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Comparative Study between Targeted Retinal Photo coagulation With and Without Single Intravitreal Bevacizumab Injection Versus Conventional Panretinal Photocoagulation for Proliferative Diabetic Retinopathy Treatment

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Abstract

Background: Proliferative diabetic retinopathy (PDR) has traditionally been addressed with conventional panretinal argon laser photocoagulation (PRP). However, it may cause anatomical and functional adverse events arousing the need to explore alternative treatment modalities.

Aim of Study: The study's objective was to examine and compare the effectiveness of targeted retinal photocoagulation (TRP) alone or in combination with a single intravitreal bevacizumab injection and regular conventional PRP alone in the management of individuals with naive mild to moderate PDR without macular edema.

Patients and Methods: A prospective interventional randomized study that enrolled cases with naïve mild to moderate PDR but no high-risk characteristics (HRC) or macular edema. Forty eyes have completed the study. 20 eyes received PRP and the other 20 eyes had targeted retinal photocoagulation (TRP), 9 eyes of which were injected with single intravitreal bevacizumab injection one week after the laser treatment). Baseline and three months postoperative data were registered, including Best Corrected Visual acuity (BCVA), detailed fundus examination, fundus fluorescein angiography (FA) with photomontaging of seven 30 degrees standard images to assess the neovascular process and SD-OCT Macula; to assess the Central Sub Field Foveal Thickness (CSFT) using the ETDRS Map.

Results: 20 eyes were treated with conventional PRP with mean age of 45.85±10.93. The mean duration of diabetes was 21.25±7.73 with mean HBA1c of 8.62±1.19. Mean baseline (BCVA) was 0.27±0.16 log MAR which increased to 0.26 ± 0.16 logMAR (p-value=0.671). Mean baseline CSFT was 228.40±31.04µm which increased to 270.25±57.85µm (p-value=0.004) after 3 months. Regression of proliferative state was achieved in 75% (15 eyes) at the end of third month following PRP.

While regarding the TRP group, the average age was 46.2 ±9.29 with average diabetes duration of 17.4±8.03 with mean HBA1c of 8.96±1.63. Baseline mean LogMar BCVA was 0.49 ±0.31 which increased to 0.48±0.3 log (p-value=0.868). Baseline mean CSFT was 248.50±39.05µm which increased to 262.15±35.34µm (p-value=0.018) at 3 Months. The mean percentage of change in CSFT was 19.14% following PRP and 6.52% following TRP. Post treatment CSFT was different among both groups (p-value=0.007). Regression of the proliferative state was achieved in 90% (18 eyes) of the TRP group after 3 months (p-value=0.407).

Conclusion: TRP is not inferior to conventional PRP in control of the neovascular process and achieving regression of the proliferative state either used alone or in combination of single intravitreal injection of bevacizumab. Vision was almost not affected by neither PRP nor TRP, however the percentage of induced change in the CSFT caused by TRP was definitely less than that was caused by PRP.

Key Words: *Proliferative diabetic retinopathy – Optical coherence tomography – Panretinal photocoagulation.*

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Introduction

Microvascular consequences of diabetes can result in diabetic retinopathy, which represents the most common preventable cause of blindness [1]. PDR with vitreous hemorrhage or tractional retinal detachment and macular edema or ischemia are considered the major causes of diminution of vision among diabetics.

PDR is identified by the presence of growing new vessels. The main factor for neovascularization is retinal ischemia brought on by vascular blockage. Vascular endothelial growth factors (VEGF) and up-regulation of their associated receptors [2] are the key mediators of angiogenesis, which can enhance vascular permeability and cause the development of aberrant and leaky new capillaries [3].

Until recent years, PDR patients were often treated with pan-retinal photocoagulation (PRP). Considering severe PDR cases with high-risk characteristics (HRC), PRP showed almost 50% reduction in the incidence of severe visual loss [4].

We still don't fully understand how PRP causes the neovascularization of the retina to regress. However, it is believed to increase retinal oxygenation because the removal of the highly oxygen-consuming outer retina reduces oxygen demands, which in turn increases choroidal diffusion of oxygen and improves the hypoxic state by reducing the production of cytokines and endothelial growth factors [5,6]. However, there is a chance of developing macular edema and a temporary or permanent decline in visual acuity. In addition to affecting the peripheral field and contrast sensitivity, macular edema that is already present may get worse after PRP [7].

