Half Fluence Photodynamic Therapy in Peripapillary Circumscribed Choroidal Hemangiomas

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Research Article

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Abstract

Purpose

To evaluate the safety and efficacy of half fluence photodynamic therapy (PDT) as treatment for symptomatic peripapillary circumscribed choroidal haemangiomas (CCHs).

Methods

In this prospective, interventional case series; 11 patients with symptomatic peripapillary CCHs presenting to a single centre were treated with half fluence PDT using verteporfin 6 mg/m2 with fluence of 25 mJ/cm2 (standard is 50 mJ/cm2) and other standard settings. Patients were evaluated at baseline, four weeks, twelve weeks and twenty-four weeks post-PDT treatment with best corrected visual acuity (BCVA), ultrasonography, spectral domain- optical coherence tomography (SD-OCT), visual evoked potential and angiographic studies.

Results

Eleven patients with peripapillary CCHs received half fluence PDT. The BCVA significantly improved to 0.558 $\pm$ 0.118 at four weeks post treatment (P=0.014), to 0.494 $\pm$ 0.114 at twelve weeks (P=0.006) and 0.441 $\pm$ 0.125 at twenty-four weeks (P=0.007) from baseline levels of 1.017 $\pm$ 0.075 on log MAR scales. Similar improvement was observed in central macular thickness (CMT) of 78.50 $\pm$ 13.73 um(P=0.001) at four weeks; 114.70 $\pm$ 27.73 um(P=0.003) at twelve weeks and 174.60 $\pm$ 23.13 um(P=0.001) at twenty-four weeks post treatment. A single session of re-treatment was required in 18%(n=2) of patients which also showed complete resolution at last follow-up. No complications were observed without any significant change in retinal nerve fibre layer (RNFL) thickness at six months follow-up(P=0.088).

Conclusions

Half fluence PDT can be an effective and safe treatment option for peripapillary CCHs which results in both anatomical and functional improvements with no observable complications.

Introduction

Choroidal haemangioma is an uncommon benign vascular tumour of the choroid that can be diffuse or circumscribed depending on specific clinical characteristics [1]. The circumscribed choroidal haemangioma (CCH) has unilateral presentation, orange-red tumour colour, round, well-circumscribed shape, and location in the posterior fundus [2]. Fluorescein angiography shows hyper fluorescence, rapid early filling; confirmed on optical coherence tomography (OCT) with dome-shaped contour and absence of choriocapillaris compression [3]. CCH can cause significant visual impairment when exudative activity leads to the development of macular oedema and/or serous retinal detachment and, eventually, photoreceptor loss. Treatment of symptomatic or exudative CCH should be considered in order to preserve vision.

CCHs can be treated with laser photocoagulation, cryotherapy, radiotherapy, proton beam radiotherapy, external beam radiotherapy, plaque radiotherapy and transpupillary thermotherapy [4-9]. These treatments are associated with the potential risk of damage to the overlying retina as well as optic nerve. Many authors exhibited safety and efficacy of photodynamic therapy (PDT) using full fluence in treatment of CCHs with Singh et al reporting choroidal atrophy as possible complication in their study [10-11]. Alkin et al reported reduced complication rate and better efficacy in half fluence PDT treated patients of chronic central serous chorio-retinopathy [12]. Wong et al also found similar efficacy in patients of polypoidal choroidal vasculopathy (PCV) treated with half fluence PDT [13]. Since PDT target abnormal vascularised tissue within the choroid making, it a logical and safe option in the management of CCH as described for PCV or CSCR patients even with low or half fluence settings. Moreover, targeting peripapillary haemangiomas with standard full fluence or bolus PDT can lead to inadvertent damage to vascular supply of optic nerve head resulting in optic atrophy.

Therefore, we conducted present study to evaluate the safety and efficacy of half fluence photodynamic therapy in treatment of symptomatic peripapillary circumscribed choroidal haemangiomas (CCHs).

