Original Article

Reduced-fluence photodynamic therapy and anti-vascular endothelial growth factor for polypoidal choroidal vasculopathy in an Indian population

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Aims: The aim was to study the efficacy of combined therapy with reduced-fluence photodynamic therapy (RFPDT) and intravitreal bevacizumab/ranibizumab from the Indian subcontinent. **Settings and Design:** This was a single-center, retrospective interventional study. **Methods:** Thirty-five eyes of 34 patients diagnosed with polypoidal choroidal vasculopathy were included. All the patients underwent RFPDT, followed by intravitreal bevacizumab/ranibizumab. **Statistical Analysis Used:** SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA) was used to compare the logarithm of the minimal angle of resolution visual acuity at presentation and final follow-up. $P < 0.05$ was considered statistically significant. **Results:** Regression of polyps after a single session of RFPDT was seen in five eyes; multiple sessions of treatment were required in thirty eyes. An average number of intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections given were 4 ± 1.9 and average number of PDT sessions were 1.2 ± 0.5. Visual acuity improvement was seen in 21 (60%) eyes ($P < 0.001$), decrease in visual acuity was seen in 7 (20%) eyes ($P = 0.016$), and in 7 eyes (20%), vision remained stable. Regression of polypoidal lesions was seen in 80% of cases. No complications of massive subretinal hemorrhage or breakthrough vitreous hemorrhage were noted in our patients. The mean follow-up period was 18 months (range, 12–24 months). **Conclusions:** RFPDT with anti-VEGF is safe and effective treatment with polyp regression and vision improvement in 80% of cases, without any complication of subretinal hemorrhage/vitreous hemorrhage.

Key words: Anti-vascular endothelial growth factor, photodynamic therapy, polypoidal choroidal vasculopathy, reduced fluence

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Polypoidal choroidal vasculopathy (PCV) was first described by Yannuzzi *et al*. in 1990 as having two distinct components of branching vascular network (BVN) and terminal aneurismal dilatations or "polyps" associated with or without serous/hemorrhagic detachment of retinal pigment epithelium (RPE).[1-3] Clinically, the features of PCV masquerade age-related macular degeneration (AMD) and may account for nearly 10%–40% of the eyes presumed to have AMD.[4] The natural history of patients with PCV may be favorable in 50%, while in the remaining, the disorder may persist for a long time with recurrent subretinal bleeding and exudation resulting in macular scarring and finally visual loss.[5]

Various treatment options for PCV include observation, thermal laser, standard fluence photodynamic therapy (SFPDT), reduced-fluence PDT (RFPDT), and anti-vascular endothelial growth factor (anti-VEGF).[6-10] Koh *et al*. have consolidated practical management guidelines for PCV based on current evidence.[7] Where thermal laser has been used for extrafoveal lesions, PDT has been reserved for subfoveal polyps.[6,8-9] Recurrent or new polypoidal lesions have been seen after successful PDT, which necessitate repeated PDT sessions increasing the risk of RPE tears and choroidal ischemia following PDT.[7,11] Furthermore, massive subretinal hemorrhage has been reported in 3%–19% of treated patients.[11]

Anti-VEGF therapy reduces the subretinal fluid (SRF) but has been found to be less effective in occluding the choroidal polyps.[12,13] Combination therapy of PDT and intravitreal anti-VEGF has been preferred by many for treatment of PCV, considering the synergetic effects.[14] It resulted in favorable outcomes, including improved visual acuity, reduced recurrence rate, and low complications.[14] Decreased incidence of subretinal hemorrhage has been reported, following RFPDT in recent reports.[15] However, there are very few reports in literature on the efficacy of combined therapy with RFPDT and intravitreal bevacizumab/ranibizumab, especially from the Indian subcontinent.[16-18] We report our series of patients who received combination therapy with intravitreal ranibizumab/bevacizumab and RFPDT with verteporfin for PCV in Indian eyes.

