TREATMENT OF DIABETIC MACULAR EDEMA BY MICROPULSE LASER – INITIAL FINDINGS

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SUMMARY

Introduction: Diabetic macular edema (DME) is the most common cause of a visus dicrease in patients suffering type 2 diabetes. DME originates in abnormal macula capillars permeability. This study presents the findings of observing patients with DME after by micropulse laser therapy with the wavelength of 577 nm.
Methods: The study covers 23 eyes of 15 patients with focal or difuse DME. In all patients we performed a 577 nm micropulse laser therapy of the macula, proceeding by a technique of placing spots next to each other in the shape of EDTRS optotype letters. In average we performed 3 treatments per eye.
Results: Best-corrected visual acuity (BCVA) was 61,8 of a letter at the beginning, 62,5 of a letter after 3 months, 59,5 of a letter after 6 months, 57,6 of a letter after 9 months and 59,2 of a letter after 12 months. The average difference between BVAC at the beginning and after a year was -2.7 of a letter. A T-test does shows statistically insignificant difference.
The average central retinal thickness (CRT) was 380,4 µm at the beginning, 368,1 µm after 3 months, 327,5 µm after 6 months, 329,2 µm after 9 months and 301,0 µm after 12 months. The difference between the average CRT at the beginning and after 12 months was -79,5 µm. A T-test shows statistically significant difference.
Discussion: Our studied group reported visus improvement or stabilization in 61% of eyes and decrease or stabilization of DME in 83% of eyes. Without treatment a deterioration would occur due to the progressive nature of the disorder. Taking into account these results and relevant literature we resolved to change our treatment methods in favour of placing laser spots as close as possible. An evaluative study of this method will follow.
Conclusion: In the studied group the average CRT improved and the average BCVA remained virtually equal. Treating DME by means of a micropulse laser has proven to be an effective method. It does not leave scars on retina and thus prevents creating scotoms. If the edema is higher or a resistent cyst occurs in the macula, it is recommended to combine laser and anti-VEGF therapies. In case of insufficient effects of a laser therapy there is a possibility of combining it with an anti-VEGF treatment.

Key words: diabetic macular edema, laser treatment, micropulse laser

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INTRODUCTION

Diabetic retinopathy (DR) and diabetic macular edema (DME) are serious complications of diabetes (DM). DME is the most common manifestation of DR, which causes a deterioration of vision. At the same time, DME is the most common cause of deterioration of central visual acuity in the population aged under 50 years in developed countries. It therefore represents a serious social and economic problem.

The aim of the study was to present the results of observation of patients with DME following treatment with a micropulse laser with a wavelength of 577 nm.

Epidemiology: Worldwide there is a large number of studies dealing with the epidemiology of DR, DME and clinically significant DME (CSME). CSME is defined as DME which immediately threatens the fovea and central visual acuity [13]. The prevalence of DME and CSME is dependent upon the type of DM, the length of its duration, age of the patient and ethnic group [20]. The prevalence of edema increases not only with the length of the disease, but also with a higher level of glycated haemoglobin and proteniuria [16]. Clinically significant DME afflicts 6 to 10% of patients with DM [4]. According to the Czech Statistical Office, a total of 841 227 diabetics (442 388 women and 398 839 men) were recorded in the Czech Republic in 2012, forming 8% of the population [22]. The incidence of DME is not statistically monitored in the Czech Republic, but active screening for DR and DME is performed [5, 6]. On an assumption of 6-10 % prevalence of CSME in patients with DM, it is possible to expect that the number of patients who will be affected by CSME during their lives in the Czech Republic will be between 50 and 84 thousand (0.5% to 0.6 % of the population).

Pathophysiology: DME is caused by abnormal permeability of the macular capillaries. The seriousness of the vascular pathology is significantly influenced by the genetic disposition of the individual, and is modified by further metabolic (hyperglycaemia, dyslipidemia and insulin resistance) and haemodynamic factors (hypertension) [12]. Cataract surgery is considered an ocular risk factor. By contrast, a protective effect is attributed to chorioretinal scars, amblyopia and probably also high myopia. A protective mechanism is evidently loss of the ganglion cells and the

attendant reduced metabolic activity of the retina, as well as haemo-modulating changes upon chorioretinal tension of the capillaries, which is one of the principles of laser treatment of DR [17].

