Transpupillary Thermotherapy With Indocyanine Green Dye Enhancement for the Treatment of Occult Subfoveal Choroidal Neovascularization in Age-Related Macular Degeneration

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**BACKGROUND AND OBJECTIVES:** Transpupillary thermotherapy (TTT) with indocyanine green (ICG) dye enhancement (TTT+) and TTT alone were compared for safety and effectiveness as a treatment of occult subfoveal choroidal neovascularization in age-related macular degeneration.

**PATIENTS AND METHODS:** Twenty-one patients were randomized to receive TTT (12 eyes) or TTT+ (9 eyes) and observed for at least 6 months. ETDRS visual acuity and fluorescein and ICG angiography were obtained every 3 months.

**RESULTS:** The median initial visual acuity was 20/80 in the TTT group and 20/100 in the TTT+ group. At 6 months, loss of less than 3 lines of visual acuity was present in 7 of 12 eyes (58%) in the TTT group and 5 of 9 eyes (56%) in the TTT+ group. At the final examination, there was no active choroidal neovascularization exudation in 6 of 12 eyes (50%) in the TTT group and 5 of 9 eyes (56%) in the TTT+ group. The median final visual acuity was 20/125 in the TTT group and 20/160 in the TTT+ group. Ocular or systemic complications were not encountered in either group.

**CONCLUSION:** TTT with ICG dye enhancement was as safe and effective as TTT alone in this study. However, modifications of treatment protocol would be needed to see whether there is any advantage to using ICG dye enhancement.

INTRODUCTION

The majority of severe vision loss associated with age-related macular degeneration is a result of choroidal neovascularization (CNV). Most patients with neovascular age-related macular degeneration present...
with minimally classic or occult forms of CNV. The Verteoporf in Photodynamic Therapy (VIP) study demonstrated that photodynamic therapy with verteporfin resulted in a higher rate of stabilization of vision compared with placebo for patients with subfoveal occult CNV, especially for lesions of less than 4 disc areas or visual acuity worse than 20/50 at baseline. However, for larger occult lesions, photodynamic therapy was not recommended. Furthermore, photodynamic therapy is limited by the need for multiple treatments, the need to avoid sunlight exposure, costliness, and stabilization rather than improvement of vision. Pegaptanib sodium has been approved for treatment of all subtypes of CNV, including minimally classic and occult forms. However, this treatment modality requires repeated intraocular injections and has risks of endophthalmitis and retinal detachments.

Another potential treatment option for occult CNV is transpupillary thermotherapy (TTT). It uses a long pulsed, low frequency infrared diode laser that produces choroidal hyperthermia without a photocoagulation effect. Its effectiveness in treatment of CNV may be due to (1) induction of apoptosis in the endothelial cells of neovascularization; (2) free radical reactions in vascular tissues, causing thrombosis of abnormal vessels; (3) increased temperature, causing inhibition of vascular endothelial growth factor and enhancement of other inhibitors of angiogenesis; and (4) induction of heat shock proteins and protection of the neurosensory retina during TTT.

A multicenter, randomized prospective trial called TTT4CNV hoped to elucidate the therapeutic effect of TTT. It found that treatment with TTT was no better than observation, except in eyes with baseline visual acuity of 20/100 or worse. Although this trial did not find treatment benefit, some modifications to current TTT treatment can be considered for increased efficacy.

One variation of TTT treatment is to use indocyanine green dye (ICG) as a photosensitizing agent during treatment. Because the absorption peak of ICG dye (805 nm) is similar to the diode laser emission peak (810 nm), there is a theoretical advantage that ICG dye-enhanced laser photocoagulation may permit use of lower energy and yet allow selective ablation of ICG-retaining CNV, resulting in relative sparing of damage to surrounding tissues. Furthermore, because ICG is relatively inexpensive compared to verteporfin used in photodynamic therapy or repeated injections with pegaptanib sodium, the potential therapeutic effect of TTT enhanced by ICG dye is economically attractive worldwide.

