

CLINICAL SCIENCE

The effects of dorzolamide on choroidal and retinal perfusion in non-exudative age related macular degeneration

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Aim: To comprehensively evaluate the effects of dorzolamide on the choroidal and retinal circulation in patients with age related macular degeneration (AMD).

Methods: In this randomised, double masked, parallel study, 36 non-exudative AMD patients were randomised in a 2 to 1 fashion to placebo versus topical dorzolamide and underwent assessment of their choroidal and retinal circulation. Scanning laser ophthalmoscope indocyanine green angiograms (ICGA) were analysed by a new area dilution analysis technique. Four areas in the perifoveal region and two areas in the temporal peripapillary region were evaluated by plotting intensity of fluorescence of each area over time. The means of the choroidal filling times and the heterogeneity of the filling times were assessed. Scanning laser ophthalmoscope fluorescein angiography (FA) was evaluated for retinal arteriovenous passage (AVP) times by plotting intensity of fluorescence of retinal vessels over time. Assessment was performed at baseline and at 4 months.

Results: Compared to placebo, AMD patients treated with dorzolamide showed a significantly increased rapidity of choroidal filling in the superior and inferior peripapillary regions ($p=0.007$, $p=0.02$, respectively). No significant difference in choroidal filling times was found in any of the perifoveal areas ($p=0.9$). Also, on FA assessment, treatment with dorzolamide showed no statistical differences in AVP times ($p=0.19$).

Conclusions: Dorzolamide may increase peripapillary choroidal perfusion in non-exudative AMD patients. Further studies are merited.

The pathogenesis of age related macular degeneration (AMD), the leading cause of irreversible visual loss in the United States, remains elusive. Several theories have been proposed and these include primary retinal pigment epithelium (RPE) senescence,^{1,2} genetic defects such as ABCR gene mutations (which encodes retinal rod photoreceptor protein),³ and primary ocular perfusion abnormalities.⁴ Several previous studies demonstrated ocular perfusion abnormalities in AMD.^{5–14} It is unclear if these choroidal perfusion abnormalities can be affected pharmacologically. In the current study, new analysis techniques were applied to indocyanine green angiography (ICG) and fluorescein angiography (FA) to objectively evaluate the effect of dorzolamide on choroidal and retinal perfusion in subjects with non-exudative AMD.

METHODS

Study subjects

Study subjects were eligible for inclusion if they showed non-exudative macular degeneration, defined according to the international classification system as a degenerative disorder in patients older than 50 years with "soft drusen greater than 63 microns, hyperpigmentation and/or hypopigmentation of the RPE, . . . or geographic atrophy of the RPE."¹⁵ Exclusion criteria included exudative macular degeneration in the study eye defined according to the international classification system as the presence of "RPE and associated neurosensory retinal detachment, (peri)retinal hemorrhages, or (peri)retinal fibrosis on masked analysis of fundus photos or evidence of choroidal neovascularisation (CNV) on fluorescein angiography."¹⁵ In subjects with non-exudative AMD bilaterally, the eye with the best corrected visual acuity was chosen as the study eye, in order to maximise fixation during angiographic analysis.

Exclusion criteria for study 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. The institutional review board of the Indiana University School of Medicine approved all protocols. Thirty six AMD patients were randomised in a 2 to 1 fashion to placebo versus topical dorzolamide (Trusopt) 2% three times a day. They were randomised in this manner in order to ensure sufficient material to develop a data set for the untreated AMD population for additional study in the future. All assessments were performed at baseline and at 4 months.

Ophthalmic evaluations

In all subject, intraocular pressure was measured by Goldmann tonometry. Fluorescein angiography was performed before study entry on all subjects to rule out evidence of CNV.