Targeted laser delivery (TRD) and/or anti-VEGF medicines have recently been developed as therapeutic modalities for the treatment of PDR, reducing the requirement for traditional PRP and resolving its problems.

The goal of targeted LASER photocoagulation (TRP) is to preserve perfused retina by treating only ischemic retinal regions and nearby areas that show leakage in patients with PDR. Therefore, compared to traditional PRP, TRP is linked to less laser-induced scarring [8]. Although TRP to the peripheral ischemic retina slows leakage from new vessels, VEGF continues to be produced by glial and Muller cells [9,10].

The Diabetic Retinopathy Clinical Research Group Study Network (DRCR.net) compared the effects of intravitreal injection of Ranibizumab to PRP and revealed outstanding results in the treatment of PDR (protocol S) [11]. However, several intravitreal injections are frequently required. These pricey procedures come with a risk of consequences like endophthalmitis, an increase in intraocular pressure or damage to intraocular structures (such as a traumatic cataract) with each injection.

Combination therapy using intravitreal anti-VEGF injection and selective PRP could take advantage of the benefits of the two treatment modalities and increase patient safety by reducing the risks associated with conventional PRP while reducing the need for additional intravitreal injections.

Patients and Methods

Sample size of twenty eyes for each arm was estimated which was increased by 10% to be 22 in each group to compensate for the number of dropped out cases and to increase the power of the study. The study started with 44 eyes in subjects with PDR without macular edema (DME) as confirmed with fundus fluorescein angiography. Cases were randomly allocated into 2 groups:

- Group A received conventional pan retinal photocoagulation (PRP).
- Group B received targeted retinal photocoagulation (TRP). It was further divided into 2 sub-groups.

- *Subgroup B-1:* The patients in this sub-group received TRP in addition to single intravitreal bevacizumab injection within one week of the laser session.
- *Sub-group B-2:* Patients received only TRP.

This is study was conducted at Kasr Al-Ainy Hospital Cairo University From February 2020 February 2022.

The patients were chosen from the retina sub-specialty clinic at Kasr Al-Ainy Hospital, Cairo University. Before beginning any study procedure, subjects gave their informed consent. The research ethical committee of Faculty of medicine, Cairo University amended the study protocol. That was adherent to the principles of Helsinki Decleration.

Patient selection:

Inclusion criteria:

- Naïve PDR (no previous retinal photocoagulation) with no high risk characteristics of PDR according to Early Treatment Diabetic Retinopathy Study Scale of Diabetic Retinopathy Severity.
- Mild PDR is <0.5 disc diameter area of NVEs in one or more quadrant.
- Moderate PDR is defined to have more than 0.5 disc diameter areas of NVES in 1 or more quadrants or NVDs more than 0.25 to 0.33 disc diameter.

Exclusion criteria:

- Previous PRP or previous intravitreal injections.
- High-risk characteristics (HRC) of PDR: Cases with NVD > one third disc's diameter, NVD one third to one fourth of the disc's diameter with co-existing pre-retinal hemorrhage/vitreous hemorrhage, and NVE with co-existing pre-retinal haemorrhage/vitreous hemorrhage.

- Macular edema or increased central foveal thickness >300µm.
- Any vitreo-retinal traction.
- Previous vitreo-retinal surgery or cataract extraction.
- Significant media opacity hindering visualization or interfering with the optical coherence tomography (OCT) imaging.
- Other Ocular Pathologies: Uveitis, other vascular retinal disorders, and Age-Related Macular degeneration, epi-macular membrane or tractional retinal detachment.

Pre-treatment evaluation:

Demographic data were registered such as age, gender, diabetes type and duration, presence of associated risk factors as hypertension and smoking, presence of comorbidities related to diabetes as neuropathy or nephropathy in addition to any systemic drug intake. Patients were asked also about History of previous surgeries, retinal laser treatment and intravitreal injection of Anti-VEGF.