Several studies have tested the feasibility of combining TTT with ICG dye enhancement. Reichel et al. reported a case series of 10 patients in whom diode laser photoocoagulation enhanced by ICG dye was used for treatment of occult CNV. In this study, multiple small spot size laser photoocoagulation was applied confluent to treat the lesion. Costa et al. have used TTT and ICG dye as a photosensitizer for the photodynamic occlusion of normal choriocapillaries in pigmented rabbits. They also reported a beneficial treatment effect of TTT enhanced by ICG dye in 2 patients with occult CNV.

We report our experience with TTT with ICG dye enhancement for the treatment of occult subfoveal CNV in age-related macular degeneration compared to the standard TTT, and discuss points to explore when considering TTT with ICG dye enhancement.

**PATIENTS AND METHODS**

Institutional Review Board approval was obtained prior to patient enrollment at the Medical College of Wisconsin. Patients with predominantly or entirely occult CNV due to age-related macular degeneration with 3 mm or less in greatest linear dimension, documented visual loss or onset of metamorphopsia within less than 3 months, and ETDRS visual acuity between 20/32 and 20/400 were enrolled. They were randomized to receive TTT or TTT with ICG dye enhancement (TTT+) at initial treatment and observed prospectively every 3 months for a minimum of 6 months. A complete ophthalmologic examination including ETDRS visual acuity, fundus photographs, fluorescein angiography, and ICG angiography was obtained on each visit.

Using a Goldmann macular lens, TTT was delivered with an infrared diode laser (IRIDEX Corporation, Mountain View, CA) at a wavelength of 810 nm with a 3-mm spot size, a duration of 60 seconds, and a power of 800 mW. The patients who were randomized to the TTT+ group were given a bolus of ICG dye (0.5 mg/kg) infusion followed by a 5-mL flush of sterile normal saline. Treatment began 5 minutes later with a 3-mm spot size, a duration of 60 seconds, and a power of 500 mW. One spot encompassed the entire
CNV in all patients. At each 3-month visit, if leakage or growth of CNV was present, treatment was repeated according to the initial randomization protocol. Outcome measures were proportion of eyes with less than 3 lines of visual acuity loss, number of re-treatments, and final exudative response based on clinical examination, fluorescein angiography, and ICG angiography.

RESULTS

A total of 21 eyes in 21 patients were treated. The mean age of the 12 patients treated with TTT was 79 years (range: 63 to 93 years). The mean age of the 9 patients treated with TTT+ was 77 years (range: 62 to 93 years). The median initial visual acuity was 20/80 (range: 20/32 to 20/200) for the TTT group and 20/100 (range: 20/50 to 20/125) for the TTT+ group.

During or immediately following treatment, complications such as retinal whitening, immediate loss of vision, macular infarction, retinal pigment epithelial tear, or hemorrhages did not occur in either group. There were no complications related to ICG injection, and bolus injection of ICG was well tolerated by all of the patients in the TTT+ group.

The number of treatments in both groups ranged between 1 and 3. More than 1 treatment was needed in 5 of 12 (42%) eyes in the TTT group (mean: 2) and 7 of 9 (77%) eyes in the TTT+ group (mean: 2). All eyes had at least 6 months of follow-up. For the TTT group, less than 3 lines of visual acuity loss was present in 7 of 12 (58%) eyes at 6 months, 6 of 9 (67%) eyes at 12 months, and 4 of 6 (67%) eyes at 18 to 24 months of follow-up. For the TTT+ group, less than 3 lines of visual acuity loss was seen in 5 of 9 (56%) eyes at 6 months, 4 of 6 (67%) eyes at 12 months, and 3 of 3 (100%) eyes at 18 to 24 months of follow-up. In the final examination, there was no active CNV exudation based on clinical examination and fluorescein angiography in 6 of 12 (50%) eyes of the TTT group and 5 of 9 (56%) eyes of the TTT+ group. The median final visual acuity was 20/125 (range: 20/50 to 20/800) in the TTT group and 20/160 (range: 20/40 to 20/800) in the TTT+ group.

