

Comparison of photodynamic therapy and transpupillary thermotherapy for the management of occult subfoveal choroidal neovascularization secondary to age-related macular degeneration

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Abstract

Aim: To compare the visual outcomes of photodynamic therapy with verteporfin and transpupillary thermotherapy for subfoveal occult choroidal neovascularization secondary to age-related macular degeneration.

Patients and methods: Patients with subfoveal occult choroidal neovascularization caused by age-related macular degeneration were included in this non-randomized open-label prospective comparative clinical trial. Standardized refraction, visual acuity testing, serial color photography, and fundus fluorescein angiography were performed to evaluate the effects of treatment in 16 eyes of 15 patients who underwent photodynamic therapy and 15 eyes of 13 patients who underwent transpupillary thermotherapy using standardized treatment protocols. Follow-up was carried out at 1, 3, and 6

months. Retreatment was carried out after 3 months, if indicated.

Results: There was no significant difference in visual acuity pre- and post-treatment for patients undergoing photodynamic therapy and transpupillary thermotherapy at 1, 3, and 6 months. In patients with visual acuity $\geq 6/12$ and lesions >4 disc area, there was a significant risk of severe visual loss with photodynamic therapy ($p = 0.0005$).

Conclusion: For patients with subfoveal occult choroidal neovascularization with visual acuity $\geq 6/12$ and lesions >4 disc area, there is a significant risk of severe visual loss with photodynamic therapy. However, if the visual acuity is $<6/12$, both photodynamic therapy and transpupillary thermotherapy are effective for short-term preservation of visual acuity.

Key words: Macular degeneration, Hyperthermia, induced, Photochemotherapy

Introduction

Age-related macular degeneration (AMD) is the commonest cause of visual loss in patients older than 65 years in the western world.¹ AMD is a significant cause of ocular morbidity for elderly people,² and the poor prognosis for untreated wet AMD lesions compounds the problem. There has been considerable controversy about the treatment options for occult choroidal neovascularization (CNV) secondary to AMD. The utility of photodynamic therapy (PDT) for subfoveal occult CNV secondary to AMD has been suggested by the Verteporfin in Photodynamic Therapy (VIP) trial.³ Anecdotal reports of treatment of occult subfoveal CNV secondary to AMD by transpupillary thermotherapy (TTT) are available in the literature.⁴⁻¹¹ Although series of patients with TTT have been described in the literature, none of the reports are case-control or comparative studies.

Algvere et al evaluated 66 patients with minimally classic CNV.⁷ These authors reported stabilization or improvement for 86.3% of patients after TTT. Ahuja et al evaluated 81 eyes of 77 patients with occult subfoveal CNV, and reported an improvement for 69% of patients after TTT.⁸ Friberg et al evaluated 35 eyes of 35 patients with CNV, 28 of which had minimally classic lesions.⁹ This study showed stabilization of vision in 86% of patients after TTT. Kim et al evaluated 48 eyes with occult subfoveal CNV treated with TTT.¹⁰ This study reported stabilization or improvement of vision for 62.5% of patients. Agarwal et al evaluated 28 eyes with subfoveal CNV (classic, occult, or mixed) treated with TTT.¹¹ This study reported stabilization for 60% of patients. Although these studies provide an impression of the treatment outcomes after TTT for occult CNV, they do not compare TTT with either placebo or other treatment. For this reason, a prospective comparative trial of PDT versus TTT for Indian patients with occult subfoveal CNV was performed.

Patients and methods

The study was a prospective non-randomized open-label comparative clinical trial. Thirty one eyes of 28 age-matched patients with subfoveal occult or minimally classic CNV secondary to AMD who attended the retinal clinic at Dr Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India, were included in the trial. All patients participating in this study were given a choice of either PDT or TTT after explanation of the costs, benefits, and risks of each treatment. This approach provided a measure of random allocation, although true randomization was not possible.

The inclusion criteria for patients evaluated in the trial were age older than 50 years, fluorescein angiographic evidence of subfoveal occult CNV due to AMD, greatest linear dimension (GLD) of the entire lesion $\leq 5400 \mu\text{m}$, and the nasal side of the CNV located $500 \mu\text{m}$ from the temporal border of the optic nerve head. All the patients included in the study had to have a best corrected visual acuity between $\geq 3/60$ and $\leq 6/9$, with sufficiently clear ocular media to perform

examination and treatment. The principle exclusion criteria were CNV due to other causes, previous history of central serous retinopathy, concurrent ocular pathology, history of prior laser photocoagulation, severe hepatic, renal, or neurological disease, or uncontrolled hypertension. Patients with other illnesses that could independently affect visual acuity such as diabetic retinopathy, hypertensive retinopathy, collagen vascular diseases, and retinovascular diseases were excluded from the study. Patients were followed up for 6 months.