Examination:

Every case underwent a thorough evaluation, which included:

- Testing best corrected visual acuity (BCVA) on the Snellen VA chart.
- Slit-lamp examination; this includes checking the condition of the crystalline lens and looking for neo-vessels in the iris (NVI)
- Using Goldman applanation tonometry to quantify intraocular pressure (IOP).
- Detailed fundus examination using binocular indirect slit-lamp bio microscopy and indirect ophthalmoscopy (VOLK 90 D lens, Mentor, Ohio, USA) to assess the condition of the macula and to grade diabetic retinopathy stage.
- Initial Fundus Fluorescein Angiography (FFA) with a TRC 50DX TOPCON retinal camera; to validate the proliferative state, montaging of 8 directions photos to create a broader field image of the periphery.
- Optovue RTVue model-based Spectral Domain Optical Coherence Tomography (SD-OCT) Macula (RT100, Optovue, Inc., Fermont, CA). For the CSMT, five-line raster and EMM5 scans were used to find the ETDRS map.

Intervention:

Group A (PRP):

PRP was performed for the patients in this group using VISULAS 532s - Zeiss green Laser machine applying parameters that produced retinal reaction that was standardized to grayish white reaction (100 millisecond duration, 200µ spot size and 200mW power were usually required).

Technique of Pan Retinal Photocoagulation for each patient:

- Topical anesthesia eye drops (e.g. Benoxinate Hydrochloride 0.4%) were instilled.
- Quadrispheric Volk lens was applied.
- Standard Scatter pan retinal photocoagulation was done. Dead nasal and dead temporal positions were avoided to preserve the long ciliary nerves. The total number of applied shots ranged from 1500 to 2500 in two or three sessions.
- All patients took post PRP treatment in the form of Nepafenac 0.1% eye drop 3 times daily till the next session and for up to 2 weeks after the last session, plus systemic analgesics as needed.

Group B (TRP):

The same laser parameters for PRP were followed. The area targeted by laser was guided by the constructed photo of FFA, laser was applied only to ischemic areas and adjacent intermittent areas showing leakage. The patients in this group were further divided into 2 sub-groups:

- *Subgroup B-1:* In which the patients received TRP in addition to single intravitreal bevacizumab injection within one week of the laser session.
- *Sub-group B-2:* In which the patients received only TRP.

Intravitreal injection:

Setting: Intravitreal injections were given in operating theatre.

*Preparation:*Confirmed written consent (after explaining the purpose of injection, risks and potential complications).

Procedure:

The correct eye to be injected was confirmed followed by sterilization then topical anesthetic drops (Benoxinate hydrochloride 0.4%) and 5% povidone iodine instillation. Surgical drape and lid speculum were applied. The injecting syringe was prepared immediately before injection to ensure any air is expelled. Injection site was 3.5-4mm post to the limbus in either supero temporal or inferotemporal quadrants. The needle (27-30) was inserted perpendicularly towards the center of the globe followed by injection of bevacizumab 0.05ml (1.25mg) with careful removal of syringe and counter pressure using sterile cotton tipped applicator. Paracentesis was done if needed in case of significant increase of IOP. The speculum was

removed then sterile eye patch was applied. All patients were prescribed topical antibiotic (Gatifloxacin 0.3% eye drops) for a week.

Follow-up:

First follow-up was done within 2 days to exclude infection and persistence increase in IOP in the subgroup that received IVB. Full ophthalmological examination was done after 1 month of treatment. Examination included BCVA, IOP measurement, anterior segment evaluation, fundus examination and FFA. The same evaluation was also performed after 3 months in addition to SD-OCT.

Outcomes of the study:

Primary outcome: Regression of proliferative state at 4 weeks and 12 weeks.

Secondary outcomes:

The safety of the three treatments arms regarding BCVA and development of macular edema.

Statistical methods:

All of the study data were managed using SPSS version 28 (Statistical Package for the Social Sciences). Log Mar BCVA was translated from Snellen BCVA. Regarding categorical data, frequency (count) and relative frequency (%) were calculated. The mean, standard deviation, median, minimum, and maximum were considered for quantitative data. To compare quantitative variables, the non-parametric Kruskal-Wallis and Mann-Whitney tests were utilized. The Wilcoxon signed rank test was performed to compare serial measures taken from each individual.