Materials And Methods

This prospective interventional study was carried out at tertiary care referral eye hospital in North India. Institutional ethical committee clearance was obtained and study adhered to the principles of the Helsinki Declaration. All patients who were aged 18 and above and had symptomatic peripapillary circumscribed haemangiomas reporting between June 2019 to May 2020 were included after obtaining written informed consent. Patients with history of previous treatment in form of laser, anti-VEGF injections or PDT for haemangioma or any other concurrent retinal diseases were excluded. Initial diagnosis was made based on fundoscopy, Spectral domain-optical coherence tomography (SD-OCT), fundus fluorescein angiography (FFA) and/or indocyanine green angiography (ICG). Baseline visual acuity in log MAR was recorded and SD-OCT scans were performed before treatment and repeated at subsequent observation intervals. OCT scanning was performed using spectral domain OCT (Carl Zeiss Meditec, Inc., 5160 Hacienda Drive, Dublin, CA 94568 USA), with both radial and line OCT scanning of macula as well as optic disc cube scans were obtained. The baseline visually evoked potential (VEP)evaluation before treatment and at six-month follow-up was carried out in all patients. The typical fundus appearance, ultrasonographic features, SD-OCT images and baseline retinal nerve fibre layer thickness maps (case 2) are shown in Fig 1. After informed consent, half-fluence PDT was performed. A standard dose of 6 mg/m2 intravenous Visudyne (Verteporfin) was used and infused over 10min. The laser power (Quantel PDT laser) was set at half fluence of 25 mJ/cm2 (standard is 50 mJ/cm2) and was applied over 83s. The laser was applied 15min after the commencement of infusion using a ×1.6 magnification contact lens (Volk® PDT lens; Volk Optical Inc., Mentor, OH, USA) as a single spot. The laser spot size varied in each patient, related to the size of the treated area. Laser spot was adjusted to cover lesion area with distance of 200um from disc margin as safety measure in each patient. At follow up visits, BCVA assessment, SD-OCT imaging for measurement of central macular thickness (CMT) as well as retinal nerve fibre layer (RNFL) thickness and VEP recordings were repeated. Patients were evaluated at 04

weeks, 12 weeks and 24 weeks. In cases of sub-foveal fluid persistence or recurrence at 03 months, repeat half fluence PDT was performed with same laser settings as initial treatment.

Statistical Analysis

Standard weighted one-way analysis of variances (ANOVA) was performed to identify any relationship between the change in log MAR visual acuity and central macular thickness from pre-treatment and follow-up visits at 04 week, 12 weeks and 24 weeks. Paired T-test was used to compare effect of half fluence PDT on pre and post-treatment RNFL thickness. The p-value of $\geq$ 0.05 was considered statistically significant.

Results

Of the total of 13 patients with symptomatic peripapillary circumscribed haemangiomas, who were subjected to half fluence PDT during study period only 11 completed the required follow-up of six months post intervention. The average age of patients was 54.72 $\pm$ 9.96 years(n=11) with male preponderance (n=7; 63%). All patients were symptomatic with diminution of vision and had macular serous detachment. The demographic and clinical features of patients are included in **Table 1**. The structural as well as functional improvement was seen in all patients (n=11; 100%) as well as on imaging evaluation as shown in case 2 [Fig 2].

The average BCVA in pre-treatment group was 1.017 $\pm$ 0.075 which significantly improved to 0.558 $\pm$ 0.118 at four weeks post treatment(**P=0.014**). The BCVA further improved to 0.494 $\pm$ 0.114 at twelve weeks (**P=0.006**) and 0.441 $\pm$ 0.125 at twenty-four weeks post treatment(**P=0.007**) from baseline levels [Fig 3]. The change in BCVA was not statistically significant in comparison between 04 weeks and 12 weeks(P=0.058).

All patients(n=11;100%) were visually symptomatic with presence of serous macular detachment and mean CMT at baseline was 564.60 $\pm$ 18.485um. Patients showed statistically significant reduction in CMT at four weeks of 78.50 $\pm$ 13.73 um(**P=0.001**); 114.70 $\pm$ 27.73 um(**P=0.003**) at twelve weeks and 174.60 $\pm$ 23.13 um(**P=0.001**) at twenty-four weeks post treatment from baseline [Fig 4]. Two patients(n=2;18%) had minimal reduction in subretinal fluid which required repeat single session of half fluence PDT at 12 weeks post initial treatment with complete resorption of subretinal fluid. The change in CMT was not statistically significant when compared between 04 weeks and 12 weeks(P=0.088).

No adverse events or complications of treatment were noted in any patient. The baseline average RNFL thickness before treatment was 120.68 $\pm$ 5.372 um. At twenty-four weeks post treatment, average RNFL thickness was 116.86$\pm$ 4.38(P=0.62) which was not statistically significant from pre-treatment levels [Fig5]. The comparison of VEP measurements pre- and post-PDT treatment did not show increase in P100 latency or decrease in amplitude in any patient.

