Original Article

Optic nerve head perfusion changes in eyes with proliferative diabetic retinopathy treated with intravitreal ranibizumab or photocoagulation: a randomized controlled trial

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ABSTRACT

Background: Proliferative diabetic retinopathy (PDR) is a serious sight-threatening disease, and half of the patients with high-risk PDR can develop legal blindness within 5 years, if left untreated. This study was aimed at comparing panretinal photocoagulation (PRP) and intravitreal ranibizumab injections in terms of radial peripapillary capillary (RPC) density on optical coherence tomography angiography (OCTA) in patients with treatment-naive PDR.

Methods: This open-label, prospective, randomized clinical trial included 50 patients with treatment-naive PDR with optic disc neovascularization and randomized them into two groups: group 1, with patients undergoing two sessions of PRP 2 weeks apart, and group 2, with patients received three intravitreal ranibizumab injections (0.5 mg) 1 month apart for 3 consecutive months. Patients underwent a full ophthalmological examination, including best-corrected distance visual acuity (BCDVA) measurement in the logarithm of minimal angle of resolution (logMAR) notation and OCTA before intervention and monthly after the last laser session or the first intravitreal ranibizumab injection for 3 months of follow-up. Visual field (VF) was tested at the beginning and end of 3 months.

Results: Forty-two (84%) eyes completed the 3-month follow-up, including 22 eyes in the PRP group (88%) and 20 (80%) eyes in the ranibizumab group. The two groups were comparable in terms of demographic characteristics, diabetes duration, baseline BCDVA, glycated hemoglobin level, OCTA parameters, VF indices, and intraocular pressure (all $P > 0.05$). The RPC density change from baseline to the 3-month follow-up was significantly lower in the PRP group than in the ranibizumab group (mean difference in RPC density change: - 3.61%; 95% confidence interval: - 5.57% to - 1.60%; $P = 0.001$). The median (interquartile range) logMAR change from baseline to the 3-month follow-up (0.0 [0.2]) was significantly higher in the PRP group than in the ranibizumab group (- 0.15 [0.3]; $P < 0.05$). The median changes in central foveal thickness from baseline to the 3-month follow-up differed significantly between the two groups ($P = 0.001$).

Conclusions: In eyes with PDR and neovascularization of the disc RPC density on OCTA increased in the ranibizumab group and decreased in the PRP group. Visual acuity gain was higher in the ranibizumab group than in the PRP group. Future multicenter trials addressing our limitations are required to verify the findings of this study.

KEYWORDS

diabetic retinopathies, lucentis, intravitreal injection, optical coherence tomography, optic nerves, photocoagulation, laser ablation, laser therapies

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INTRODUCTION

Proliferative diabetic retinopathy (PDR) is a serious, sight-threatening disease. Half of the patients with high-risk PDR can develop legal blindness within 5 years, if left untreated [1]. Panretinal photocoagulation (PRP) has been established for over 40 years as an effective treatment for high-risk PDR [1]. However, it causes many complications, such as decreased visual acuity (VA), visual field (VF) defects [2], color vision deficiency [3], macular edema, formation of an epiretinal membrane [4], vitreous hemorrhage, and retinal detachment [1].

These complications indicate that alternative safe treatments, such as ranibizumab, which is used to manage hereditary [5] or non-hereditary retinal diseases [6, 7], could be desirable. Using a different treatment protocol, the Diabetic Retinopathy Clinical Research (DRCR) network [1] found that intravitreal ranibizumab injection (0.5 mg) was non-inferior to PRP after 2 years of follow-up. VA and VF were worse in the PRP group. The rate of vitrectomy and development of diabetic macular edema were more common in the PRP group. The number of eyes without active neovascularization was comparable between the two treatment modalities after 2 years of follow-up [1].

Radial peripapillary capillaries (RPCs) form a vascular network in the retinal nerve fiber layer (RNFL). They are parallel and radial in direction and longer than the average capillary without anastomosis [8]. RPC density decreases with increased severity of diabetic retinopathy and is correlated with VA [9], VF, and RNFL thickness [10, 11]. Assessing RPC density can help study microvasculature changes, particularly in the presence of macular edema [12], which leads to segmentation errors, misidentification of retinal layers, and consequent errors in macular vessel density (VD) measurement compared to healthy eyes [13].

This study was aimed at comparing RPC density between eyes with PDR treated with intravitreal ranibizumab injection and those treated with PRP using optical coherence tomography angiography (OCTA).

METHODS

This prospective, randomized clinical trial was conducted at the Ophthalmology Department, Ain Shams University Hospitals, Cairo, Egypt. All eligible participants attending ophthalmology outpatient clinics were selected in the recruitment period between June 2019 and June 2022. The study was registered in the Pan African clinical trial registry (registration number: PACTR202206535473146). It adhered to the tenets of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Ain Shams University. Informed consent was obtained from all participants for enrollment in the study after a full explanation of the nature of the testing procedures.

We included treatment-naive eyes with PDR and neovascularization of the disc (NVD) and excluded eyes with media opacity, retinal or optic nerve diseases other than diabetic retinopathy, previous intravitreal anti-vascular endothelial growth factor (anti-VEGF) or steroid injection, previous PRP, tractional retinal detachment (TRD), glaucoma, any form of optic neuropathy, and poor-quality OCTA images due to weak signal intensity. The treating ophthalmologists or patients were not blinded. However, those who were involved in gathering data, image acquisition (VF and OCTA), carrying out examinations such as testing best-corrected distance VA (BCDVA) and measuring intraocular pressure (IOP), and performing analysis were masked.