The Chi-square test was performed to compare categorical data. Instead, Fisher's exact test was performed if frequency was <5. p-values of 0.05 or lower were considered significant.

Results

31 patients (44 eyes) were investigated in the study while 29 patients (40 eyes) completed the 12 weeks follow-up. 20 eyes had conventional PRP treatment while 9 eyes received TRP with injection and 11 eyes were treated with TRP alone.

Base line characteristics:

The baseline variables of age, HbA1c, duration of diabetes, and CFT did not significantly differ between the two groups. However, pretreatment BCVA revealed a substantial difference (p=0.018).

Table (1): Baseline characteristics.

	PRP				TRP				p-value
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum	
Age	45.85	10.93	29.00	62.00	46.20	9.29	29.00	58.00	1.000
HBA1c	8.62	1.19	6.40	10.80	8.96	1.63	6.50	13.20	0.620
Duration of DM	21.25	7.73	7.00	35.00	17.40	8.03	4.00	30.00	0.192
Pre-ttt LOG MAR BCVA	0.27	0.16	0.00	0.70	0.49	0.31	0.00	1.00	0.018*
CFT pre	228.40	31.04	158.00	270.00	248.50	39.05	164.00	295.00	0.056

*Significant.

Table (2): Systemic and ocular associations of the study participants.

	Group				p-value
	PRP		TRP		
	Count	%	Count	%	
HTN:					
Yes	9	45.0	8	40.0	0.749
No	11	55.0	12	60.0	
Smoking:					
Yes	3	15.0	5	25.0	0.695
No	17	85.0	15	75.0	
Comorbidity (nephropathy, neuropathy, diabetic foot, cerebrovascular stroke and ischemic heart disease):					
Yes	13	65.0	8	40.0	0.113
No	7	35.0	12	60.0	
Cataract:					
Yes	6	30.0	9	45.0	0.327
No	14	70.0	11	55.0	

Associated medical and ocular conditions.

Regression of the proliferative state and FFA leakage:

With or without injection, insignificant difference among the two study arms was noted regarding regression of the disease.

BCVA:

The average baseline BCVA was 0.27±0.16 log MAR in the PRP arm while it was 0.49±0.31 log MAR in the TRP group. Baseline BCVA differed significantly between the two arms. (p=0.018). Subgroup analysis revealed that mean baseline BCVA in TRP with IVI subgroup was 0.4±0.34 log MAR and 0.55±0.28 log MAR in the TRP alone (p=0.45).

After 3 months, the average BCVA was 0.26± 0.16 log MAR in the PRP arm and 0.48±0.3 log MAR in the TRP arm with no significant difference in relation to the baseline. (p=0.671 and 0.868 for PRP and TRP, respectively). The induced change magnitude of BCVA log MAR was 4.3% in PRP group and 3.81% in the TPR. It was statistically insignificant among the two arms (p=0.603).

Table (3): Summery of number of eyes in which regression of proliferative state was reached at one and three months post-treatment.

	PRP		TRP/injection		TRP		p-value
	Count	%	Count	%	Count	%	
Regression after 1 month:							
Regression	9	45.0	2	22.2	6	54.5	0.374
No regression	11	55.0	7	77.8	5	45.5	
Regression after 3 months:							
Regression	15	75.0	8	88.9	10	90.9	0.557
No regression	5	25.0	1	11.1	1	9.1	

At 3 months, mean BCVA in the TRP with IVI subgroup was 0.41±0.36 log MAR (p=0.725) while the in TRP alone subgroup was 0.54±0.25 log MAR (p=0.527). The two subgroups did not significantly differ from one another in log MAR post-procedure (p=0.333). The magnitude of induced change in subgroup analysis was 6.46 % in TRP with injection subgroup and 1.88% in the TRP alone subgroup.

Central Subfield-Foveal Thickness (CSFT):

Baseline mean ± SD CSFT (µm) was 228.40± 31.04 and 248.50±39.05 in the PRP and TRP groups respectively. The two groups did not significantly differ from one another. Regarding baseline CSFT (p=0.056). Subgroup data showed that the mean baseline CSFT in the TRP with IVI subgroup was 223.00±36.75µm and in the TRP alone subgroup was 269.36±27.43µm (p=0.01).

