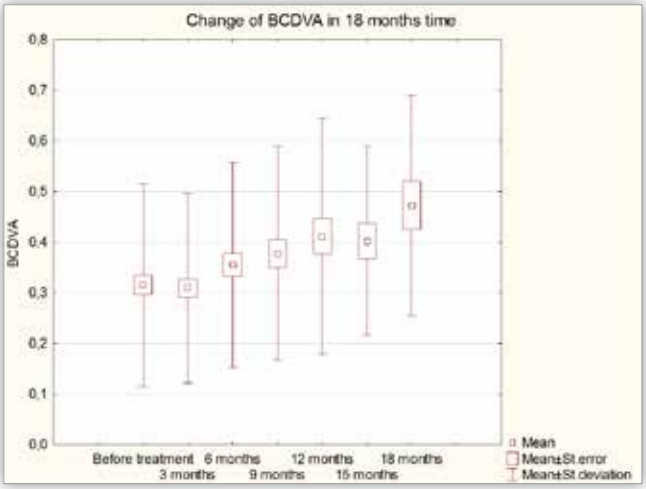

Fig. 2. Change of BCDVA in 18 months time.
Ryc. 2. Zmiana BCDVA w ciągu 18 miesięcy.

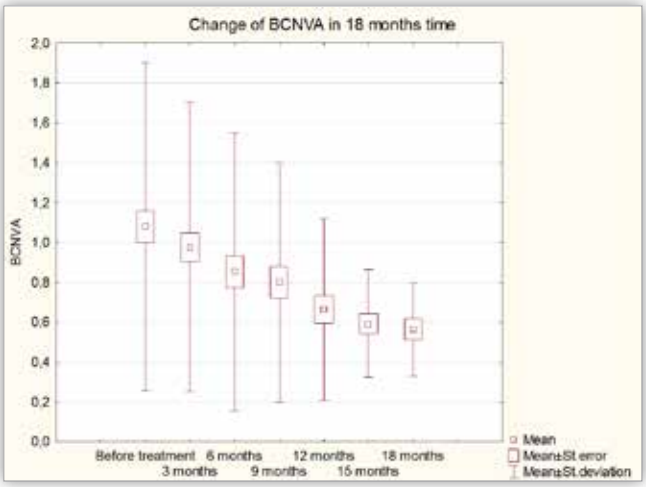

Fig. 3. Change of BCNVA in 18 months time.
Ryc. 3. Zmiana BCNVA w ciągu 18 miesięcy.

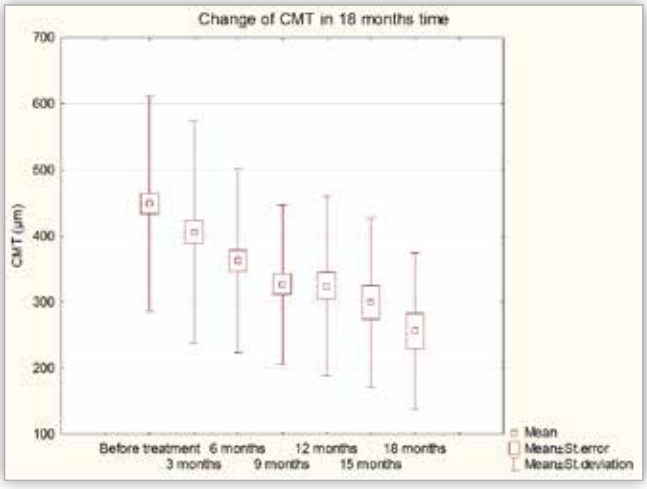

Fig. 4. Change of CMT in 18 months time.
Ryc. 4. Zmiana CMT w ciągu 18 miesięcy.

were statistically significant negative correlation between baseline BCDVA and baseline CMT (p=0.00) and statistically significant positive correlation between baseline BCNVA and baseline CMT (p=0.00). There was statistically significant negative correlation between HbA1c level and patients' age (p=0.01). There was no statistically significant correlation between HbA1c level and disease duration, baseline BCDVA, BCNVA, CMT (p=0.94, p=0.39, p=0.41, p=0.44, respectively) and final BCDVA, BCNVA and CMT (p=0.93, p=0.69, p=0.25, respectively). The laser treatment was performed in 7 patients one time, in 16 – two times, in 73 – three times, and in 16 – four times. We found the reduction of the CMT in 75.32% of patients (84 eyes), stabilization in 16.88% (19 eyes) and worsening in 7.8% (9 eyes). There was no statistically significant differences in: duration of diabetes mellitus, HbA1c level and the degree of vision damage between male and female patients. Finally, no retinal damage was observed.