Participants underwent complete general and ophthalmological history-taking and full ophthalmologic examination, including autorefraction (Shin-Nippon Bon Auto Refractometer, Accuref 8001, Rexxam), measurement of BCDVA using the Landolt C VA chart and then converted to logarithm of the minimum angle of resolution (logMAR) notation, detailed slit-lamp examination (LS Ophthalmic Slit Lamp; ChongQing Medical Sunkingdom Medical Instruments Co., Ltd., ChongQing, China) of the anterior segment, posterior segment assessment using a + 90 D biconvex lens (VOLK Optical Inc., Mentor, Ohio, USA), and IOP measurement in mmHg using Goldman applanation tonometry (AT900, Haag-Streit, Koeniz, Switzerland). Baseline glycated hemoglobin (HbA1c) testing, VF testing, and OCTA were performed for all participants at the beginning of the study.

The included eyes were randomized by computerized sequence generation using software [14] into two groups, with 25 eyes in each group: group 1, including eyes that underwent PRP in two sessions 2 weeks apart, and group 2, including eyes that received intravitreal ranibizumab (0.5 mg; Lucentis, Genetec Inc., San Francisco, CA, USA) monthly injections for 3 consecutive months. Full ophthalmological examination, including BCDVA

and OCTA, was performed monthly for 3 consecutive months. The first follow-up was performed 1 month after the second laser session and 1 month after the first intravitreal ranibizumab injection. Subsequently, follow-ups were performed monthly for 2 months. VF was tested at the 3-month follow-up.

An OCT-A RTVue XR Avanti (AngioVue; Optovue Inc., software version 2017, Fremont, CA, USA) machine was utilized in this study [15]. A 6 × 6-mm grid centered on the fovea was used to scan the macular area. A 4.5 × 4.5-mm grid centered on the optic disc was chosen to scan the peripapillary area [16].

Each 6 × 6-mm scan was automatically segmented with the following boundaries: the superficial capillary plexus (SCP) was segmented from 3 μm beneath the internal limiting membrane (ILM) to 15 μm beneath the inner plexiform layer (IPL). The deep capillary plexus (DCP) was segmented from 15 μm beneath the IPL to 70 μm beneath the IPL. In the peripapillary region, the scan was automatically segmented at the RPC layer level. The RPC layer was defined as the layer between the ILM layer and the outer limit of the RNFL [17].

The following parameters were assessed on OCTA: VD was measured in the macular area within the three rings of the Early Treatment Diabetic Retinopathy Study (ETDRS) grid centered on the fovea. The foveal area was measured as the central 1-mm ring centered on the fovea. The parafoveal area was measured as the zone between the 1- and 3-mm-diameter concentric rings centered on the fovea. The perifoveal area was measured as the zone between the 3- and 6-mm-diameter concentric rings centered on the fovea. Grid location was manually corrected to the center of the fovea when the default position defined by the software was incorrect. All VD measurements were obtained at the levels of SCP and DCP. The foveal avascular zone (FAZ) was automatically measured using the FAZ measurement function of the OCTA software applied to the retinal slab. Central foveal thickness (CFT) was measured corresponding to the retinal thickness in the central 1-mm diameter ring of the ETDRS. A grid centered at the optic disc within the 4.5 × 4.5-mm rectangle scan of OCT angiograms to scan the peripapillary area. The inner circle was fit to the disc margin on the en-face OCT image. The inner optic disc area was measured as the area outlined by the disc margin, as detected by Bruch's membrane opening. Inside the disc, the whole image and peripapillary vascular density were measured [16, 18, 19].

To quantitatively assess new vessels on a 4.5 × 4.5 optic disc en-face OCTA scan, NVD area was manually defined. The neovascular area (NVA) and neovascular flow area (NVFA) were calculated using software [20] (Figures 1).

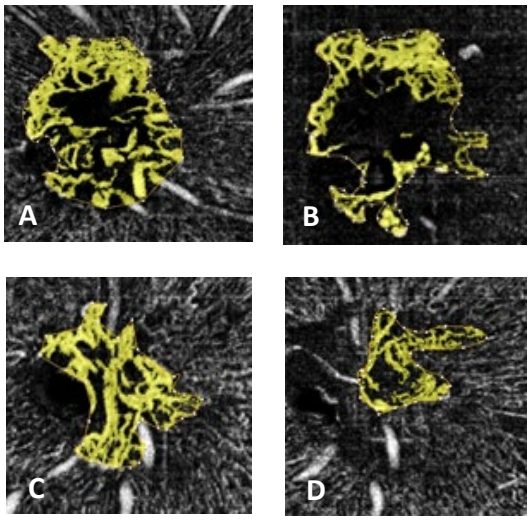

Figure 1. Quantitative evaluations of pre- and post-treatment neovascularization and flow areas of neovascularizations of the disc (NVDs) with optical coherence tomography (OCT) angiograms using the OCT-angiography RTVue XR Avanti (AngioVue; Optovue Inc., 2017, Fremont, CA, USA) machine. (A, B) OCT angiograms of treatment-naive NVD in an eye in group 1. (A) Before panretinal photocoagulation, neovascularization and flow areas of NVD were 2.44 and 1.23 mm², respectively. (B) Three months after panretinal photocoagulation, neovascularization and flow areas decreased to 2.18 and 0.83 mm², respectively. (C, D) OCT angiograms of treatment-naive NVD in an eye in group 2. (C) Before intravitreal injections of 0.5 mg ranibizumab (Lucentis, Genetec Inc, San Francisco, CA, USA), neovascularization and flow areas of NVD were 1.08 and 0.68 mm², respectively. (D) After three consecutive intravitreal injections of ranibizumab monthly, neovascularization and flow areas decreased to 0.62 and 0.31 mm², respectively. Note: Eyes in group 1 underwent panretinal photocoagulation divided into two sessions 2 weeks apart; Eyes in group 2 received intravitreal injections of 0.5 mg ranibizumab monthly for 3 consecutive months.