At three months, the PRP group's CSFT significantly rose to 270.25±57.85µm (p=0.004), whereas the TRP group's CSFT grew to 262.15±35.34 µm (p=0.018). In the PRP arm, the average percentage of change in CSFT was 19.14%, whereas in the TRP group, it was 6.52%. Between the two arms, a statistically significant difference was detected (p=0.007).

At 3 months, subgroup analysis showed that mean CSFT was 251.33±34.01 µm in TRP with in IVI subgroup (p=0.008). In the TRP alone subgroup, CSFT was 271±35.45µm (p=1). The Percentage of change in CSFT in TRP with IVI was 13.95% and in the TRP alone subgroup it was only 0.45%.

Complications among the two groups:

No patient experienced any major adverse effects due to intravitreal injection during the course of the study period, and there was no clinical indication of uveitis or endophthalmitis. The treatment was also well tolerated. Additionally, neither the state of the crystalline lens nor the intraocular pressure showed any appreciable alterations.

Number of laser sessions during study period:

In the PRP group, 16 eyes (80%) had 3 sessions while 4 eyes (20%) received 4 sessions. Meanwhile in TRP group, 18 eyes (90%) received either one or two sessions and the other two eyes needed

three sessions to achieve regression. The number of sessions varied significantly between the two arms. (p=0.001).

Intra group analysis revealed insignificant difference between TRP alone and TRP with IVI regarding the laser sessions number required to reach regression. In TRP with IVI subgroup, 3 eyes (33.3%) received only one session, 5 eyes (55.6%) had two sessions while one eye (11.1%) had three sessions. However, in the TRP alone subgroup, 6 eyes (56.5%) received one session, 4 eyes (36.4%) required two laser sessions and only one eye (9.1%) received three laser sessions.

Discussion

The conventional, effective treatment for PDR has been PRP. Alternative techniques are preferred despite the fact that it is effective because it can exacerbate macular edema, induce loss of peripheral vision, and reduce contrast sensitivity and night vision [12].

All retinal regions, including those that are typically perfused in addition to capillary dropout angiographic and ischemic sites, are subjected to laser treatment in conventional PRP techniques. TRP, on the other hand, entails ablating ischemic and non-perfused retinal regions while sparing the better perfused regions [13].

Our study presents new treatment modalities involving TRP and TRP with intravitreal injection of bevacizumab as non-inferiority procedures compared to conventional PRP in control of the proliferative retinopathy.

Our data suggested that regression of the proliferative state was established in 75% of the PRP group and in 90.9% and 88.9% of TRP and TRP with IVI respectively at 3 months of the study indicating the efficiency of the two latter treatment modalities to control mild to moderate PDR with no high risk characteristics.

Similar outcomes were reported in 2018, when Association for Research in Vision and Ophthalmology (ARVO) annual meeting concluded UWF-FA guided TRP as an effective treatment for PDR and severe NPDR without HRC with disease progression in 93.3% at 6 months [14].

Muqit et al., (2013) conducted a prospective, non-randomized trial to examine pattern scan TRP in PDR. A single-session of Pascal 20ms duration TRP technique was used on 28 eyes to apply 1500 burns on sites with moderate retinal ischemia and retinal capillary non-perfusion. This procedure was assisted by wide-field fluorescein angiography (Optos). At 12 weeks, 76% of patients had PDR regression; at 24 weeks, 37% developed complete regression of the disease; and 33% showed partial disease regression. Supplementary PRP was scheduled for 30% of patients with active PDR [13].

Also selective photocoagulation to non-perfusion areas in pre-proliferative diabetic retinopathy was found effective in prevention of progression to PDR in a multi-centered randomized controlled clinical trial involved 69 patients conducted by Young et al., [15].

In our study, patients who received TRP had less number of sessions of laser treatment improving their experience of treatment and perceived pain.

Our data showed the two study arms differ significantly in their baseline BCVA (Log MAR). This is mostly attributed to the following reasons: Percentage of eyes with cataract in TRP group was higher than the PRP groups (45% & 30% respectively), presence of ischemic maculopathy, mean age and HBA1c were lower in the PRP. Moreover, mild and moderate PDR cases were pooled together without categorization. However, the magnitude of induced change in BCVA and log MAR after treatment was statistically insignificant in the two groups.

