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Original Research Article

Comparision of central retinal layer thickness in patients with PDR treated with intravitreal ranibizumab vs ranibizumab plus PRP

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ABSTRACT

Background: Diabetic retinopathy (DR) is the primary cause of blindness in the working population worldwide and is a common consequence of type 2 diabetes (T2DM).
One significant risk factor for serious vision loss in individuals with diabetes mellitus is retinal neovascularization (NV). Since the 1980s, retinal photocoagulation (PRP) has been the gold standard for treating diabetic retinopathy (DR) because it increases the availability of oxygen to the retina and reduces the subsequent release of vascular endothelial growth factors (VEGF), which prevents the progression of diabetic retinopathy. Intravitreal anti VEGF therapy show combine anti-angiogenic and anti-edematous properties and significantly altered the course of DR.
The purpose of this study is to assess the central retinal thickness (CRT) of eyes from patients with proliferative diabetic retinopathy (PDR) receiving intravitreal ranibizumab versus ranibizumab with pan retinal photocoagulation (PRP).
Materials and Methods: Thirty patients with proliferative diabetic retinopathy were split into two groups for this prospective randomized control trial. Fifteen eyes in Group A received intravitreal ranibizumab, while fifteen eyes in Group B received intravitreal ranibizumab plus panretinal photocoagulation (PRP). The study was carried out over a six-month period. Using paired T tests and analysis of variance, visual acuity and central retinal thickness (CRT) were assessed at baseline, week 4, and week 8.
Results: Best corrected visual acuity and Central Retinal thickness show a significant difference statistically (p value <0.05) between the two groups. Group A had a baseline visual acuity of 0.85 ± 0.10 compared to Group B 0.98 ± 0.14 with p value 0.007. By week 8, Group A showed a visual acuity of 0.34 ± 0.07 versus 0.26 ± 0.07 in Group B with p value 0.0012. Additionally, Group A's baseline CRT was 258.33 ± 20.33 μm compared to Group B's 267.40 ± 29.40 μm (p = 0.00002), and by week 8, it measured 217.26 ± 10.49 μm versus 228.00 ± 15.69 μm (p = 0.032).
Conclusion: Compared to intravitreal ranibizumab alone, the combination of pan retinal photocoagulation with intravitreal ranibizumab is a more successful treatment for proliferative diabetic retinopathy. Central retinal thickness, macular edema, and neovascularization are reduced more significantly with combination therapy, potentially reducing the need for injections.

1. Introduction

The most prevalent cause of blindness in the working population worldwide is diabetic retinopathy (DR), a common consequence of type 2 diabetes (T2DM). The

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estimated national prevalence of diabetic retinopathy in India is between 12.5% and 21.7%, and the rate of vision-threatening diabetic retinopathy (VTDR) is between 4.0% and 3.4% (3.4%–4.8%). There are no appreciable changes in the prevalence of diabetic retinopathy between urban and rural areas. [1,2]

Retinal ischemia predisposes to angiogenesis ie. Proliferative diabetic retinopathy (PDR) which is largely mediated by VEGF (Vascular endothelial growth factor). [3]

Pan retinal photocoagulation (PRP) offers a promising early intervention in which around 60% of Proliferative diabetic retinopathy (PDR) patients experience neovascularization regression within three months of Pan retinal photocoagulation (PRP). [4] However, the need for additional laser treatments and, in some cases (4.5%), vitrectomy highlights the limitations of PRP. [5] PRP, often reported as painful, can potentially lead to peripheral vision loss and even increase the risk of macular edema. [6]

Intravitreal Anti-VEGF treatments due to their combined anti-angiogenic and anti-edematous properties, significantly altered the course of diabetic retinopathy (DR). [7] Anti-VEGF medications, such as pegaptanib and ranibizumab, are presently being tested in a number of clinical trials with promising preliminary findings to treat macular edema and retinal neovascularization in diabetic patients. Compared to PRP, intravitreal ranibizumab (RBZ) did not aggravate PDR in eyes with PDR; this was notably true for eyes that were not needed to receive ranibizumab for center involving diabetic macular edema (CI-DME). [8,9]

