

Low power vs standard power transpupillary thermotherapy in patients with age-related macular degeneration and subfoveal choroidal neovascularization ineligible for photodynamic therapy

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Abstract

Aim To assess the effect of standard power vs low power transpupillary thermotherapy (TTT) in patients with active subfoveal choroidal neovascularization secondary to age-related macular degeneration ineligible for photodynamic therapy (PDT) by original treatment of age-related macular degeneration with photodynamic therapy (TAP) study group recommendations.

Methods Retrospective review of 79 patients with active predominantly occult subfoveal choroidal neovascularization or predominantly classic subfoveal choroidal neovascularization but Snellen visual acuity <20/200. All patients were treated with TTT administered via a Mainster wide field fundus contact lens with a retinal power/diameter coefficient of 248 mW/mm in the standard power ($n = 27$) and 181 mW/mm in the low power group ($n = 52$). The primary outcome was stabilization (<1 Snellen line change) or improvement (two or more Snellen lines) in visual acuity. Clinical and fluorescein angiographic resolution of overlying exudation was documented.

Results At 24 month follow-up, 17 patients (63%) in the standard power and 36 patients (69%) in the low power group achieved stable or improved vision. Improved vision (mean

three lines) was observed in 22% of the standard power and 23% of the low power group. Overlying exudation was reduced clinically with minimal or no leakage on fluorescein angiogram in 85% of standard power and 90% of low power group. Subgroup analysis in the low power group demonstrated a visual benefit in patients with subfoveal lesions, which had any classic component. **Conclusions** Low power TTT is as effective as standard power in stabilizing or improving vision and reducing overlying exudation in patients with active subfoveal choroidal neovascularization ineligible for PDT.

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Introduction

Age-related macular degeneration (AMD) is responsible for progressive central visual loss, which affects the majority of our activities of daily living. The hallmark of neovascular AMD is the development of choroidal neovascularization (CNV), which ultimately leads to the destruction of the macular

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photoreceptors and is responsible for severe central visual loss, accounting for 88% of AMD patients who are blind.¹ The recent Beaver Dam Eye study² reported the cumulative incidence of neovascular AMD in at least one eye as 1.4% in the aged population. At present the only proven treatments, conventional argon laser photocoagulation³⁻⁵ and photodynamic therapy (PDT),^{6,7} have limitations. The immediate profound central scotoma following conventional laser for subfoveal CNV has rendered it an unacceptable clinical treatment modality. The Treatment of age-related macular degeneration with photodynamic therapy (TAP) study group^{6,7} demonstrated stabilization or improved vision following PDT with verteporfin in patients with predominantly classic subfoveal CNV lesions and recent findings from the Verteporfin in Photodynamic Therapy (VIP) study⁸ demonstrated a visual benefit in small purely occult CNV lesions. Patient eligibility for PDT remains limited by visual acuity requirements, angiographic characteristics, and lesion size.

The majority of patients presenting with new onset active subfoveal CNV have occult or minimally classic lesions and are therefore not eligible for current proven treatments. Furthermore, the natural history of these lesions is a progressive increase in the lesion size and concomitant visual loss. Transpupillary thermotherapy (TTT) has been used for the treatment of small posterior choroidal melanomas,⁹ retinoblastoma,¹⁰ and choroidal haemangiomas¹¹ since the mid 1990s. Recent interest has focused on the potential therapeutic effect of TTT on subfoveal CNV secondary to AMD following observations by Reichel *et al*¹² in 1999 and more recent publications.¹³⁻¹⁵ TTT has been shown to stabilize vision and reduce overlying exudation in both classic and occult subfoveal CNV.¹²⁻¹⁶ The exact treatment parameters have not yet been elucidated. Based on previous clinical experience, Goldmann type contact lens is most commonly used generating a power retinal/diameter coefficient of 248 mW/mm. Despite being usually well-tolerated, concerns exist about the risk of a retinal pigment epithelium (RPE) tear, macular ischaemia, and possible longer term RPE atrophy particularly with repeat treatments.

During the time parameters of this study PDT in our unit was restricted to those patients whose visual acuity and lesion characteristics conform to the TAP criteria.^{6,7} This study aimed to assess the outcomes of low power TTT compared to a previously treated group of standard power TTT in patients with subfoveal CNV not eligible for PDT.

Materials and methods

Retrospective review of patients with a recent diagnosis of subfoveal CNV secondary to AMD, ineligible for PDT

according to the TAP protocol, and who received TTT was performed. Patients with predominantly classic CNV had visual acuity <20/200. Patients were not offered treatment if they clinically had a large amount of serous subretinal fluid overlying the neovascular complex, cystic retinal changes predisposing to macular hole development, or greater than 50% of the CNV complex comprising of haemorrhage.