Discussion

PDT is considered to be the treatment of choice for choroidal haemangioma, as it selectively targets abnormal choroidal vessels without damaging the overlying neurosensory retina. It is indicated in symptomatic patients resulting due to macular oedema or subretinal fluid [14]. The various protocols for PDT described for the treatment of choroidal haemangioma are; 'standard', 'bolus' and 'high fluence' protocols; which use standard dose of verteporfin but vary in additional settings [15-18]. The tumour control; usually defined as the elimination of exudation rather than complete tumor shrinkage can be achieved in the vast majority of the patients with every protocol. But, there is significant potential for choroidal atrophy and other adverse events following PDT as observed by multiple researchers [10, 19] with varying rate of success with single session of treatment. The optic disc vasculature can also be at risk of potential ischemia; especially in peripapillary choroidal haemangiomas.

The present study; is first attempt at evaluating efficacy and safety of half fluence PDT for symptomatic CCHs. It showed that half-fluence PDT can have a significant effect on improvement of a patient's visual acuity, in resolving SRF and reducing central retinal thickness. Tumour control was observed in all patients with significant improvement in BCVA at all observation points and last follow-up at six-months. The significant visual improvement in present study were similar to earlier studies where standard, bolus or high fluence protocols were used [19-22]. Many of these studies required multiple session of PDT treatment but additional session of half fluence PDT in our study was required in only two cases (18%). Similarly, successful anatomical outcomes in form of resolution of macular oedema or subretinal fluid with single session treatment was observed in nine patients (82%) at twelve weeks follow-up and complete resolution at six-month follow-up in all patients with additional session of half fluence PDT. Similar positive results were also seen with half fluence PDT in other choroidal pathologies like central serous chorioretinopathy and polypoidal choroidal vasculopathy which also predominantly affect choroidal vascular permeability [12,13].

Vision threatening complications in form of choroidal atrophy, choroidal effusion and perifoveal haemorrhage has been reported with standard PDT protocols [10,19,23]. None of these complications were seen in present study. Moreover, effect of half fluence PDT was further assessed with comparison of pre and post-treatment RNFL thickness and visually evoked potential (VEP). No adverse effect of half fluence PDT on RNFL thickness as well as VEP values was observed in our study. This probably resulted from lesser energy delivered per unit area due to half fluence PDT protocol as well as single laser spot used with a safety margin of 200um from optic disc margins. Bernstein et al also reported successful resolution of peripapillary choroidal neovascular membrane with PDT treatment which included application over optic disc also without any clinical evidence of optic nerve damage. However, objective assessment of optic nerve damage with OCT imaging study was not performed [24].

Our study is not without its limitations, as it has small number of patients and lacks a control group. The strengths of our study are that it includes long-term follow up of a cohort of patients who received half-fluence PDT. Patients were followed up for a considerable long period following treatment without any observable long term ill effects. Moreover, a new variable in form of change in RNFL thickness was studied to validate safety of half fluence protocol of PDT treatment.

In summary, our study provides considerable information that half fluence PDT can be used to successfully treat symptomatic circumscribed choroidal haemangiomas (CCHs) without any observable complications. However, we recognise that a large, prospective, comparative study would provide more significant evidence as to whether present protocol is safe and effective treatment modality.

Declarations

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Conflict of interest: - The Authors declare that there is no conflict of interest.

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Ethics approval: - Obtained from institutional ethical committee

Patient's Consent: - *Obtained from patient for participation as well as publication of manuscript.*

References

1. Karimi S, Nourinia R, Mashayekhi A. Circumscribed choroidal hemangioma. J Ophthalmic Vis Res 2015;10(3):320–8.
2. Krohn J, Rishi P, Froystein T, Singh AD. Circumscribed choroidal haemangioma: Clinical and topographical features. Br J Ophthalmol 2019.
3. Shields JA, Shields CL. Intraocular tumors. An atlas and textbook. 3rd ed. Lippincott Wolters Kluwer; 2016. p. 247–63.
4. Sanborn GE, Augsburger JJ, Shields JA. Treatment of circumscribed choroidal hemangiomas. Ophthalmology 1982; 89:1374–80.
5. Humphrey WT. Choroidal hemangioma: response to cryotherapy. Ann Ophthalmol 1979; 11:100–4.
6. Schilling H, Sauerwein W, Lommatzsch A. Long term results after low dose ocular irradiation for choproidal hemangioma. Br J Ophthalmol 1997; 81:267–73.
7. Ritland JS, Eide N, Tasujo J. External beam irradiation therapy for choroidal hemangiomas. Visual and anatomical results after a dose of 20–25 Gy. Acta Ophthalmol Scand 2001; 79 :184–6.
8. Hannouche D, Frau E, Desjardins L, Cassoux N, Habrand JL, Offret H. Efficacy of proton therapy in circumscribed choroidal hemangiomas associated with serious retinal detachment. Ophthalmology 1997; 104:1780–4.
9. Kamal A, Watts AR, Rennie IG. Indocyanine green enhanced transpupillary thermotherapy of circumscribed choroidal hemangioma. Eye 2000;14:701–5.
10. Singh AD, Kaiser PK, Sears JE, Gupta M, Rundle PA, Rennie IG: Photodynamic therapy of circumscribed choroidal haemangioma. Br J Ophthalmol 2004;88:1414–1418.

