ORIGINAL ARTICLE

RESULTS OF TREATMENT OF DIABETIC MACULAR EDEMA BY PASCAL LASER SYSTEM

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SUMMARY

Objective: To evaluate functional, anatomical and clinical efficacy, and safety of the pattern scanning laser (PASCAL®) photocoagulation in patients with diabetic macular edema and absence of proliferative diabetic retinopathy.
Methods: From 2008 to 2013 84 eyes of 58 patients (30 men, 28 women) were treated with pattern laser photocoagulation at the Ophthalmology Department at University Hospital Ostrava. Average age at the baseline visit was 65 years. The inclusion criteria included non-proliferative diabetic retinopathy (84 eyes), focal DME (14 eyes), diffuse exudative DME (70 eyes). All the eyes were „treatment naive". The average duration of diabetes was 18 years, average baseline HbA1c value was 8,4%. Either focal laser photocoagulation or grid photocoagulation was performed with the PASCAL photocoagulator. Best corrected visual acuity (BCVA), central retinal thickness (CRT), fundus photography, biomicroscopy and complications were evaluated during the minimum 12months follow-up period. Statistical analysis using parametrical and nonparametrical tests with p less than 0,05 was done.
Results: Mean baseline BCVA was 0,43 logMAR. Values 0,38, 0,37, 0,38 a 0,38 logMAR were observed in the follow-up intervals in the 4th, 6th, 12th and 18th month. In 4 eyes (5%) improvement of more than 3 lines was observed, in 26 eyes (31%) improvement from 0 to 3 lines was observed, in 52 eyes (62%) decrease from 0 to 3 lines was observed and in 2 eyes (2%) decrease of more than 3 lines was observed. Mean baseline CRT was 398 µm, values 370 µm, 362 µm, 349 µm and 338 µm were observed in the follow-up intervals in the 4th, 6th, 12th and 18th month. At the 12th month visit 76 eyes (90%) were stabilized, and in 8 eyes (10%) progression of the disease was observed. No complications were observed during the first 12 monhts follow up.
Conclusion: Pattern scanning laser photocoagulation of DME lead to BCVA and clinical stabilization. In addition to this, it lead to decrease of the CRT. The efficacy was comparable to traditional laser systems with no apparent benefit to the traditional systems. The efficacy was inferior to modern intraocular anti-VEGF (vascular endothelial growth factor) drugs.
Key words: diabetic macular edema, pattern scanning laser, short pulse duration

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INTRODUCTION

Diabetic macular edema (DME) is a significant complication of diabetes and a cause of severe loss of sight in productive age in developed countries including the Czech Republic [14, 15]. To date, the protocol from the Diabetic Retinopathy Study (DRS) and Early Treatment Diabetic Retinopathy Study (ETDRS) is considered the standard technique for performing laser photocoagulation of the retina. This protocol was based on the technical prerequisites of the available laser systems, and its effectiveness was supported by therapeutic results, and especially by the above-stated randomised trials [9, 10, 29, 30]. For DME the recommended procedure is either focal direct treatment of individual microaneurysms or of areas of percolation by individual points, or performance of grid photocoagulation of the retina in the area of retinal thickening – macular edema of "non-ischemic" type. According to the above-stated studies, performance of laser photocoagulation of the retina for non-ischemic type DME is effective.

In the last decade new technologies have been introduced into industry and medicine, leading to the development of a new generation of laser systems. These are capable of producing individual laser impulses in far shorter durations (0.01 s and shorter). At the same time, these impulses are directed in quick sequence in "patterns". These innovations enable alteration of the standard therapeutic protocols. However, data about the short-term and long-term effectiveness of such performed procedures, and also about the safety of these procedures, is not yet available.

The objective of the submitted study is to present our experience with the performance of laser photocoagulation by means of a laser system using patterns and short impulse durations on patients with DME with absence of PDR.

