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To compare the short-term efficacy and safety of combination therapy with standard fluence and reduced fluence PDT in polypoidal choroidal vasculopathy

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ABSTRACT

Purpose: To evaluate and compare the efficacy of reduced-fluence photodynamic therapy (PDT) with standard-fluence photodynamic therapy in treating polypoidal choroidal vasculopathy.

Materials and Methods: Twenty-eight eyes (27 patients) with polypoidal choroidal vasculopathy were retrospectively analysed; 14 eyes received Indocyanine green angiography-guided standard-fluence (SF) PDT (50 J/cm^2) and 14 eyes received Indocyanine green angiography-guided reduced-fluence (RF) PDT (25 J/cm^2). Primary outcome measured after 6 months of treatment were the changes in mean BCVA, polyp regression, polyp PED height, central choroidal thickness (CCT), post PDT intravitreal anti VEGF injection need and complications.

Results: Results of both the groups were comparable at 6 months follow up. Mean change in log mar visual acuity at 6 months for the SF PDT group was 0.12 compared to 0.13 for the RF PDT group (p = 0.919). Mean change in PED height at 6 months for the SF PDT group was 159 μm compared to 172 μm for the RF PDT group (p = 0.06). Mean change in CCT at 6 months for the SF PDT group was 45μm compared to 10μm for the RF PDT group (p = 0.96). While the SF PDT group needed a mean of 2 injections post PDT, the RF PDT group required a mean of 3 injections during the course of 6 months follow up. Neither of the group reported any adverse effects following the procedure.

Conclusions: Our study demonstrated that reduced-fluence PDT is at least on par with standard-fluence PDT in management of PCV.

1. Introduction

Polypoidal choroidal vasculopathy (PCV), a form of wet age-related macular degeneration (AMD), is characterized by an abnormal choroidal vascular network and extension of their endings to form polyps.[1] The APOIS PCV workgroup updated nomenclature of PCV and recommended using the terms polypoid lesion and branch vascular network (BVN) to describe the two components within the PCV complex.[2]

Although typically wet AMD is treated with anti-VEGF monotherapy, EVEREST study found that verteporfin Photo Dynamic Therapy (PDT) when administered as monotherapy or in combination with intravitreal anti VEGF (ranibizumab) had higher rates of polyp regression when compared to intravitreal anti VEGF therapy alone in PCV eyes.[3] In EVEREST study, verteporfin was administered at 6 mg/m^2 for 83 seconds using standard fluence PDT (light dose 50 J/cm^2, dose rate 600mW/cm^2, wavelength 689 nm).[3] Standard fluence PDT has been reported to cause vision-threatening complications like sub-retinal haemorrhage, vitreous haemorrhage, supra-choroidal haemorrhage and RPE tears.[4,5] It is believed that PDT causes chorio-capillary thrombosis, resulting in choroidal ischemia and up regulation of VEGF expression which ultimately results in atrophy or development of CNVM.[6]

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A less-intensity protocols of PDT treatment has been proposed by many authors to reduce the risk of complications with standard PDT. These protocols include either reducing the dose of verteporfin dye administered or reducing one of the laser parameters to achieve reduced laser fluence.[7,8] Various authors have described the success of these less-intensive regimens, theoretically reducing the risk of complications.[7,8] In this study, we sought to compare the clinical efficacy & safety of reduced-fluence (RF) PDT to standard-fluence (SF) PDT in treatment of PCV eyes in a series of South Indian population.