11. Porrini G, Giovannini A, Amato G, Ioni A, Pantanetti M. Photodynamic therapy of circumscribed choroidal haemangioma. Ophthalmology 2003; 110: 674–680.
12. Alkin Z, Perente I, Ozkaya A, Alp D, Agca A, Aygit ED, Korkmaz S, Yazici AT, Demirok A. Comparison of efficacy between low-fluence and half-dose verteporfin photodynamic therapy for chronic central serous chorioretinopathy. Clin Ophthalmol. 2014 Apr 5;8: 685-90.
13. Wong IY, Shi X, Gangwani R, Iu LP, Fung N, Li Q, Ng ALK, Li X. One-year results of half-versus standard-dose photodynamic therapy combined with ranibizumab for polypoidal choroidal vasculopathy.
14. Singh AD, Kaiser PK, Sears JE, Gupta M, Rundle PA, Rennie IG. Photodynamic therapy of circumscribed choroidal haemangioma. Br J Ophthalmol. 2004;88(11):1414–8.
15. Boixadera A, García-Arumí J, Martínez-Castillo V, Encinas JL, Elizalde J, Blanco-Mateos G, Caminal J, Capeans C, Armada F, Navea A, Olea JL. Prospective clinical trial evaluating the efficacy of photodynamic therapy for symptomatic circumscribed choroidal hemangioma. Ophthalmology. 2009 Jan;116(1):100-105.
16. Verbraak FD, Schlingemann RO, de Smet MD, Keunen JE. Single spot PDT in patients with circumscribed choroidal haemangioma and near normal visual acuity. Graefes Arch Clin Exp Ophthalmol. 2006;244(9):1178–82.
17. Verbraak FD, Schlingemann RO, Keunen JE, de Smet MD. Longstanding symptomatic choroidal hemangioma managed with limited PDT as initial or salvage therapy. Graefes Arch Clin Exp Ophthalmol. 2003;241(11):891–8.
18. Blasi MA, Tiberti AC, Scupola A, Balestrazzi A, Colangelo E, Valente P, Balestrazzi E. Photodynamic therapy with verteporfin for symptomatic circumscribed choroidal hemangioma: five-year outcomes. Ophthalmology. 2010 Aug;117(8):1630-7.
19. Schmidt-Erfurth UM, Michels S, Kusserow C, Jurklies B, Augustin AJ. Photodynamic therapy for symptomatic choroidal hemangioma: visual and anatomic results. Ophthalmology. 2002;109(12): 2284–94.
20. Barbazetto I, Schmidt-Erfurth U. Photodynamic therapy of choroidal hemangioma: two case reports. Graefes Arch Clin Exp Ophthalmol 2000;238:214–21.
21. Madreperla SA. Choroidal hemangioma treated with photodynamic therapy using verteporfin. Arch Ophthalmol 2001;119:1606–10.
22. Robertson DM. Photodynamic therapy for choroidal hemangioma associated with serous retinal detachment. Arch Ophthalmol 2002;120:1155–61.
23. Landau IM, Steen B, Seregard S. Photodynamic therapy for circumscribed choroidal haemangioma. Acta Ophthalmol Scand 2002;80:531–6.
24. Bernstein PS, Horn RS. Verteporfin photodynamic therapy involving the optic nerve for peripapillary choroidal neovascularization. Retina. 2008 Jan;28(1):81-4.

Tables

Table 1: Demographic and clinical features of patients with juxta-papillary circumscribed choroidal haemangiomas (CCHs)

Case	Age	Sex	Pre-treatment BCVA (log MAR)	Pre-treatment CMT (um)	Retreatment required or not	Any Adverse events or complications
1	63	F	1	563	No	Nil
2	55	M	1	568	No	Nil
3	41	M	0.8	559	Yes; Half fluence PDT repeated	Nil
4	56	M	1.3	704	No	Nil
5	54	M	1	510	No	Nil
6	62	F	1.3	542	No	Nil
7	65	M	1.07	524	No	Nil
8	59	F	0.6	503	No	Nil
9	37	M	0.8	611	No	Nil
9	66	F	1.3	553	Yes; Half fluence PDT repeated	Nil
10	44	M	1	572	No	Nil
11	63	F	1	563	No	Nil