In their study on high-risk PDR eyes, Filho et al. found that adjunctive IVR to PRP considerably reduced the foveal leakage area (FLA) after 48 weeks, or around 11 months, which may have mitigated the mild deterioration in visual acuity and thickening of the macular tissue that were seen with PRP alone. [10,11] In comparison to PRP alone, Figueira et al. study shown that over the course of a year, the combination of RBZ and PRP improved the regression of aberrant blood vessels (NV) in patients with high-risk proliferative diabetic retinopathy (HR-PDR). [12,13]

The main purpose of our study is to assess the central retinal thickness (CRT) of eyes treated with intravitreal ranibizumab alone and in combination with pan retinal photocoagulation (PRP) in patients diagnosed with proliferative diabetic retinopathy (PDR).

2. Materials and Methods

A prospective randomised control trial was conducted in the Ophthalmology Outpatient Department (OPD) of a tertiary care centre between June 2023 and November 2023. The study complied with the principles of the Declaration of Helsinki, having been examined and approved by the Institutional Research Ethics Committee (ASRAMS BHR-EC/Approval No.3/2023).

Prior to data collection, all participants provided their informed consent. Patients diagnosed with proliferative diabetic retinopathy (PDR), who visited the outpatient department consecutively were divided into two study groups: Group A: Intravitreal Ranibizumab injections were administered to 15 patients. Group B: Panretinal photocoagulation (PRP) and intravitreal ranibizumab injections were administered to 15 patients.

3. Materials and Methods

3.1. Sample size

Thirty patients with proliferative diabetic retinopathy (PDR) who met particular criteria as defined by EDTRS standards were included in the study. The patients were split into two groups of fifteen individuals each using simple randomization technique.

Patients in Group A received intravitreal injections of ranibizumab.

Patients in Group B received intravitreal injections of ranibizumab in addition to panretinal photocoagulation (PRP).

3.2. Inclusion criteria

Patients with proliferative diabetic retinopathy (PDR) meeting the specific criteria defined as per EDTRS guidelines as follows:

1. Presence of neovascularization at the disc (NVD) greater than EDTRS standard photograph 10A.
2. Presence of neovascularization at the disc (NVD) associated with vitreous or pre retinal hemorrhage or
3. Neovascularization elsewhere (NVE) with more than a half disc area associated with vitreous or pre retinal hemorrhage.

3.3. Exclusion criteria

Exclusion criteria included the following:

1. Patients with significant media opacity.
2. Patients with history of prior laser treatment or vitrectomy in the study eye.
3. Patients with Tractional retinal detachment.
4. Patients with histories of ophthalmic disease other than diabetic retinopathy and cataract.
5. Patients who underwent intraocular surgery except for cataract extraction.

3.4. Study procedure

The study comprised of patients who satisfied the inclusion and exclusion criteria. All the patients included in the study underwent a thorough comprehensive eye examination at the start of the study or the baseline. This included

best corrected visual acuity (BCVA) in LogMAR format using Snellen's test types, intra ocular pressure (IOP) measurements by tonometry using Goldmann Applanation Tonometer (GAT), anterior segment evaluation with slit lamp biomicroscope and dilated fundus examination with direct ophthalmoscope or +90D or indirect ophthalmoscope in case of media haziness after pupillary dilatation with 1% tropicamide eye drops. Spectral Domain Optical coherence tomography (SD-OCT) was performed using retinal thickness map analysis to display numeric averages of measurements for each of the nine EDTRS sub fields to measure central retinal thickness (CRT).

A single, masked expert used ETDRS protocol to assess the severity of diabetic retinopathy. Additionally, basic blood tests for blood sugar (RBS) and long-term sugar control (HbA1c) were performed.

Both groups received 0.5mg of IVR in 0.05ml at baseline, week 4, and week 8. Group B received additional standard PRP treatment delivered by a single experienced retinal specialist using a NIDEK GREEN LASER with a 532nm frequency. PRP was performed in two sessions with 15 days apart, targeting non-perfused areas. Each session included laser shots with a pulse duration of 0.2s for a total of 1200-2000 burns.

3.5. Follow-up

Complete ophthalmic examinations were performed on all patients at baseline, week 4, and week 8. Spectral-domain optical coherence tomography (SD-OCT), dilated fundus examination, and best-corrected visual acuity (BCVA) were among the tests performed.