METHOD

In the period from 1 June 2008 to 30 June 2013, 84 eyes of 58 patients treated at the Department of Ophthalmology at the University Hospital Ostrava were selected for inclusion in the study cohort. All had presence of exudative clinically significant DME demonstrated by fluorescence angiography, fundus photography and biomicroscopic examination of the fundus, initial best corrected visual acuity on a logMAR scale within the range of 0.00 – 1.00, presence of mild to advanced NPDR, and length of duration of DME up to 24 months. Focal laser treatment or macular grid at impulse durations of 20 ms and use of patterns was performed on all the patients. For all patients an anamnesis was taken, vision with best corrected distance vision was determined on Precision Vision optotypes with notation for testing at 4 meters – ETDRS chart 1,2,R + Illuminator Cabinet Mod. 2425E (Precision Vision, First Street, La Salle, IL, USA), the result was converted according to the conversion table to logarithm of minimal angle of resolution (logMAR), and examination of the anterior segment was performed on a slit lamp. Afterwards the fundus was examined biomicroscopically in artificial mydriasis with a 90D Superfield NC® lens (Volk Optical, Inc., Ohio, USA), photography of the posterior pole was performed using a camera FF450 Plus IR, Carl Zeiss with Visupac Digital Imaging System (Carl Zeiss Meditec, Inc., Dublin, California, USA), and fluorescence angiography was also performed using this camera. At the same time spectral OCT macular module was performed on OCT Spectralis (Heidelberg Engineering, Inc., Carlsbad, California, USA).

Laser photocoagulation of the retina was performed using a Pascal Photocoagulator (Topcon Medical Laser Systems, Inc., Santa Clara, CA, USA). First of all the output required for the production of one spot was titrated, the duration of an individual impulse was 20 ms, size of the spot 100 µm and the output was progressively increased until a grey coloured laser spot was attained or up to direct photocoagulation of percolating microaneurysms. Upon focal treatment of the macula, either individual microaneurysms or the area of clinically significant macular edema were photocoagulated.

In the case of diffuse exudative edema, a complete or incomplete macular grid was performed. A quadrant or semi-quadrant circular section was used, and treatment of the surface of the retina indicated for photocoagulation was performed.

During the course of the observation period, the parameters illustrated in table no. 1 were observed at regular time intervals.

At subsequent follow-up examinations the functional, anatomical and clinical effect of treatment was evaluated, and in addition the frequency of complications was analysed in the groups.

BCVA and a change thereof in comparison with the initial visit was evaluated at individual intervals. The objective was to stabilise visual acuity in the sense of improvement or absence of a deterioration at subsequent follow-up examinations in comparison with the initial examination. Additionally the proportions of patients were evaluated according to the change of BCVA (improvement by more than 3 rows, improvement within the range of 0.01 – 3 rows, deterioration within the range of 0 – 3 rows and deterioration by more than 3 rows according to ETDRS optotypes).

The development of central retinal thickness was also evaluated on OCT. The objective was to demonstrate reduction or at least stabilisation of retinal thickness in comparison with the initial visit.

The clinical effect was evaluated as fulfilling the purpose of laser photocoagulation of the retina – stabilisation. Regression of DME or its persistence with the same CRT was evaluated as stabilisation (S). A condition in which there was a worsening of DME together with an increase in CRT was evaluated as progression (P). From this group a sub-group of "failure of treatment" (F) was further detached, in which even further therapeutic intervention did not bring about a stabilisation of the disease and it was not possible to influence the condition further therapeutically. A further therapeutic intervention was performed in the case of progression (multiple repetition/supplementation of laser photocoagulation, pars plana vitrectomy or anti-VEGF treatment) and the evaluation was completed.

The clinical effect was also assessed by means of an evaluation of the complications in the study cohort (onset and/or progression of another serious ocular pathology influencing the results of the examination – e.g. cataract, vitreomacular traction syndrome etc.).

We first of all provided a description of the variables by methods of descriptive statistics. Numerical characteristics were designated for joint variables (arithmetical average, median, standard deviation), and a box graph was plotted. Nominal variables (sex, stabilisation of biomicroscopic finding, type of treatment etc.) were described by their absolute and relative frequencies. A Shapiro-Wilk normality test was also conducted for joint variables.

To determine the significance of changes during the observation period for joint variables, a dispersion analysis was used for repeated measurements or a Friedman test, depending on their normality.