Again, subgroup analysis revealed that no significant change in BCVA at 3 months between TRP alone and TRP with injection.

Similar outcomes were discovered by Soman et al., who conducted PRP on 76 eyes of 68 cases with PDR but no macular edema. Of these patients, 81.58% reported improved or stable vision, whereas 18.42% reported worsening vision 3 months later [12]. In addition, McDonald et al., analyzed 175 PDR-diagnosed and PRP-treated eyes and included pre-, post-, and follow-up exams as well as fluorescein angiography; they found that 25% of these eyes lost 2 lines of vision in an average follow-up of 15 months [7].

According to Shimura et al., analysis of 64 eyes having PDR with non HRC or severe NPDR and undergoing PRP treatment, 84% of the eyes maintained their VA at 24 weeks, 5% of the eyes experienced a drop in vision over the first 0-8 weeks after PRP but later recovered their baseline values, and 11% of the eyes showed a drop in visual acuity that worsened during follow-up [16]. In another study, three months following PRP, 15 eyes (75%) of cases of PDR with no co-existing macular edema

had improved or stable vision, whereas 25% had impaired vision. These results were found in an Egyptian research conducted in Al-Azhar University and published in 2020 **[17]**.

According to the Diabetic Retinopathy Study, PRP caused vision loss in 10% of the eyes. Considering other studies, between 25% and 43% of eyes experienced visual alterations or loss after PRP. Nevertheless, most of these researches included also cases suffering from macular edema **[18]**.

Back to our study, TRP group showed that 40% had improved their visual acuity (from 0.5126 log Mar to 0.4 log MAR), 30% preserved a stable vision (average 0.6 log MAR) and 30% experienced reduction in visual acuity from 0.333 to 0.4667 log MAR.

Sub group analysis revealed that in TRP with IVI sub group, improvement was noticed in 44.44% of eyes (from 0.35 to 0.25 log MAR), stable vision of average 0.65 log MAR in 22.22% and 33.33% had a worsen VA from 0.3 to 0.4667 log MAR. While in the TRP alone subgroup 36.36% of eyes improved their VA from 0.675 to 0.55 log MAR, stable VA was in 36.35% of average 0.575 log MAR and only 27.27% their VA diminished from 0.3367 to 0.4667 log MAR.

The TRP strategy in the Manchester Pilot Study utilized 20ms duration multi-spot Pascal® 4*4/5*5 arrays. TRP (1,500 shots) were only delivered to sites of peripheral retinal ischemia in a single session (SS). Widefield Optos® Angiography was done to document intermediate retinal ischemia and non-perfusion. In that study, 26 eyes (18 PDR and 8 DME) were enrolled, and the findings showed that VA significantly increased by +4 letters at four weeks (n=26) and twelve weeks (n=16) (p 0.05) **[19]**.

In a randomised clinical trial comparing Pascal-targeted retinal photocoagulation (TRP), reduced fluence/minimally traumatic panretinal photocoagulation (MT-PRP), and standard-intensity PRP (SI-PRP) for PDR management, Muiqt et al., (2013) found no significant differences in vision among the study groups **[20]**.

In a prospective, non-randomized trial, 28 cases of naive (PDR) were treated using a single session, 20-ms duration Pascal TRP approach that involved delivering 1500 laser shots to areas of intermediate retinal ischemia and non-perfused sites guided by wide-field FA (Optos).They reported an increase in ETDRS VA by +3 letters at six months (p< 0.0001) **[13]**.

In our study, baseline average (CSFT) (µm) was 228.40±31.04 in the PRP group with all patients having pre-laser CSFT less than 300µm. After three month, there was a significant increase in CSFT post-treatment to 270.25±57.85µm (p-value=0.004), the average change percentage of CSFT was 19.14%.

Similar outcomes were noticed by Soman et al., Mean preoperative CSFT was 222.05±59.11 µm, and after four weeks (p=0.01) and twelve weeks (p=0.04), these values considerably rose to 264.05 ±102.56mm and 256 x 101.38µm, respectively. **[12]**.

