Indocyanine Green Mediated Photothrombosis (IMP) with Intravitreal Bevacizumab (IVB) for Treatment of Choroidal Neovascular Membrane (CNV) due to ARMD

Anisha Seth¹, Bhanu Pangtey², Neha Goel³, Basudeb Ghosh⁴
¹Delhi Retina Centre, Chowdhary Eye centre, Daryaganj, New Delhi, India
²Aravind eye hospitals and postgraduate institute of ophthalmology, Madurai, Tamil Nadu, India
³ICARE eye hospital and postgraduate institute, NOIDA, U.P., India
⁴Guru Nanak Eye Centre, Maulana Azad Medical College, New Delhi, India

Abstract

Purpose: Choroidal neovascular membrane (CNV) is one of the leading causes of blindness among elderly patients. Anti-Vascular endothelial growth factors (VEGF) and photodynamic therapy (PDT) are the only treatment options available for subfoveal and juxtafoveal CNV but are extremely costly. Indocyanine Green Mediated Photothrombosis (IMP) has been successfully used for subfoveal CNV due to ARMD and is much cheaper than PDT. Our study aims to evaluate IMP followed by intravitreal Bevacizumab in subfoveal and juxtafoveal CNV due to ARMD.

Methods: This prospective interventional study consisted of 15 eyes with subfoveal and juxtafoveal CNV due to ARMD. IMP was performed with low power diode laser augmented with indocyanine green dye (ICG) and followed 24 hours later with intravitreal bevacizumab 1.25 mg/0.05ml. Subjects were followed up at 6 weeks, 12 weeks and 16 weeks for BCVA, IOP, lens status assessment on slit lamp, fundus examination, FFA and SD-OCT.

Results: Mean visual acuity improved from 0.136 preoperatively to 0.177 at 6 weeks, to 0.183 at 12 weeks and 0.185 at 16 weeks. Mean pre-treatment mean macular thickness (MMT) varied from 284.1 µm to 261.2 µm at 4 weeks post-treatment, to 268.8 µm at 12 weeks and to 267 µm at 16 weeks post-treatment. 10 eyes showed stabilization of vision with treatment till 16 week post treatment. Five eyes showed improvement in vision which was sustained till 16th week post treatment. No eye showed decrease in vision by the end of follow up. The difference was statistically significant at all visits.

Conclusion: IMP in combination with intravitreal Bevacizumab is an effective treatment modality for CNV in ARMD.

Keywords: indocyanine mediated photothrombosis, Choroidal Neovascular Membrane, ARMD

Introduction

Age Related Macular Degeneration (ARMD) is one of the leading causes of blindness among elderly patients in developed and developing countries. The major cause of visual loss is choroidal neovascularization (CNV) along with its corresponding fluid accumulation, haemorrhage, lipid exudation and fibrosis.

The Macular photocoagulation study (MPS) showed that Argon and Krypton laser therapy resulted in better visual outcomes in patients with juxtafoveal and extrafoveal CNV respectively. However, in subfoveal CNV it led to immediate, profound decrease in the visual acuity and is therefore not accepted as a treatment modality in these cases. Photodynamic therapy (PDT) with Verteporfin causes less collateral damage. However, its high cost, questionable effect in minimally classic and occult subfoveal CNV and side effects, limit its utility. It can be used in combination with steroids and anti-vascular endothelial growth factor (VEGF) therapy as a multi pronged approach to tackle CNV. Anti-VEGF therapy, though beneficial in improving visual acuity, is unlikely to cause sustained and complete resolution of CNV by itself. Currently, treatment with these agents requires multiple injections, leading to high cost and risk of systemic adverse events. Indocyanine Green Mediated Photothrombosis (IMP) which uses low power diode laser augmented with Indocyanine green dye (ICG) has been successfully used in a variety of conditions including subfoveal CNV due to ARMD. It causes selective intraluminal photothrombosis and is much cheaper than PDT. Our study aims to evaluate the treatment efficacy of IMP followed by intravitreal Bevacizumab in subfoveal and juxtafoveal CNV due to ARMD.