Table 1 Evaluated parameters and time intervals of follow-up examinations in study cohort (M - month)

	0	4M	6M	12M	18M	24M	30M	36M	42M	48M
BCVA	x	x	x	x	x	x	x	x	x	x
OCT	x	x	x	x	x	x	x	x	x	x
FA	x									
Fundus photography	x	x	x	x		x		x		x
Biomicroscopy	x	x	x	x	x	x	x	x	x	x

Total change of BCVA was divided into the categories of improvement by more than 3 rows, improvement within the range of 0.01 – 3 rows, deterioration within the range of 0 – 3 rows and deterioration by more than 3 rows. A comparison of the structure of frequency of these categories within the framework of the individual methods was conducted using an $\chi 2$ test or Fisher's exact test. The structure of stabilisation of the biomicroscopic finding was similarly compared. The selected observation period constituted 18 months. A longer observation period was selected only for evaluating the stabilisation of the biomicroscopic finding, namely 48 months.

All the statistical tests were conducted bilaterally on a 0.05 level of significance. The statistical analysis was conducted with the help of the software IBM SPSS Statistics version 22.

RESULTS

The general characteristics of the study cohort are illustrated in table no. 2.

Best corrected visual acuity

Initial average BCVA was 0.43 logMAR, at subsequent follow-up examinations in the 4th month 0.38, in the 6th month 0.37, in the 12th month 0.38 and in the 18th month 0.38 logMAR. The development of BCVA is illustrated graphically including the median and the 1st and 3rd quartiles in fig. 1 and 2.

Parametric and non-parametric (Friedman test) statistical tests also demonstrated that the distribution of values of initial BCVA and BCVA at subsequent examinations is not the same, on the contrary it is statistically significantly improved at the subsequent examinations in comparison with the initial visit.

Table no. 3 illustrates an independent evaluation of the distribution of patients with an improvement by more than 3 rows, improvement within the range of 0.01 – 3 rows, deterioration within the range of 0 – 3 rows and deterioration by more than 3 rows of ETDRS optotypes 18 months from the beginning of observation.

Central retinal thickness

Initial average CRT was 398 µm, at subsequent follow-up examinations in the 4th month 370 µm, in the 6th month 362 µm, in the 12th month 349 µm and in the 18th month 338 µm. The development of CRT including the median and the 1st and 3rd quartile is illustrated graphically in fig. 3.

Parametric and non-parametric (Friedman test) statistical tests also demonstrated that the distribution of values of initial CRT and CRT at subsequent examinations is not the same, on the contrary it is statistically significantly improved at all the subsequent examinations in comparison with the initial visit and at the examination in the 18th month.

Effectiveness and treatment of complication

In the period up to 6 months from the beginning of observation, stabilisation of the clinical finding was observed in all patients included in the study cohort. In the period between the 6th and 12th month of observation there was a progression of the pathology in 8 eyes. Table no. 4 illustrates the numbers of eyes and an evaluation of the effectiveness of treatment in the individual observation intervals and the proportion of stabilisation, progression and failure of treatment.

The clinical effect of treatment (stabilisation of biomicroscopic finding – BM) in all eyes during the course of the entire observation period is illustrated by the graph in fig. 4.

No complications were noted during the 12 months of the observation period.

DISKUSE

In the selection of subjects for the study cohort we included patients who did not have entirely uniform characteristics of the overall pathology (diabetes mellitus type 1 and type 2 and degree of compensation of diabetes) and the type of DME. Such a uniform study cohort would be difficult to select even within the framework of a global multicentric prospective randomised trial, which was not our ambition. Our ambition was rather to demonstrate set targets in a smaller group approximating regular clinical practice with the use of regular statis-

Tab. 2 General characteristics of study cohort (N - number of eyes; HbA1c - glycated haemoglobin; M - month)

Characteristics	Patients (n=84)
Age – median (25, 75 percentile)	65 (57.70)
Men	41 (48.8%)
Women	43 (51.2%)
DM 1	11 (13.1%)
DM 2	73 (86.9%)
focal DME	14 (16.7%)
diffuse DME	70 (83.3%)
Duration of diabetes	18 (12.24)
HbA1c – median (25, 75 percentile)	8.4% (7.1 9.2)
Follow-up – median (from, to)	24 M (18.48)