Therapy: In addition to laser therapy, current options for treatment of DME also include intravitreal application of vascular endothelial growth factor (VEGF) blockers or cortiocosteroids, or the performance of pars plana vitrectomy (PPV) [18]. At present, treatment by laser, PPV and the anti-VEGF preparation ranibizumab and aflibercept is approved in the Czech Republic. Laser treatment of DME can be performed by the classic method of focal photocoagulation in the case of a focal edema or grid photocoagulation in the case of diffuse DME [7]. Another possibility of treatment is modern micropulse photocoagulation. The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated a 50% reduction of the danger of incidence of medium-severe deterioration of vision in patients after photocoagulation for DME, although it is possible to expect an improvement by more than 15 letters in only approximately 3% of patients after 3 years of observation [13, 14]. The effect of focal photocoagulation may be in part thanks to the occlusion of percolating microaneurysms, but the precise reduction of edema following photocoagulation is unknown [15].

Principle of micropulse laser treatment of DME: The laser pulse is not continual, but is divided into 100 micropulses, in which the length of the "on" and "off" mode is adjustable. Upon selection of a "5% duty cycle", the entire length of exposure shall be 10 ms out of a total pulse length of 200 ms. Thermic damage to the retina does not occur using this method, and no clinically detectable scar forms – biomicroscopically, by autofluorescence, fluorescence angiography or optical coherence tomography (OCT). The principle of "true sub-threshold photocoagulation" means that the scar is not detectable by any method either during the period of treatment or in the future [9]. In laboratory tests on mice it has been demonstrated that upon use of a 6% duty cycle of a laser at 810 or 532 nm it was difficult to histologically distinguish any impairment of the retina or damage to retinal pigment epithelium (RPE) in the area of the laser spot [21].

STUDY COHORT

Patients for whom treatment for DME using micropulse mode of laser was commenced at our department between February 2012 and October 2013 were included in the study. The observation period was 12 months.

CHARACTERISTICS OF STUDY COHORT

The cohort included 23 eyes of 15 patients (12 men and 3 women). In 7 patients only one eye was monitored (in the other eye of one patient the condition was after pars plana vitrectomy and MLI peeling, in another patient the condition was after central retinal vein occlusion, in one patient the condition was after branch retinal vein occlusion and another 4 patients had DME in only one eye). The study cohort did not include patients for whom therapy with anti-VEGF preparations was possible or who were transferred to this therapy during the course of observation. The average age of the patients was 67.7 years (standard deviation (SD) 10.1 years, median 68 years). Two patients were treated for type 1 DM, 13 patients for type 2 DM. The duration of DM was from 2 to 31 years, on average 18.8 years, SD 8.2 years, median 20 years. A total of 7 patients were treated with peroral antidiabetic drugs, 5 patients with insulin and 3 patients with a combination of antidiabetic drugs and insulin. 11 patients had been treated for arterial hypertension in their anamnesis, 3 had experienced myocardial infarction and 1 patient had experienced a stroke. Glycated haemoglobin (HbA_1C) at the beginning of observation was on average 68.1 mmol/mol, SD 17.2 mmol/mol, median 66 mmol/mol (min. 45, max. 115 mmol/mol). After 6 months average HbA_1C was 65.5 mmol/mol, SD 16.4 mmol/mol, median 65 mmol/mol (min. 40, max. 108 mmol/mol). At the end of the observation period HbA_1C was on average 66.3 mmol/mol, SD 13.7 mmol/mol, median 63 mmol/mol (min. 50, max. 95 mmol/mol). At the beginning and the end of observation, 6 patients had $HbA_1C \leq 60$ mmol/mol.