3.6. Statistical analysis

Paired t-tests and analysis of variance were used to compare the mean change from baseline to week 4 and week 8 for the following continuous variables:

Best-corrected visual acuity (BCVA) assessed in LogMAR format.

Central retinal thickness (CRT) was measured from Spectral-Domain OCT (SD-OCT).

The Mann-Whitney U test was used to compare the distribution of severity scores for diabetic retinopathy (assessed by ETDRS) between the two groups at baseline and follow-up visits, as severity is an ordinal variable.

Statistical package for social sciences (SPSS) of version 20.0 was used to conduct the statistical analysis. Statistical significance was defined as a p-value of less than 0.05.

4. Results

Following evaluation using the EDTRS protocol, thirty patients diagnosed with proliferative diabetic retinopathy (PDR) who met the inclusion and exclusion criteria were split into two groups of fifteen patients each. Intravitreal ranibizumab was administered to patients in group A, while intravitreal ranibizumab plus pan retinal photocoagulation was administered to patients in group B. Regarding the study sample, the mean age of the patients was 63.20 ± 6.14 years for group A and 63.80 ± 5.34 years for group B. In group A, 33.33% of the participants were female, and 66.66% were male; in group B, 46.66% of the participants were female, and 53.33% were male.

At baseline, the mean best corrected visual acuity was 0.85 ± 0.10 in group A and 0.98 ± 0.14 in group B respectively measured in LOGMAR format, while the mean best corrected visual acuity at week 4 was 0.56 ± 0.15 and 0.53 ± 0.14 respectively (p value – 0.03) and at week 8 is 0.34 ± 0.07 and 0.26 ± 0.07 respectively (p value – 0.0012). (Table 1)

The mean central retinal thickness at baseline was 258.33 ± 20.33 and 267.40 ± 29.40 in group A and B respectively (p value – 0.0002) while the mean central retinal thickness at week 4 in both groups was 228.00 ± 14.83 and 247.26 ± 21.04 respectively (p value – 0.01) and at week 8 was 217.26 ± 10.49 and 228.00 ± 15.69 respectively (p value – 0.032). (Table 2)

Figure 1 shows evolution of BCVA in both the groups at baseline, week 4 and week 8 in logMAR format. Significant improvement of BCVA is seen in group B compared to group A.

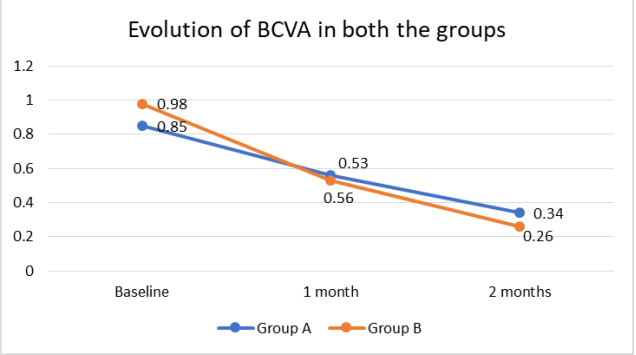

Figure 1: Evolution of BCVA in both the groups

5. Discussion

In this study, patients diagnosed with proliferative diabetic retinopathy treated with intravitreal ranibizumab alone and with intravitreal ranibizumab plus pan retinal photocoagulation (PRP) were compared for best corrected visual acuity and central retinal thickness (CRT). When compared to patients in the intravitreal ranibizumab group alone, the mean best corrected visual acuity (BCVA) of patients in the intravitreal ranibizumab with pan retinal photocoagulation (PRP) group demonstrated a significant improvement in visual acuity at weeks 4 and 8. When assessed over the course of the study, the additional use of

Table 1: Shows demographic details of mean best corrected visual acuity in patients form group 1 and group 2

Visual Acuity (Mean ± Standard Deviation)	Group A (Intravitreal Ranibizumab)	Group B (Intravitreal ranibizumab with pan retinal photocoagulation	p value
Baseline	0.85 ± 0.10	0.98 ± 0.14	0.007
Week 4	0.56 ± 0.15	0.53 ± 0.14	0.03
Week 8	0.34 ± 0.07	0.26 ± 0.07	0.0012