We excluded poor-quality images from the study with any of the following characteristics: an automatic image quality index < 6, visible artifacts, poor clarity due to the presence of cataract, corneal opacity, vitreous hemorrhage, or optic disc edema. When the automatic segmentation was inaccurate, manual segmentation was performed.

The patients underwent standard automated perimetry for VF testing using Humphrey's threshold-24 - 2 test of the Swedish interactive thresholding algorithm pack with the Humphrey Field Analyzer (Carl Zeiss Meditec Inc., Dublin, CA, USA). Unreliable results were excluded, and participated were motivated to repeat the VF test for that eye. Mean deviation (MD) and pattern standard deviation (PSD) values were reported [21].

For eyes in group 1, PRP was performed using a green laser photocoagulator system (GYC-1000, Nidek Co., Ltd., Japan). After dilatation of the patient's pupil with tropicamide 0.5% (Tropixal, DEMO SA Pharmaceuticals, Kryoneri, Greece) and phenylephrine 5% (phenylephrine, Cooper, Athens, Greece), a laser attached to a typical ophthalmic slit-lamp was delivered in a coaxial fashion. A Volk QuadrAspheric contact lens (VOLK, Mentor, Ohio, USA) with a laser spot magnification of 1.97 and 120°/144° field of view was placed against the cornea with a clear coupling agent. Conventional continuous wave laser therapy was performed in two sessions 2 weeks apart, with an exposure time of 100 ms, spot size of 200 μm, and power from 350 to 900 mV until the desired effect was reached. The total number of shots reached approximately 2000 – 3000 laser burns, with a 1-burn width apart, outside the vascular arcades nasal to the disc at 2- and 3-disc diameters temporal to the macula in two sessions: lower and nasal followed by upper and temporal. The goal was to produce gray burns and avoid dense white burns, and all settings were adjusted to achieve the desired effect [2, 22].

For eyes in group 2, 0.5 mg ranibizumab was intravitreally injected monthly for 3 consecutive months under sterile surgical conditions using a 29-gauge needle 3.5 and 4.0 mm posterior to the limbus in pseudophakic and phakic eyes, respectively [23].

Data were statistically analyzed using IBM Statistical Package for Social Sciences Statistics for Windows (version 20.0; IBM Corp., Armonk, N.Y., USA). Normality of data distribution was tested with the Kolmogorov – Smirnov test. Descriptive statistics of quantitative variables were calculated as mean (standard deviation [SD]) for normally distributed variables analyzed with independent-samples *t*-test and median and interquartile range (IQR) for non-normally distributed variables analyzed with the Mann – Whitney U test. Split-plot repeated-measures analysis of variance (ANOVA) was used to evaluate changes in RPC density over 3 months. In all statistical analyses, a *P*-value < 0.05 was considered to be statistically significant**.**

RESULTS

We enrolled 50 eyes of 50 participants, including 32 (64%) women and 18 (36%) men, and randomized them into two groups: group 1, including 25 eyes that underwent PRP, and group 2, including 25 eyes that received intravitreal injections of 0.5 mg ranibizumab monthly for 3 consecutive months. Forty-two (84%) eyes completed 3 months of follow-up, including 22 (88%) eyes in the PRP group and 20 (80%) eyes in the ranibizumab group (Figure 2). The two groups were comparable in terms of demographic characteristics, baseline BCDVA, HbA1c, OCTA parameters, VF indices, and IOP (all $P > 0.05$; Table 1).

Changes in the mean (SD) RPC density from baseline to 1-, 2-, and 3-month follow-ups differed significantly between the two groups (all $P < 0.05$; Table 2). Mean (SD) RPC density changes from baseline to the 3-month follow-up were significantly higher in the PRP group than in the ranibizumab group (- 2.16% [3.55%] versus 1.45% [2.59%]; $P = 0.001$; Table 2). RPC density differed significantly between the two groups (mean difference: - 3.61%; 95% confidence interval: - 5.57 to - 1.60; Figure 3).

Split-plot repeated-measures ANOVA was performed on the RPC density at baseline and 3 consecutive months. The main effect of grouping was significant (split-plot ANOVA, $F_{1, 40} = 7.40$, $P = 0.010$). The group interaction was also significant (split-plot ANOVA, $F_{3, 120} = 4.44$, $P = 0.005$). The main effect of time was insignificant (split-plot ANOVA, $F_{3, 120} = 0.52$, $P = 0.669$; Figure 4).

As a secondary outcome, the median (IQR) BCDVA changes from baseline to the 3-month follow-up in the PRP and ranibizumab groups were 0.0 (0.2) and - 0.15 (0.3) logMAR, respectively, showing a significant difference ($P < 0.05$; Table 2). Similarly, the median (IQR) BCDVA changes from baseline to the 1-month follow-up (0.0 [0.1] versus - 0.2 [0.2] logMAR; $P < 0.05$; Table 2).