Treatment protocol

Standardized protocol refraction, visual acuity testing, ophthalmic examination of the anterior and posterior segment by direct and indirect ophthalmoscopy, slit-lamp biomicroscopy for evaluation of the fundus, and fluorescein angiography were performed to evaluate the effects of treatment in 15 patients (16 eyes) who underwent PDT with verteporfin and 13 patients (15 eyes) who were treated by TTT using standardized treatment protocols.

Follow-up was performed 4 weeks, 12 weeks, and 6 months after the treatment. At each follow-up visit, visual acuity, slit-lamp biomicroscopy, and fundus fluorescein examination were performed to rule out any adverse effects. Retreatment, if indicated, was performed 3 months after the initial treatment using the same treatment regimen.

Stabilization of visual acuity was defined as visual acuity equal to or better than baseline, or loss of visual acuity ≤ 3 lines (treatment of age-related macular degeneration with photodynamic therapy [TAP] trial criteria).

Transpupillary thermotherapy

TTT was delivered through a dedicated slit lamp (Oculight Slx, Infrared diode laser [810 nm]; Iridex Corporation, Mountain View, USA) mounted and modified to provide a spot size $\leq 3 \text{ mm}$. The power setting was adjusted according to the lesion size and patient characteristics. The spot size was adjusted according to the lesion size, to cover the entire lesion. If the lesion was $>3 \text{ mm}$, multiple confluent spots, centering on the first 3-mm spot on the entire foveal avascular zone, were applied. A quadrispheric lens with antireflective coating was used for each patient. The endpoint was no visible reaction at the end of treatment. The time of the initial spot was 60 seconds. Test spots in the inferior quadrant of the eye were used to titrate the final power, which was 10% less than the power that gave a visible reaction to the test spot.

Photodynamic therapy

The standard therapeutic regimen for PDT described in the TAP trial was performed. Verteporfin was injected intravenously at a dose of 6 mg/m^2 body surface area — the drug was reconstituted by adding sterile water 7 mL to achieve a concentration of 2 mg/mL and the required amount of drug was diluted in 5% dextrose to reach a final volume of 30 mL. The drug was injected over a 10-minute period using an infusion pump. After 5 minutes, diode laser irradiation at 689 nm was performed via a slit-lamp delivery system, to deliver 50 J/cm^2 at an intensity of 600 mW/cm^2 over 83 seconds to

Table 1. Demographic data of patients undergoing photodynamic therapy with verteporfin or transpupillary thermotherapy.

	Photodynamic therapy	Transpupillary thermotherapy	p Value
Number of patients	15	13	0.9
Number of eyes	16	15	
Sex			
Male	9	11	0.001
Female	6	2	
Mean age (years)	65.6	62.2	
Mean lesion size [GLD; μm] (SD)	4248.7 (887.8)	3556.6 (1031.0)	

Abbreviation: GLD = greatest linear dimension.

a spot size that was 1000 μm greater than the GLD of the lesion (to provide a margin of additional treatment area to compensate for any eye movement during treatment).

Results

The study included 16 eyes of 15 patients (9 men and 6 women) that underwent PDT and 15 eyes of 13 patients (11 men and 2 women) that underwent TTT. The mean age of the patients undergoing PDT and TTT was 65.6 years (range, 51 to 80 years) and 62.2 years (range, 51 to 75 years), respectively. The mean lesion size for patients treated with PDT and TTT was 4248.7 μm (SD, 887.8 μm ; range, 1980 to 5010 μm) and 3556.6 μm (SD, 1031.0 μm ; range, 2010 to 5100 μm), respectively. **Table 1** shows the demographic data of the study patients.

The baseline mean letter score, according to the Early Treatment of Diabetic Retinopathy Study chart, was 49.69 (SD, 17.80) for patients treated with PDT and 41.67 (SD, 12.05) for those treated with TTT. There was no statistically significant difference between the 2 groups. There were no statistically significant differences in visual acuity for patients undergoing either PDT and TTT before treatment and at 1, 3, and 6 months follow-up (**Table 2**).

Characterization of individual patients who achieved stabilization of visual acuity was similar for both groups and at each follow up. Four patients had a loss of ≥ 15 letters after treatment with PDT (**Figure 1**). For patients with a loss of ≥ 15 letters after treatment with PDT, there was a highly significant chance of loss of vision if the pretreatment letter score was ≥ 70 ($p = 0.0005$). Post-treatment stabilization was better with TTT than with PDT at 6 months (**Figures 2**

Table 2. Mean visual acuity letter score changes at 1, 3, and 6 months following treatment with photodynamic therapy with verteporfin or transpupillary thermotherapy.