In Lee et al., study, prior to PRP, the central macular thickness measures had a mean of 196± 13µm, and at 1, 3, 6, and 12 months following PRP, they were 210±14, 213±19, 225±47, and 220± 18µm, respectively **[21]**.

In the Egyptian research conducted in Al-Azhar University, the mean pre- PRP central foveal thickness (CFT) was 253.05±18.53µm (ranging from 227-281 µm), increased significantly to 281.45± 28.71µm (ranging from 240-344µm) at 3months' follow-up (p<0.001) **[17]**.

Shimura et al., 2003 stated that central retinal thickness was significantly increased following weekly treatment (p=0.012); while insignificant difference occurred following biweekly treatment **[16]**.

According to those investigations, one or more sessions of standard PRP resulted in a significant, modest thickening of the macular tissue relative to baseline.

However, the effects of pattern scan PRP using shorter wavelengths of 20ms have been suggested by several studies. Muqit et al., compared single spot, 100ms, multisession PRP (MS-PRP) with multispot, 20ms single session PRP (SS-PRP) in the Manchester Pascal Study. The mean CFT increased significantly with MS-PRP (22mm at 4 weeks; 20mm at 12 weeks; p .001) but not significantly with SS-PRP **[19]**. Mukhtar et al., also showed a significant reduction in central macular thickness following two sessions (2500-3000 burns) of PASCAL PRP laser PRP **[22]**. In addition to the improvement in vision noticed in that study, decrease in central macular thickness gives an idea about the possible benefits of PASCAL laser over conventional argon laser.

In our study, as regard the effect of TRP on the CSFT, baseline CSFT was 248.50±39.05µm which increased to 262.15±35.34µm (p-value=0.018).

The average percentage of change in CSFT was 6.52%. This is different than what was reported in Manchester pilot study. The central retinal thickness (CRT) significantly decreased with follow-ups (10.4µm at 3 months, p=0.007; 12.1 µm at 6 months, p=0.0003) [19].

At 12 weeks, Mquit et al., (2013) found that TRP and MT-PRP significantly reduced CRT compared to SI-PRP and TRP. The base line mean CRT was 251±35.8µm; range 173-297). Over time, CRT decreased significantly (7µm at 4 weeks, p=0.027; 10.4µm at 12 weeks, p=0.007; 12.1 µm at 24 weeks, p=0.0003). No reports of substantial retinal edema requiring laser treatment after TRP sessions were detected [13]. The previously mentioned studies used shorter duration of 20ms pattern scan TRP which explains their effect on CSFT.

Back to our subgroup analysis, mean CSFT was 251.33±34.01 µm in TRP with in IVI subgroup (p-value=0.008). In the TRP alone subgroup CSFT was 271±35.45 µm (p-value=1). The Percentage of change in CSFT in TRP with IVI was 13.95% and in the TRP alone subgroup it was only 0.45 at 3 months of study.

While in a three armed randomized clinical trial (CTPDR 2022), 207 eyes of naive diabetic patients were recruited and randomized into 3 arms: first arm received conventional PRP, second arm had 4 monthly injections of intravitreal injections of bevacizumab and third that received modified laser therapy and two monthly IVB injections.

They compared neovascularization leakage area and BCVA among the three groups at one year follow-up. They discovered that the BCVA between the groups did not differ significantly (p=0.77). The lowest final leakage area was in the modified combination group (p=0.006), new onset macular edema was not different between injection and combination arm (p=0.23), however more visits were needed in the injection arm (p=0.001). They concluded that combination and IVB protocols can be suggested to patients with PDR, particularly when macular edema coexists [23].

One more network meta-analysis (NMA) study evaluated PRP alone, anti-VEGF alone, and combined therapy in randomized clinical trials (RCTs). The main outcomes of this NMA, which included 12 RCTs with a 12-month follow-up, were the regression of the neovascularization area, BCVA, and CMT. It revealed that the neovascularization regression did not significantly differ among all arms, but that the anti-VEGF group and the combined group had better visual results than PRP [24].