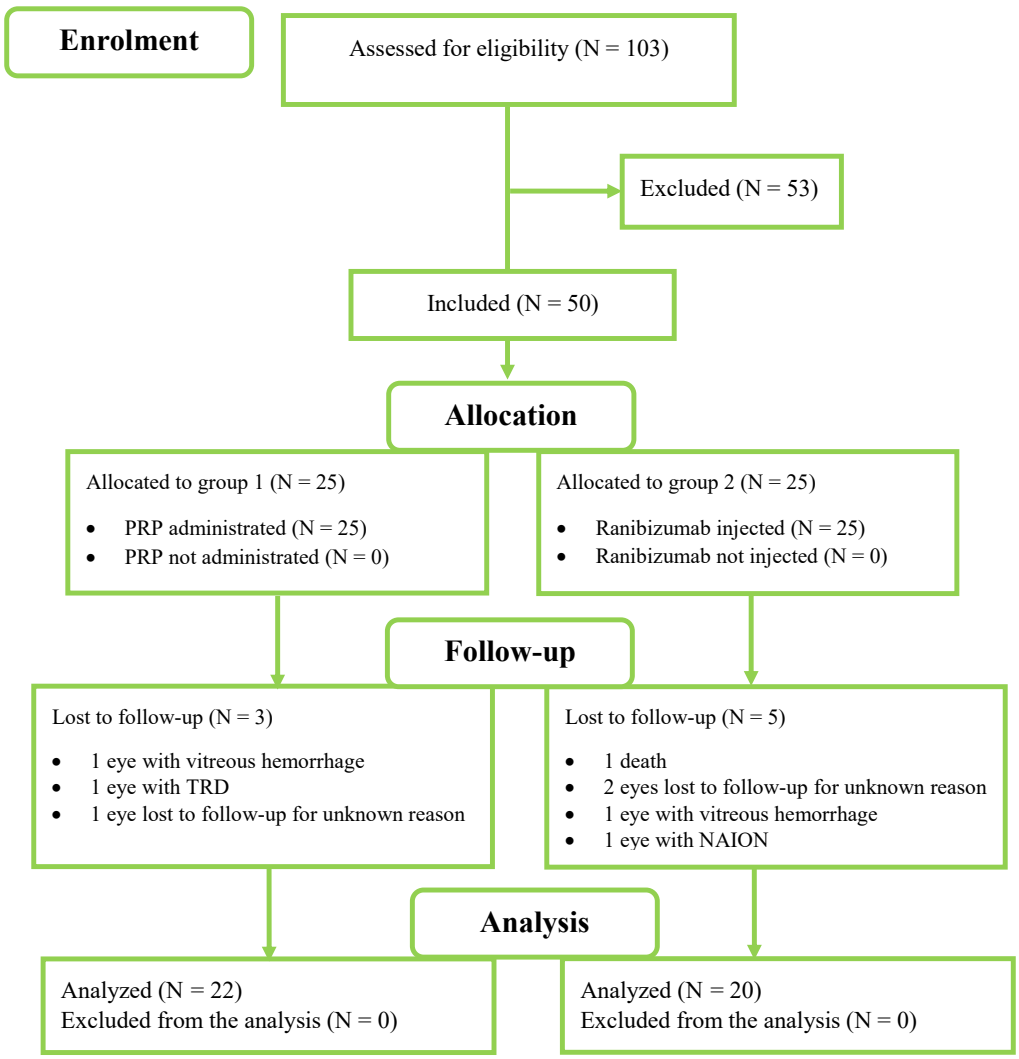

Figure 2. CONSORT flow diagram of the study process. Allocation of participants to group 1 or 2. Abbreviations: N, number of eyes; TRD, tractional retinal detachment; NAION, non-arteritic anterior ischemic optic neuropathy. Note: Eyes in group 1 underwent panretinal photocoagulation divided into two sessions 2 weeks apart. Eyes in group 2 received intravitreal injections of 0.5 mg ranibizumab (Lucentis, Genetec Inc., San Francisco, CA, USA) monthly for 3 consecutive months.

Table 3 shows comparison results of changes in other parameters obtained from OCTA, VF testing, and IOP measurement from baseline to the 3-month follow-up between the two groups. The median (IQR) changes in whole-image optic disc vascular density from baseline to the 3-month follow-up differed significantly between the two groups (- 1.45% [4.15]) in the PRP group and 1.45% [2.6] in the ranibizumab group; $P = 0.001$) (Table 3). However, changes in inside-disc vascular density, NVA, or NVFA from baseline to the 3-month follow-up did not differ significantly between the two groups (all $P > 0.05$) (Table 3).

Among macular OCT parameters, the median (IQR) changes in CFT from baseline to the 3-month follow-up differed significantly between the two groups (12.5 [71.5] μm in the PRP group and - 13 [58.75] μm in the ranibizumab group; $P = 0.001$; Table 3). However, changes in the FAZ area; foveal, parafoveal, or perifoveal vascular density; or whole-image macular VD did not differ significantly between the two groups (all $P > 0.05$; Table 3). Changes in IOP, MD, or PSD did not differ significantly between the two groups (all $P > 0.05$; Table 3).