	Photodynamic therapy Mean (SD)	Transpupillary thermotherapy Mean (SD)	p Value
Baseline	49.69 (17.80)	41.67 (12.05)	0.14
1 month	48.13 (19.31)	41.00 (12.28)	0.4
3 months	48.13 (17.50)	45.30 (16.20)	0.58
6 months	44.69 (16.40)	45.67 (16.70)	0.75

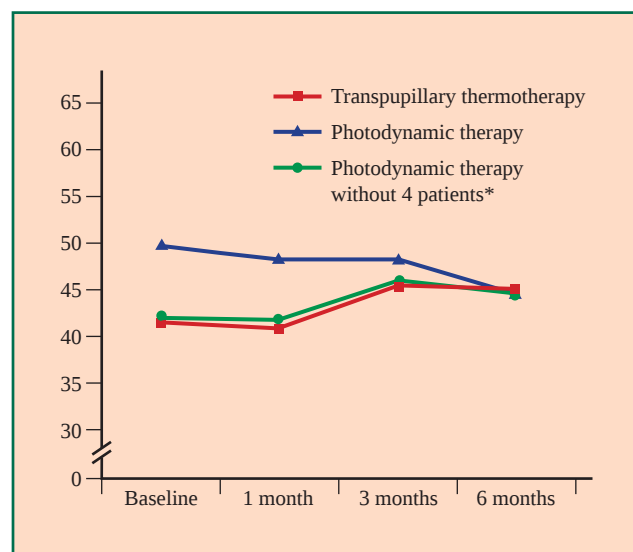


Figure 1. Letter score of patients with vision loss >3 lines after treatment with photodynamic therapy or transpupillary thermotherapy.

* Four patients had a loss of ≥ 15 letters after treatment with photodynamic therapy.

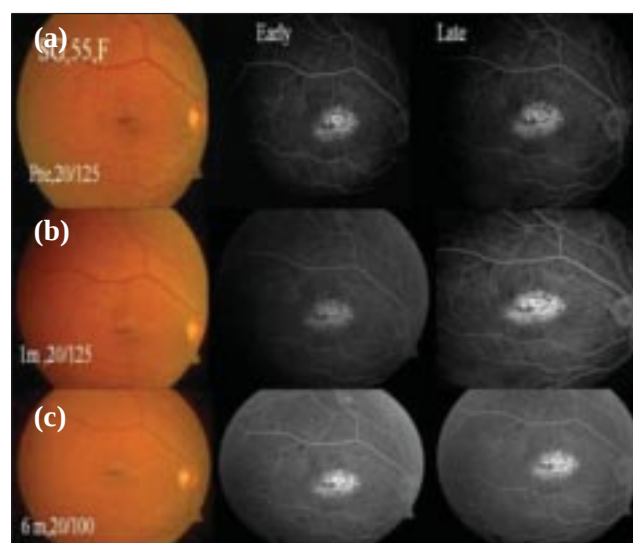


Figure 2. Pre- and post-transpupillary thermotherapy for subfoveal occult choroidal neovascularization secondary to age-related macular degeneration at (a) baseline; (b) 1 month; and (c) 6 months by colored fundus photography and fundus fluorescein angiography of the early and late phases in a 55-year-old woman. Note the stabilization of visual acuity and no increase in hyperfluorescence of the lesion.

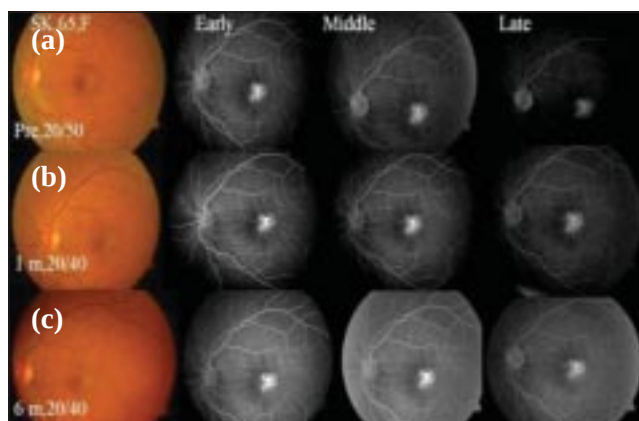


Figure 3. Pre- and post-photodynamic therapy with verteporfin for subfoveal occult choroidal neovascularization secondary to age-related macular degeneration at (a) baseline; (b) 1 month; and (c) 6 months by colored fundus photography and fundus fluorescein angiography of the early, middle, and late phases in a 65-year-old woman. Note the stabilization of visual acuity and no increase in hyperfluorescence of the lesion.