ICG angiography

ICG angiography was performed with the scanning laser ophthalmoscope (Rodentstock SLO 101) at baseline and at 4 months. Red-free images were first obtained with a 488 nm argon laser at 40° to locate the macula relative to the optic disc. The argon laser was shut down, and a 795 nm near infrared laser was used to perform the angiogram. The ICG was prepared by dissolving 25 mg of ICG into 2 ml of solvent and 1 ml of this solution was then injected per examination. The small volume of dye allows a rapid injection time of less than

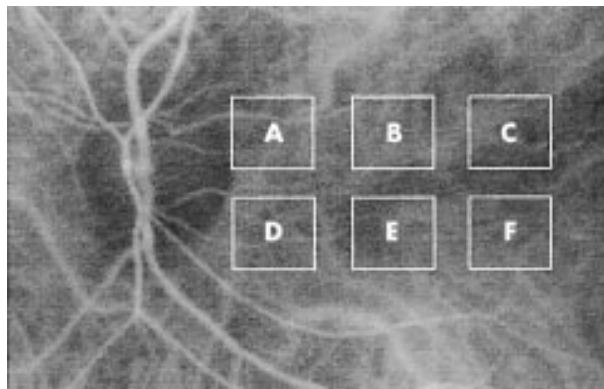


Figure 1 ICG area dilution analysis. A 40 degree indocyanine green choroidal angiogram using scanning laser ophthalmoscopy. Six locations, each a 6° square, on the image are identified for area dilution analysis. A and D for peripapillary choroid and B, C, E, and F for macular area.

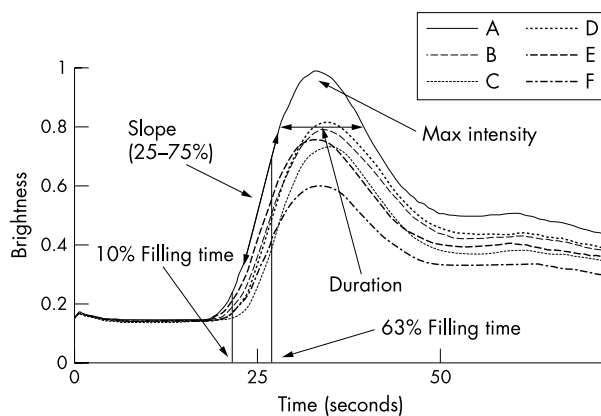


Figure 2 ICG area dilution analysis: haemodynamic parameters in area dilution analysis of indocyanine green choroidal angiography using scanning laser ophthalmoscopy. Area dye dilution analysis identifies five parameters from the brightness maps: 10% filling time, 36% filling time, the slope of each curve, the duration of the each curve, and the maximum intensity of brightness. The 10% and 36% filling time (seconds) is the amount of time required to reach a brightness 10% and 36% above baseline. The slope (arbitrary unit: intensity/s) is calculated by dividing the intensity change by the time lapsed between 25% and 75%. The duration (seconds) is the time between 75% in the ascending and descending curves.

1 second. The injection is immediately followed by a 2 ml saline flush. Verbal commands were used to guide subject fixation so that the nasal edge of the disc was at the edge of the video frame centred vertically and the macula towards the centre of the screen. The examination was recorded on S-VHS video tape and processed off line.

S-VHS recordings of ICG angiograms were digitised using a Scion Imaging frame grabber with customised Scion Image software (Scion Corporation, Frederick, MD, USA), running on a Mac G4 image processing workstation. Every eighth image was opened resulting in an analysis temporal resolution of 3.75 images per second. Area dilution analysis has been described in detail in the literature.⁶ Six locations, each a 6° square, were identified for analysis (Fig 1). Four areas around the fovea and two areas in the temporal peripapillary retinal area were evaluated. The average brightness of the area contained in each box was computed for each frame of the angiogram. Area brightness was plotted with time on the x axis and brightness on the y axis (Fig 2). A red-free image was used to identify the precise location of the macula. Transparent screen overlays were used to ensure consistent sample

