Transpupillary Thermotherapy for Subfoveal Occult Choroidal Neovascularization: Effect on Ocular Perfusion

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Purpose. To perform a descriptive analysis of the effects on ocular blood flow of transpupillary thermotherapy (TTT) for occult subfoveal choroidal neovascular membranes (CNVMs) in age-related macular degeneration (AMD).

Methods. Eleven subjects with occult subfoveal CNVM due to AMD were assessed in a masked fashion by color Doppler imaging (CDI) within 24 hours before, 24 hours after, and 1 month after undergoing TTT.

Results. In the posterior ciliary arteries (PCAs), there were no statistically significant changes observed in the peak systolic velocity (PSV), end diastolic velocity (EDV), or resistive index (RI) at 24 hours. At 1 month, the mean EDV decreased 36% ($P = 0.0105$) and the mean RI increased 3.8% ($P = 0.0305$) in the nasal PCA. Although there was a similar trend in the temporal PCA, the differences did not reach statistical significance. In the central retinal artery (CRA), the mean PSV decreased 16% ($P = 0.0137$), and the mean EDV decreased 21% ($P = 0.0222$) at 24 hours after treatment. There were no statistically significant differences in the CRA blood flow indices at 1 month after treatment. In the ophthalmic artery, there were no statistically significant differences observed in the mean PSV, EDV, or RI at 24 hours or 1 month after treatment.

Conclusions. TTT is associated with transiently decreased volumetric blood flow in the retinal circulation 24 hours after treatment. In the posterior ciliary arteries that supply the choroid, there were no changes observed at 24 hours, but at 1 month, there was a decrease in the mean EDV and an increase in the RI in the nasal and temporal PCAs, reaching statistical significance in the nasal PCA only. This study suggests that TTT could lead to alterations in choroidal blood flow, as assessed by CDI. Further study is warranted. (*Invest Ophthalmol Vis Sci.* 2001;42:3337–3340)

Transpupillary thermotherapy (TTT) is a laser photocoagulation protocol characterized by large-spot, long-pulse, and low-irradiance infrared (810 nm) laser exposure. TTT has been used to successfully treat occult subfoveal choroidal neovascular membranes (CNVMs) in age-related macular degeneration (AMD).[1] In this application, TTT is administered as subthreshold photocoagulation with no visible endpoint and no ophthalmoscopically apparent chorioretinal change, which has been observed to result in closure of CNVM and resorption of intraretinal and subretinal fluid, with little or no damage to the overlying retina. In an uncontrolled retrospective series of 16 eyes of 15 patients undergoing TTT for occult subfoveal CNVM, 94% of the eyes showed decreased exudation on fluorescein angiography, and no eyes showed any deleterious effects.[1] A multicenter randomized prospective clinical trial is currently in progress. The mechanism of action of TTT, however, is currently unclear. One possible mechanism includes thermally induced changes in ocular blood flow.

In this study, we evaluated the ocular blood flow in subjects before and after they underwent TTT to descriptively analyze the effect of TTT on ocular perfusion. Eleven subjects with occult subfoveal CNVM were assessed by color Doppler imaging (CDI) within 24 hours before, 24 hours after, and 1 month after undergoing TTT. This ocular perfusion assessment before and after TTT has not been performed previously. It should be noted that this study was not designed to assess the efficacy of TTT; this is under evaluation in a large, prospective, randomized trial, as discussed earlier.

Methods

Study Subjects

Study subjects were eligible for inclusion if they showed exudative macular degeneration, defined according to the International Classification System[2] as a degenerative disorder in patients more than 50 years of age with "RPE and associated neurosensory retinal detachment, (peri)retinal hemorrhages, or (peri)retinal fibrosis on masked analysis of fundus photographs or evidence of choroidal neovascularization on fluorescein angiography." Only subjects who had predominantly occult subfoveal CNVM, defined according to the Macular Photocoagulation Study[3] as a fibrovascular pigment epithelial detachment or as late leakage of undetermined source were deemed eligible for the study. The study protocol adhered to the tenets of the Declaration of Helsinki, and color Doppler assessment of ocular blood flow in AMD was approved by the IRB at Indiana University.