At the initial and each subsequent clinic visit, patients underwent measurement of best-corrected visual acuity on either a 2 m logMAR chart or a Snellen chart and detailed macular examination with high magnification slit lamp biomicroscopy. Visual acuity tested on a 2 m logMAR chart was converted to Snellen equivalent. Colour fundus photography and fluorescein angiography (sodium fluorescein 5 ml, 10%) were performed at each visit. The lesions were classified based on fluorescein characteristics. Baseline lesion characteristics including presence of haemorrhage, fibrosis, and retinal pigment epithelium (RPE) changes were documented (Table 1).

TTT was delivered using a slit lamp mounted modified infrared diode laser (Iridex, Mountain View, California) at 810 nm via a hand held contact lens (Mainster Wide Field) with a magnification power of 1.5 using a 2.0 or 3.0 mm slit lamp spot. The initial group of 29 patients were treated with power settings of 740–1100 mW generating a power retinal/diameter coefficient of 248 mW/mm. In the subsequent low power group ($n = 52$), power settings of 530–800 mW were employed generating a power retinal/diameter coefficient of 181 mW/mm. Duration of treatment was for 1 min with no visible retinal whitening. Lesions with linear dimensions greater than 4.5 mm were treated with overlapping spots.

Follow-up visits were planned at 6 weeks and thereafter 3 monthly. The primary outcome was stabilization of vision, defined as less than one Snellen line change. Improved visual acuity was defined as an increase in Snellen visual acuity of two or more lines from baseline. Worse visual acuity was defined as loss of two or more Snellen lines of visual acuity from baseline. We assessed avoidance of moderate (<3 line) and severe (<6 line) visual loss. Clinical and fluorescein angiogram outcomes were documented (Table 2). The mean of the figures obtained after calculation of the logarithm of the minimal angle of resolution (Snellen visual acuity) was converted to the antilog in order to obtain the average visual acuity. Visual acuity outcomes were compared by conversion to logMAR using a paired two-tailed Student's *t*-test. Visual outcomes between subgroups of differing lesion size and differing lesion component were compared using a χ^2 test (Table 3).

Table 1 Baseline Characteristics *n* = 79

Characteristic	Standard power (<i>n</i> = 27)	Low Power (<i>n</i> = 52)
<i>Age (years)</i>		
60–69	6 (22%)	9 (17%)
70–79	12 (44%)	19 (37%)
80–89	8 (30%)	22 (42%)
90 +	1 (4%)	2 (4%)
<i>Sex</i>		
Female	18 (67%)	38 (73%)
Male	9 (33%)	14 (27%)
<i>Snellen visual acuity</i>		
20/40–20/80	4 (15%)	8 (15%)
20/100–20/200	13 (48%)	26 (50%)
20/250-counting fingers	10 (37%)	18 (35%)
<i>Lesion type</i>		
Pure occult	20 (74%)	38 (73%)
Minimally classic	7 (26%)	8 (15%)
Predominantly classic	0	6 (12%)
<i>Haemorrhage (%)</i>		
0	11 (41%)	23 (44%)
<50%	16 (59%)	29 (56%)
≥50%	0	0
<i>Fibrosis (%)</i>		
0	1 (33%)	17 (33%)
<50%	3 (61%)	32 (61%)
≥50%	3 (6%)	3 (6%)
<i>RPE atrophy (%)</i>		
0	2 (48%)	25 (48%)
<50%	27 (52%)	27 (52%)
≥50%	0	0
<i>Lesion size</i>		
<3600 μm	19 (70%)	35 (67%)
≥3600 μm	8 (30%)	17 (33%)

Results

In all, 79 eyes of 79 patients who received TTT were included in the study. Baseline characteristics including sex, age, and presenting visual acuity were similar in both groups. (Table 1) Follow up in the standard power group (mean 25 months) was longer than in the low power group (mean 21 months). Mean number of treatments per patient was 1.2 (range 1–3) in both.