BCVA, best corrected visual acuity; **log MAR**, logarithm of minimum angle of resolution; **CMT**, central macular thickness; **PDT**, photodynamic therapy

Figures

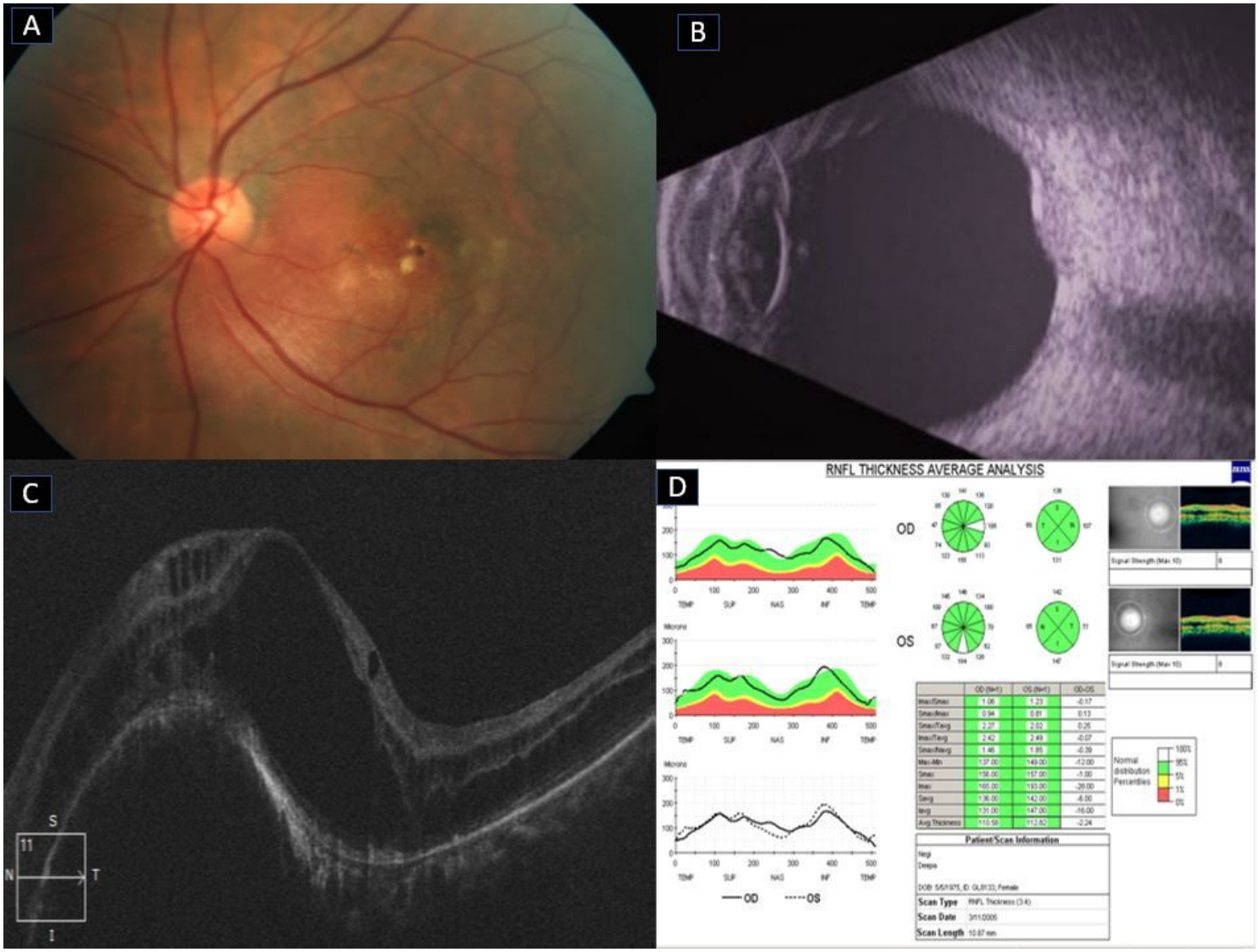

Figure 1

A. Fundus photo of left eye of patient showing round, well-circumscribed, orange red colour circumscribed choroidal haemangioma extending from disc margin till foveal centre. B. USG-B scan of same eye confirming peripapillary choroidal haemangioma. C. SD-OCT of same patient showing dome shaped contour elevation due to haemangioma with large pocket of subretinal fluid. D. SD-OCT retinal nerve fibre layer thickness analysis of same patient revealing normal average thickness in both eyes with a value of 112.4um in left eye.