Materials And Methods

This was a prospective interventional pilot study consisting of 15 eyes diagnosed with subfoveal and juxtafoveal CNV due to ARMD in vitreo-retina clinic of Guru Nanak Eye Centre. After institutional ethical committee approval, a written informed consent was obtained from each study participant. All patients underwent detailed history taking and clinical examination. A complete ocular evaluation, including measurement of best corrected visual acuity (BCVA) with the Snellen chart, slit-lamp biomicroscopy, IOP (intraocular pressure) using Applanation tonometer,
fundus photography, fundus fluorescein angiography (FFA) and spectral-domain optical coherence tomography (SD-OCT) were performed at baseline.

**Inclusion Criteria**

Patients were included in the study if there was a presence of well defined, subfoveal or juxtafoveal, minimally classic or occult CNV due to ARMD on FFA (according to MPS criteria) that showed activity on OCT and had the greatest linear diameter (GLD) of the entire lesion was ≤ 7500µ on FFA.

**Exclusion Criteria**

Patients were excluded if they had choroidal neovascular membranes (CNVM) due to any other cause, extensive subretinal haemorrhage, history of previous treatment of CNV in the preceding 6 months, presence of co-morbid conditions (i.e. cataract, media opacities, vitreous haemorrhage) that could affect the visual acuity or preclude view of the fundus, history of hypertension, cerebrovascular disease, liver disease or allergic reaction to Fluorescin or Indocyanine Green dye.

**Methodology**

IMP was performed as an outpatient procedure under topical anaesthesia with adequate cycloplegia. A slit lamp integrated Diode photocoagulator using 810 nm wavelength (Iris Medical OcuLight SLx, IRIDEX Corporation) was used. A 4 ml Indocyanine Green (ICG) aqueous solution reconstituted with distilled water at a dose of 2 mg/kg was divided into two equal parts. The first part was administered as an intravenous bolus, followed immediately by a 5 ml saline flush. Thirty minutes later, the second part of the dose was administered, followed by a 5.0 ml saline flush. Two minutes after the start of the second infusion, a laser was applied to the lesion for 100 seconds using a spot size with a diameter approximately 1000µm larger than the greatest linear dimension of the entire neovascular complex, through a Mainster standard contact lens (Ocular Instruments, Bellevue) of 1.5× magnification. A test spot applied to the retina nasal to the optic disc decided the power of the laser. Twenty-four hours later, all eyes were given a single intravitreal injection of 1.25 mg/0.05 ml of Bevacizumab. Topical anaesthesia was obtained with 0.5% Proparacaine eye drops followed by standard per operative cleaning and draping. 5% Povidone-Iodine solution was applied to the periocular areas, eyelids, eyelashes and conjunctival sac. Bevacizumab was injected into the vitreous with a 30 gauge needle 3.5 mm posterior to limbus in pseudophakic and 4 mm posterior to limbus in phakic eyes in inferotemporal quadrant. Tamponade was applied with sterile cotton tipped applicator to the needle track as it was withdrawn. Indirect ophthalmoscopy was done to confirm intravitreal location of the suspension and perfusion of the optic nerve head. Our spot size for the laser treatment was limited to 0.8, 1.2, 2, 3 and 4 mm. In cases, that required larger area to be covered, we irradiated the remaining lesion area with the desired spot size for another 100 seconds without lapse of any time so as to irradiate the lesion when the ICG dye concentration was high in the choroidal circulation. In many cases, larger area was irradiated due to the spot sizes available to us. The laser parameters were taken from the study by Arevalo et al and power was reduced by 25% and modified according to the spot sizes available to us. The power reduction was done to avoid the adverse effect on RPE as the retina of the Indian population is more pigmented as compared to Europeans. (Table 1) All patients were examined next day after intravitreal injection for evaluation of BCVA, IOP evidence of any intraocular inflammation/infection or any other complication. Topical antibiotics were prescribed for 1 week. Subjects were followed up at 6 weeks, 12 weeks and 16 weeks for BCVA, IOP, slit lamp examination for lens status assessment and fundus examination, FFA and SD-OCT. Main outcome measures were change in BCVA and Central macular thickness (CMT). Statistical analysis was done using SPSS (IBM SPSS version 22). Wilcoxon signed rank test was used for pre and post-treatment comparison. A p-value ≤ 0.05 was considered statistically significant.