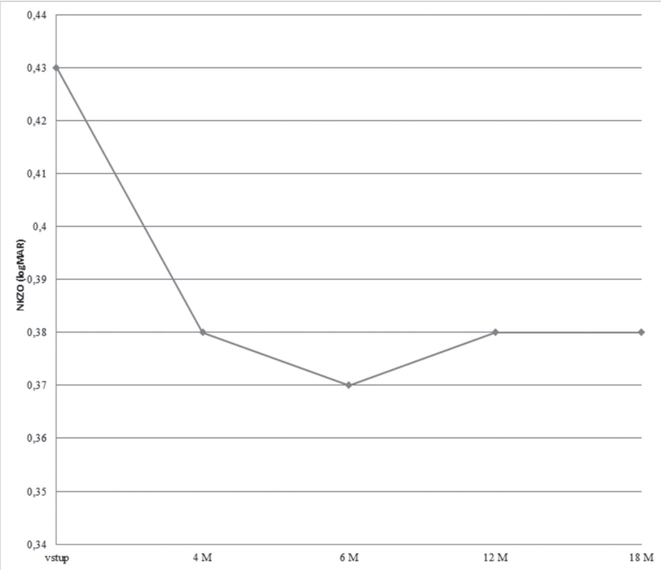

Fig. 1 Development of average BCVA in individual intervals (M – month)

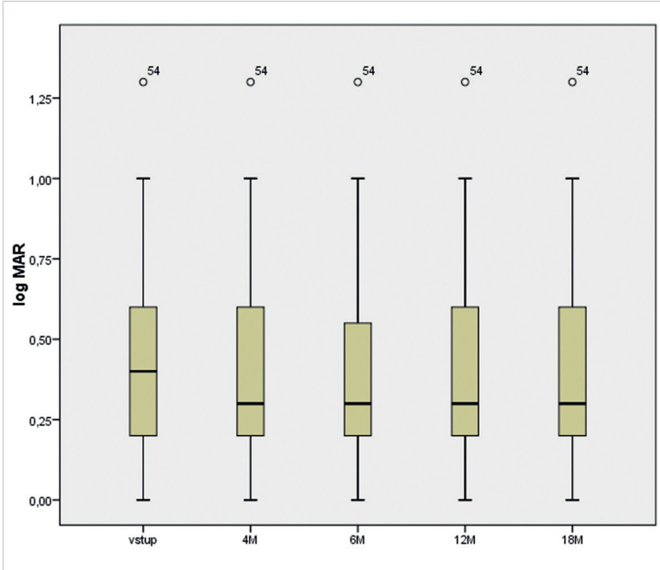

Fig. 2 BCVA values at follow-up visits in 4th, 6th, 12th and 18th month (M - month)

Tab. 3 Distribution of BCVA in individual categories (ETDRS charts)

	Improvement	Improvement	Worsening	Worsening	Total
	≥ 3 lines	0,01 - 3 lines	0-3 lines	> 3 lines	
Number of eyes	4	26	52	2	84
Percentage	4.8%	31,0%	61,9%	2,4%	100,0%

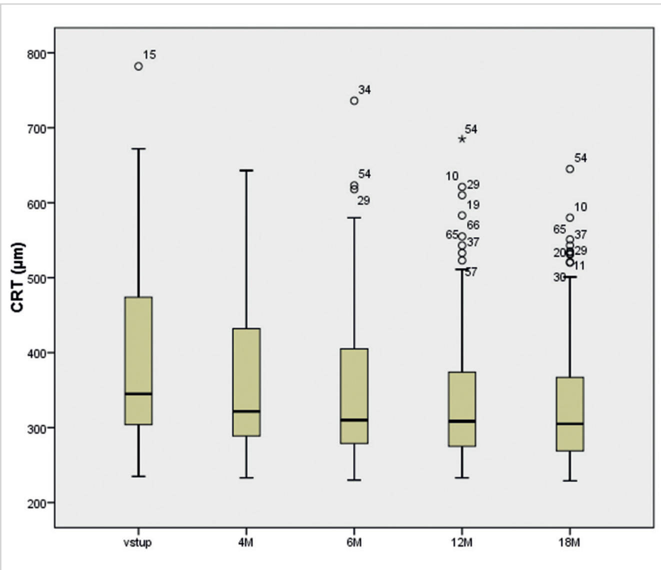

Fig. 3 CRT values at follow-up visits in 4th, 6th, 12th and 18th month (M - month)