Medium-advanced non-proliferative DR (NPDR II) was diagnosed in 9 eyes, severe non-proliferative DR (NPDR III) in 13 eyes and incipient proliferative DR (PDR I) in one eye. Before the beginning of micropulse treatment of the macula, focal photocoagulation (PC) of the retina outside of the macula was performed in the 9 eyes with NPDR II, and panretinal photocoagulation (PRPC) was performed in the other 14 eyes. PRPC was completed always more than 3 months before the commencement of micropulse treatment. Focal PC of the medium periphery of the retina was performed also before micropulse PC, and was supplemented in the case of necessity. The total period from the first photocoagulation of the retina up to the commencement of treatment of DME by micropulse laser was within an interval from 3 months to 11 years, on average 4.1 years, SD 3.6 years, median 3 years. The duration of maculopathy was from 1 month to 10 years, on average 2.2 years (SD 2.4 years, median 1.3 years). Focal DME was described in 8 eyes, and diffuse DME in 15 eyes (table 1). Before the beginning of micropulse PC, focal PC of the macula was performed on 15 eyes. Focal PC was always performed at least 3 months before micropulse PC. On average focal PC of the macula was performed 10.8 months before micropulse PC (SD 6.7 months, median 11 months).

METHOD

Photocoagulation of the macula was performed on all patients using a yellow diode laser with a wavelength of 577 nm, model IQ 577™ IRIDEX. A 5% duty cycle mode of micropulse laser beam was used. This means that upon a total exposure of 200 ms, the effective dose of the laser was divided into 100 micropulses, the sum length of which is 5%, i.e. 10 ms. Each micropulse lasted 2.0 ms, in which the laser was activated for 0.1 ms and switched off for 1.9 ms. The dosing of energy was performed within an area nasally from the papilla by continual mode of the laser, a spot with a diameter of 100 µm was used, time 100 ms and energy initially 50 mW. The energy was progressively increased up to a level when a visible spot

Tab. 1 Characteristic

Characteristic	value
Age - mean, SD, median (years)	67,3 ±10,13 68
Number of mens	12
womans	3
DM type 1 - number of patients	2
type 2 - number of patients	13
Duration DM - mean, SD, median (years)	17,4 ±8,2 18
Treatment of DM: PAD - number of patients	7
insulin - number of patients	5
PAD and insulin - number of patients	3
Anamnesis: hypertension - number of patients	11
heart atack in anamnesis - number of patients	3
stroke in anamnesis - number of patients	1
nefropathy	3
HbA_1C baseline -mean, SD, median (mmol/mol)	68,1 ±17,3 66
6 months - mean, SD, median (mmol/mol)	65,5 ±16,4 65
12 months - mean, SD, median (mmol/mol)	66,3 ±13,7 63
DR moderate nonproliferative - number of eyes	9
severe nonproliferative - number of eyes	13
mild proliferative - number of eyes	1
Duration of laser treatment - mean, SD, median (years)	4,1 ±3,6 3
Duration of maculopathy - mean, SD, median (years)	2,2 ±2,4 1
DME focal - number of eyes	8
diffuse- number of eyes	15
Baseline central retinal thickness (µm)	≥200
Baseline BCVA (number of ETDRS letters)	≥85

remained on the retina. A micropulse mode of 5% duty cycle was set, exposure 200 ms and energy 2-3 times greater than the energy measured upon dosing. The spots were placed alongside each other as ETDRS letters, i.e. the gap between the spots is the same size as the laser spot. The spots are not visible on the retina, orientation is possible only according to memory. Micropulse photocoagulation was performed always according to the current condition of the macula, and as a result upon improvement of the finding it was not performed at each follow-up examination.

Vision was measured with best correction on ETDRS optotypes, and is presented in the results in letters of ETDRS optotypes (hereinafter "letters") as best corrected visual acuity (BCVA).

Retinal thickness was measured on OCT from the beginning of the study on a Zeiss Stratus instrument, and from February 2014 on a Spectralis instrument. In both cases, measurement was set to the distance between the membrana limitans interna and the Bruch's membrane. The observation interval was 3 months.