Methods

This is a retrospective, interventional study conducted at a tertiary eye care center in South India from January 2006 to October 2012. Thirty-five symptomatic eyes of 34 patients

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with subfoveal PCV as diagnosed on fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA), and optical coherence tomography (OCT) were included. Patients with any contraindication to FFA, ICGA, or verteporfin were excluded. Eyes with the presence of RPE tear or other maculopathies such as AMD, diabetic macular edema, or high myopia were excluded. All participants received a comprehensive ocular examination including best-corrected visual acuity (BCVA) and dilated fundus examination. The study adhered to the Declaration of Helsinki.

PCV was clinically classified into exudative form - presence of exudation without hemorrhage, subretinal lipid exudation and hemorrhagic form - presence of subretinal hemorrhage or hemorrhagic pigment epithelial detachment (PED) with or without exudation.[7] FFA and ICGA were performed at baseline and as and when required. OCT characteristics were noted using time domain (version 3.0, Carl Zeiss Meditec, Germany) and Cirrus OCT (Carl Zeiss Meditec, Dublin, California, USA). Diagnosis was based on the presence of stippled hyperfluorescence on FFA and polypoidal lesions with or without BVN seen on ICGA in early frames. The presence of dome-shaped steeply protruding RPE on OCT further corroborated the diagnosis of polyps. The ICGA-based greatest linear diameter (GLD) of the lesion was determined to cover the polypoidal lesions and surrounding BVN. The total area of PED and subretinal hemorrhage was not included in GLD. RFPDT was done using light energy of 25 J/cm^2 for 83 s (300 mW/cm^2) after 6 mg/m^2 verteporfin injection. It was followed by 1.25 mg of bevacizumab (Avastin; Genentech Inc., South San Francisco, California, USA) or 0.5 mg of ranibizumab (Lucentis, Genentech Inc., South San Francisco, California, USA), given intravitreal 3.5 mm from limbus using a 30-gauge needle under topical anesthesia with strict aseptic precautions 24–48 h after RFPDT. Patients were given the choice to choose between bevacizumab and ranibizumab. The choice for bevacizumab was done by patients primarily to minimize the financial burden.

Retreatment

OCT was done on monthly follow-ups. The intravitreal anti-VEGF injection was repeated at 4–6 weeks intervals if persistent SRF was seen on OCT. If active polypoidal lesions associated with SRF or subretinal hemorrhage were seen on ICGA at 3 months, retreatment with RFPDT combined with intravitreal bevacizumab was performed using the same method as described above.

Outcome measures

Outcome measures included resolution of fluid on OCT and regression of polypoidal lesions on ICGA. Comparison of baseline and final BCVA was done. The number of RFPDT/anti-VEGF injections required was recorded. Any ocular or systemic adverse event was noted.

Statistical analysis

The BCVA at presentation and final follow-up was converted to the logarithm of the minimal angle of resolution (logMAR) equivalents for analysis. These values thus obtained were compared using Wilcoxon signed-rank test. Stepwise regression analysis was also done to determine the factors that affected the BCVA at final follow-up. The factors included were age, gender, baseline BCVA, and GLD. The number of cases developing hemorrhage after RFPDT was also recorded. Statistical analysis was performed using SPSS software (SPSS version 17.0; SPSS Inc., Chicago, IL, USA).

Results

Thirty-five eyes of 34 patients received combination therapy with RFPDT and intravitreal anti-VEGF injection. On analysis, 20 were female (one bilateral presentation) and 14 were male with female to male ratio of 1.4:1. The average age of the patients was 66 ± 9.5 years for male and 60 ± 8.4 years for female (P = 0.07), with more than 50% of the patients being in the 51–60 years of age group. Nearly 25% patients had a bilateral disease though only one patient had active disease in both eyes at presentation. Bilateral RFPDT was done at the same session for this patient. Exudative PCV was seen in 63% and hemorrhagic PCV in 37% of cases [Table 1]. Subretinal orange-colored nodules were visible ophthalmoscopically in 50% of cases.