2. Materials and Methods

We retrospectively analysed 28 eyes of PDT-naive patients diagnosed with type 1 aneurysmal choroidal neovascularisation (PCV) who underwent verteporfin PDT from November 2016 to December 2018 in a tertiary Ophthalmology referral centre in South Kerala. Our inclusion criteria included all the diagnosed cases of polypoidal choroidal vasculopathy including treatment naïve patients with a minimum follow up of 6-month period post PDT. Those with co-existing other ocular diseases like diabetic retinopathy, pathologic myopia, uveitis, glaucoma etc were excluded from study. Type 1 aneurysmal choroidal neovascularisation was diagnosed by reading-centre certified retinal specialists using dynamic fluorescein (FA) and indocyanine green angiograms (ICGA) (Heidelberg Spectralis, Germany) using the diagnostic criteria adopted by the EVEREST and EVEREST II studies[3,9] i.e. early sub retinal ICGA hyper fluorescence occurring within the first 6 mins, and at least one of the following diagnostic criteria: 1) Nodular appearance of the polyp on stereoscopic viewing, 2) Hypo fluorescent halo around the nodule, 3) Abnormal vascular channel(s) supplying the polyps, 4) Pulsatile filling of polyps, 5) Orange sub-retinal nodules corresponding to the hyperfluorescent area on ICGA, 6) Massive sub macular haemorrhage.[3] Spectral-domain optical coherence tomography (SD-OCT) (Heidelberg Spectralis, Germany) was performed in all cases to obtain thickness measurements used in the secondary outcomes described below.

Two PDT approaches were compared; Standard-fluence PDT (SF PDT-689 nm, 50 J/cm2; 83 s) and reduced-fluence PDT (RF PDT-689 nm, 25 J/cm2; 83 s).[3] Outcomes studied included best corrected visual acuity (BCVA), polyp regression, foveal fluid, polyp PED height, central choroidal thickness(CCT), post PDT intravitreal anti VEGF injection requirement and complications at 6 months. Polyp regression was defined based on tomographic evidence.

3. Results

Patients were divided into two groups for analysis based on their PDT regimen. 28 eyes of 27 patients (males 51.8%) were analysed in this study. Out of these, 14 (50.0%) eyes were treated with SF PDT while other 14 eyes were treated using RF PDT. The mean age of the patients was 62.03 ± 8.1 years (range 40–81 years). Mean age in SF PDT group was 61.35 ±7.7 years and 63.06 ± 8.44 years in RF PDT group. These patients were followed-up for a period of 6 months.

We compared baseline visual acuity (VA), and OCT characteristics of both the groups (Table 1). Overall, both the groups gained vision compared to baseline for 6 months follow up period. At 6-months, the baseline mean log mar VA in the SF PDT group was increased from 0.40 + 0.23 to 0.28 + 0.14, and in the RF PDT group, it changed from 0.39 + 0.18 to 0.26 + 0.23. Mean change in BCVA at 6 months for the SF PDT group was 0.12 compared to 0.13 for the RF PDT group. There was no statistically significant difference in mean VA increase between the two groups (p=0.919) at 6-month follow-up.

The mean PED height & CCT at baseline and 6 months follow up visit are illustrated in Table 1. The mean reduction in PED size from baseline was comparable in both groups at 6 months, with no significant difference between them. From baseline, mean PED height decreased in SF PDT group from 361±203μm to 202 ±167.08 μm while in RF PDT group it decreased from 353±147 μm to 181±14 μm. Mean change in PED height at 6 months for the SF PDT group was 159 μm compared to 172 μm for the RF PDT group (p = 0.06).

Mean CCT was 316±69 μm at baseline and decreased to 271.92 ±32 μm at 6 months follow up in SF PDT group while in RF PDT group it decreased from 293.28 ±57 μm to 283 ±59 μm. Mean change in CCT at 6 months for the SF PDT group was 45μm compared to 10μm for the RF PDT group (p = 0.96). In 12 patients (8 in the SF PDT group and 4 in the RF PDT group), PED resolved or become flat irregular (FIPED).

Overall, 86% patients in both PDT groups received at least one intravitreal anti VEGF injection after PDT. 2 patients each (14.2%) in the standard-fluence (SF) and reduced-fluence (RF) groups received PDT mono-therapy only (p = 0.55). While the SF PDT group required an average of 2 injections after PDT, the RF PDT group required an average of 3 injections during the follow-up period of 6 months.

None of the patients in the SF PDT or RF PDT groups experienced major complications such as massive bleeding, RPE tears, or severe vision following PDT in our study.