Regarding adverse events, the PRP group included one eye with TRD and one eye with vitreous hemorrhage. The ranibizumab group included one eye with vitreous hemorrhage, one eye with non-arteritic anterior ischemic optic neuropathy (NAION), and one patient who died from unknown causes. None of the patients in the PRP group developed systemic complications. One patient in the PRP group and two patients in the ranibizumab group were lost to follow-up (Figure 2).

Table 1. Comparison of demographic data and baseline characteristics between study groups

Variables	Group 1 (n = 25)	Group 2 (n = 25)	*P*-value
Age (y), Mean ± SD	51.24 ± 9.4	46.84 ± 8.39	0.088
Sex (Male / Female), n (%)	11 (44.0) / 14 (56.0)	7 (28.0) / 18 (72.0)	0.239
DM duration (y), Median (IQR)	15 (10)	10 (7)	0.286
HbA1c (%), Median (IQR)	8.5 (1.75)	8 (1.1)	0.447
BCDVA (logMAR), Median (IQR)	0.5 (0.43)	0.5 (0.50)	0.514
PAFDD (%), Mean ± SD	45.07 ± 4.99	47.28 ± 5.46	0.143
PFDD(%), Mean ± SD	41.90 ± 4.55	43.77 ± 3.79	0.120
FDD(%), Mean ± SD	30.79 ± 10.12	26.90 ± 9.25	0.162
PAFDS(%), Mean ± SD	39.97 ± 6.23	41.26 ± 5.78	0.461
PFDS (%), Mean ± SD	43.29 ± 4.65	44.27 ± 4.58	0.455
FDS(%), Median (IQR)	20.50 (10.2)	17.30 (16.4)	0.367
WIMDR6 (%), Mean ± SD	46.60 ± 4.46	48.23 ± 5.52	0.204
FAZ (mm^2), Median (IQR)	0.33 (0.13)	0.38 (0.27)	0.383
NVFA (mm^2), Median (IQR)	1.11 (2.14)	0.57 (0.86)	0.054
NVA (mm^2), Median (IQR)	1.82 (4.77)	1.05 (2.02)	0.064
RPC density (%), Mean ± SD	46.14 ± 4.12	47.97 ± 4.93	0.161
VD inside disc (%), Median (IQR)	53.4 (10.7)	49.1 (5.6)	0.426
VD in whole image (%), Mean ± SD	44.98 ± 3.09	46.20 ± 6.39	0.203
CFT (µm), Median (IQR)	277 (51)	263 (93)	0.634
PSD (dB), Mean ± SD	6.23 ± 3.22	5.90 ± 2.74	0.703
MD (db), Median (IQR)	- 9.62 (14.41)	- 8.14 (9.28)	0.877
IOP (mmHg), Median (IQR)	17.96 (2.60)	17.56 (2.90)	0.588

Abbreviations: y, years; SD, standard deviation; n, numbers; %, percentage; IQR, Interquartile range; HbA1c, glycated haemoglobin; BCDVA, best-corrected distance visual acuity; logMAR, logarithm of the minimum angle of resolution; PAFDD, parafoveal vascular density deep plexus; PFDD, perifoveal vascular density deep plexus; FDD, foveal density deep plexus; PAFDS, parafoveal density superficial plexus; PFDS, perifoveal density superficial plexus; FDS, foveal density superficial plexus; WIMDR6, whole image macular density 6 mm whole retina; FAZ, foveal avascular zone; NVFA, neovascular flow area; mm^2, square millimeter; NVA, neovascular area; RPC density, radial peripapillary capillary density; VD, vessel density; CFT, central foveal thickness; µm, micrometer; PSD, pattern standard deviation; dB, decibels; MD, mean deviation; IOP, intraocular pressure; mmHg, millimeter of mercury. Note: Group 1, Eyes in group 1 underwent panretinal photocoagulation divided into two sessions 2 weeks apart; Group 2, Eyes in group 2 received intravitreal injections of 0.5 mg ranibizumab (Lucentis, Genetec Inc., San Francisco, CA, USA) monthly for 3 consecutive months.

Table 2. Comparison of changes in BCDVA and RPC density from baseline to 1- , 2-, and 3-month post-treatment follow-up between study groups

Variables	1-month			2-month			3-month		
	Group 1	Group 2	*P*	Group 1	Group 2	*P*	Group 1	Group 2	*P*
BCDVA(log-MAR), Median (IQR)	0 (0.1)	- 0.2 (0.2)	**0.005**	0 (0.12)	- 0.15 (0.2)	0.062	0 (0.2)	- 0.15 (0.3)	**0.031**
RPC density (%), Mean ± SD	- 2.12 ± 3.88	0.60 ± 10.18	**0.013**	- 1.70 ± 2.72	0.15 ± 2.93	**0.015**	- 2.16 ± 3.55	1.45 ± 2.59	**0.001**

Abbreviations: BCDVA, best-corrected distance visual acuity; RPC, radial peripapillary capillary; logMAR, logarithm of the minimum angle of resolution; IQR, Interquartile range; %, percentage; SD, standard deviation. Note: *P*, *P*-values < 0.05 are shown in bold; Group 1, Eyes in group 1 underwent panretinal photocoagulation divided into two sessions 2 weeks apart; Group 2, Eyes in group 2 received intravitreal injections of 0.5 mg ranibizumab (Lucentis, Genetec Inc., San Francisco, CA, USA) monthly for 3 consecutive months.