Regression of polyps after a single session of RFPDT and intravitreal anti-VEGF injection was seen in five eyes [Fig. 1]. Multiple RFPDT sessions and/or multiple anti-VEGF injections were required in thirty eyes. In five eyes that had large PED at presentation, the anti-VEGF injection was given 3–4 weeks before RFPDT to reduce the risk of RPE rip and make treatment safer [Fig. 2]. In two eyes with a large area of subretinal hemorrhage at presentation, pneumatic displacement of subretinal hemorrhage was done using intravitreal injection of 0.3 ml C3F8. This allowed better visualization of the polyps on ICGA after 2–3 weeks. This was followed by combination therapy with RFPDT and intravitreal anti-VEGF.

An average number of intravitreal anti-VEGF injections given were 4 ± 1.9 and average number of RFPDT sessions required were 1.2 ± 0.5. Intravitreal bevacizumab was given in 21 eyes and ranibizumab in 14 eyes. Average GLD was 2.1 ± 1.02 (range, 0.76–4.34). Average GLD in patients responding to a single session of RFPDT with anti-VEGF injection was 1.4 ± 0.6, whereas in those needing multiple session was 2.2 ± 1.02; (P = 0.08) [Table 2].

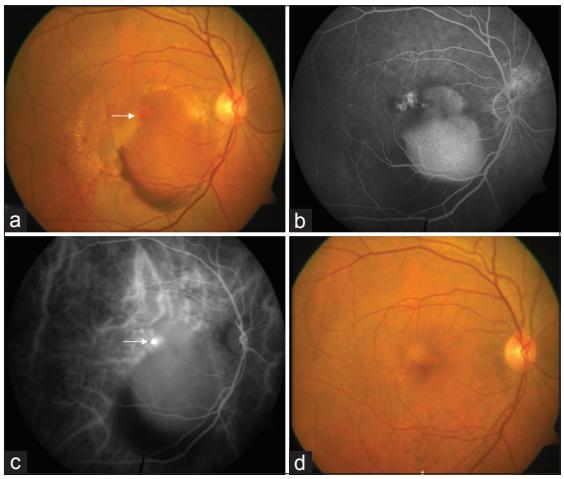

Figure 1: Color fundus (a) of 58-year-old female showing orange colored nodule (polyp) at the edge of subretinal pigment epithelium hemorrhage and hyperfluorescent lesion corresponding to the polyp on fundus fluorescein angiography (b) and indocyanine green (c) showing a good response to single session of combination therapy* (d). *Photodynamic therapy + anti-vascular endothelial growth factor (bevacizumab/ranibizumab)