Discussion

Our study showed that subthreshold micropulse yellow laser treatment significantly improved BCDVA and BCNVA in patients with diffuse cystic DME (p=0.00 and p=0.00 respectively). Results of other studies are presented in Table I.

Similar outcomes were reported by Othman et al. after 12 months (15). Fazel et al. obtained significant BCVA improvement after 4 months, however, in DME with CRT (Central Retinal Thickness) lower than 450 μm (16). Mansouri et al. reported significant improvement of BCVA only in patients with CRT lower than 400 μm (17). Our study determined the clinical efficiency of subthreshold micropulse laser in macular edema with CMT ranging from 369 to 875 μm. We found statistically significant negative correlation between baseline BCDVA and baseline CMT (p=0.00) and statistically significant positive correlation between baseline BCNVA and baseline CMT (p=0.00).

In our opinion, the most important for final outcomes were baseline distance and near visual acuity. This means that the earlier the treatment and the better initial visual acuity, the better the results. Statistical analysis of our study confirmed this thesis. Our outcomes correlate with observations of the ETDRS (Early Treatment Diabetic Retinopathy Study), that showed that the output better visual acuity determined the better final visual acuity (18).

We found no statistically significant correlation between HbA1c level and final BCDVA, BCNVA and CMT. The lack of statistically significant correlation between HbA1c level and final outcomes seems surprising because it is known that poor glycemic control is a bad prognostic factor for progression of diabetic retinopathy and maculopathy. On the other hands, the better HbA1c level the better the prognosis of diabetic retinopathy. However, in our study, most patients (n=94) had poor glycemic control and HbA1c level > 7mg% at the beginning of the treatment and that fact could distort the results. According to the American Diabetes Association, HbA1c should be kept within the limits of 6.5-7mg% (19). Perhaps, a different correlation would occur between final BCDVA and BCNVA and final HbA1c, but we did not carry out such measurements. In our study, HbA1c was measured only at the beginning of treatment.

Similarly, the duration of diabetes affects the progression of diabetic maculopathy and retinopathy. In our study, the outcomes did not confirm this, although the mean duration of the disease in our patients was 14.4±8.75 years (range 1 to 39 years).

Authors/ publication year	Number of treated eyes (n)	Material and duration of follow-up	Results
Othman et al. 2014 (15)	Group 1 – SMPLT alone (n=187) Group 2 – SMPLT post conventional laser (n=33)	Two groups of non-ischemic DME 12 months	Group 1 – significant BCVA improvement Group 2 – stabilization of BCVA, no improvement Significant CRT reduction in both groups
Luttrull et al. 2014 (20)	n=39	Central DME with good BCVA ≥ 20/40 4-7 months	Mean BCVA improvement (by 0.03 logMAR) Significant CRT reduction
Mansouri et al. 2014 (17)	Group 1 – CRT< 400μm (n=33) Group 2 – CRT> 400μm (n=30)	Two groups 12 months	Group 1 – significant BCVA improvement (by 0.2 logMAR) and CRT reduction Group 2 – no significant change of BCVA, CRT
Vujosevic et al. 2015 (14)	Group 1 – Yellow SMPLT n=26 Group 2 – Infrared SMPLT n=27	Two groups DME<400μm 6 months	No significant changes of BCVA, CRT, CCT,MV significant improvement of retinal sensivity in both groups
Fazel et al. 2016 (16)	Group 1 – SMPLT n=34 Group 2 – conventional laser n=34	Two groups DME<450μm 4 months	Significant CRT reduction in both groups (higher in group 1) Significant BCVA improvement in Group 1 (by 0.07 logMAR)

Tab. I. Micropulse laser treatment studies.
Tab. I. Wyniki leczenia MPLT w dostępnym piśmiennictwie.

Because we found surprising statistically significant positive correlation between baseline BCNVA and baseline CMT (p=0.00), it is possible that a careful analysis of the change in retinal thickness in all ETDRS spots in the macula and their correlation with change in the retinal sensitivity in the microperimetry may be a better tool for assessing the effectiveness of MPLT treatment. This thesis requires further research.

Conclusions

Subthreshold micropulse yellow laser showed long-term efficacy in diffuse diabetic macular edema treatment in reducing central macular thickness and improving visual acuity. The level of HbA1c did not correlate significantly with the initial and final BCDVA, BCNVA and CMT. The SMPLT is a very safe procedure, because no retinal damage was observed after laser treatment.

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