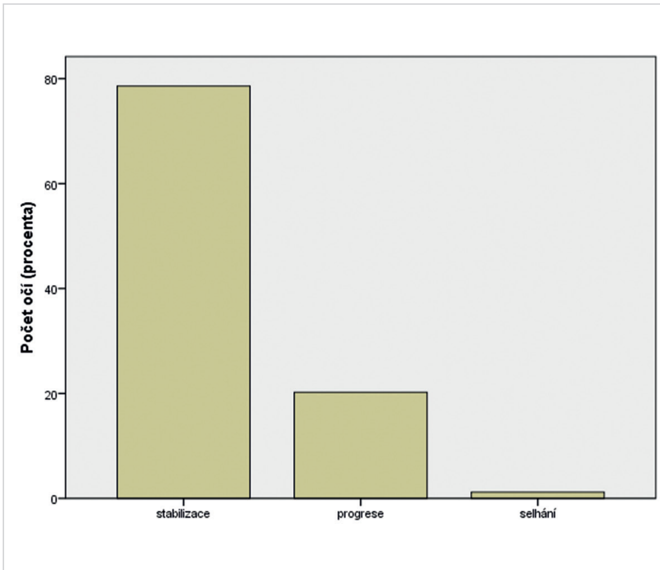

Fig. 4 Clinical effect of treatment

Tab. 4 Efficacy of treatment in individual intervals (N – number of eyes)

	12M	18M	24M	30M	36M	42M	48M	Total	Total %
n	84	76	65	36	32	6	5	84	100%
stabilization	76	73	61	35	31	5	5	66	78.6%
progression	7	3	4	1	1	1	0	17	20.2%
failure	1	0	0	0	0	0	0	1	1.2%

tical and analytical methods of medicine, based on evidence.

From the analysis of BCVA it is possible to judge that stabilisation of BCVA was significant in all patients. A deterioration of visual acuity occurred especially in patients who at the beginning of the study had BCVA in logMAR units on the boundary of 1.0.

For several decades, classic laser photocoagulation of diabetic macular edema was the gold standard of treatment of this clinical unit, the foundations of which were laid by the ETDRS study. In the case of early photocoagulation of the retina, a loss of 3 and more rows occurred in 5% of eyes after 1 year, in 7% of eyes after 2 years and in 12% after 3 years. Improvement by 3 or more rows was observed in 3% of eyes. ETDRS also examined retinal thickening, which was observed in 74% of eyes with CSME at the beginning of treatment and only in 35% of treated eyes following early focal photocoagulation, and in 63% of eyes following deferred focal photocoagulation [8-10]. In recent years the effectiveness of laser therapy has been compared especially with the application of antibodies to counter endothelial growth factor (anti-VEGF) into the vitreous body. In large randomised trials a change of logMAR has been observed at 12 months from -0.02 to 0.03 as well as a reduction of CRT from 57 to 103 µm following laser treatment. A gain of 3 or more rows was observed in the above-stated studies in 8 – 15% of patients, and a loss of 3 or more rows in 4 – 10% of patients [2, 6, 7, 12, 19]. We consider these results comparable with our observation. Similar conclusions ensue from a study comparing the "modified" ETDRS protocol and "mild macular grid" (change up to + -0,02 logMAR and reduction by 49 - 88 µm) [31]. Upon use of a micropulse diode laser, the change of BCVA during the observation period was +0.13 logMAR [17]. The effectiveness of the laser with use of a very short impulse duration and patterns has the potential to ensure a lower risk of occurrence of scarring and collateral damage to tissue [6, 22]. In recent years, studies have also been published on the use of lasers with short impulse durations and patterns in diabetic retinopathy and DME. However, these studies either aimed to describe morphological changes on the retina or had substantially less patients, a shorter observation period and less examined parameters [13, 16, 20, 21, 27]. Upon the use of patterns in the macula we did not observe any complications, nevertheless in certain cases it was not possible to use the entire macular pattern at once partially due to poor patient co-operation and a higher risk of iatrogenic damage to the patient, and partially due to asymmetrical macular edema, in which it was difficult to titrate the output necessary for the creation of a spot. Any time saving in this case is also minimal. During the treatment we did not observe any complications of the character of clouding into the foveola or rupture of blood vessels, retinal pigment epithelium (RPE), haemorrhage in the macular region etc. In the literature "stabilisation" upon use of conventional lasers is evaluated especially in relation to visual acuity. However, we consider stabilisation of visual acuity and stabilisation of the pathology with regard to our definition, which in our cohort was 78.6%, to be comparable data, which corresponds to the observed experiences of other authors [3, 5, 18, 23]. In their cohort of 111 eyes, Řehák et al. observed stabilisation of visual acuity in 74 – 78 % of patients over the course of 1 – 5 years following the commencement of photocoagulation of the retina [25]. Improvement by 2 or more rows over 2 years was observed in 17% of eyes. It is possible to achieve comparable results by means of "sub-threshold" lasers or selective lasers [26]. A certain weakness of the study could be the absence of a sub-analysis of the results of treatment of focal and diffuse DME. In our study cohort there was a pronounced predominance of diffuse DME, and so the results correspond rather to the treatment of this type of DME. For a valid analysis of patients with focal DME it would be necessary to include more patients with this type of DME in the study cohort.