Table 3. Comparison of changes in parameters obtained with OCTA, VF testing, and IOP measurement from baseline to 3-month post-treatment follow-up between study groups

Variables	Group 1 (n = 22)	Group 2 (n = 20)	*P*-value
PAFDD (%), Median (IQR)	- 1.95 (7.17)	0.45 (6.8)	0.273
PFDD (%), Median (IQR)	- 2.7 (7.73)	- 0.55 (5.90)	0.650
FDD (%), Median (IQR)	1.2 (18.68)	- 1.550 (7.25)	0.940
PAFDS (%), Median (IQR)	- 1.0 (10.2)	- 1.2 (7.73)	0.338
PFDS (%), Median (IQR)	- 3.5 (6.67)	0.25 (7.08)	0.054
FDS(%), Median (IQR)	- 2.05 (21.25)	- 2.3 (8.4)	0.546
WIMDR6 (%), Mean ± SD	- 2.35 (7.82)	- 0.7 ± 6.3	0.674
FAZ (mm^2), Median (IQR)	- 0.0005 (0.19)	0.0 (0.17)	0.762
NVFA (mm^2), Median (IQR)	- 0.20 (0.89)	- 0.22 (0.42)	0.669
NVA (mm^2), Median (IQR)	- 0.23 (1.46)	- 0.30 (0.53)	0.513
VD inside disc (%), Median (IQR)	- 2.75 (9.20)	- 1.05 (5.52)	0.442
VD in whole image (%), Median (IQR)	- 1.45 (4.15)	1.45 (2.6)	**0.001**
CFT (μm), Median (IQR)	12.15 ± 71.5	- 13 (58.75)	**0.001**
PSD (dB), Median (IQR)	0.38 (3.45)	- 0.18 (1.04)	0.134
MD (dB), Median (IQR)	0.96 (3.87)	0.66 (2.16)	0.668
IOP (mmHg), Median (IQR)	- 1.00 (3.0)	- 1.00 (5.0)	0.391

Abbreviations: OCTA, optical coherence tomography angiography; VF, visual field; IOP, intraocular pressure; PAFDD, parafoveal vascular density deep plexus; %, percentage; IQR, Interquartile range; PFDD, perifoveal vascular density deep plexus; FDD, foveal density deep plexus; PAFDS, parafoveal density superficial plexus; PFDS, perifoveal density superficial plexus; FDS, foveal density superficial plexus; WIMDR6, whole image macular density 6 mm whole retina; SD, standard deviation; FAZ, foveal avascular zone; mm^2, square millimeter; NVFA, neovascular flow area; NVA, neovascular area; VD, vessel density; CFT, central foveal thickness; μm, micrometer; PSD, pattern standard deviation; dB, decibels; MD, mean deviation; mmHg, millimeter of mercury. Note: Group 1, Eyes in group 1 underwent panretinal photocoagulation divided into two sessions 2 weeks apart; Group 2, Eyes in group 2 received intravitreal injections of 0.5 mg ranibizumab (Lucentis, Genetec Inc., San Francisco, CA, USA) monthly for 3 consecutive months.

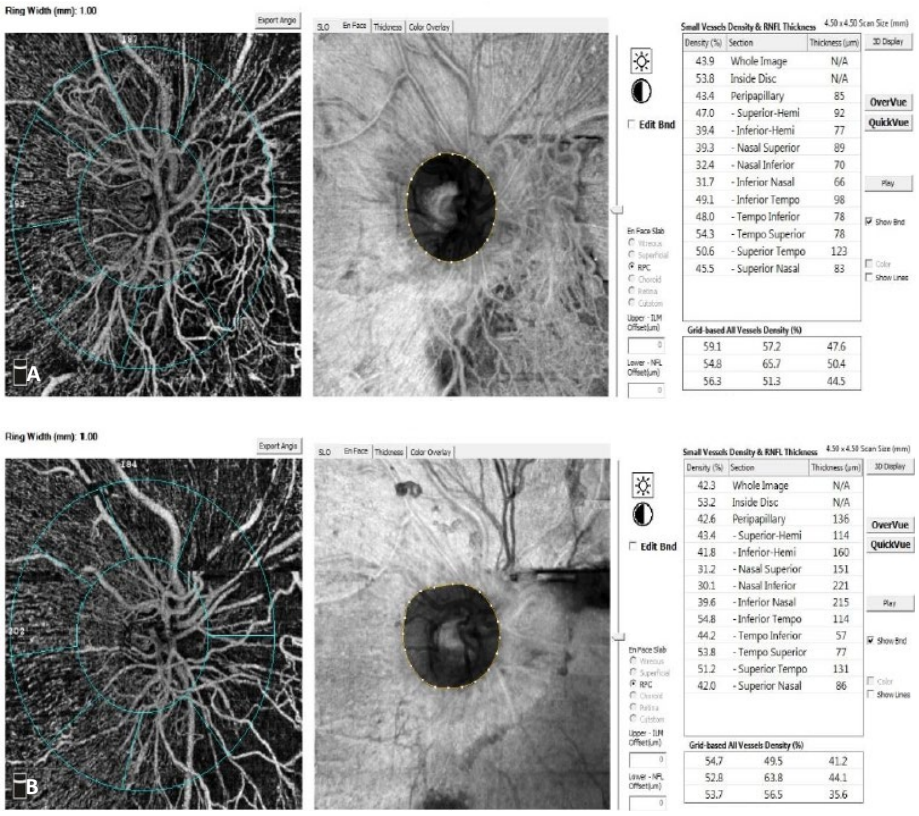

Figure 3. Typical 4.5 × 4.5-mm optical coherence tomography angiograms using the OCT-angiography RTVue XR Avanti (AngioVue; Optovue Inc., 2017, Fremont, CA, USA) machine of an eye in the panretinal photocoagulation group, show a decrease in radial peripapillary capillary density from (A) 43.4% at baseline to (B) 42.6% at 3-month post-panretinal photocoagulation follow-up. Note: Eyes in group 1 underwent panretinal photocoagulation divided into two sessions 2 weeks apart.

