

Original Article

Transpupillary Thermotherapy for Treatment of Choroidal Neovascularisation Secondary to Age-Related Macular Degeneration in Indian Eyes

Manish Nagpal, MS, FRCS (Ed); Kamal Nagpal, MS; Shobhana Sharma, MS; Jyoti Puri, DO; Pran N Nagpal, MS, FACS

Aim: To evaluate the efficacy of transpupillary thermotherapy (TTT) for treatment of subfoveal choroidal neovascularisation (CNV) secondary to age-related macular degeneration (AMD), and to define accurate power settings for this procedure in Indian eyes.

Methods: A prospective, nonrandomised study of 160 eyes of 144 patients with subfoveal CNV. The laser settings included 2mm spot and 300mw power or 3mm spot and 400-600mw power. Two separate 3mm spots were used in larger lesions. The treatment was given for 60 seconds at each point.

Results: Ninety-nine eyes had classic membranes and 61 eyes had occult membranes. Following treatment, 79 of 99 (79.8%) classic and 52 of 61 (85%) occult membranes regressed. Visual improvement (> 2 lines) was seen in 29 (29.3%) eyes and 12 (19.6%) eyes; visual stabilisation (1 line) in 39 (39.4%) eyes, and 35 (57.4%) eyes; and reduction of vision (< 2 lines) in 31 (31.3%) eyes and 14 (22.9%) eyes with classic and occult membranes respectively. Mean follow-up was 12 months. One patient suffered inadvertent foveal burn.

Conclusion: TTT is effective in the management of subfoveal membranes in Indian eyes. They respond to lower energy levels compared to the Caucasian eyes.

Key Words: Transpupillary thermotherapy (TTT), Choroidal neovascular membrane (CNV), Age related macular degeneration (AMD), Ocular pigmentation

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Age-related macular degeneration (AMD) is the leading cause of irreversible visual loss among the elderly across the globe.^{1,8} Its prevalence increases sharply after the age of 65. Several epidemiological studies have found a 1.2% to 1.5% incidence of exudative age-related macular degeneration.^{6,8} Although far less common than the non-exudative form of AMD, exudative or neo-vascular AMD is responsible for most cases of severe visual loss.⁹

Laser photocoagulation is the only therapy proven effective for selected patients with neo-vascular age-related macular degeneration.¹⁰ The Macular Photocoagulation Study (MPS) group,^{11,12} has shown that it reduces the incidence of severe visual loss in patients with classic extrafoveal and juxtafoveal

membranes. However, the MPS showed an immediate precipitous decline in central vision following laser treatment of subfoveal CNV, due to damage to the overlying neurosensory retina.¹³ Also, a large proportion of the sub-foveal CNV seen clinically are occult, too large, or ill-defined. These are typically associated with poorer prognosis and do not meet the MPS guidelines for laser treatment.^{14, 15} Therefore, CNV complicating AMD often remains an untreatable blinding disorder.

As a consequence, considerable effort is being directed towards developing novel treatment strategies for neovascular AMD. On one hand, laser prophylaxis to high-risk drusens, in order to prevent the formation of CNV is being investigated.¹⁶⁻¹⁸ On the other, the use of laser in a non-photocoagulative mode such as the photodynamic therapy has been attempted.^{19,22} Radiation therapy with its known antiangiogenic properties has been explored.^{23,24} Pharmacological agents used for inhibition of angiogenesis such as interferon-alpha,²⁷ fumagillin derivatives,²⁸ interleukin 12,²⁹ thalidomide, etc are undergoing trials for their potential beneficial role in AMD. Subretinal surgery with removal of subretinal blood and CNV^{30,33} and the more recent macular translocation surgery^{34,37} are further attempts to deal with this problem.

Retina Foundation: Ahmedabad, India

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Reprint requests to Dr. Manish, Nagpal, Retina Foundation, Near Shahibag under bridge, Shahibag, Ahmedabad - 380 009, Gujarat, India. E-mail: <manishadl@sancharnet.in>

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Lately, there have been clinical trials of the use of low irradiance, long pulse diode laser irradiation termed "transpupillary thermotherapy" (TTT) for the management of occult and classic CNV due to ARMD.^{m*} In this procedure, heat is delivered to the choroid and the retinal pigment epithelium through the pupil using a modified diode (810 nm) laser. This wavelength has low-absorption in xanthophyll *and* is poorly absorbed by haemoglobin. These factors minimise the retinal nerve fibre layer damage and provide easy penetration through pre- and subretinal blood respectively. Its main site of absorption is the choroid, thereby offering an effective treatment for choroidal lesions.