Subjects were deemed ineligible if they had a history of diabetic retinopathy, ophthalmic or retinal artery occlusion, retinal vein occlusions, hypertensive retinopathy, choroidopathy, or known history of significant carotid stenosis. In addition, no subjects were using warfarin at the time of the study and no subject had a history of vasculitis. Additional exclusion criteria for both study and control subjects included glaucoma, optic neuropathy, macular dystrophies, ocular inflammatory disease, retinal detachment, or media opacity sufficient to preclude examination and follow-up. In addition, subjects were excluded if they were unable to give informed consent or had a history of allergy to fluorescein, radiographic dyes, shellfish, or iodine.

Eligible subjects were asked to sign an informed consent before undergoing angiography, CDI, and TTT. Each subject was evaluated before and after TTT to compare pretreatment with posttreatment CDI measurements to evaluate the short-term longitudinal effect on ocular

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perfusion. In particular, 11 subjects with occult subfoveal CNVM were assessed by CDI within 24 hours before, 24 hours after, and 1 month after undergoing TTT. The pretreatment CDI measurements therefore functioned as a baseline control, with which the posttreatment CDI measurements were compared in a longitudinal fashion.

Color Doppler Imaging

A CDI system (Quantum 2000; Siemens Quantum, Inc., Issaquah, WA) with a 7.5-MHz linear probe was used to perform all measurements. This system analyzes a sample of pulsed Doppler signal from within a small sample volume (1.2 × 1.2 mm) to calculate blood flow velocities. Ultrasonographic evaluation was performed by an experienced ultrasonographer who was masked to each subject's treatment status.

The evaluation was initiated with a CDI of the optic nerve, which provides the most useful landmark for the identification of the several retrobulbar vessels. The ophthalmic artery (OA) is situated either above or below the optic nerve in the posterior orbit, before passing forward in the nasal orbit in a horizontal plane slightly superior to that of the optic nerve. This vessel was examined approximately 25 mm behind the globe in the straighter portion of the vessel in the nasal orbit where the most reliable results are obtained. The central retinal artery (CRA) is detectable within the retrolaminar portion of the optic nerve for approximately 10 mm. In this region the vessel maintains a straight course and angle-of-incidence corrections may readily be applied. Together with the central retinal vein, the artery yields a band of blue and red pixels within the optic nerve shadow, at an angle approximately 15° to the anteroposterior meridian. This technique was consistently applied to both the control and study subjects to evaluate these vessels. The short posterior ciliary arteries (PCAs) commence as trunks approximately 10 to 20 mm behind the globe. It is at this point, before these vessels form multiple branches surrounding the optic nerve in its retrobulbar portion, that operator detection is most reproducible, and this area was consequently chosen as a CDI study locus. It is possible to identify and reliably assess the nasal and temporal posterior ciliary vessels, and these vessels were therefore studied in all subjects.

In each vessel, PSV and EDV were calculated from the Doppler signal. PSV refers to the highest blood flow velocity achieved during systole and is calculated from the frequency of the peak in the Doppler-shifted waveform. EDV refers to the lowest velocity occurring during diastole and is calculated for the frequency of the trough in the waveform. In addition, the Pourcelot resistance index (RI), a measure of peripheral vascular resistance, was calculated for each vessel. RI is calculated as: RI = (PSV − EDV)/PSV. Paired *t*-tests were used to compare PSV, EDV, and RI in each vessel before and after treatment.

Transpupillary Thermotherapy

TTT was delivered through a slit lamp using an infrared (810 nm) diode laser photocoagulator with a beam diameter adjustable from 0.5 to 3.0 mm (IRIS Medical OcuLight SLx; Iridex Corp, Mountain View, CA). A standard Goldmann-type fundus contact lens, antireflective (AR)-coated for use with the diode laser, was placed on the eye after topical anesthesia with 0.5% proparacaine. Continuous observation through the slit lamp was maintained to ensure fixation and the absence of ophthalmoscopically apparent chorioretinal change during treatment.

Treatment was initiated with one 3.0-mm diameter spot for a 60-second duration and a power setting of 800 mW. If a retinal color change was observed, treatment was immediately stopped and restarted at a reduced power setting (20% decrements) to complete the full 60-second treatment. In general, there was no color change seen as a treatment endpoint, or there was a barely detectable light-gray appearance to the lesion.