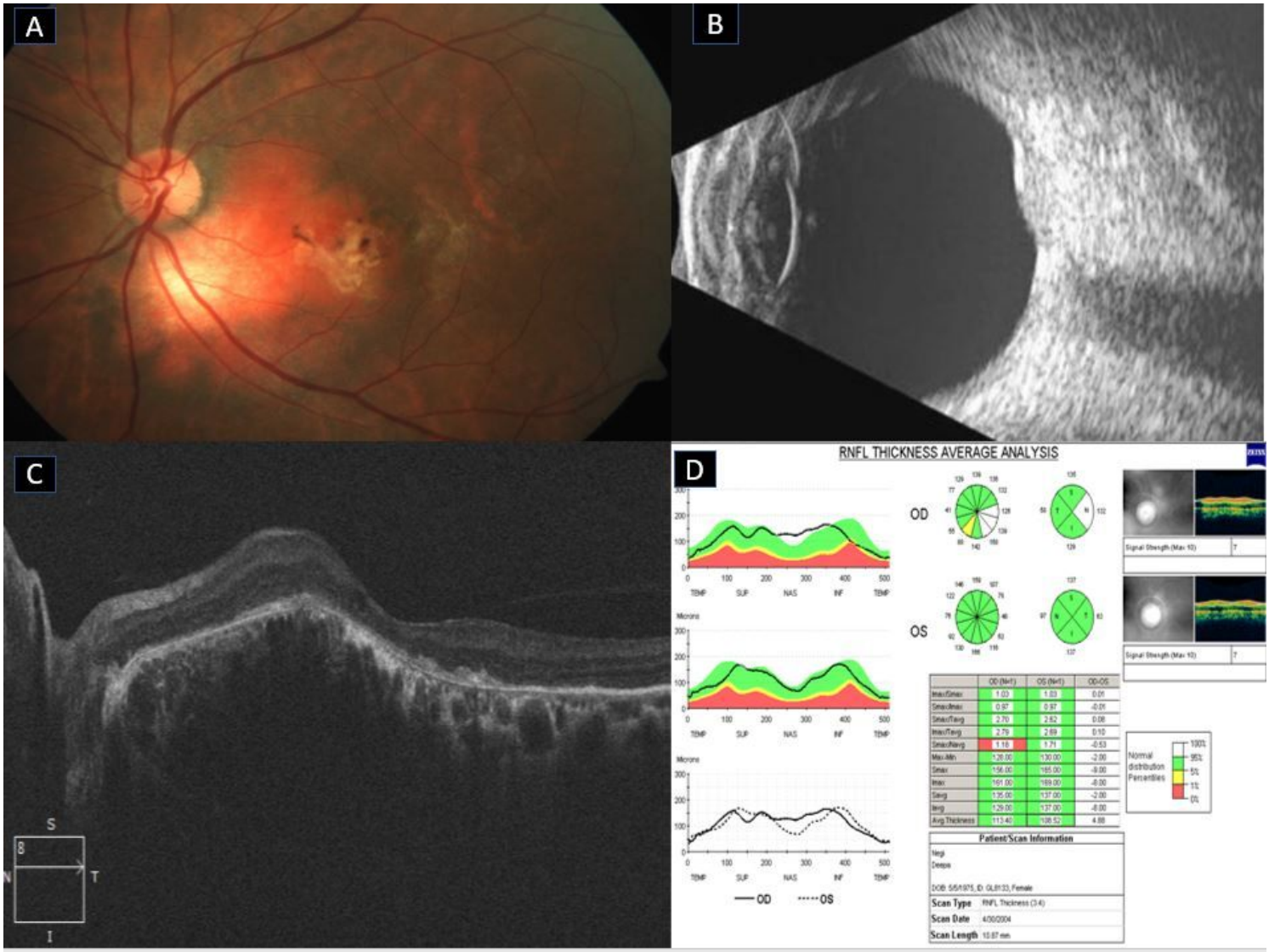

Figure 2

A. Fundus photo of left eye twenty four weeks post photodynamic therapy(PDT) treatment showing significant hemangioma regression with well delineated tumor margins and absence of sub-foveal fluid. B. USG-B scan of same eye confirming decrease in size of peripapillary choroidal haemangioma. C. SD-OCT of same patient showing significant resolution of dome shaped elevation as well as resorption of subretinal fluid. D. SD-OCT retinal nerve fibre layer thickness analysis of same patient revealing normal average thickness intreated eye with a value of 108.6um.