DISCUSSION

ICG dye has been shown to be a weak photosensitizing agent. It is considered to be a relatively non-diffusible dye within the normal retinal vasculature because of its relatively large molecular weight, and is 98% bound to plasma proteins such as albumin, globulins, and lipoproteins. These characteristics may promote increased intravascular ICG dye retention, even in CNV. Because TTT allows deeper penetration at 810 nm and ICG dye can act as a photosensitizer at that wavelength, selective treatment of CNV with lower energy and less damage to the surrounding tissues is thought to be possible.

In our study, the baseline vision, lesion size, and age of patients were well balanced. In the final analysis, there was no significant difference in visual outcome or the number of treatments required between the TTT and TTT+ groups during the course of follow-up with the chosen treatment protocol. Although more patients in the TTT+ group seemed to require two or more treatments, both groups did not differ in the mean or the range of number of treatments.

In addition to this pilot study having small sample size, reasons for lack of difference between the two groups and no apparent benefit from use of ICG to enhance TTT may include the timing of laser application following ICG infusion, laser power, or sub-optimal ICG concentration. Each of these factors will be discussed for the benefit of those considering future studies using this modality of treatment for CNV.

The disappearance rate of ICG in healthy human subjects is 18% to 24% per minute. The normal biological half-life was determined to be from 2.5 to 3 minutes, so single blood samples taken from healthy subjects 20 minutes after injection should contain no more than 4% of the initial concentration of dye, eliminating the need for a period of limited light exposure as required with verteporfin. Given this rapid clearance, we chose to give a bolus injection to maximize the effect of ICG in the circulation.

Furthermore, because of the rapid clearance of ICG, treatment with TTT should be done relatively soon after bolus ICG injection. Reichel et al. chose to treat within 2 to 5 minutes after intravenous administration because this time range represented the maximal fluorescence observed in the choriocapillaries with minimal leakage of ICG into the retina. Ho et al. demonstrated by digital ICG videoangiography that there is a delayed onset of intraocular cystoid pooling of ICG dye occurring between 14 and 34 minutes after
injection in some patients with occult CNV. Furthermore, work by Peyman et al. on rabbits showed that no effective lesions were noted when TTT followed ICG pretreatment by less than 1 minute or more than 7 minutes. We chose to begin our treatment 5 minutes after the ICG dye injection. We believe it should not be delayed any further to maximize ICG concentration effect and to avoid further damage to the retina from ICG that leaks out from CNV.

On the other hand, delayed treatment may be preferred if there is indeed a preferential pooling of ICG within CNV compared to the rest of circulation. Costa et al. have developed a protocol that they call indocyanine-mediated thrombosis, using sequential ICG injection. They believe that the first ICG infusion acts as a loading dose that leads to ICG staining of the walls of CNV. The second infusion is given 20 minutes later and the laser treatment is performed 2 minutes following the second ICG infusion. They propose that laser uptake is preferentially occurring in those vessels that have been formerly “ICG loaded.” Obana et al. used ICG bolus injection followed by continuous infusion. The rationale for continuous infusion was based on their observation that there was a wide variation in intravascular ICG concentration among patients after bolus injection. However, the continuous infusion of ICG maintained a steady plasma concentration for approximately 5 minutes. Larger studies are required to assess the efficacy of these variations.