All 79 CNV lesions were subfoveal. In the standard power group, 74% were pure occult and 26% were minimally classic. In the low power group, 73% were pure occult, 15% were minimally classic, and 12% were predominantly classic. There was haemorrhage present in 56% of the lesions in both groups at presentation. There was no significant difference in mean visual acuity

Table 2 Outcomes *n* = 52

	Standard power (<i>n</i> = 27)	Low power (<i>n</i> = 52)
Mean Pre-TTT vision	20/180	20/200
Mean Post-TTT vision	20/220	20/190
<i>Vision outcomes</i>		
Improved	6 (22%)	12 (23%)
Stable	11 (41%)	24 (46%)
Decreased	10 (37%)	16 (31%)
Avoided moderate visual loss	18 (67%)	38 (73%)
Avoided severe visual loss	25 (93%)	49 (94%)
<i>Clinical exudative response</i>		
Decreased	23 (85%)	47 (90%)
Increased	4 (15%)	5 (10%)
<i>Fluorescein angiogram outcomes</i>		
Closed	20 (74%)	36 (69%)
Minimal leakage	3 (11%)	11 (21%)
Progression of leakage	4 (15%)	5 (10%)
<i>Lesion characteristics</i>		
<i>Haemorrhage (%)</i>		
0		39 (75%)
<50%	22 (81%)	12 (23%)
≥50%	5 (19%)	1 (2%)
	0	
<i>Fibrosis (%)</i>		
0		3 (6%)
<50%	0	36 (69%)
≥50%	19 (70%)	13 (25%)
	8 (30%)	
<i>RPE atrophy (%)</i>		
0	0	37 (71%)
<50%	22 (81%)	2 (4%)
≥50%	5 (19%)	

Table 3 Subgroup analysis (*n* = 52)

Characteristic	Stable/improved vision	Decreased vision	P-value*
<i>Lesion size</i>			
<3600 μm (<i>n</i> = 35)	25	10	
≥3600 μm (<i>n</i> = 17)	11	6	NS
<i>Lesion type</i>			
Pure occult (<i>n</i> = 38)	22	16	
Any classic (<i>n</i> = 14)	13	1	≤0.03

* χ^2 test.

before and after TTT in the standard power group (20/180 vs 20/220) or the low power group (20/200 vs 20/190) (Table 2).

In total, 63% (standard power) and 69% (low power) achieved the primary outcome of stable or improved

vision, respectively. Of those, 22% (standard power) and 23% (low power) had improved vision by two or more lines (mean three lines). Patients in the standard power group (37%) had worsened vision of two or more lines as compared to patients in the low power group (31%). In total, 67% (standard power) *vs* 73% (low power) avoided moderate visual loss and 93 *vs* 94% avoided severe visual loss, respectively.

Two patients in the standard power group and three patients in the low power group lost more than six lines of vision. Massive exudation with the development of a cystoid macular hole was responsible for vision loss in one patient in the standard power group and in two patients in the low power group. One patient in each group lost six or more lines of vision due to significant central RPE atrophy.

Subgroup analysis of the low power group (Table 3) demonstrated that patients with any classic component in their lesion had stable or improved vision compared to those with pure occult lesions. No significant difference in visual outcomes was noted for smaller ($<3600\ \mu\text{m}$) or larger lesion ($\geq 3600\ \mu\text{m}$) subgroups.

On fluorescein angiogram, minimal or no leakage was observed in 85% of the standard power and 90% of the low power TTT-treated eyes at latest follow-up. During the procedure, no patient reported any discomfort and no whitening of the lesion was noted in any case. No patient developed an RPE tear following treatment. No serious adverse event occurred during or immediately after treatment in any patient.

Discussion

The most important finding from this study is that visual acuity was stable or improved in 69% of patients following low power TTT, which compares favourably to standard power TTT, PDT, and natural history outcomes. Reichel *et al*¹² in 1999 first showed that TTT for AMD reduced the amount of subretinal fluid overlying a CNV complex in 94% and appeared to stabilize or improve visual acuity in 75%. Other TTT trials have demonstrated angiographic membrane closure following standard power TTT for CNV in 78%¹³ with stabilization of visual acuity in 62.5–86%.^{12–16} The exact optimal treatment parameters are unknown; the initial 29 patients in this series were treated based on previous clinical experience. Power settings of 720–1100 mW were used with a Mainster wide field lens to achieve a power/retinal diameter coefficient of approximately 248 mW/mm. Thach *et al*¹⁵ more recently demonstrated that large spot size TTT is effective in stabilizing or improving visual acuity in 71% of a series of 69 patients with predominantly occult membranes. The power used in this series ranged from 600 to 1000 mW generating a

power/retinal diameter coefficient of between approximately 169 and 266 mW/mm. In our series of 52 patients, lower power (530–800 mW, power/retinal diameter coefficient 181 mW/mm) TTT achieved stabilization or improvement in vision (69%) and reduction in subretinal exudation (90%) overlying the CNV complex comparable to the standard power group and similar to previously reported data.