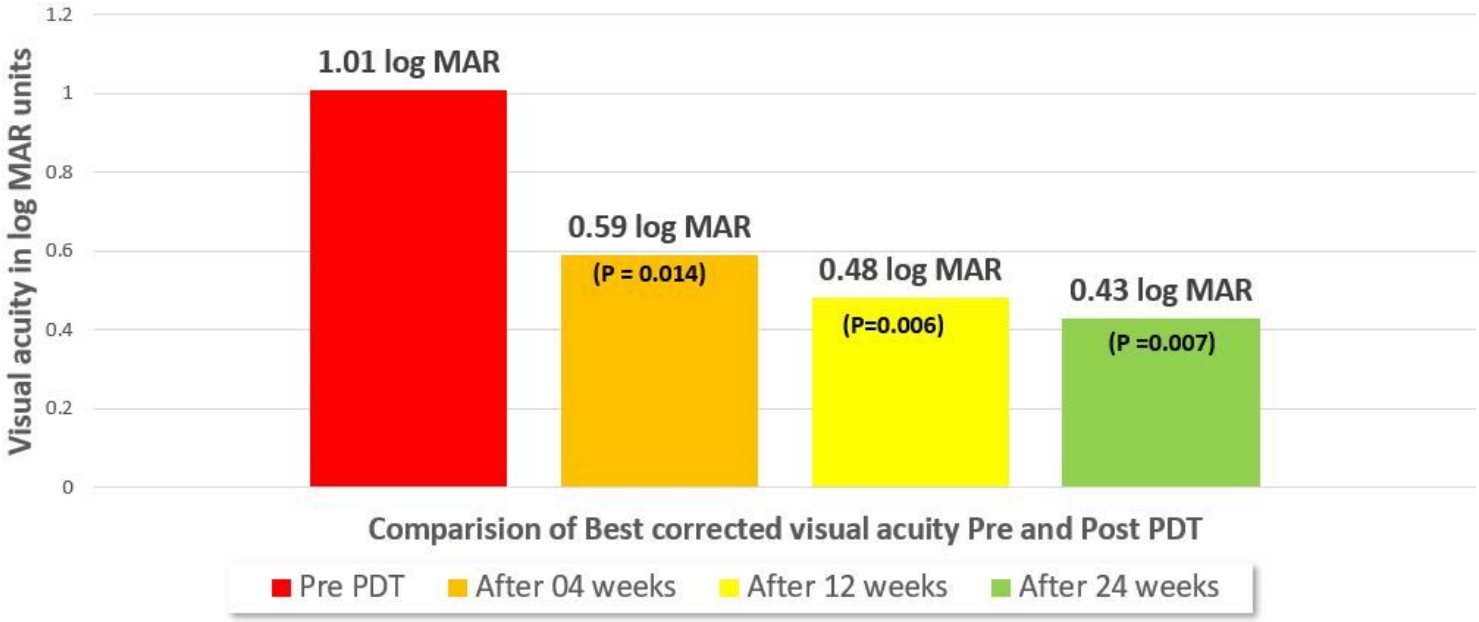

Figure 3

A bar chart depicting progressive improvement in best corrected visual acuity photodynamic therapy (PDT) treatment at different observation point from baseline.

