Efficacy and side effects of individualized panretinal photocoagulation

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Running head:

Same efficacy for less retinal laser in PDR

Abbreviations:

Dark adaptation (DA)

Diabetic retinopathy (DR)

Panretinal photocoagulation (PRP)

Proliferative diabetic retinopathy (PDR)

Retinal quality of life (RQOL)

Vascular endothelial growth factor (VEGF)

Visual fields (VF)

Visual function questionnarie-25 (VFQ-25)

Abstract

This was a pilot study, where we demonstrated comparable efficacy and side effects of less extensive versus standard panretinal photocoagulation in patients with treatment-naïve proliferative diabetic retinopathy.

Panretinal laser photocoagulation (PRP) is considered the standard treatment of PDR[1], but given the invasive nature of the treatment, side-effects like loss of visual fields (VF)[2] and night vision[3] as well as diabetic macular edema (DME)[4] can be expected.

To address this, we conducted a prospective, single-blinded randomized clinical trial (RCT) of patients with treatment-naïve PDR, where we investigated efficacy, side effects and retinal quality of life (RQOL) of patients treated with individualized PRP (targeting only affected retinal quadrants) as compared to standard (all quadrants) PRP.

The current study was a six-month 1:1 single-blinded RCT (https://clinicaltrials.gov, identifier: NCT03113006) including 53 eyes of 47 patients with treatment-naïve PDR. Patients were randomized to navigated retinal photocoagulation (Navilas®, OD-OS GmbH, Teltow, Germany) performed as standard treatment for all retinal quadrants (n=27) or individualized PRP addressing only quadrant(s) with retinal neovascularization (n = 26) (Fig. S1 available at www.ophthalmologyretina.org). The treatment was performed in two sessions, with one week in between treatments, at baseline (BL) in both groups. Participants were included at Odense University Hospital, Odense, Denmark between June 1st, 2017 and February 1st, 2019. Exclusion criteria were DME in the affected eye (central subfields thickness >300 μm), age <18 years, pregnancy and/or hazy optic media that could prevent PRP. Randomization was performed by Research Electronic Data Capture (REDCap) database under Open Patient data Explorative Network (OPEN). The study was conducted in accordance with the Helsinki Declaration II and in accordance with good clinical practice. Patients provided both written and oral consent to participation. The project was approved by the Research Ethics Committee of Southern Denmark (Project-ID: S-20160168) and The Danish Data Protection Agency.

Principal endpoint was defined as progression of PDR as given by disease progression, vitreous hemorrhage, need for additional retinal photocoagulation, or need for vitrectomy. Disease progression was evaluated at month (M) 3 and 6 by lesion growth (assessed by ophthalmoscopy and wide-field fundus photo) or increasing leakage by ultra-wide-field fundus fluorescein angiography (UW-FFA, Optos, Dunfermline, United Kingdom).

To evaluate side-effects at M6, we measured development in visual fields (VF, 30-2 perimetry, ZEISS Humphrey® Field Analyzer 3, Carl Zeiss, Oberkochen, Germany) and in dark adaptation (DA, Goldmann-Weekers dark adaptometer, Haag-Streit Holding, Köniz, Schweiz), while covering the fellow-eye. Mean Deviation (MD) and Visual Field Index (VFI) were recorded for VF. A validated Danish version of Visual Function Questionnarie-25 (VFQ-25) including the appendix VFQ-39 [5] was filled out by the patients at BL and M6.

Mann-Whitney U test and Wilcoxon signed-rank test were used as appropriate to analyze differences between groups and time points. Chi2 test was used to evaluate if there were any differences in number of patients who progressed in the two groups.

A total of 53 eyes of 42 patients were included. Patients did not differ according to age (years), distribution of sex, ethnicity, body mass index (kg/m^2), diabetes type, diabetes duration (years), smoking status, central retinal thickness (μm), blood pressure (mmHg), HbA1c (mmol/mol), or blood lipids (mmol/L) (Table S1, available at www.ophthalmologyretina.org).

Progression of PDR did not differ between patients treated by individualized and standard PRP (48.0% vs. 59.3%, p=0.27, Table 1), even though the former by protocol received fewer photocoagulation spots (1524±1096 vs. 2165±915, p=0.006).

Visual fields and dark adaptation were obtained in 44 (individualized: 24, standard: 20) and 42 (individualized: 23, standard: 19) eyes, respectively. VF did not differ between the individualized and standard group at M6 in either VFI (92.5±7 vs. 95.5±8, p=0.13) or MD (-4.70±4.23 vs. -3.47±4.22, p=0.25). Dark adaptation analysis (log unit) showed no differences between the individualized and standard group at M6 (0.41666±0.051 vs. 0.41340±.0.059, p=0.76).

VFQ-25 were obtained in 26 patients (individualized: 15, standard: 11). There were no differences between groups at M6 (90.9±2.4 vs. 89.6±10.4, p=0.41). Though, a statistically significant worsening between BL and M6 was found in the individualized group (93.5±7.55 vs. 90.9±2.40, p=0.04). However, in post-hoc analysis excluding the VFQ-39 appendix, we found no differences in the groups from BL to M6 (individualized p=0.71, standard p=0.69), or between the groups at M6 (89.1±9.3 vs. 86.5±10.9, p=0.45).

In this prospective RCT of patients with treatment-naïve PDR, we found that individualized PRP, targeting only affected retinal quadrants, had the same efficacy as full PRP. Furthermore, side effects and RQOL did not differ between the two groups.

VF and DA ability are determined by the function of the photoreceptor cells. In an earlier study, VF and DA were found to be affected in patients with PDR both before and after PRP[2]. In PRP, the retinal pigment epithelium and photoreceptors are altered and replaced by scar-tissue. A previous study reported that navigated laser leads to more uniform laser burns compared to conventional pattern scan laser[6], and this might explain our results that were somewhat in opposition to the results of DRCR.net Protocol S that reported of VF-loss secondary to PRP[7].

We conclude a less intensive, individualized retinal photocoagulation, targeting only retinal quadrants with retinal neovascularization, has a similar efficacy as standard PRP in patients who are regularly seen in the clinics. In addition, limited side-effects, balanced between groups, could indicate a gentler approach performed by the navigated laser system used in both treatment arms. This pilot-study adds to the ongoing discussion of individualizing and balancing efficacy and side-effects in PDR. While VA-loss was prevented at M6 in our study, we cannot speculate to the long-term sustainability of results. Hence, upcoming randomized trials, addressing long-term VA and treatment efficacy, and including additional relevant endpoints like electroretinography, would be important to confirm these findings.

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