Results

Eleven subjects with occult subfoveal CNVM were included in the study. Table 1 summarizes the demographics of the study population. In brief, all subjects were white, three were men and eight were women, and the mean age was 78 years. All patients were assessed by CDI within 24 hours before, 24 hours after, and 1 month after undergoing TTT. Table 2 summarizes the results. Overall, there were statistically significant differences in the retrobulbar blood flow indices in the CRA at 24 hours and in the nasal PCA at 1 month.

Table 1. Demographics

Parameter	
Number of patients	11
Race	White
Mean age (y)	78 ± 8*
Gender	Eight women, three men
Cigarette-smoking history	Nine never smoked; two with a prior history of smoking
History of hypertension	Seven with hypertension treated with medication
Average systolic blood pressure (mm Hg)	150 ± 18*
Average diastolic blood pressure (mm Hg)	77 ± 9.9*
Pulse (beats/min)	72 ± 10*
Average intraocular pressure (mm Hg)	16 ± 4*
Fellow-eye status	Eight with nonexudative AMD, three with exudative (two predominantly occult, one mixed-classic and occult)

* Mean ± SD.

In particular, in the posterior ciliary arteries, which supply the choroid, there were no statistically significant changes observed in the PSV, EDV, or RI at 24 hours. At 1 month, however, statistically significant changes were noted. In particular, the mean EDV in the nasal PCA measured 2.254 ± 0.723 cm/sec before treatment, compared with 1.440 ± 0.092 cm/sec 1 month after treatment, yielding a 36% decrease ($P = 0.0105$). The PSV was not significantly altered in the nasal PCA at 1 month after treatment. The mean RI in the nasal PCA measured 0.730 ± 0.063 cm/sec before treatment, compared with 0.758 ± 0.044 cm/sec 1 month after treatment, yielding a 3.8% increase ($P = 0.0305$). Although there was a similar trend in the temporal PCA, the differences did not reach statistical significance.

In the CRA, the mean PSV measured 9.208 ± 1.974 cm/sec 24 hours before treatment and 7.689 ± 1.418 cm/sec 24 hours after treatment, yielding a 16% decrease, which was statistically significant ($P = 0.0137$). The mean EDV in the CRA measured 2.117 ± 0.690 cm/sec before treatment compared with 1.681 ± 0.477 cm/sec at 24 hours after treatment, yielding a 21% decrease ($P = 0.0222$). There was no statistically significant difference in the CRA RI at 24 hours after treatment. Consequently, this concurrent decrease in the PSV and EDV at a constant RI implies decreased volumetric blood flow in the CRA at 24 hours after treatment. This decrease was not sustained, however; there were no statistically significant differences in the CRA blood flow indices at 1 month after treatment.

In the ophthalmic artery, there were no statistically significant differences observed in the mean PSV, EDV, or RI at 24 hours or 1 month after treatment.

Discussion

TTT involves slowly heating the subfoveal choroidal neovascular complex with infrared (810 nm) diode laser light to cause