In all, 73% of patients in the low power group avoided moderate visual loss and 94% avoided severe visual loss which compares favourably with the outcomes from the TAP^{6,7} and VIP⁸ studies. The 24-month outcomes of the VIP study group⁸ demonstrated stable (no change) or improved vision (≥ 1 line) in only 28% of verteporfin and 20% of placebo group with pure occult subfoveal CNV. In addition, vision decreased (≥ 1 line) in 72% of verteporfin-treated and in 80% of the placebo-treated group in the VIP study. In our low power group, only 16 patients (31%) had reduced visual acuity of two or more Snellen lines. Subgroup VIP study analysis suggests PDT is of greater benefit to patients with smaller lesions (four disc areas or less) and lower levels of visual acuity.⁸ In our low power group, no significant difference in visual outcomes was demonstrated between patients with smaller ($<3600\ \mu\text{m}$) or larger ($\geq 3600\ \mu\text{m}$) lesions (Table 3), suggesting TTT as effective for both. Predominantly, occult neovascular membranes are often large and 17 (33%) of the lesions in our low power group had a greatest linear dimension of at least 3600 μm (equivalent to 4 MPS disc areas). The Mainster wide field lens, which generates a large retinal spot size, permits total coverage of these large lesions. As PDT has not been of any proven benefit for large occult lesions,⁸ TTT offers a therapeutic option for these patients.

Our visual acuity and exudative outcomes following low power TTT also compare favourably with the natural course of occult subfoveal CNV. One study¹⁷ demonstrated that, after 9–12 months of follow-up, 32% of occult lesions more than double their size, the median loss in visual acuity was 2.5 lines and approximately 50% of pure occult lesions developed classic CNV.

Subgroup analysis of the low power group showed that patients with any classic component had stable or improved vision ($P < 0.03$) following TTT compared to patients with purely occult CNV (Table 3). Neither the TAP^{6,7} nor VIP⁸ study demonstrated any benefit with PDT for patients with minimally classic lesions or predominantly classic lesions but vision less than 20/200. Unfortunately, the majority of patients with subfoveal CNV have pure occult or minimally classic leakage and often larger lesions. This study has shown a treatment benefit following low power TTT for this large patient population that are ineligible to conventional forms of therapy.

TTT was well tolerated by patients in both groups with no retinal whitening observed and no pain reported by any patient during the procedure. Following treatment, three patients developed increased exudation and angiographic leakage with a cystoid macular hole. No predisposing factors were evident in these patients, thus it is unclear if these effects were directly related to the treatment. Overall, 26 patients between both groups lost more than two lines of Snellen visual acuity, despite a marked improvement in associated overlying exudation in 20 of these eyes.

The main risk with TTT identified in the short term is the development of an RPE tear. Following standard power TTT, the rate of RPE tears has varied from 0% to as high as 8%.^{12–16,18} No patient developed an RPE tear in the standard or lower power groups. Benner *et al*¹⁹ recently reported two cases of macular infarction following TTT in a case series of 107 patients (1.9%), however, both these patients had possible predisposing factors; a pre-existing laser scar and an area of geographic atrophy. None of the patients in our series developed this problem. This low rate of adverse effects also compares well with the documented complication rate following PDT. The rate of acute severe vision loss after PDT (four or more lines on a logMAR chart within 7 days of treatment) was reported as 4.4% in the VIP study.⁸ None of the patients in our series reported a severe visual loss following initial or any repeat treatment. The long-term potential damaging effects of PDT on RPE cells, particularly in patients requiring multiple treatments, may become a limiting factor in its use.

In practice, TTT is a less invasive form of treatment than PDT for the patient and is not as cost prohibitive. TTT is a straightforward procedure that can easily be carried out in a short time in an outpatient clinic. No medication is transfused during TTT, unlike during PDT, lessening the potential for adverse effects or patient unsuitability. The cost of TTT is restricted to the initial purchase of the portable diode laser and no other specialized equipment is required, in comparison to the administration of PDT. The frequency of repeat treatments after TTT is low as a reduction in exudation is achieved in the majority of cases. The majority of patients in the low power group (77%) required one treatment only. This favourably compares with the repeat treatment rate following PDT particularly in the first year; the average number of treatments during the first year of the TAP study was 3.7.⁶

Data interpretation from this study has limitations as it is a retrospective review, Snellen and not logMAR visual acuity charts were used and follow up is relatively short. Thus, direct comparison to prospective, randomised studies such as the TAP and VIP cannot be made.

However, it does provide further supporting evidence for the role of low power TTT in predominantly occult CNV and for those patients with predominantly classic subfoveal CNV but with lower levels of vision rendering them ineligible for PDT. Proof of a therapeutic benefit is being assessed by a prospective randomised trial, the TTT4CNV trial currently underway.

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