Table 2: Shows the mean central retinal thickness in patients from group 1 and group 2

Central Retinal Thickness (Mean ± Standard Deviation)	Group A (Intravitral Ranibizumab)	Group B (Intravitreal Ranibizumab With Pan Retinal Photocoagulation)	p value
Baseline	258.33 ± 20.33	267.40 ± 29.40	0.00002
Week 4	228.00 ± 14.83	247.26 ± 21.04	0.01
Week 8	217.26 ± 10.49	228.00 ± 15.69	0.032

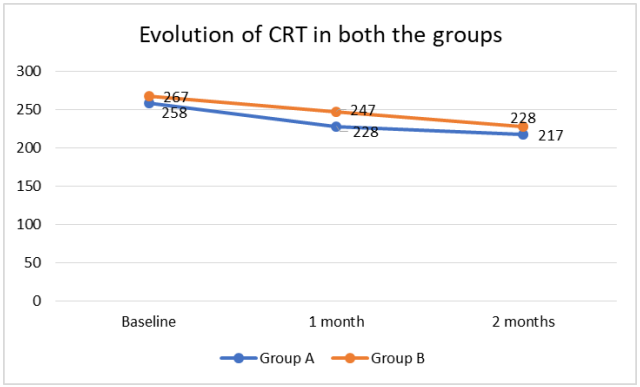

Figure 2: Evolution of CRT in both the groups

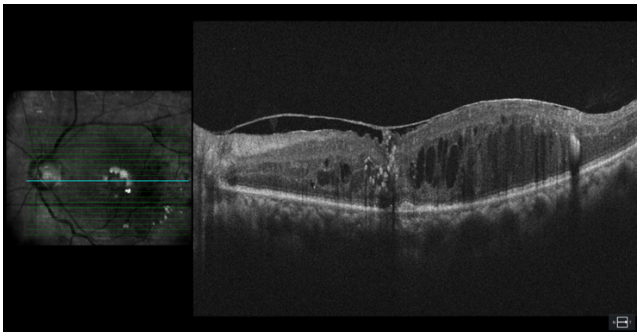

Figure 3: OCT at baseline in group A (intravitreal ranibizumab) pre treatment

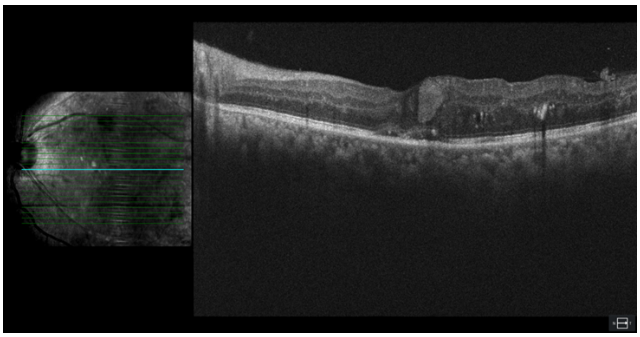

Figure 4: OCT of group A (intravitreal ranibizumab) post treatment showing decreased central retinal thickness and edema

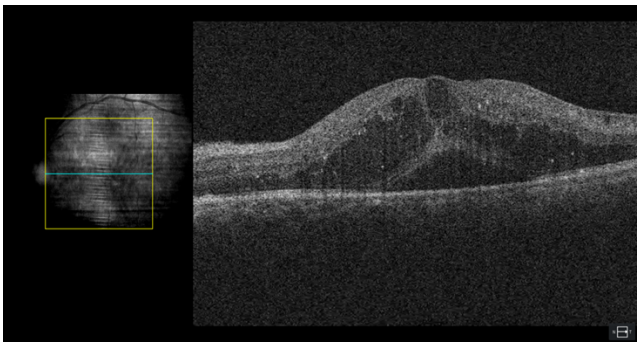

Figure 5: OCT picture of group B (intravitreal ranibizumab with pan retinal photocoagulation) at baseline pre treatment

PRP revealed no inferiority outcome of changes in visual acuity between the patients of two groups.