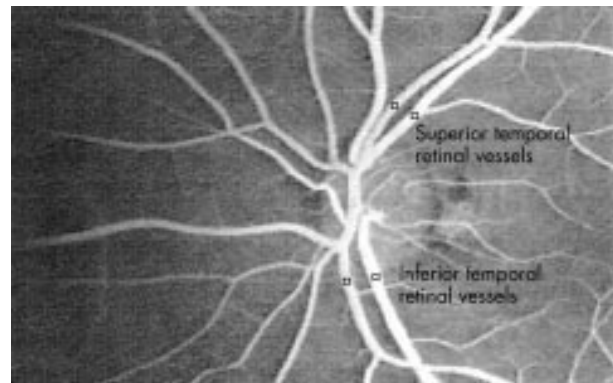


Figure 3 FA assessment of arteriovenous passage (AVP) time. AVP time, analogous to mean circulation time, can be computed by comparing the times of dye arrival at the measuring point on the artery with that on the vein.

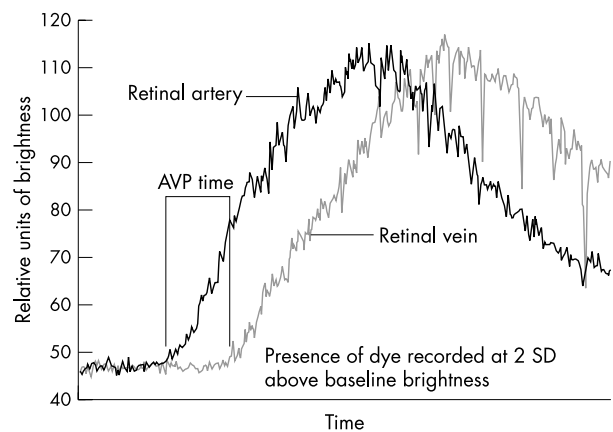


Figure 4 FA assessment of arteriovenous passage (AVP) time. The brightness of the dye within the analogous artery and vein can be plotted over time. The presence of dye recorded at two standard deviations above baseline brightness is used as a reference point to calculate the AVP time.

window placement to confirm that the same area of tissue was analysed between visits.

Intensity curves were analysed by quantifying the dye arrival times (amount of time required to rise to 10% and 63% above baseline), the slope of the filling portion of the curves, and the duration of fluorescence at 70% maximum and beyond (Fig 2). The slope correlates with the speed of blood entrance into the choroid. Each haemodynamic parameter can be evaluated by performing individual area analysis, mean analysis of the four perifoveal or six total areas, and analysis of the regional spread (maximum minus minimum) to determine haemodynamic homogeneity.

The average fluorescence within six areas of the choroid was measured. The brightest point of all six slopes was set to 1, normalising the curve so that the slope was dependent on how fast the dye arrived in the eye and eliminated the contribution of disruptions in optical qualities. Dye dilution curves were then created (average brightness versus time) and used to determine the 10% and 63% (tau) times, the slopes of each curve, and the duration time of the dye within the choroid. Duration was estimated by the amount of time that the curve exceeds 70% of total brightness. Each parameter from each individual curve was compared by a paired *t* test. The results from each of the six areas were averaged to determine the mean. Further, the two areas near the disc, and the four areas surrounding the fovea were averaged for comparison of peripapillary and perifoveal choroidal haemodynamics.

Table 1 Demographics

Characteristic	Treated	Placebo
Number	5	12
Mean age (years)	75 (8)	78 (6.4)
Sex (male/female)	2/3	8/4
Systolic blood pressure (mm Hg)	141 (9)	132 (19)
Diastolic blood pressure (mm Hg)	79 (10)	74 (8)
Pulse (bpm)	71 (10)	70 (4)

Fluorescein angiography

Fluorescein angiography (Fig 3) can be analysed to obtain retinal haemodynamic measurements such as arteriovenous passage (AVP) time. AVP time, analogous to mean circulation time, can be computed by comparing the times of dye arrival at the measuring point on the artery with that on the vein. Only with high temporal resolution (0.03 seconds) could AVP be performed. The brightness of the dye within the analogous artery and vein can be plotted over time. The presence of dye recorded at two standard deviations above baseline brightness is used as a reference point to calculate the AVP time (Fig 4). AVP times were assessed at baseline and at 4 months.