Table 1: Clinical characteristics of patient

Case number	Age/sex	Type	Visual acuity		Treatment		Outcome	
			Baseline	Final visit	RFPDT (GLD)	Anti-VEGF	Fundus status at final follow-up	Status of vision
1	75/male[P]	H	6/12	6/12	3.92	Rx2	Stable	S
2	53/female[P]	H	6/12	6/12	2.15	Bx4	Stable	S
3	51/female	E	6/9	6/5	0.9	Rx1	Stable	I
4	53/female	E	6/9	6/6	2.11	Bx1	Stable	I
5	59/male	E	6/9	6/6	1.08	Bx1	Stable	I
6	54/male	E	6/9	6/6	1.92	Bx1	Stable	I
7	75/female	E	6/24	6/12	0.8	Bx1	Stable	I
8	72/female	H	6/9	6/60	3.2	Bx5	CNVM	R
9	77/male	E	CF - 3 m	CF - ½ m	1.68	Rx3, Bx5	CNVM	R
10	59/female	H	6/36	6/45	1.54	Rx2, Bx2	CNVM	R
11	68/female	E	6/6	6/24	2.1	Bx8	CNVM	R
12	52/female	E	6/18	6/6	1.54	Bx3	Stable	I
13	61/female	H	6/18	6/12	0.76	Bx1	Stable	I
14	58/female	E	6/60	6/18	2.5	Bx7	Stable	I
15	52/female	E	6/24	6/9	1.54	Bx4	Stable	I
16	52/male	H	6/12	6/12	(2T, 2S) 2.24, 1.88 1.85, 1.4	Bx4	Stable	S
17	66/male	E	6/18	6/18	(2T) 2.02	Bx7	Stable	S
18	69/female	H	6/12	6/24	3.54	Bx4	SRF+	R
19	48/female	E	6/15	6/24	(3T) 1.41, (2T) 4.34	Rx3, Bx3	SRF+	R
20	81/male	H	6/24	6/18	1.54	Bx4	Stable	I
21	70/male	E	6/9	6/7.5	2.96	Bx3	Stable	I
22	73/male	H	6/9	6/18	(2S) 2.9, 0.5	Bx5	SRF+	R
23	59/female	H	6/36	6/36	(2S) 1.0, 1.0	Bx3	Stable	S
24	68/female	E	6/9	6/9	1.8	Bx3	Stable	S
25	59/female	E	6/9	6/6	1.95	Bx2	Stable	I
26	59/female	E	6/18	6/12	1.49	Bx2	Stable	I
27	76/female	H	1/60	1/60	1	Rx1	Stable	S
28	55/female	H	6/12	6/6	1.1	Rx3	Stable	I
29	53/female	E	6/9	6/5	1.33	Bx3	Stable	I
30	78/male	E	6/9	6/6	2.02	Rx4, Bx1	Stable	I
31	60/male	E	6/12	6/6	(2T) 1.25, 2.4	Bx4	Stable	I
32	57/male	H	6/9	6/6	0.76	Bx3	Stable	I
33	59/male	E	6/9	6/6	2.12	Bx5	Stable	I
34	67/male	E	6/12	6/9	(2T) 1.58, 2.3	Bx7	Stable	I
35	67/male	E	6/18	6/9	2.1	Bx3	Stable	I

[P]Pneumatic displacement. RFPDT: Reduced-fluence photodynamic therapy, GLD: Greatest linear diameter, H: Hemorrhagic, E: Exudative, 2T: 2 PDT sessions, 2S: 2 laser spots, R: Ranibizumab, B: Bevacizumab, x number: Number of injections, SRF: Subretinal fluid, +: Present, S: Visual acuity stable, I: Visual acuity improved, R: Visual acuity reduced, PDT: Photodynamic therapy, VEGF: Vascular endothelial growth factor, CNVM: Choroidal neovascular membrane

Visual outcomes

Visual acuity improvement was seen in 21 (60%) eyes (0.4 ± 0.2 logMAR units to 0.1 ± 0.2 logMAR units; $P < 0.001$ Wilcoxon signed-rank test). Decrease in visual acuity was seen in seven (20%) eyes (0.4 ± 0.5–1.0 ± 0.7 logMAR units; $P = 0.016$; Wilcoxon signed-rank test). In seven eyes (20%), vision remained stable [Table 1]. Furthermore, the patients who showed good response following a single treatment session were younger, (mean age 58 ± 9.4 years vs. 63 ± 9.1 years; $P = 0.2$) had better BCVA at presentation (0.3 ± 0.17 logMAR units vs. 0.5 ± 0.4 logMAR units), and ended up with a significantly better BCVA (0.0 ± 0.15 logMAR units vs. 0.4 ± 0.5 logMAR units) at final follow-up as compared to eyes which had multiple injections or RFPDT for resolution of the disease [Table 2].

Tomographic and angiographic outcomes

Regression of polypoidal lesions was seen in 80% of cases at the last follow-up. Persistent SRF was seen in three eyes (8.57%) and development of choroidal neovascular membrane (CNVM) was seen in four eyes (11.42%) at the last follow-up [Table 1 and Fig. 3]. Of the four patients who