**Table 1: Laser parameters used in IMP**

| CURRENT STUDY | SPOT SIZE (mm) | POWER (mW) | SPOT SIZE (mm) | POWER (mW) |
|---------------|---------------|------------|---------------|------------|
| 0.8           | 90            | 1.5        | 1.2           | 150        |
| 1.2           | 150           | 1.88       | 2             | 220        |
| 2             | 220           | 2.82       | 3             | 320        |
| 3             | 320           | 4.7        | 4             | 420        |
| 4             | 420           | 8.09       | 8             | 1210       |
Results

**Patient demographics**
The study included 15 eyes of 15 patients with mean age 62 years (range 48 - 78 years). Six were male and nine were female.

Four patients had history of cataract surgery and posterior chamber intraocular lens implantation in the studied eye, 5 had clear lens and remaining 6 had early immature cataract. No patients had cataract significant enough to preclude the view of the fundus. Eleven eyes had predominantly classic CNVM on FA while 4 eyes had occult CNVM.

**Visual acuity**
The BCVA improved in 33% of eyes after treatment. Mean visual acuity improved from 0.136 preoperatively to 0.177 at 6 weeks, to 0.183 at 12 weeks and 0.185 at 16 weeks. (Figure 1) However, this improvement was statistically significant only at 16 weeks (p= 0.03). 10 eyes showed stabilization of vision with treatment till 16 weeks post treatment. Five eyes showed improvement in vision, which was sustained till 16th week post treatment. No eyes showed decrease in vision by the end of follow up.

Before treatment, 5 eyes had BCVA better than 6/60 while 10 eyes had BCVA less than 6/60. At 16 weeks, 8 eyes had BCVA better than 6/60 while only 7 eyes had BCVA less than 6/60. Out of the 4 eyes with occult CNVM, 3 eyes showed stabilization of BCVA post treatment and one eye showed increase in BCVA.

**SD-OCT**
The mean macular thickness (MMT) decreased maximally in the first 6 weeks and then stabilised by 16th week. (Figure 2) Mean pre-treatment MMT varied from 284.1 µm to 261.2 µm at 4 weeks post-treatment, to 268.8 µm at 12 weeks and to 267 µm at 16 weeks post-treatment. The difference was statistically significant at all visits (p<0.05), but was maximum at 4 weeks (p=0.002). Six eyes (40%) showed complete resolution of CNVM on OCT. Out of these, 4 eyes were initially predominantly classic type of CNVM while 2 were occult CNVM.

**FFA**
At the end of 16 weeks, 5 eyes showed no leakage on FFA while 3 eyes showed a decrease in leakage. In one eye, decrease in leakage was noted at 6 weeks but thereafter, it remained the same till 16 weeks of follow-up. Two eyes showed an initial decrease in leakage at 6 weeks but on subsequent follow up at 12 weeks, an increase in leakage was noted which continued to increase till 16 weeks of follow-up. In 3 eyes, leakage did not increase or decrease after the treatment

**IOP and lens status**
The mean preoperative IOP was 16.4 ± 1.59 mmHg while the mean postoperative IOP was 16.6 ± 1.58 mmHg. The difference was not statistically significant (p=0.08). No patient developed rise in IOP > 21 mm of Hg. None of the 11 phakic eyes showed evidence of cataract development or progression.
Discussion

PDT with Verteporfin has been an advancement in the treatment of CNV due to AMD and has been found to be effective for subfoveal predominantly classic CNV. It requires intravenous administration of tetrypyrrol derivative benzoporphyrin Verteporfin (Visudyne). This photo-sensitizer has a long absorption wavelength at 690 nm therefore allowing deeper penetration of laser for more effective treatment. However, it is an expensive treatment modality and thus is not affordable to many patients.