4. Discussion

Polyp regression rates up to 80% in PCV eyes after standard PDT have been well documented in several studies.[4,5]

Table 1: Comparing efficacy of RF and SF photodynamic therapy in treatment of PCV

Baseline characteristic	PDT treatment regime				Change in mean value over 6 months		P value
	SF-PDT (n = 14)	SF-PDT (n = 14)	RF-PDT (n = 14)	RF-PDT (n = 14)	SF-PDT	RF-PDT	
LogMAR mean visual acuity	0.40 ±0.23	0.28 ±0.14	0.39 ±0.18	0.26±0.23	0.12	.13	0.919
PED height(μm)	361±203	202± 167.08	353±147	181±141	159	172	0.06
Central choroidal thickness (μm)	316±69	271.92±32	293.28±57	283±59	45	10	0.96

EVEREST I and EVEREST II studies reported a higher rate of polyp regression using SF PDT in combination with intra-vitreal anti VEGF (ranibizumab) therapy compared to intra-vitreal anti VEGF injection alone.[3,10] Many authors have reported complications like severe bleeding, exudation, and choroidal ischemia following standard fluence PDT, which may result in visual acuity loss up to 11.0-30.8% of the eyes.[11,12] Our study reported no such major complications after PDT in both the groups. To reduce the adverse effects of PDT, many authors have suggested alternative PDT protocols that are less intensive by either decreasing the laser fluence or by decreasing the dosage of verteporfin dye administered.

Photo dynamic therapy acts by the initiation of photo chemical processes at target sites. Intra-venous administration of verteporfin dye followed by laser application leads to a cascade of chemical reactions that results in cytotoxic free radical release causing endothelial damage, blood flow stagnation and ultimately shutdown of vasculature.[13] Favourable concentration of verteporfin dye in polyps and BVNs minimizes collateral damage of tissues.[13] There is a direct correlation between the phototoxic effects of PDT with the dosage of drug administered and exposed light dose. For example, reducing the dose of a drug requires increasing the amount of light required to achieve a similar effect, and vice versa. Hence, the phototoxic effect can be modified by either adjusting the dosage of drug or the light dose.[13] In our study, we chose to vary the fluence by shortening the duration of laser irradiation while keeping the dose rate constant. A practical advantage of reducing the time of laser application, rather than the dose rate, to achieve reduced fluence was that it reduced the overall treatment time required.

In our study, we found that RF PDT was comparable to SF PDT in the management of PCV in terms of visual outcomes. Overall, both groups gained VA in 6 months follow up time. In SD-OCT, RF PDT (Figure 1) also resulted in similar reductions in PED height and central choroidal thickness (CCT) (Figure 2) when compared to SF PDT (Figure 3). In addition to improving visual acuity, polyp regression is also important because of the risk of recurrent bleeding from patent polyps which may result in significant vision loss later.[14] RF PDT was also comparable to SF PDT when compared with respect to mean number of intra-vitreal anti-VEGF injections given after PDT treatment.

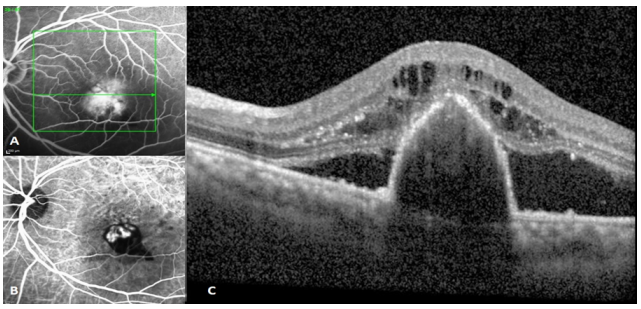

Fig. 1: Baseline images showing polyps in combined FFA+ ICGA (**A & B**) with corresponding tall peaked PED with internal reflectivity, SRF & IRF in SD-OCT (**C**)