Our study demonstrated a significant reduction in central retinal thickness (CRT) at 1 month in proliferative diabetic retinopathy (PDR) patients treated with intravitreal ranibizumab (IVR) along with pan retinal photocoagulation (PRP) compared to intravitreal ranibizumab (IVR) alone. These findings are consistent with previous studies by Filho et al. (40 patients) and Figueira et al. (87 patients), who reported that the combination of intravitreal ranibizumab (IVR) and pan retinal photocoagulation (PRP) resulted in a larger reduction in macular edema (FLA) and greater neovascularization regression compared to PRP alone.[10,12]

Filho et al. specifically showed that intravitreal ranibizumab (IVR) after PRP was associated with a larger reduction in macular edema at week 48 compared to pan retinal photocoagulation (PRP) alone in eyes with high-risk

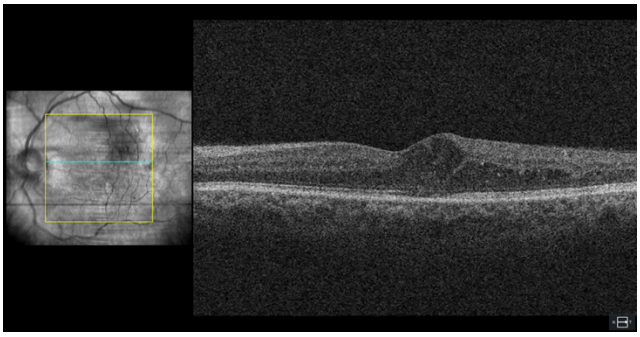

Figure 6: OCT picture of group B (intravitreal ranibizumab with pan retinal photocoagulation) post treatment showing decreased central retinal thickness and macular edema

proliferative diabetic retinopathy (PDR) patients.[10]

Figueira et al. found that IVR along with PRP was more effective than PRP monotherapy for neovascularization regression in high-risk PDR participants over 12 months. Our results further support these observations, suggesting that the combination therapy may be more effective for reducing CRT at an earlier time point (1 month).[12]

Chatziralli et al. (47 patients) investigated the use of IVR for PDR with coexistent diabetic macular edema (DME). They concluded that both IVR alone and IVR combined with PRP could be effective for treatment. While they did not observe a difference in best-corrected visual acuity (BCVA) and CRT at the 24-month follow-up between the two groups, the combination group showed greater regression of neovascularization and required fewer injections. Our study focused solely on PDR without DME; however, our findings regarding the effectiveness of combination therapy for reducing CRT align with Chatziralli et al.'s observations on neovascularization regression.[14]

A randomized control trial involving 305 patients with PDR was examined by Gross JG et al. to determine whether ranibizumab was not less effective than PRP in terms of vision outcomes.[15] The study found that after two years, ranibizumab treatment did not produce visual acuity that was worse than PRP treatment in eyes with PDR. Ranibizumab may be a reasonable treatment alternative for patients with PDR, at least for the first two years, even though longer-term follow-up is necessary.

6. Limitations

Our study has the following limitations. First, the sample size was relatively small, potentially limiting the generalizability of our findings. Second, the follow-up duration was short (1 month), precluding assessment of long-term effects on vision and retinal morphology. The treatment modalities precluded the masking of participants and clinicians; however, the grouping was done with unbiased masking. The limitation of the treatment modalities and strict adherence to the treatment protocols has limited the bias of the study. Cost effectiveness with other treatment strategies when compared with the similar results was beyond the study.

Future research with larger, prospective cohorts and longer follow-up periods is necessary to definitively determine the optimal treatment strategy for PDR, considering both short-term improvements in macular edema and long-term visual outcomes. Additionally, studies evaluating the cost-effectiveness of combination therapy compared to IVR alone would be valuable for informing healthcare decision making.

7. Conclusion

In conclusion, our study and previous studies by Filho et al., Figueira et al., and Chatziralli et al. collectively suggest that the combination of intravitreal ranibizumab and pan retinal photocoagulation is a more effective treatment for proliferative diabetic retinopathy compared to intravitreal ranibizumab alone. The combination therapy leads to a greater reduction in central retinal thickness, macular edema, and neovascularization, potentially with a reduced need for injections.

The research aids in risk assessment, patient counselling, and evaluation of the visual status following therapy for proliferative diabetic retinopathy. It evaluates the necessity of routine intravitreal medication and monthly clinic visits.

8. Source of Funding

Nil.

9. Conflict of Interest

None.

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