The optimal TTT laser setting in the presence of ICG enhancement is unknown. Previous studies have shown that pretreatment with ICG reduces the power needed to create clinical and angiographic threshold lesions in pigmented and non-pigmented rabbits, and the authors concluded that it is related to the photosensitizing effect of ICG. Assuming that ICG may enhance the effect of the infrared diode laser, the power used in the TTT+ group was lowered by approximately one-third. We decreased the laser power from 800 mW for the TTT group to 500 mW for the TTT+ group, in hopes of avoiding potential and previously reported complications such as macular infarction, vascular occlusions, retinal pigment epithelial tears, and geographic atrophy. We did not encounter any adverse effects with this lowered laser setting, but it is possible that laser power reduction may have been too great and resulted in no apparent benefit of ICG enhancement. On the other hand, one-third reduction in power setting with ICG enhancement was at least as effective as TTT alone at a higher power setting.

Currently, TTT is applied to the CNV for 60 seconds. Based on studies with other photodynamic agents, a duration of 60 seconds may be sufficient to result in activation of ICG as a photosensitizer. Treatment is usually performed until no visible change or a slight graying of the retinal pigment epithelium is achieved. This end point can certainly be subjective and may result in overtreatment or undertreatment. Variable pigmentation and melanin concentration of the patient, as well as presence of subretinal hemorrhage or pigment clumping, will affect laser setting parameters. Ibarra et al. found that threshold power settings for visible lesions in albino rabbits were 10 times greater than in pigmented rabbits. The power settings required to produce threshold lesions in albino rabbits caused retinal temperature increases in pigmented rabbits that were 5 times higher than in the albino rabbits. Furthermore, temperature increases in albino rabbits were 1.5 times higher with subretinal blood than without blood.

We decided to treat all patients with settings similar to those for the TTT4CNV trial but watching carefully for any retinal discoloration. None of our patients had subfoveal hemorrhage prior to treatment. Even with identical laser settings within each group of patients, we did not encounter any retinal complications in our mostly homogeneous group of patients. However, we believe that more studies are needed to elucidate the most optimal power and duration settings based on the fundus pigmentation of the patient and the type of lesion being treated.

Furthermore, the optimal ICG dose needs to be considered. The maximum recommended human dose is 5 mg/kg. In our study, we chose 0.5 mg/kg to avoid potential retinal complications secondary to possible ICG-enhanced photosensitivity, as well as the volume of ICG that needed to be infused in a bolus fashion. Reichel et al. had used 25 to 50 mg of bolus ICG in their study. Costa et al. used 1.5 mg/kg of ICG in a 2.5-mL bolus, followed by a 5-mL saline flush.

Finally, it is important to note that Peyman et al.’s histologic specimens of pigmented and non-pigmented rabbits that received threshold TTT fluences showed full-thickness retinal damage with or without ICG enhancement. Their results suggest that visible funduscopic or angiographic lesions after TTT in humans...
may also represent damage of the overlying retina. A slight graying of the retinal pigment epithelium may actually result in significant full-thickness retinal damage. Therefore, it is important to select a treatment parameter that will not result in any visible retinal discoloration. It is unclear whether TTT with ICG enhancement will allow use of reduced fluence and limit retinal damage, yet result in treatment of CNV. Further studies on methods to enhance selective damage to CNV with reduced energy delivery to the surrounding tissues are needed.

Obstacles to using TTT or ICG as a photosensitizing enhancer for TTT include lack of an objective and consistent end point in treatment. Several authors have published reports on possible methods of accurately titrating TTT by measuring choroidal temperature.21-24 Methodologies currently under investigation include focal electoretinography, microthermocouple, magnetic resonance imaging, and thermosensitive liposomes. Each of the aforementioned modalities has potential but is not currently clinically applicable.

Our study, despite its inherent weaknesses of small sample size and failure to show benefit of the TTT+ group, at least has shown that TTT with ICG dye enhancement can be as safe and efficacious as TTT alone, even with a lower laser power setting. Better methods of monitoring the end point to individualize treatment parameters, which may be strongly influenced by the patient's fundus pigmentation and the type of lesion being treated, and elucidating the safest and most effective treatment protocol using ICG will require further studies.

REFERENCES

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