IMP is based on the same principle as PDT but is much cheaper. It uses Indocyanine green, an anionic tricarbocyanine photosensitive dye, that has selective intravascular retention and peak absorption at about 805 nm, which is close to the peak emission of the conventional diode laser. Infrared light penetrates tissue deeper than red light, which thereby increases the membrane selectivity and spares the inner retinal layers.28 The mechanism of IMP is considered to be occlusion of the choroidal vasculature by inducing damage to the endothelial cell lining of the vessel with subsequent thrombus formation. The normal biological half time of ICG has been determined to be 2.5 to 3 minutes and eliminates the need for 24-hours period of limited light exposure, which is required in PDT with Verteporfin.29 It also has low skin phototoxicity. Safety of ICG is well documented in humans, with severe adverse reaction occurring only in 0.05% recipients.30 Its maximum recommended human dose is 5mg/kg.

In 1994, Reichel E et al first used Indocyanine green dye-enhanced diode laser photocoagulation for treatment of poorly defined subfoveal CNVM due to AMD.13 In their study, 9 out of 10 patient had a stable visual acuity after treatment. One patient had a marked, immediate decline of visual acuity directly attributable to the effects of laser photocoagulation. In 1999, Obana A et al conducted a retrospective pilot study of Indocyanine Green enhanced diode laser photocoagulation for subfoveal CNVM associated with AMD.14 Occlusion of CNV was achieved in 35 of 38 eyes (92%), and 7 eyes (18%) showed recurrence, which were occluded by retreatment in all but 1 eye. Ten eyes (26.3%) showed improvement of visual acuity; 16 (42.1%) showed no change; and in 12 eyes (31.6%) visual acuity deteriorated. Following this, Costa et al conducted various studies using IMP in various types of CNVM and found it to be effective in stabilisation of vision.22,23,27 Farah M et al also used only IMP for the treatment of classic CNV due to AMD, and found that 55% eyes showed stabilization of vision and improvement of more than 2 ETDRS lines was noted in 33% eyes.15

However, similar to PDT, collateral damage of the adjacent structures leading to choriocapillaris hypoperfusion and retinal pigment epithelium (RPE) atrophy may lead to less favourable results.8,9 The associated collateral damage has been shown to result in retinal edema and release of angiogenesis factors such as VEGF, leading to failure of the treatment.9 Hence, IMP was combined with intravitreal Triamcinolone because of its anti-inflammatory anti-VEGF action. However, to the best of our knowledge, there has been no study yet, to evaluate the effect of IMP with intravitreal Bevacizumab on CNVM due to AMD.

Arevalo et al in 2005 conducted a pilot study to determine the feasibility, safety and effect of treating subfoveal CNV due to AMD with IMP with and without intravitreal Triamcinolone.16 BCVA showed stability in 6 eyes (66.7%), improvement in 2 eyes (22.2%) and worsening in 1 eye (11.1%) in the group which was treated with IMP with intravitreal Triamcinolone. In the group which was treated only with IMP, 9 eyes showed stability (90%) and 1 eye showed worsening (10%).

In our study, 5 eyes showed improvement in vision ten eyes had shown stabilization of vision with treatment till the 16 week post treatment. No eyes showed decrease in vision till the end of follow up. The MMT decreased minimally in the first 6 weeks and then stabilised by the end of 16 weeks. Six eyes (40%) showed complete resolution of CNVM on OCT. The early decrease in retinal thickness may be due to the combined effect of both IMP and intravitreal Bevacizumab. Mild increase in retinal thickness at 12th week visit may represent the weaning of effect of intravitreal Bevacizumab leading to mild retinal edema. Final visit, possibly represents the effect of IMP in decreasing the retinal thickness.

Though the results involving the occult CNVM were not statistically significant due to very few number of cases, it appears that the combination of IMP with intravitreal Bevacizumab shows promising result in occult CNVM as well. In the study by Arevalo et al, 9 eyes had occult pattern of presentation.18 After the treatment, 5 eyes (55.6%) had stabilization of the visual acuity, 1 eye (11.1%) showed improvement and 3 (33%) had worsening of the vision. Change in vision by 2 lines from pre-treatment status was considered as significant in their study. We, in our study, also used the same criteria and noticed that 3 eyes with occult pattern of leakage had stabilization of vision and 1 had improvement in vision. None of the eyes showed worsening of vision after treatment.