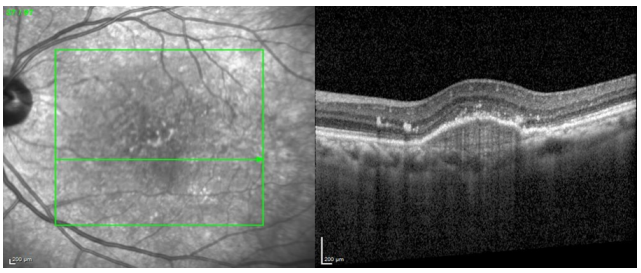

Fig. 2: Follow up SD-OCT images after reduced fluence PDT of same patient showing regression of polyps and resolution of activity after 6 months

Other studies have described the use of PDT with reduced fluence by shortening the laser exposure time to treat PCV.[7,15] They also reported improvements of log mar VA ranging from 0.17–0.24,[7,15] mean CCT reduction of 208 μm[15] and polyp regression rate of 58.3–79%.[7,15] Wong et al. reported visual acuity improvement (log mar 0.23) and good polyp regression rates (42.1%) with administration of reduce fluence PDT.[16] Similarly, there have been reports

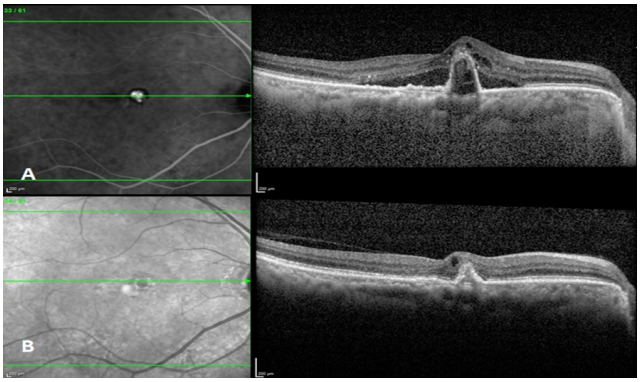

Fig. 3: Baseline images showing polyps in ICGA (**A**) with corresponding SD-OCT images showing thumb shaped PED with SRF and IRF. (**B**) Follow up OCT images after 5 months of standard fluence PDT showing regression of polyps with resolution of SRF and IRF

of the use of low fluence PDT, which resulted in an improvement in log mar VA ranging from 0.13 to 0.3, a mean reduction in foveal thickness of 87 to 281μm, and a reduction in polyp regression rates ranged from 71.4% to 92.8%.[8,16] These results are comparable to those of our study. Fan et al. also showed that RF PDT combined with intravitreal anti VEGF therapy would improve the visual acuity at 6 months, with minimal lipid exudation and retinal haemorrhages when compared to SF PDT alone.[7]

One of the major safety concerns of SF PDT is that it causes choriocapillaris thrombosis leading to choroidal ischemia, chorio-retinal thinning and atrophy.[6,17] Choroidal capillary injury after standard fluence PDT has been reported to result in areas of hypo perfusion shown by ICGA.[17] Although it would be ideal to compare the size of hypoperfused area as determined by ICGA between the two treatment groups, this was not the primary aim of our study. Therefore, we measured CCT as a surrogate marker of chorio-retinal atrophy over 6 months. No significant difference in CCT reduction was seen between the two treatment groups.

5. Conclusion

Limitations of our study include small sample size, selection bias due to its retrospective nature and lack randomization in assigning the treatment arms. Generally, SF PDT is not preferred to large PEDs in PCV due to increased risk of RPE rips. Hence, selection bias would be a major confounding factor due to small sample size in this study. Large sample size and proper randomisation of study groups would have given more reliable results. To counteract this, we performed a case-control comparison by including the same number of eyes with similar baseline characteristics in both treatment groups. Furthermore, this is one of the few studies comparing RF PDT with SF PDT in the treatment of PCV, and the results provide some 'real-world' data into the efficacy of different PDT regimens.

In summary, the results of our study showed that reduced-fluence PDT is at least on par with standard-fluence PDT in the treatment of PCV.

6. Source of Funding

None.

7. Conflicts of Interest

Nil.

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