TABLE 2. Velocity and RI Measures

Measure	Orbital Artery	Before TTT	After TTT	*P*
Twenty-four hours after TTT				
PSV (cm/sec)	OA	23.520 ± 3.770	24.859 ± 3.621	0.314
	CRA	9.208 ± 1.974	7.689 ± 1.418	0.013*
	NPCA	8.524 ± 2.002	8.370 ± 2.139	0.471
	TPCA	7.746 ± 2.718	8.330 ± 1.515	0.379
EDV (cm/sec)	OA	4.618 ± 1.686	4.113 ± 1.469	0.593
	CRA	2.117 ± 0.690	1.681 ± 0.477	0.022*
	NPCA	2.254 ± 0.723	2.040 ± 1.055	0.463
	TPCA	2.221 ± 0.643	2.093 ± 0.284	0.072
RI	OA	0.801 ± 0.073	0.831 ± 0.057	0.061
	CRA	0.770 ± 0.052	0.781 ± 0.037	0.122
	NPCA	0.730 ± 0.063	0.756 ± 0.098	0.688
	TPCA	0.703 ± 0.077	0.742 ± 0.056	0.221
One month after TTT				
PSV (cm/sec)	OA	23.520 ± 3.770	30.333 ± 11.141	0.115
	CRA	9.208 ± 1.974	8.308 ± 2.577	0.348
	NPCA	8.524 ± 2.002	6.084 ± 0.825	0.059
	TPCA	7.746 ± 2.718	6.463 ± 2.540	0.294
EDV (cm/sec)	OA	4.618 ± 1.686	5.875 ± 1.207	0.350
	CRA	2.117 ± 0.690	1.554 ± 0.453	0.078
	NPCA	2.254 ± 0.723	1.440 ± 0.092	0.011*
	TPCA	2.221 ± 0.643	1.760 ± 0.471	0.171
RI	OA	0.801 ± 0.073	0.790 ± 0.071	0.449
	CRA	0.770 ± 0.052	0.805 ± 0.043	0.232
	NPCA	0.730 ± 0.063	0.758 ± 0.044	0.031*
	TPCA	0.703 ± 0.077	0.713 ± 0.064	0.659

Data are mean ± SD. OA, ophthalmic artery; CRA, central retinal artery; NPCA, nasal posterior ciliary artery; TPCA, temporal posterior ciliary artery.

* Statistically significant.

occlusion of the CNVM. Treatment is performed with a large single spot that covers the entire complex. The infrared wavelength is thought to penetrate the retina and RPE to maximally affect the CNVM, while minimizing thermal injury to the outer retina. The mechanism of action of TTT, however, is currently unclear. One possible mechanism involves thermally induced changes in ocular blood flow, both globally and locally. Several studies have demonstrated perfusion abnormalities in AMD, including delayed choroidal filling, using conventional angiographic techniques.[4–6] Delayed choroidal filling may have histologic significance, because it may correlate with diffuse thickening of Bruch's membrane.[7] This sign also has functional significance, because eyes with this symptom harbor discrete areas of increased threshold on static perimetry[8] and are at risk for loss of vision.[9] Recently, new technologies have been used to corroborate the existence of choroidal perfusion anomalies in AMD, including laser Doppler flowmetry,[10] CDI,[11–13] and indocyanine green (ICG) angiography.[14,15] The role of these ocular perfusion changes in the pathogenesis of AMD is unclear.[16]

The present study revealed statistically significant differences in the retrobulbar blood flow indices in the CRA at 24 hours and in the nasal PCA at 1 month. In the CRA, there was a concurrent decrease in the PSV and EDV at a constant RI, implying decreased volumetric blood flow in the CRA at 24 hours after treatment. This decrease was not sustained, however, at 1 month after treatment. As noted, the infrared wavelength of TTT is absorbed maximally by the deep choroidal tissues and minimally by the retina. Consequently, it is unclear whether this transient alteration in retinal blood flow represents an unanticipated direct effect on the retinal circulation or a secondary autoregulatory process by the retinal circulation.

In the posterior ciliary arteries, which supply the choroid, there were no changes observed at 24 hours, but at 1 month, there was a decrease in the mean EDV and an increase in the RI in the nasal and temporal PCA, reaching statistical significance in the nasal PCA only. It is possible that a larger sample size would have led to statistical significance in the temporal PCA as well. Alternatively, it is possible that there is regulatory shunting of blood from the nasal to the temporal choroid in response to TTT, leading to preferential alterations in the nasal choroidal circulation.

The mechanism by which TTT leads to alterations in choroidal blood flow is unclear. However, if TTT leads to complete or partial occlusion of occult CNVM, choriocapillaris, or both, then an increase in the RI would be expected. Unfortunately, it is difficult to accurately assess blood flow through the CNVM, before and after TTT, for several reasons. In particular, it is very difficult to quantify choroidal blood flow angiographically, given the overlying retinal and multilayered choroidal circulations that complicate analysis. In addition, the limited sample size of this study prevents meaningful analysis of the angiograms with respect to perfusion of the occult CNVM and choriocapillaris. Although this study suggests that TTT can lead to alterations in choroidal blood flow, which may be consistent with complete or partial occlusion of occult subfoveal CNVM as suggested by other investigators,[1] further study is warranted.

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