In conclusion, the findings from our study advocate the use of IMP in combination with intravitreal Bevacizumab for the treatment of CNV in ARMD. However, a larger group of patients with a control group and a longer follow up are required to validate our results.

Cite This Article as: Seth A, Pangtey B, Goel N, Ghosh B. Indocyanine Mediated Photothermolysis (IMP) with Intravitreal Bevacizumab (IVB) for Treatment of Choroidal Neovascular Membrane (CNV) due to ARMD. Delhi J Ophthalmol 2016;26:180-4.

Acknowledgements: None

Date of Submission: 28.10.2015 Date of Acceptance: 24.11.2015

Conflict of interest: None declared

Source of Funding: Nil
References

1. Mitchell P, Smith W, Attebo, Wang JJ. The prevalence of age related maculopathy in Australia: The Blue Mountain Eye Study. *Ophthalmology* 1995; 102:1450-60.
2. Ferris FL, Fine SL, Hyman LA. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol* 1984; 102:1640-2.
3. Bressler NM, Bressler SB, Fine SL. Age-related macular degeneration. *Surv Ophthalmol* 1988; 32:375-413.
4. Macular Photocoagulation Study Group: Subfoveal neovascular lesions in age-related macular degeneration. Guidelines for evaluation and treatment in the Macular Photocoagulation Study. *Arch Ophthalmol* 1991;109:1242-57.
5. Macular Photocoagulation Study Group. The use of fundus photographs and fluorescein angiograms in the identification and treatment of choroidal neovascularization in the Macular Photocoagulation Study. *Ophthalmology* 1989; 96:1526-34.
6. Treatment of age-related macular degeneration with Photodynamic Therapy (TAP) Study Group: Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: 1-year results of two randomized clinical trials. TAP Report I. *Arch Ophthalmol* 199; 117:1329-45.
7. Sharma S, Brown GC, Brown MM, Hollands H, Shah GK. The cost-effectiveness of photodynamic therapy for the fellow eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology* 2001; 108:2951-9.
8. Chan WM, Lai TYY, Wong AL, Tong JP, Liu DTL, Lam DSC. Combined photodynamic therapy and intravitreal triamcinolone injection for the treatment of subfoveal choroidal neovascularisation in age related macular degeneration: a comparative study. *Br J Ophthalmol* 2006; 90:337-41.
9. Smith BT, Dhalla MS, Shah GK, Blinder KJ, Ryan EH Jr, Mittra RA. Intravitreal injection of bevacizumab combined with verteporfin photodynamic therapy for choroidal neovascularization in age-related macular degeneration. Retina 2008;28:675-81.
10. Kabeel MM, El-Batarny AM, Tameesh MK, Abou El Enien MA. Combined intravitreal bevacizumab and photodynamic therapy with verteporfin for management of choroidal neovascularization secondary to age-related macular degeneration. *Clinical Ophthalmology* 2008; 2:159-66.
11. Spaide RF, Luid K, Fine HE, Klancnik J, Meyerle C, Yannuzzi LA et al. Intravitreal bevacizumab (Avastin) treatment of choroidal Neovascularisation secondary to neovascular age related macular degeneration: a comparative study. *Br J Ophthalmol* 2006; 90:337-41.
12. Smith BT, Dhalla MS, Shah GK, Blinder KJ, Ryan EH Jr, Mittra RA. Intravitreal injection of bevacizumab combined with verteporfin photodynamic therapy for choroidal neovascularization in age-related macular degeneration. *Retina* 2008;28:675-81.
13. Reichel E, Pflaufflo CA, Ducker JS, Guyer DR. Indocyanine Green Dye-Enhanced Diode Laser Photocoagulation of Poorly Defined Subfoveal Choroidal Neovascularization. *Ophthalmic Surgery* 1994; 25:195-201.