RESULTS

At the beginning of observation, CRT was on average 380.4 µm (SD 146.0 µm, median 380 µm). After 3 months CRT was on average 368.1 µm (SD 141.6 µm, median 320 µm). After 6 months CRT was on average 327.5 µm (SD 105.6 µm, median 323 µm). After 9 months CRT was on average 329.2 µm (SD 113.2 µm, median 317 µm). After 12 months CRT was on average 301 µm (SD 110.6 µm, median 288 µm). The difference between initial average CRT and the average after 12 months was -79,5 µm. According to the t-test the difference is statistically significant on a 1% level of significance (table 2, graph 1).

A reduction of CRT by more than 30 µm was achieved in a total of 13 eyes (57%) during the course of observation. In 6 eyes (26 %) the difference between the first and last measurement was less than or equal to ± 30 µm, and in 4 eyes (17 %) there was a worsening by more than 30 µm.

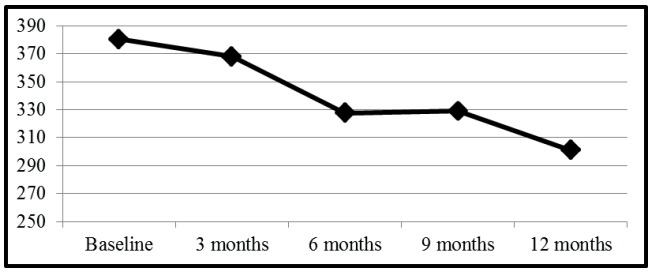
At the beginning of observation, average BCVA was 61.8 letters (SD 14.2, median 60 letters). After 3 months 62.2 letters (SD 14.4, median 65 letters). After 6 months 59.5 letters (SD 13.6, median 60 letters). After 9 months 57.6 letters (SD 12.8, median 58 letters). After 12 months 59.2 letters (SD 14.2, median 60 letters). The average difference between initial BCVA and after 12 months was -2.7 letters. The difference according to the t-test is not significant (table 3, graph 2).

In a total of 5 eyes (22 %) there was an improvement of BCVA by at least 5 letters during the course of observation. In 9 eyes (39%) BCVA remained unchanged and in 9 eyes (39%) there was a deterioration by more than 5 letters (fig. 1). In two eyes there was a deterioration by 15 letters or more of ETDRS, specifically 1x by 15 letters and 1x by 16 letters.

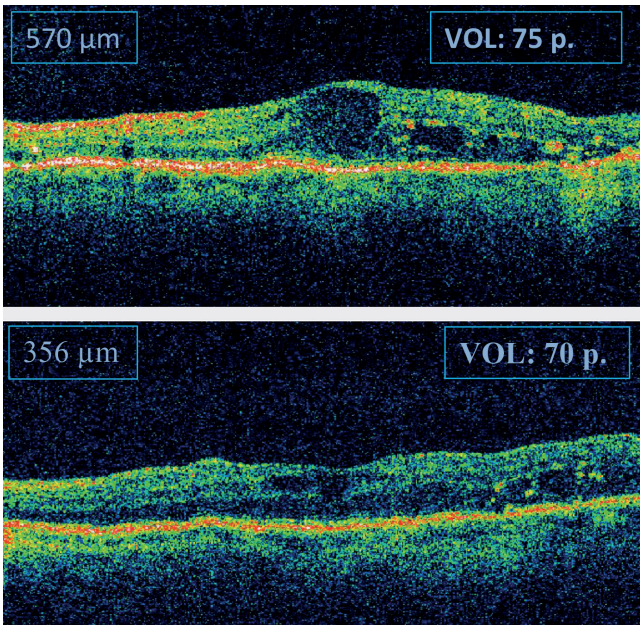
The average number of photocoagulation sessions was

Table 2 Central retinal thickness (CRT)

CRT (µm)	Průměr	SD	Medián
N=23	Mean	SD	Median
Baseline	380.4	146.0	380
3 months	364.1	141.6	320
6 months	327.5	105.6	323
9 months	329.2	113.2	317
12 months	301.0	110.6	288



Graph 1 Central retinal thickness (µm)



Obr. 1 Příklad OCT: snížení CRT po roce o 214 µm, ale došlo ke zhoršení vízu o 5 písmen.