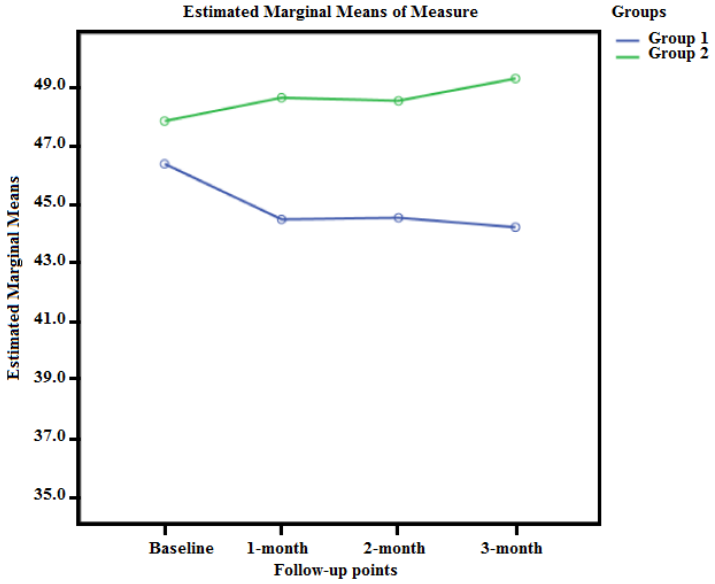

Figure 4. Split-plot analysis of variance for repeated measurements of radial peripapillary capillary (RPC) density shows reduced RPC density in group 1 (panretinal photocoagulation group) and increased RPC density in group 2 (ranibizumab group) over a follow-up of 3 months. Note: Eyes in group 1 underwent panretinal photocoagulation divided into two sessions 2 weeks apart; Eyes in group 2 received intravitreal injections of 0.5 mg ranibizumab (Lucentis, Genetec Inc., San Francisco, CA, USA) monthly for 3 consecutive months.

DISCUSSION

This study showed that RPC and whole-image optic disc VD increased in the ranibizumab group and decreased in the PRP group, with statistically significant differences. The mean difference in RPC density was - 3.61% (95% confidence interval: - 5.57 to - 1.6) at the 3-month follow-up. The VA gain was higher in the ranibizumab group than in the PRP group.

In contrast, Zhao et al. reported no significant difference in changes in papillary VD (whole-scan, inside-disc, and peripapillary) between eyes with PDR that underwent PRP and those that underwent intravitreal conbercept (IVC) treatment [24]. Their study was non-randomized, retrospective, and comparative, with 12 months of follow-up. They compared PRP and 3+ IVC as needed regimen. IVC was administered when neovessels recurred after three loading doses [24]. The difference between the two studies could be attributed to the use of different types of anti-VEGF, numbers of intravitreal injections, or follow-up durations.

Mendrinos et al. used interactive vessel analysis software to measure the width of the retinal vessels on a digital retinal image [25]. PRP had a significant vasoconstrictive effect on retinal arterioles in patients with severe non-proliferative or PDR after 48 (5) days [25]. Although we did not measure the width of the retinal vessels, we found that RPC and whole-image optic disc VD were significantly lower in the PRP group.

Amanat et al. [26] showed that optic nerve blood flow was lower in PRP-treated eyes than in non-PRP-treated eyes on OCTA. They reported that 85.72% of the eyes showed decreased blood flow to the optic nerve at the 1-month follow-up [26]. In the present PRP group, RPC change from baseline to the 3-month follow-up was - 2.16%. Nicolai et al. [12] found increased peripapillary and inside-disc VD in hypertensive patients with central retinal vein occlusion 1 and 4 months after loading intravitreal injections of ranibizumab [12], suggesting an effect of ranibizumab on PDR. In the present study, eyes with PDR received intravitreal injections of 0.5 mg ranibizumab monthly for 3 consecutive months, and the RPC change from baseline to 3 months was 1.45%.

The present study also showed better BCDVA outcomes in the ranibizumab group, which may be related to increased optic disc perfusion or decreased CFT. Zhao et al. [24] found that the mean BCDVA was significantly lower in the PRP group and higher in the IVC group [24]. Sivaprasad et al. [27] found that the aflibercept group was non-inferior and superior to PRP in terms of BCDVA [27].

The median (IQR) CFT showed inconsistent results. It increased in the PRP group by 12.5 (71.5) μm and decreased in the ranibizumab group by 13 (58.75) μm. These findings were similar to those of Zhao et al. [24], who

reported CFT increase in the PRP group and decrease in the ranibizumab group. Similarly, Sivaprasad et al. found that CFT was significantly higher in the PRP group than in the aflibercept group [27]. Unlike the present study, Zhao et al. [24] and Sivaprasad et al. [27] excluded patients with macular edema.