and 3) when either the TAP study criteria (<3-line loss) or baseline pretreatment vision levels were considered. However, these differences were not statistically significant

Discussion

The main purpose of this study was to compare the efficacy of PDT and TTT for the treatment of occult subfoveal CNV due to AMD. TTT for CNV secondary to AMD is performed in India for financial rather than scientific reasons. Although there are independent studies of PDT and TTT, there are no studies available comparing these 2 modalities. Furthermore, there are no studies comparing TTT with placebo. This study is the first prospective clinical trial comparing PDT with TTT. The trial could not be double-blind since there was only a small subset of patients who could choose PDT, due to financial constraints. Since conventional modes of randomization were not feasible, it was decided to offer PDT to all patients, and those who refused PDT were offered TTT. Although true randomization was not possible, the protocol provided some degree of random allocation of treatment.

There has been a large long-term randomized double-blind trial of PDT with verteporfin.³ In this trial, the primary outcome was similar for the verteporfin-treated and placebo-treated eyes at 12 months, although a number of secondary visual and angiographic outcomes were significantly more favorable for the verteporfin-treated group. Between 12 and 24 months, the treatment benefit increased such that at 24 months, the verteporfin-treated eyes were significantly less likely to have moderate or severe vision loss. These results were consistent between the total population and the subgroup of patients with a baseline lesion composition identified as occult CNV with no classic component. This subgroup included 166 of the 225 verteporfin-treated patients (74%) and 92 of the 114 placebo-treated patients (81%). Ninety one of the verteporfin-treated group (55%) lost at least 15 letters compared with 63 of the placebo-treated

group (68%) [$p = 0.032$]. In the study described here, 75.0% of the patients treated with verteporfin lost <15 letters at 6 months compared with 93.3% of patients in the TTT group. However, this difference was not statistically significant.

After 6 months, the mean letter score for the PDT group decreased to 44.69 (SD, 16.40) from the pretreatment value of 49.69 (SD, 17.80). For the TTT group, the mean letter score increased to 45.67 (SD, 16.70) from the pretreatment value of 41.67 (SD, 12.05). The mean change in letter score in both groups at 1 and 3 months was not significantly different from the pretreatment values. Although there was no significant difference between the 2 modalities at 6 months, PDT showed a downward trend. However in subfoveal occult CNV with visual acuity <6/12, there were no statistically significant differences in visual outcomes between the 2 modalities of treatment at 6 months follow-up ($p = 0.75$).

In subfoveal occult CNV with visual acuity $\geq 6/12$ and lesion >4 disc area, there is a significant risk of severe visual loss with PDT. In a subgroup analysis, 4 patients had severe visual loss following PDT. All 4 patients had a pretreatment letter score >70 and 3 of the 4 patients had GLD >4 disc area. This finding was highly statistically significant ($p = 0.0005$). In the VIP trial,³ patients with occult CNV with a large lesion (4 disc area or a GLD >2 disc diameter) and good pretreatment vision also had an increased risk of severe vision loss. As the VIP trial suggested, and these study results indicate, verteporfin treatment was not beneficial for eyes with occult CNV with no classic lesions that were both large and had better levels of visual acuity. Perhaps because of the relatively benign natural history of many of these lesions, it may be prudent to withhold verteporfin therapy unless a recent documented history of vision loss can be established. Recently, some researchers have used combined treatment of standard verteporfin PDT and 25 mg crystalline intravitreal triamcinolone (IVTA) for occult CNV. Augustin and Schmidt-Erfurth treated 41 eyes of 41 patients with combined therapy and concluded that the combined treatment may improve the outcome of standard verteporfin PDT for the treatment of occult CNV secondary to AMD, and lower the retreatment rate compared with monotherapy.¹² Nicolo et al treated 11 eyes of 10 patients with occult with no classic CNV with combined standard verteporfin PDT and IVTA.¹³ In this study, 45.5%, 63.6%, 63.6%, and 36.3% of patients showed improved visual acuity of at least 3 lines at 1, 3, 6, and 12 months, respectively. There was also a decrease in fluorescein leakage at subsequent examinations. The role of combined treatment needs further studies for validation.

The study described here is the first prospective comparative trial of PDT and TTT for treatment of occult subfoveal CNV using a standardized protocol. The study showed that there was no significant difference in the mean visual acuity between the 2 groups at 6 months. The study also strongly suggests that treatment by PDT should be avoided for patients with larger lesion size (>4 disc area) and good initial visual acuity (>20/40; letter score 70).

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