Statistical analysis

Unpaired *t* tests were used to compare demographic and haemodynamic parameters between the treatment and

control groups. Paired *t* tests were used to compare between haemodynamic parameters at baseline and 4 months.

RESULTS

Thirty six AMD patients were randomised in a 2 to 1 fashion to placebo versus topical dorzolamide and underwent assessment of their choroidal and retinal circulation. Approximately half of the subjects in each group could not maintain adequate fixation for analysis. The demographics of the subjects who underwent complete analysis are summarised in Table 1. The mean age of the 12 untreated controls was 78 (SD 6.4) years and the mean age of the five dorzolamide treated subjects was 75 (SD 8) years, with no statistically significant difference. There were also no statistically significant differences in blood pressure or pulse.

Using the ICGA analysis technique, the effect of dorzolamide on the choroidal blood circulation (Tables 2 and 3) were assessed. Compared to the control group ($n=9$), patients treated with dorzolamide ($n=5$) showed increased rapidity of filling in the superior peripapillary region (area A, 124.5% increase, $p=0.0066$), and in the inferior peripapillary region (area D, 43.3% increase, $p=0.0206$). The overall peripapillary region combining the superior and inferior regions showed a significant increase of 83.9% ($p=0.0015$). In the four individual perifoveal regions, there were no significant difference in the rapidity of filling: with *p* value of 0.9, 0.6, 1.0, and 0.9 for area B, C, E, and F, respectively. In the total perifoveal

Table 2 ICG area dilution analysis results: peripapillary choroidal circulation

Area	Treatment (number of subjects)	Mean change of slope (%)	Standard error	<i>p</i> Value
A	Placebo (9)	-9.706	21.845	-
A	Dorzolamide (5)	124.523	38.994	0.0066
D	Placebo (9)	-19.667	11.104	-
D	Dorzolamide (5)	43.343	25.176	0.0206
Peripapillary area	Placebo (9)	-14.687	16.016	-
Peripapillary area	Dorzolamide (5)	83.933	13.810	0.0015

Table 3 ICG area dilution analysis results: perifoveal choroidal circulation

Area	Treatment (number of subject)	Mean change of slope (%)	Standard error	<i>p</i> Value
B	Placebo (12)	7.979	33.164	-
B	Dorzolamide (5)	14.302	25.999	0.9096
C	Placebo (11)	41.396	44.319	-
C	Dorzolamide (5)	4.197	21.919	0.5955
E	Placebo (12)	21.851	23.163	-
E	Dorzolamide (5)	21.801	20.996	0.9990
F	Placebo (11)	-2.833	29.368	-
F	Dorzolamide (5)	-7.984	29.368	0.9103
Total perifoveal area	Placebo (12)	13.301	27.209	-
Total perifoveal area	Dorzolamide (5)	8.079	7.241	0.9054

Table 4 FA analysis results

Area	Treatment (number of subject)	Mean AVP time (s)	Standard error	<i>p</i> Value
Superior temporal	Placebo (12)	2.048	8.115	-
Superior temporal	Dorzolamide (5)	-20.937	19.327	0.2081
Inferior temporal	Placebo (12)	-0.464	10.261	-
Inferior temporal	Dorzolamide (5)	-18.972	17.627	0.3574
Combine superior and inferior	Placebo (12)	0.074	6.334	-
Combine superior and inferior	Dorzolamide (5)	-20.546	18.111	0.1884

area (combination of area B, C, E, and F), neither dorzolamide nor placebo significantly altered the rapidity of filling time with no significant difference between the two ($p=0.9054$).

To study the haemodynamic of the retinal blood flow, FA was utilised to assess the effect of dorzolamide on the AMD patients (Table 4). Compared to the placebo group ($n=12$), subjects treated with dorzolamide ($n=5$) showed no statistically significant decrease in AVP times: 20.9% decrease in AVP time in the superior temporal vessels ($p=0.2081$) and 19.0% decrease in the inferior temporal vessels ($p=0.3574$).