Overall we evaluate the advantages of the Pascal laser system for diabetic macular edema as markedly limited for a number of reasons. The potential risk of damage to tissue upon unintentional damage to the centre of the foveola may be higher, whereas the time saving in comparison with application in one point in this case is negligible. At the same time, the required energy is more difficult to titrate with regard to the different thickness of the retina both in the physiological state and in the area of irregular diffuse macular edema. In addition it is necessary to try to avoid application of laser points into the area of hard exudates or haemorrhage, which is often impossible upon use of a pattern. There remains "only" the advantage of the short impulse duration. However, the main limiting factor is the high efficacy of intraocular pharmaceuticals used in the field of macular pathologies, which in certain recommended procedures have already rendered laser therapy the method of second or lower choice, or a choice within combined treatment [1, 11]. Satisfactory effectiveness upon treatment of DME by laser can be expected only upon treatment of focal DME with initial good visual acuity. By contrast, laser photocoagulation of DME is no longer considered the method of first choice for diffuse DME [1, 11]. At present it has been replaced by pharmacotherapy using steroids – frequently depot steroids (e.g. dexamethasone or fluocinolone) – and especially anti-VEGF substances – ranibizumab, aflibercept and bevacizumab. In the case of these preparations it is possible to expect not only a stabilisation of visual acuity and the finding following the commencement of treatment, but in particular a clinical and functional improvement [24, 28]. At this point it is necessary to state that in the Czech Republic at present anti-VEGF treatment is covered only upon the fulfilment of a range of indication criteria, and as the method of second choice after laser treatment fails. The depot preparations dexamethasone and fluocinolone are not paid for from public health insurance in the Czech Republic whatsoever in the indication of DME. Bevacizumab does not have registration for administration to the vitreous body, and its application thereto may be accompanied by ocular and general adverse effects. The patients included in our study cohort were initially treated by laser because treatment with intraocular pharmaceuticals was not available at the time of their inclusion in the cohort. Overall, however, it is possible to conclude unequivocally that laser photocoagulation with the use of patterns and shorter impulse duration alone does not currently bring any significant benefit either in comparison with conventional lasers, and especially in comparison with pharmacotherapy.

CONCLUSION

The performance of laser photocoagulation of DME using patterns and far shorter impulse durations led to a stabilisation and improvement of BCVA (on average by 1 row of ETDRS optotypes) in patients with DME, in 5% of patients there was an improvement by 3 rows of ETDRS optotypes during the observation period of 4 – 18 months. Following the performance of laser photocoagulation of DME using patterns and far shorter impulse durations there was a significant reduction of CRT during the observation period of 4 – 18 months. The impact on CRT was comparable with conventional photocoagulation of the retina. Following the performance of laser photocoagulation of DME with the use of patterns and far shorter impulse durations, stabilisation of the clinical finding was achieved in 79% of afflicted eyes within an observation period of 6 – 48 months, and no complications were noted during this observation period. The impact on laser photocoagulation on BCVA, CRT and stabilisation of the clinical finding was comparable to that of conventional photocoagulation of the retina.

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