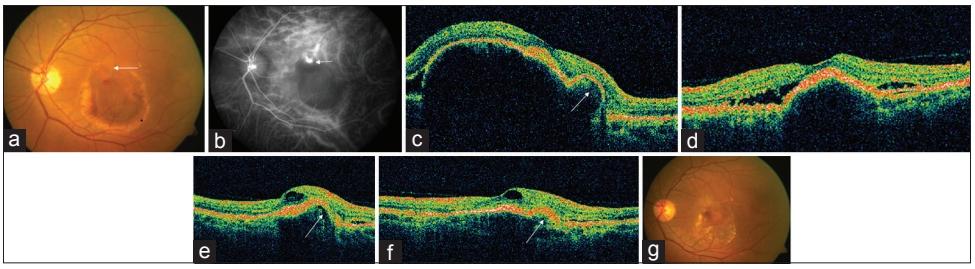

Figure 2: Color fundus photo (a) of 52-year-old female having a large hemorrhagic pigment epithelial detachment with polyp seen on indocyanine green (b) and optical coherence tomography (c) after three injections of bevacizumab showing reduction in the height of pigment epithelial detachment (d) and then after combination therapy* with regressed polyp (e) and resolved pigment epithelial detachment at last follow-up (f). *Photodynamic therapy + anti-vascular endothelial growth factor (bevacizumab/ranibizumab) (g) color fundus photo on resolution of polyp and hemorrhagic pigment epithelial detachment

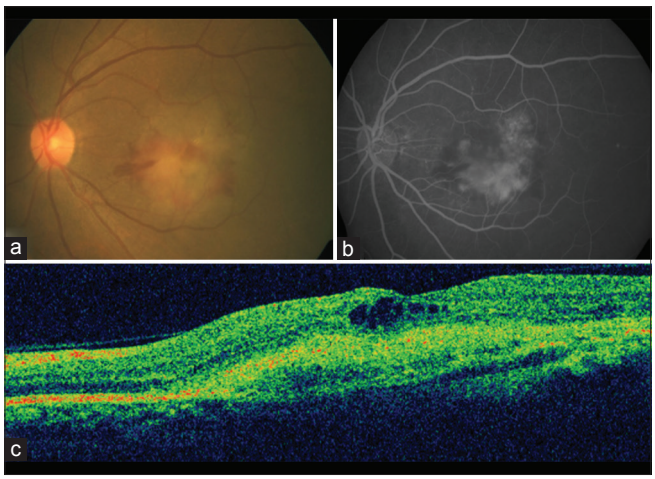

Figure 3: Color fundus photo (a) of 68-year-old female who had worsening of vision inspite of combination therapy* and multiple anti-vascular endothelial growth factor because of the development of choroidal neovascular membrane as seen on fundus fluorescein angiography (b) and optical coherence tomography (c). *Photodynamic therapy + anti-vascular endothelial growth factor (bevacizumab/ranibizumab)

Table 2: Age, spot size, and visual acuity for single sessions and multiple sessions of treatment

Rx	Age	GLD μm	Baseline BCVA	Final BCVA
Single session	58±9.4	1.4±0.6	0.3±0.17	0.0±0.15
Multiple session	63±9.1	2.2±1.02	0.5±0.4	0.4±0.5
P	0.2	0.08	0.18	0.03

GLD: Greatest linear diameter, BCVA: Best-corrected visual acuity

developed CNVM, average number of PDT sessions was 1.6 and average number of intravitreal injections was 6.5. All these cases had a poor visual outcome with the mean vision dropping from 0.6 ± 0.7 to 1.2 ± 0.8 logMAR unit in spite of maximal treatment given.

Ocular side effects

Over an average follow-up of 18 months ranging from 12 to 24 months, no case of massive subretinal hemorrhage or breakthrough vitreous hemorrhage was seen. No systemic or ocular adverse events were noted during the course of the study.