DISCUSSION

In this study, which partially addresses the heterogeneous nature of AMD by specifically excluding patients with exudative AMD, new analysis techniques were applied to ICG and fluorescein angiography to objectively evaluate the effects of dorzolamide on choroidal and retinal perfusion in subjects with non-exudative AMD compared with placebo. These techniques have been previously described.^{16,17} In brief, the entire 40 degree ICG angiogram is divided into a number of small regions (Fig 1) and dilution curves (Fig 2) are created for each region. Although the exact concentration of ICG in each region cannot be determined, simultaneous acquisition of dye dilution curves from these regions within the choroid facilitates comparison of relative concentrations between these regions. Since the six analysis regions are identically positioned on each subject's angiogram, the resulting analysis represents a very objective evaluation of choroidal perfusion characteristics and does not rely on subjective assessment. In addition, ICG facilitates study of the choroidal circulation for several reasons. Firstly, ICG better delineates the choroidal circulation than fluorescein because the near infrared light absorbed by ICG penetrates the RPE better than the shorter wavelength absorbed by fluorescein. Also, unlike fluorescein, ICG is strongly bound to plasma proteins, which prevents diffusion of the compound through the fenestrated choroidal capillaries, and permits better delineation of choroidal details. The use of scanning laser ophthalmoscopy for ICG angiography further improves the technique as the confocal design eliminates scattered and reflected light, while the single spot laser illumination improves contrast.

As noted previously, previous studies have suggested choroidal perfusion abnormalities in AMD using conventional angiographic techniques. For example, delayed choroidal filling has been noted angiographically in patients with exudative AMD.⁵⁻¹⁰ More recently, newer technologies have also been employed to corroborate the existence of choroidal perfusion anomalies in AMD. One group used laser Doppler flowmetry in subjects with non-exudative AMD to show that the choroidal blood flow was decreased at the centre of the fovea compared to a control group.¹¹ Colour Doppler imaging has also been used to evaluate the retrobulbar vasculature in AMD; two groups have found statistically significant differences in the central retinal and posterior ciliary arteries in patients with AMD compared to controls.^{12,13} Pulsatile ocular blood flow has been shown to differ in AMD subjects compared to normal subjects.¹⁴ Another group recently used a new analysis technique based on indocyanine green angiography to compare the choroidal circulation in patients with AMD to a control group, and noted a statistically significant increased frequency of presumed macular watershed filling, which they described as "characteristic vertical, angled, or stellate shaped zones of early phase indocyanine green videoangiographic hypofluorescence, assumed to be hypoperfusion, which disappeared in the early phase of the angiogram."¹⁸ More recently, a study by our group, using the ICG area dilution analysis technique, has shown that subjects with non-exudative AMD exhibit significant delay and heterogeneity of filling within the perifoveal region compared to normal age matched controls.¹⁸ These differences were most

pronounced in the perifoveal regions, suggesting that the choroidal perfusion anomalies in non-exudative AMD show some preferential involvement of the perifoveal choroid.¹⁹

The current study, using high speed ICGA and FA techniques, indicate that dorzolamide may increase peripapillary choroidal perfusion in non-exudative AMD patients compared to placebo. Other studies have suggested that topical dorzolamide can enhance ocular perfusion. In one study of 11 healthy subjects, dorzolamide hastened AVP time, and increased macular and superficial optic nerve head capillary transit velocities. It did not alter flow velocities or resistance indices in the retrobulbar vessels on colour Doppler imaging.²⁰ In another study involving subjects with normal tension glaucoma, dorzolamide significantly accelerated retinal arteriovenous passage time in the inferior temporal quadrant without altering the retrobulbar flow velocities.²¹ In the current study, the mechanism by which dorzolamide affected the peripapillary choroidal circulation is unknown. The significant difference demonstrated with the small sample of patients (dorzolamide $n=5$ versus placebo $n=12$) suggests that dorzolamide could preferentially enhance the choroidal perfusion of AMD patients. However, it is unclear if improving choroidal perfusion would lead to improved function in non-exudative AMD or delayed disease progression, and the results of this pilot study must be interpreted with caution. Further study is warranted.

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