3.0 (SD 0.8, median 3 sessions). Photocoagulation of the macula was performed once on 1 eye (4%), twice in 5 eyes (22%), three times in 10 eyes (44%) and four times in 7 eyes (30%). The average number of points was 929.4 (SD 504.5, median 882.5). The average energy used for photocoagulation was 307.9 mW (SD 95.7 mW, median 300 mW).

DISCUSSION

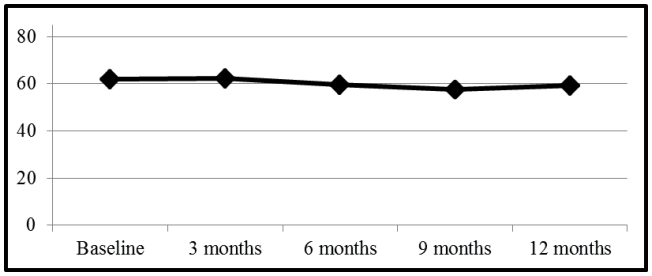
We can compare our clinical results with the results of clinical studies, here the method of classic grid photocoagulation was used. In the RESTORE study one group of patients were treated with laser monotherapy (an injection of ranibizumab was simulated), and after 12 months BCVA was improved by 0.9 letters and CRT reduced by 61.3 µm. The entrance criteria were BCVA within a range of 39 to 78 letters of ETDRS and DME reducing vision [11]. The same procedure i.e. simulation of a ranibizumab injection and active treatment by laser was used also in the study DRCR.net. Here there was an improvement of BCVA after 12 months by an average of 3 letters, and a reduction of CRT by 102 µm. The entrance criteria were BCVA between 24 and 78 letters and DME incorporating the fovea [2].

From the literature on treatment of DME by micropulse laser it is possible to conduct a comparison with the work from the universities of Rome and Padua, which presents the results of treatment of DME by a micropulse laser with a wavelength of 810 nm. Over a year-long observation period there was an improvement of BCVA by 1 letter (0.02 logMAR) and a reduction of CRT by 46.6 µm. The entrance criteria were BCVA of minimum 35 letters and CTR greater than or equal to 250 µm [19]. Another study from the university in Sao Paulo compared micropulse treatment with normal and high density of points using a laser of 810 nm. The entrance criteria were BCVA between 20/40 and 20/400 and CRT between 250 and 500 µm. Better results were attained by a branch treated with high density of points (close together), after one year they attained an improvement of BCVA by 12.5 letters and a reduction of CRT by 154 µm, against this in the branch with normal density of points there was a worsening of BCVA by 1.5 letters and CTR was reduced by 32 µm [8]. For the purpose of comparison all the BCVA results were converted to ETDRS letters [1].

In our study we also included patients with focal DME with BCVA of 85 letters and CRT lower than 250 µm. In comparison with the above-mentioned studies, we attain worse

Table 3 BCVA (number of ETDRS letters)

BCVA (number of ETDRS letters) N=23	Mean	SD	Median
Baseline	61.8	14.2	60
3 months	62.2	14.4	65
6 months	59.5	13.6	60
9 months	57.6	12.8	58
12 months	59.2	14.2	60



Graph 2 BCVA (number of ETDRS letters)

Table 4 Comparison of our observation with studies and articles about laser treatment of DME.