Reichel et al demonstrated the efficacy of TTT in 16 eyes with occult subfoveal CNV secondary to ARMD. Newsom and colleagues³⁹ assessed the effectiveness of this procedure in 44 eyes of classic and occult CNV. They concluded that TTT is able to close CNV while maintaining visual function. Herein we present our data of 160 Indian eyes that received TTT for occult and classic subfoveal membranes. These Indian subjects had greater pigmentation compared to Caucasian subjects. Therefore, we had to alter the power settings to suit these eyes and to prevent over-treatment, which is possible due to the greater pigmentation. To the best of our knowledge, this is the largest number of eyes that have undergone this procedure (Medline search).

Material and Methods

After obtaining informed consent, 144 consecutive patients (160 eyes) with classic and occult subfoveal CNV [as classified on fluorescein angiography (FA)] secondary to AMD seen at our clinic from March 1998 to July 2001 were recruited prospectively for this study in a nonrandomised fashion. Predominantly classic membranes (>50% classic on FA) were termed classic and predominantly occult membranes (>50% occult on FA) were termed as occult. Patients whose media could not permit a proper TTT were excluded. All patients were over 55 years of age. Patients had symptoms of reduced vision and/or metamorphopsia. Detailed ophthalmic examination included measurement of Snellen visual acuity, slitlamp examination of the anterior segment, intraocular pressure (IOP) measurement, indirect ophthalmoscopy and macular assessment with slitlamp biomicroscopy using a 78 D lens (Volk). Pre-treatment colour fundus photographs were taken using a non-myliatic camera (Canon Inc., Tokyo). Fluorescein angiography (using sodium fluorescein 5 ml, 10%) was done using a scanning laser ophthalmoscope based angiography unit, (Heidelberg retinal angiogram, Heidelberg Engineering GmbH, Dossenheim, Germany) in all the patients before the TTT procedure.

Treatment protocol

Patients were scheduled for TTT on the day after the first examination and initial angiography. Treatment was

carried out with a slitlamp, with a modified infrared diode 810 nm laser (Iris Medical Oculight SLx, Iridex Corporation,

Mountain View CA, USA). Patients were anaesthetised with topical 2% xylocaine. A three-mirror Goldmann contact lens coated for use with diode laser was then placed on the cornea. Targeting was achieved with a diode red beam in such a way that it covered the entire lesion and extended 100 mm beyond the borders of the lesion. The patient's fixation was monitored by observation through the slitlamp. The beam width used was either 2mm or 3 mm in order to encompass the entire lesion. Before initiating the actual treatment, a pilot shot was placed in each case outside the arcades and the result monitored. If whitening of the spot occurred, the power was reduced in steps of 100 mw till no reaction or a faint retinal graying was seen. In our experience, a power range of 400mw to 600mw was adequate to produce the desired result. Then the actual treatment was initiated. The treatment duration at a point was 60 seconds. Two adjacent 3mm spots were used if indicated, to cover larger lesions. If the beam width was reduced to 2mm, the energy level was reduced to 300mw.

Follow-up examinations

All patients were scheduled to follow-up with us at 1, 3, 6, 9, 12 and 18 months after the treatment. At the first follow-up at 4 weeks, if there was no change or there was worsening of the clinical picture objectively and subjectively, the patient was advised a more frequent follow-up of every 2 weeks in order to consider a retreatment. Patients with a minimum follow-up period of 6 months following the treatment were included in the study. At each visit, a complete ophthalmic examination, as detailed above, was carried out, including a fundus photograph. Fluorescein angiograms were obtained if indicated clinically.

Outcome assessment

The treatment outcome was assessed based on the subfoveal lesion (regressed, static or increased) and change in visual acuity (improved, stabilised, reduced). The size of the lesion was measured by FA and visual acuity by Snellen charts using the preoperative measurement parameters. Improvement of vision was defined as distant reading vision >2 lines, stabilisation as the visual acuity + one line and reduction as distant reading vision < 2 lines.

Retreatments

A repeat treatment was given if there were persisting exudates and haemorrhages, at an average interval of 8 weeks from the first treatment. The same treatment criteria as above were followed for the retreatments.