Regarding the effect of the three treatment arms on central macular thickness (CMT), several RCTs were included [25-29]. The PRP arm, anti-VEGF arm, and combination arm were each comprised of a total of 262 eyes, 161 eyes, and 140 eyes, respectively. The anti-VEGF arm fared better than the PRP group, with substantial reductions in CMT relative to the PRP arm [MD = –36.93] and combination group [MD = –26.88]. The comparison between PRP and combined arm showed no significant difference in average CMT [MD = –10.05] [24].

Our results showed that CSFT % change did not differ significantly between PRP and TRP with IVB (p=1), unexpectedly this difference was significant between PRP and TRP alone (p=0.002). This is could be related to the small sample size of the groups specially TRP with IVB subgroup which could reduce the chances to discover the true effect. Also the anti-VEGF treatment has short term effect [30], so multiple injections may be needed. Many studies adapted multiple IVI in combination with laser treatment for example, CTPDR 2022 study that used 2 monthly IVB injections with modified laser treatment and (Figueira et al., 2018) multicenter study in which patients in combined group had three monthly IVI plus conventional PRP sessions [26].

Indeed, the current study revealed some limitations. Investigation included a small sample size which could lead to low statistical power. Studied cases also included both mild and moderate PDR cases that might differ in severity and hence, outcome. Short duration of follow up is another limitation, as longer period may be needed to detect the long term efficiency of new treatment modalities and any further need of laser augmentation, IVI and even vitrectomy. Furthermore, Long duration argon laser (100ms) was used in treatment of patients with TRP. Other studies used the shorter duration 20ms pascal TRP which has a better effect on CSFT. Finally, the effect of repeated IVI was not evaluated.

Conclusion:

Considering the outcomes of our study, TRP alone or combined with a single intravitreal bevacizumab injection is not an inferior therapy option than traditional PRP for proliferative diabetic retinopathy over a three-month follow-up period. The effects of the aforementioned treatment modalities on BCVA were not significantly different from one another; however TRP had a smaller impact on CSFT than PRP.

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دراسة مقارنة بين الكى الضوئى الموجة لشبكية العين مع وبدون حقن بيفاسيزوماب واحد داخل الجسم الزجاجى مقابل الكى الضوئى التقليدى الشامل للشبكية لعلاج اعتلال الشبكية السكرى التكاثرى

يعد اعتلال الشبكية السكرى التكاثرى هو أهم أسباب ضعف فقدان البصر لدى مرضى السكرى. ويعد الكى الصوئى الكامل للشبكية من أكثر الأساليب فاعلية فى علاج الاعتلال الشبكى السكرى على الرغم من وجود بعض الأعراض الجانبية.

كان هدف هذه الدراسة التداخلية هو تسليط الضوء على طرق جديدة للكى الضوئى بحيث يشمل مناطق الشبكية التى لا يصلها الدم بكمية كافية مع استثناء المناطق المغذاة بشكل كاف. حيث أنه فى هذه الرسالة تم إدارج أربعة وأربعين عين من مرضى الاعتلال الشبكى السكرى التكاثرى البسيط والمتوسط. وتم عمل كى ضوئى كامل لنصف المرضى وكى ضوئى جزئى موجه للنصف الأخر وعلى مدار ثلاثة شهور من المتابعة وتم دراسة تأثير هذه الإجراءات العلاجية على الحد من الاعتلال الشبكى التكاثرى وحدة الإبصار ومتوسط سمك مركز الإبصار.

وقد أظهرت النتائج فاعلية الكى الضوئى الجزئى الموجة فى تراجع الاعتلال الشبكى التكاثرى مقارنة بالكى الضوئى الكلى والحفاظ على حدة الإبصار بدون تغيير واستخلص البحث أن نسبة التغيير فى سمك مركز الابصار كانت عند استخدام الكى الجزئى ٦.٥٢٪ مقارنة ب ١٩.١٤٪ فى حالة استخدام الكى الكلى.

وبناءاً على نتائج البحث يعتبر الكى الضوئى الجزئى الموجة فعالاً فى علاج الاعتلال الشبكى البسيط والمتوسط على المدى القريب بدون التأثير على النظر ونسبة التغيير فى سمك مركز الابصار فى معظم الحالات.