14. Obana A, Gohto Y, Nishiguchi K, Miki T, Nishi S, Asada A. A Retrospective Pilot Study of Indocyanine Green Enhanced Diode Laser Photocoagulation for Subfoveal Choroidal Neovascularization Associated with Age-Related Macular Degeneration. *Jpn J Ophthalmol* 2000; 44:668-76.
15. Farah ME, Cardillo JA, Luzardo AC, Calucci D, Williams GA and Costa RA. Indocyanine green mediated photothrombosis for the management of predominantly classic choroidal neovascularization caused by age-related macular degeneration. *Br J Ophthalmol* 2004; 88:1055-9.
16. Cardillo JA, Jorge R, Costa RA, Nunes SM, Lavinsky D, Kuppermann BD et al. Experimental selective choriocapillaris photothrombosis using a modified indocyanine green formulation. *Br J Ophthalmol* 2008; 92:276-80.
17. Kubicka-Trzaska A, Starzycza M. Photodynamic therapy with indocyanine green for choroidal neovascularization caused by age-related macular degeneration—a preliminary record. *Klin Oczna* 2003;105:351-4.
18. Arevalo JF, Gracia RA, Mendoza AJ. Indocyanine green-mediated photothrombosis with intravitreal triamcinolone acetone for subfoveal choroidal neovascularization in age-related macular degeneration. *Graefe’s Arch Clin Exp Ophthalmol* 2005; 243:1180-5.
19. Hussain N, Hussain A, Natarajan S. Indocyanine green dye enhanced laser photoagulation for juxtapfoveal choroidal neovascularization. *Indian J Ophthalmol* 2005; 53:183-6.
20. Navajas EV, Costa RA, Farah ME, Cardillo JA, Bonomo PP. Indocyanine green-mediated photothrombosis combined with intravitreal triamcinolone for the treatment of choroidal neovascularization in serpiginous choroiditis. *Eye* 2003; 17:563-6.
21. Malerbi FK, Huang SH, Aggio FB, Carvalho E Jr, Bonomo PP, Farah ME. Indocyanine green-mediated photothrombosis for choroidal neovascularization in angioid streaks. *Arq Bras Oftalmol* 2008; 71:311-5.
22. Costa RA, Calucci D, Teixeir LF, Cardillo JA, Bonomo PP. Selective Occlusion of Subfoveal Choroidal Neovascularization in Pathological Myopia Using a New Technique of Ingrowth Site Treatment. *American Journal of Ophthalmology* 2002; 135: 857-6.
23. Costa RA, Meirelles RL, Cardillo JA, Abrantes ML, Farah ME. Retinal capillary hemangioma treatment by indocyanine green-mediated photothrombosis. *Am J Ophthalmol* 2003; 135:395-8.
24. Ricci F, Missirolfi R, Fregin F, Grossi M, Dorin G. Indocyanine green enhanced subthreshold diode-laser micropulse photocoagulation treatment of chronic central serous chorioretinopathy. *Graefe’s Arch Clin Exp Ophthalmol* 2009; 597-607.
25. Bertelli E, Pernter H. Vasoproliferative Retinal Tumor Treated With Indocyanine Green-Mediated Photothrombosis. *Retinal Cases & Brief Reports* 2009; 3:266-71.
26. Romanowska DB, Kubicka-Trzaska A. Photothrombosis in choroidal melanoma mediated by indocyanine green. *Klin Oczna* 2009; 111:37-41.
27. Costa RA, Farah ME, Freymuller E, Morales PH, Smith R, Cardillo JA. The efficiency and collateral damage of photodynamic therapy with indocyanine green dye in the rabbit choriocapillaries layer. *Am J Ophthalmol* 2001; 132:557-65.
28. Anderson R, Parrish J. The optics of human skin. *J Invest Dermatol* 1981; 77:13-9.
29. Villeneuve JP, Huet R, Marleau D, Huet PM. Estimation of hepatic blood flow with indocyanine green: comparison between the continuous infusion and single injections methods. *Am J Gastroenterol* 1982; 77:233-7.
30. Hope-Ross M, Yannuzzi LA, Gragoudas ES, et al. Adverse reactions due to indocyanine green. *Ophthalmology* 1994; 101:529-33.

Corresponding author:
Anisha Seth MS, DNB, FCIO
Consultant Vitreoretina, Delhi Retina Centre, Chowdhary Eye Centre, Daryaganj, New Delhi, India
Email: anisha Seth@yahoo.com