Results

Patient demography

One hundred and sixty eyes of 144 patients were included in this study after obtaining informed consent. The study group involved 108 male and 36 female patients; 99 eyes (61.8%) had classic membranes and 61 eyes (38.1%) had occult membranes. The size of the lesions (at largest diameter) ranged from 1.5 mm to 3.5 mm (mean 2.0 mm) in the classic group, and from

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Table 1. Anatomical results

Number of eyes	Classic membranes(%)	Occult membranes (%)
Which responded to the first treatment	79 (79.7)	52 (85.24)
With membranes persisting after first treatment	20 (20.2)	9(14.75)
Which underwent single retreatments	9 (9.9)	9(14.75)
Which responded to the retreatment	4 (4.4)	3(4.91)
Total anatomical success	83 (83.8)	55(90.16)
Total	99	61

1.5mm to 4.5mm (mean 3.0 mm) in the occult group. The pre-treatment Snellen visual acuity ranged from counting fingers at 3 meters to 6/9. Post-treatment follow-up ranged from 6 to 18 months. 29 patients had a 6-month follow-up, 25 had a 9-month follow-up, and 42 and 48 patients had a total follow-up of 12 and 18 months respectively. The average follow-up was 12 months. 130 eyes had subretinal haemorrhages and all eyes showed associated subretinal exudation.

Treatment

All 160 eyes underwent TTT; 18 eyes underwent a second sitting of TTT. Retreatments were given only once. The retreatments were done at an average of 8 weeks from the first, (range 6-12 weeks). Five eyes were treated using 2mm beam size, and a power of 300mw while 145 eyes received treatment using a single spot of 3mm size at 400-600 mw power for 60 seconds. Ten eyes needed two separate 3 mm spots to encompass a larger lesion. Eleven patients complained of a feeling of warmth passing through the eye but none of them complained of pain. One patient had a sudden whitening of the area and the treatment was stopped at 51 seconds.

Treatment outcome

Classic membranes: The membranes regressed in 79 of 99 (79.78%) eyes. Twenty eyes (20.2%) showed persisting activity, of which nine received retreatments. After the required retreatment, the membranes closed in four eyes. Thus anatomical

Occult membranes: The membranes closed in 52 of 61 eyes (85%) and persisted in 9 eyes (15%). All the 9 eyes underwent single retreatments. CNV in 3 of these eventually closed. Thus anatomical success was achieved in 55 of 61 (90.16%) eyes with occult membranes (Table 1). Improvement of visual acuity was noted 12 eyes (19.6%). Stabilisation of vision was noted in 35 eyes (57.3%). Vision reduced in 14 eyes (22.9%). Thus there was stabilisation or improvement of vision in 47 eyes (77%) eyes (Table 2).

Pre and post-TTT colour fundus photographs of all eyes were assessed for objective signs of regression such as reduction of haemorrhages and overall exudation (Figures 1-3). Post-treatment fluorescein angiograms in eyes that responded to the treatment suggested decrease in leakage in the region of the membrane as compared to the pre-treatment hyperfluorescence (Figure 4).

Discussion

TIT closes the choroidal neovascular lesions by means of hyperthermia. The role of localised or generalised hyperthermia in the treatment of malignant lesions has been studied extensively.^{40,43} In fact TIT was also first described in 1995 for the treatment of choroidal melanomas, as an adjunct to radiation therapy.⁴⁴ In the more recent past, Shields et al studied its effectiveness alone, on the treatment of small choroidal melanomas.^{45,46} The anatomy of the eye and the ease of access of the posterior segment structures to laser treatment simplify the attainment of local hyperthermia with the help of TIT.

The role of TTT in closing down CNV secondary to AMD was first introduced by Reichel et al.³⁸ They published the effectiveness of this method for the treatment of occult sub-foveal CNV. In their study of 16 eyes of 15 patients followed up for an average of 13 months, 3 (19%) eyes experienced an improvement in visual acuity of two or more lines, 9 (56%) eyes had stabilisation of vision (no change or one line improvement) and 4 (25%) eyes showed a fall in vision by one or more lines. Recently, Newsom et al³⁹ reported the use of TIT in 12 eyes with predominantly classic and 32 eyes with predominantly occult membranes and

success was achieved in 83 (83.8%) eyes with classic membrane (Table 1). Improvement of visual acuity was noted in 29 eyes (29.3%). Stabilisation of vision was noted in 39 eyes (39.4%) There was a reduction of acuity by more than 1 line in 31 eyes (31.31%). Stabilisation to improvement of vision was noted in 68 eyes (68.7%) (Table 2).