Discussion

Stable or improved vision has been reported in 87.0% of cases by Spaide *et al*. and up to 95.0% of patients by Chan *et al*.[8,9] The absence of leakage on FFA and regression of polyps on ICGA at 1 year of follow-up following PDT alone was seen in 80% of eyes by Otani *et al*. and 86% by Gomi *et al*.[19,20]

However, despite these favorable results, several PDT-related complications, such as choriocapillaris nonperfusion, choroidal atrophy, and submacular hemorrhage, have been reported.[11] Hypoperfusion of the choroids has been seen as early as 1 week, following SFPDT.[21] RFPDT has shown to cause less collateral damage to the choroids even though it is equally effective in causing polyp regression by Yamashita *et al*. They showed improvement or stabilization of BCVA in 93% of patients with PCV following RFPDT at 1-year follow-up with mean number of treatment sessions in 1-year follow-up being 1.3 (range, 1–3).[15]

An immunologic study by Schmidt-Erfurth *et al*. reported reactive upregulation of VEGF after PDT, and this might predispose to subsequent recurrent neovascularization.[22] In the Everest study as well, combination treatment with PDT and ranibizumab was found to be superior to monotherapy with ranibizumab alone (77.8% vs. 28.6%).[14] Recent prospective studies by Sagong *et al*. concluded that RFPDT in combination with bevacizumab improved the BCVA from 0.76 to 0.46 logMAR at 1 year in eyes with PCV.[23] In a study by Ricci *et al*., 95% of cases had improvement or stabilization of vision and 94% had polyp regression following RFPDT and intravitreal ranibizumab.[24] Sakurai *et al*. also showed improvement in BCVA following combination therapy (RFPDT + ranibizumab) as well as fewer ranibizumab injections were required in 1-year follow-up as compared to the only ranibizumab group.[16] In our study, polyp regression was documented in 80% of the patients. In our study, each patient received a mean of 1.2 RFPDT sessions and 4 ± 1.99 intravitreal anti-VEGF injections during the average follow-up period of 18 months.

Subretinal hemorrhages were reported in 4.9% of the patients after combined treatment with SFPDT and 17.7% after PDT monotherapy in a study by Gomi *et al*.[20] In comparison, mild subretinal hemorrhage after monotherapy with RFPDT was seen in 21% of eyes by Yamashita *et al*.; all of which showed complete resolution at the end of the study period. No case of severe subretinal hemorrhage was seen.[15] There were no cases of subretinal hemorrhage in our study group

as well. Furthermore, we performed RFPDT based on GLD as measured on ICG and not on FFA as has been recommended by other clinicians as well.[19,25] ICGA GLD was determined to include polyps with surrounding BVN without including the PED/hemorrhage. In patients presenting with large serosanguineous PEDs, intravitreal anti-VEGF was given before RFPDT. This was done to reduce the risk of RPE rips which have been seen even with RFPDT.[26] Pai *et al*. have also reported the use of such sequential therapy with anti-VEGF followed by PDT in an Indian male with good visual outcome.[27]

In very large lesions, PDT is not possible. Lesions with a diameter of more than nine macular photocoagulation study disk areas were excluded from the Everest study.[14] Modification of protocol in our study (anti-VEGF injection before PDT) allowed some of these cases also to be treated safely. In addition, two eyes underwent pneumatic displacement of subretinal hemorrhage followed by ICGA to visualize the polyps. Similar technique for displacement of subretinal hemorrhage followed by PDT in eyes with PCV has also been used by Chawla *et al*.[28]

Spaide *et al*. reported CNV in 15.8% of eyes with PCV.[9] We saw the development of CNVM in 11.4% of our cases. All patients with CNVM in our study had a drop in vision and needed multiple treatment sessions as well as increased number of injections. Poor prognosis in these cases has also been reported by Tamura *et al*.[29]

Limitation of the study included its retrospective nature and absence of randomized comparative data with monotherapy with anti-VEGF as well as SFPDT and also the heterogeneity of the clinical picture at presentation. However, this heterogeneity is probably inherent to the nature of the disease. Future prospective randomized control trials will be necessary to determine the long-term safety and to look at the comparison between the efficacy of SFPDT vis-a-vis RFPDT.

Conclusions

RFPDT with anti-VEGF is safe and effective with polyp regression with visual improvement/stabilization seen in 80% of cases. It is safe with no cases of subretinal hemorrhage seen in our series. Treatment protocols may need to be individualized. Development of CNVM is associated with poor prognosis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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