In the present study, macular vascular density in the foveal, perifoveal, and parafoveal regions of the SCP and DCP did not differ statistically significantly between the two groups, consistent with Zhao et al.'s study [24], in which macular VD did not differ significantly between the PRP and IVC treated eyes with PDR after 12 months of follow-up [24]. However, the area of measurement was limited to the central 3 mm [2] of the macula; therefore, they could not determine the statistical significance of changes in VD in more peripheral macular regions. Alagorie et al. showed no change in macular VD after 12 months of intravitreal aflibercept treatment [28]. Consistent with the present study, Lorusso et al. found no significant change in macular VD 1 or 6 months after PRP of eyes with PDR in the foveal and parafoveal regions; however, unlike the present study, they used PASCAL short laser technology [29].

In the present study, the FAZ area did not differ significantly between the two groups, consistent with Zhao et al.'s study [24]. Similarly, Lorusso et al. showed no change in the FAZ area 6 months after PRP of eyes with PDR [29]. Conti et al. showed no change in the FAZ area or perimeter after intravitreal aflibercept treatment from baseline to the 6- or 12-month follow-up [30].

NVA or NVFA did not differ significantly between the two groups after 3 months. A study using DRCR network protocol S reported no difference between the ranibizumab and PRP groups in the percentage of eyes without active or regressed neovascularization on fundus photographs after 2 years [1]. They used digital photographs to assess neovascularization, and in the present study, we used OCTA to assess NVA and NVFA. In contrast, Ishibazawa et al. found a significant decrease in the mean NVFA on OCTA 2 months after PRP [20]. Falavarjani et al. reported a significant decrease in the NVD size and flow area on OCTA as early as 24 h after a single intravitreal injection of bevacizumab, with a continued decrease for at least 1 month [31].

The present study showed higher MD and PSD of VF in the PRP group than in the ranibizumab group, without statistical significance. In contrast, a study using DRCR network protocol S found significant VF changes between ranibizumab and PRP groups, in favor of ranibizumab [1]. This difference between the two studies in VF could be explained by the fact that the previous study had a better baseline VA (0.2 logMAR) compared to the present study (0.5 logMAR); second, the present study had a short follow-up, and damage due to PRP may take longer to be evident on VF testing [32].

In the present study, one patient in the ranibizumab group developed NAION, which raised concerns about transient vasoconstriction caused by anti-VEGF. Hosseini and Razeghinejad [33] reported a case of NAION after an intravitreal bevacizumab injection. Plausible causes are impaired autoregulatory and microcirculatory mechanisms of optic nerve circulation [34], transient IOP elevation after the intravitreal injection [35], and incidental occurrence of NAION.

In the present study, three (6%) eyes were lost to follow-up, including two eyes in the ranibizumab group, which raised the concern of compliance with longer follow-up periods, comparable to the loss of follow-up rates in randomized trials, which were approximately 5% – 10% over a 1- to 2-year observation period [1, 27].

One patient in the PRP group but none of the patients in the ranibizumab group developed TRD, similar to the study using DRCR network protocol S, which also showed that more eyes in the PRP group developed TRD and underwent vitrectomy than in the ranibizumab group [1, 36].

Two eyes in each group developed vitreous hemorrhage. The protocol S study reported vitreous hemorrhage after 2 years in 27% and 34% of the eyes in the ranibizumab and PRP groups, respectively [1]. They reported that 22% and 41% of the eyes in the ranibizumab and PRP groups, respectively, underwent vitrectomy for vitreous hemorrhage after 5 years of follow-up [36].

One patient in the ranibizumab group died from an unknown cause. The DRCR network studies [1] revealed no significant differences between groups in the number of patients with serious systemic adverse events, hospitalization, or death. In a multicenter randomized clinical trial using the DRCR network [1], non-fatal myocardial infarction occurred in three (3%) patients in the ranibizumab group and two (2%) patients in the PRP group; hospitalization occurred in 48 (47%) patients in the ranibizumab group and 40 (35%) patients in the PRP group; six (6%) and four (4%) patients in the ranibizumab and PRP groups, respectively, died from any cause; and four (4%) and 1 (< 1%) patient in the ranibizumab and PRP groups, respectively, died from potential vascular or unknown causes, without any significant difference [1].

This randomized clinical trial used multiple objective measures, such as OCTA parameters, global VF indices, and BCDVA, and showed better RPC and whole-image optic disc VD in ranibizumab-treated eyes. The VA gain was higher in the ranibizumab group than in the PRP group. However, the single-center trial design, short follow-up period of 3 months, small sample size, and absence of other subtypes of diabetic retinopathy, such as mild, moderate, and severe non-PDR, could be potential limitations of the present study. We propose that future multicenter trials address these limitations to verify the findings of this study.

CONCLUSIONS

In eyes with PDR and neovascularization of the disc RPC density on OCTA increased in the ranibizumab group and decreased in the PRP group. Thus, intravitreal ranibizumab significantly improved PDR compared to the negative effect of PRP on RPC on OCTA after 3 months of follow-up. The VA gain was higher in the ranibizumab group than in the PRP group. Future multicenter trials addressing our limitations are required to verify the findings of this study.

ETHICAL DECLARATIONS

Ethical approval: The study was registered in the Pan African clinical trial registry (registration number: PACTR202206535473146). It adhered to the tenets of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Ain Shams University, Cairo, Egypt. Informed consent was obtained from all participants for enrollment in the study after a full explanation of the nature of the testing procedures.
Conflict of interest: None.

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