Table 2. Visual results

Number of eyes	Classic membranes (%)	Occult membranes (%)
Visual improvement by 2 or more lines	29 (29.29) 39	12(19.67) 35
Stabilization of vision (same as pretreatment/ \pm 1 line)	(39.39)	(57.37)
Drop in vision by more than 1 line	31 (31.31)	14(22.95)

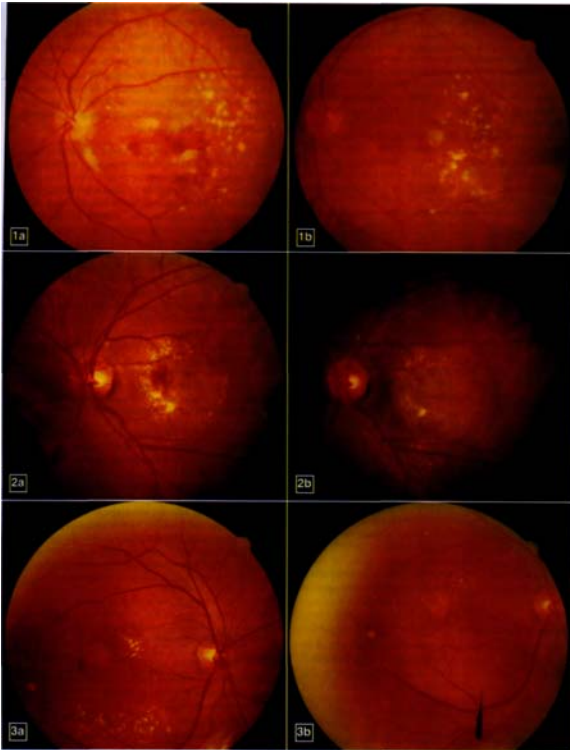
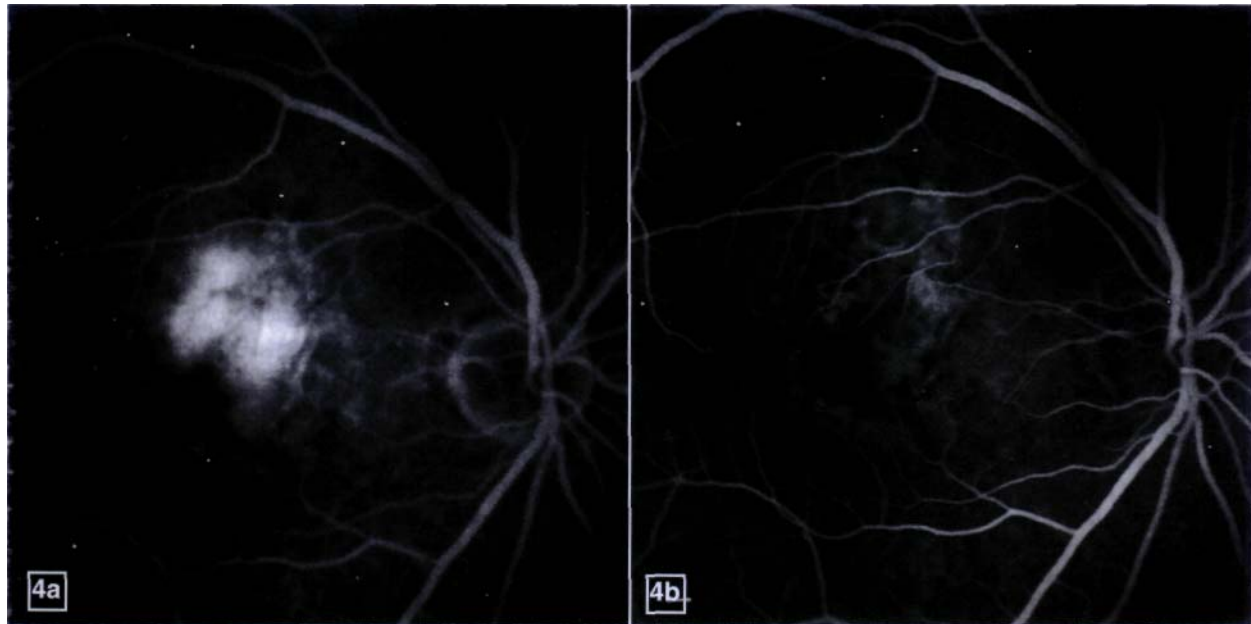


Figure 1a. Pre-thermotherapy; b. Post-thermotherapy; **Figure 2a.** Pre-thermotherapy; b. Post-thermotherapy; **Figure 3a.** Pre-thermotherapy; b. Post-thermotherapy