Study		N	Inclusion criteria		12 months	
			BCVA	CRT	BCVA	CRT
			ETDRS letters	µm	ETDRS	µm
RESTORE (sham + laser)		µm	39-78	≥ 250	+0,9	-61,3
DRCR.net (sham + laser)		293	24-78	CME in fovey	+3	-102
Vujosevic et al.		32	≥ 35	≥ 250	+1	-46,6
Lavinski et al.	high density	42	20-70	250-500	+12,5	-154
	normal density	39			-1,5	-32
Our observation	all group	23	20-85 ≥ 250	200-700	-2,7	-79,5
	subanalysis	17		-0,8	-103,8	

average results of BCVA, in which there was a reduction of BCVA by 2.7 ETDRS letters after one year. Reduction of CRT by 79.5 µm is comparable with some studies. In a sub-analysis of patients with CRT of 250 µm and higher we obtain a group of 17 eyes of 13 patients. Average BCVA at the beginning of observation was 60.1 letters and after one year 59.3 letters, the difference was a deterioration of BCVA by 0.8 letters. Average CRT at the beginning was 438.1 µm and after one year 334.3 µm, thus there was an improvement of CRT by 103.8 µm (table 4).

According to the recommendation of the laser manufacturer, use of micropulse laser therapy of DME is effective especially on patients with mild DME who have good vision and swelling around the fovea, who are not candidates for anti-VEGF injection, or for patients in whom anti-VEGF treatment fails [3]. Our group includes 6 eyes of 5 patients with an edema of 500 µm and more. At the beginning, foveal thickness was on average 573.3 µm, after 12 months 369.2 µm, thus there was an improvement of 204.2 µm. At the beginning BCVA was 55.8 letters and after 12 months 53.3 letters, the difference was thus -2.5 ETDRS letters. An improvement of CRT was achieved in all 6 eyes, but an improvement of BCVA in only 1 eye, 2 eyes remained stable and in 3 eyes there was a deterioration of BCVA. Observation in such a small group is not statistically significant, but indicates the possibility of using micropulse treatement also for more severe forms of DME.

At present, treatment of DME using the anti-VEGF preparation ranibizumab, which according to international clinical trials has higher efficacy than laser treatment [2,11], is approved and paid for by health insurance in the Czech Republic. The reason for not including the patients in our group in treatment using ranibizumab was the experience of 6 patients that in 2012 ranibizumab was not yet paid for by the health insurance company, in a further 11 the indication criteria for payment were not met at the beginning of treatment by micropulse laser, or during the course of observation. The main unfulfilled criterion was more than 12 months duration of DME upon inclusion in the group in 3 patients, in 4 patients HbA_1C was higher than 60 mmol/mol, in 3 patients central foveal thickness was lower than 300 µm and in one patient vision was better than 6/12 on Snellen‘s optotypes (which corresopnds to 4/8 on ETDRS optotypes). Since November 2014 the criteria for payment of ranibizumab for DME have been changed (HbA_1C may be up to 70 mmol/mol and length of DME up to 24 months), but our observation was terminated before this date. A further anti-VEGF preparation approved for treatment of DME in the Czech Republic is aflibercept, which at present has no stipulated payment by health insurance for the treatment of DME. Treatment of ranibizumab or aflibercept within a self-paying regime is not financially affordable for any of our patients.

In our group there was a reduction or stabilisation of DME in 83% of eyes, but an improvement or stabilisation of vision in 61% of eyes. We attribute the continuing deterioration of vision in certain patients despite the improvement of foveal thickness to progressing diabetic neuropathy.

On the basis of this observation, and in accordance with the latest recommendation [10], we have recently changed the therapeutic procedure, in which we use the technique of placing the laser spots as close together as possible. We shall present our new observations in future.

CONCLUSION

Treatment of DME by micropulse laser appears to be an effective method whose main advantage is that it does not result in the formation of scars on the retina, with attendant formation of scotomas. Its use is suitable for two groups of patients. The first group is patients with newly diagnosed DME. In the case of an insufficient effect of laser treatment it is then possible to use treatment with anti-VEGF preparations, since anti-VEGF treatment according to these criteria is possible only after the failure of laser treatment. The second group comprises patients in whom treatment with anti-VEGF is either not possible or fails, and in whom there is also no presence of adhesive membranes, as a result of which surgical solution of DME is not indicated.

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