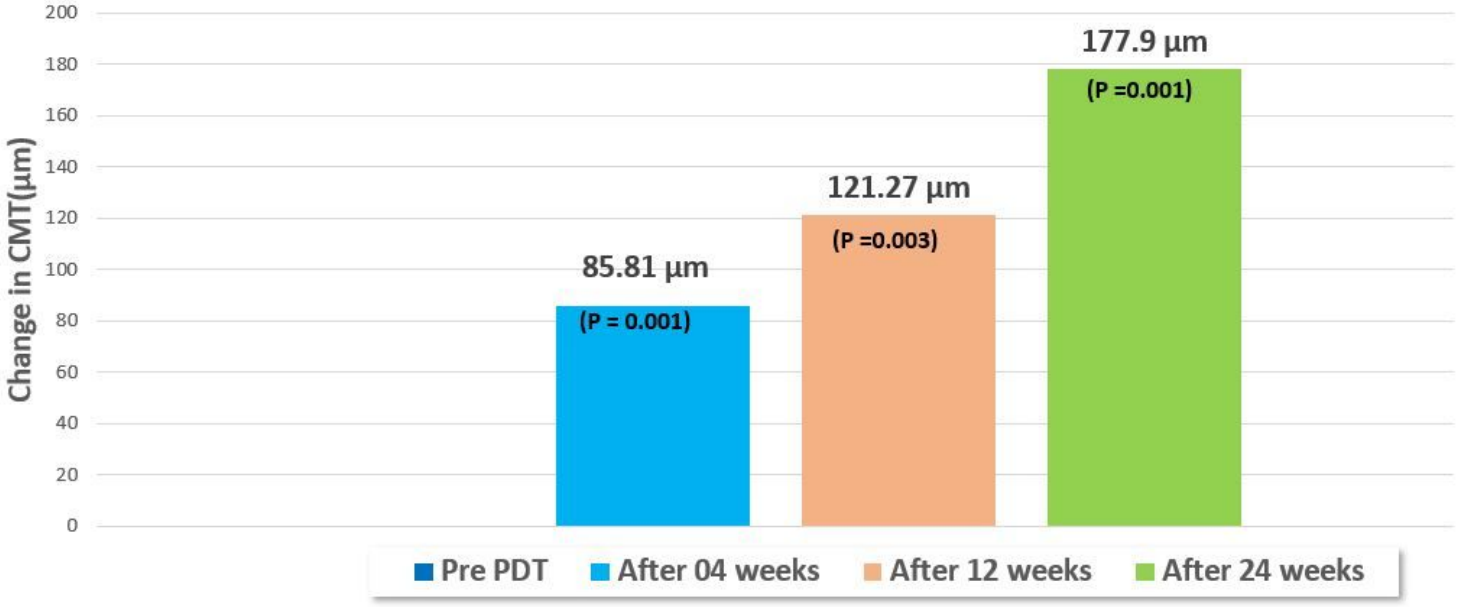

Figure 4

A bar chart depicting significant reduction in central macular thickness post photodynamic therapy (PDT) treatment at different observation point from baseline.

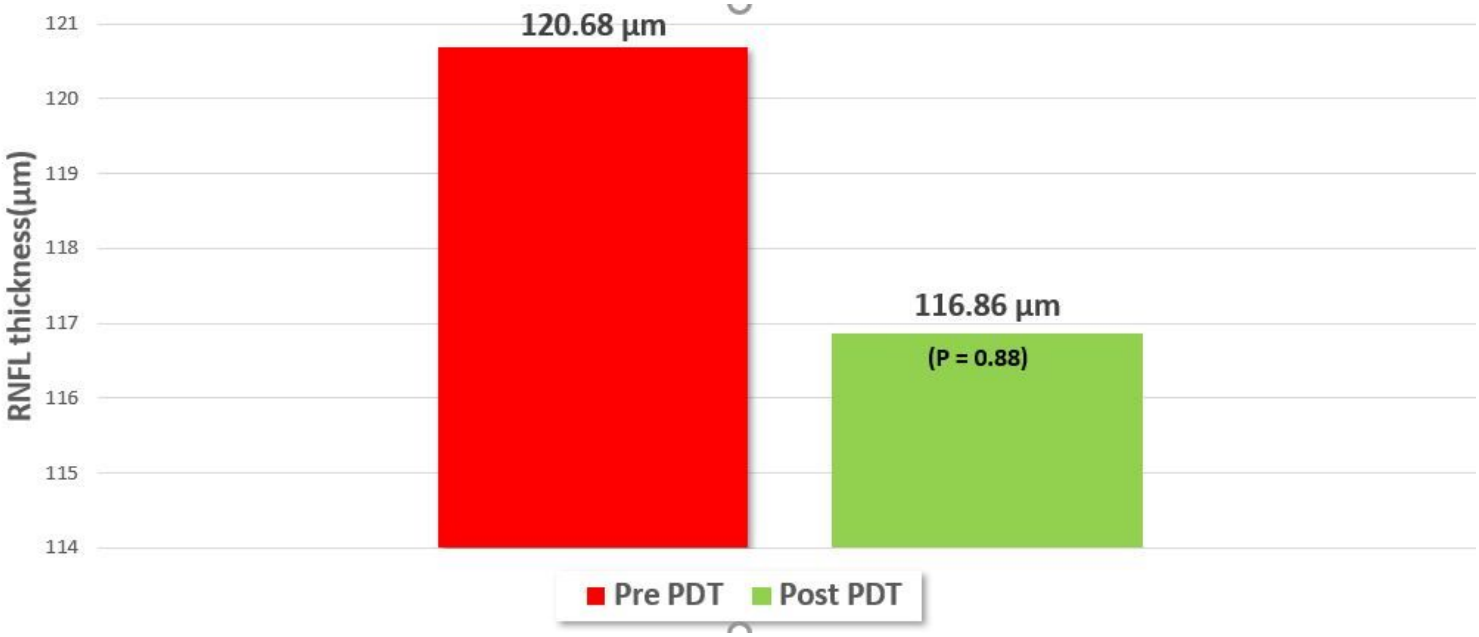

Figure 5

A bar chart showing no significant change in retinal nerve fibre layer thickness at twenty-four weeks post photodynamic therapy (PDT) treatment.