4a. Pre-thermotherapy fluorescein angiography; b. Post-thermotherapy fluorescein angiography

followed up these subjects for an average of 6.1 months. They showed that predominantly classic membranes closed in 75% of eyes and persisted in 25%. Predominantly occult membranes closed in 78% of eyes and persisted in 12.5%. There were no recurrences in the classic membranes, while occult membranes recurred in 5.1% eyes. The mean change in vision in their study group was -0.75 and -0.66 Snellen lines for the classic and occult membranes respectively. Other promising reports on the use of TTT for the treatment of occult and classic membranes, have appeared in the recent literature.⁴⁷⁻⁴⁹

Our results of closure of the membranes and visual acuity improvement after the procedure compare favourably with these studies. They also compare favourably with a natural history of occult CNV, where 63% of patients suffered three or more lines of visual loss in the first six months* and to the MPS study of classic membranes with recurrence rate of 59%.⁵¹ Also, the MPS showed that while conventional photocoagulation had a high rate of closure of classic membranes (72% at six months), this was associated with significant loss of vision in sub-foveal membranes.¹³

These results also compare well with photodynamic therapy (PDT) for subfoveal CNV treatment. The PDT using verteporfin have demonstrated stabilisation of vision (<3 lines lost) in 61.2% eyes (Vs 46% of control eyes) with classic subfoveal neovascular membrane²¹ and in 45% eyes (vs 31% control eyes) with occult subfoveal neovascular membrane.²² While the role of PDT in the treatment of sub-foveal classic membranes is

well defined, its role in the management of occult membranes is still being explored. Our results and those of the previous studies establish the efficacy of TTT in both classic and occult sub-foveal membranes. Finally, PDT is an extremely expensive procedure. Therefore, its reach to an average citizen of a developing country is limited. This has special significance in India, which needs cost-effective treatment modalities.

The importance of ocular pigmentation in this modality of treatment has been stressed by Auer et al.⁶ They reported choroidal atrophy in 5 of 32 eyes that underwent TTT. These patients were originally dark haired. A similar conclusion was also drawn by others on animal models.⁵³ Our aim was to determine the efficacy of this mode of treatment in the more pigmented Indian eyes, which are prone to over-treatment or laser burns. Therefore as a precaution, each patient received a pilot shot outside the arcades, prior to the actual treatment. We found that these eyes responded successfully to correspondingly smaller energy levels. We used 400mw to 600mw for a 3mm beam width and 300mw for a 2mm beam width, with high success rates. Reichel et al.⁵⁴ have used a range of 380-600mw for a 2mm beam width and from 360-1000mw for a 3mm beam width. Newsom and colleagues³⁹ recommend 500-700 mw energy for a 3mm beam width and 400-650 for a 2mm beam width.

The reported complications of TTT in choroidal melanoma include branch retinal artery and vein occlusion, retinal traction, retinal, choroidal and vitreous haemorrhage and retinal neovascularisation.³⁸ The

reported complications of I'll for CNV include macular infarction^M and development of a classic CNV following treatment for an occult one.⁵⁵ Benner et al⁵⁴ reported a macular infarct in 2.2% of their cases. They cautioned that presence of retinal pigment epithelial atrophy or prior laser treatment scars could contribute towards this complication. Kaga et al⁵⁵ reported the transformation of occult to classic CNV following treatment, and suggested that it may be the result of cytokine release following the treatment. McNulty et al⁵⁶ demonstrated decreased volumetric blood flow in the retinal circulation and alterations in the choroidal blood flow at 24 hours post-TTT by means of colour Doppler imaging. This was considered the mechanism for complete or partial occlusion of the CNV. The clinical relevance of this finding and its functional and visual implications however, are yet to be elucidated. In our study, we encountered one case that developed a foveal

burn despite using the similar treatment parameters, as had been used in the other eyes. Although the treatment was stopped short at 51 seconds, she subsequently developed a scar in that area with a reduction in her vision by 4 lines.

Accurate titration of the energy attains enormous significance in this procedure, where no visible end points are desirable. This is of greater importance in the heavily pigmented Indian eyes which are more prone to foveal burns. On the other hand, under-treatment will also hamper the anatomical and functional success of the procedure. Therefore a careful balance, with precautions like pilot shots in the periphery, careful monitoring of the treatment site and immediate cessation of the treatment at the first visible sign of a burn are mandatory. These measures will help maximise the benefits and reduce the complications of this procedure.

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