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Photobiomodulation in the treatment of patients with non-center-involving diabetic macular oedema

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ABSTRACT

Purpose Far-red/near-infrared phototherapy or photobiomodulation (PBM) has recently been reported to be an effective and non-invasive treatment method to inhibit lesions of diabetic retinopathy (DR) in animals. This study investigated the safety and efficacy of PBM in diabetic patients to treat non-center-involving diabetic macular oedema (NCDME).

Methods This was a non-randomised, consecutive, case series, where 4 patients with type 2 diabetes with NCDME were treated for 160 s per day with PBM for 2–9 months. Demographic data including age, sex, HbA1c%, electronic ETDRS visual acuity, and retinal and macular thickness were measured using spectral domain ocular coherence tomography (SD-OCT) before and after treatment.

Results Four eyes of 4 patients were treated, with fellow eyes serving as untreated controls. Daily PBM treatment for only 80 s per treatment twice daily caused a significant reduction in focal retinal thickening in all 4 treated eyes. No adverse effects attributable to therapy were noted by the patients or study investigators during the study period.

Conclusions PBM potentially offers a non-invasive and cost-effective therapeutic option for patients with NCDME. Further studies of this therapeutic option in DR are warranted

INTRODUCTION

The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that thickening involving the centre of the macula was an important predictor of visual loss. Roughly 10% of eyes with untreated centre-involving diabetic macula oedema (CDME) lost 3 or more lines of visual acuity over a year.[1] Current treatment options for CDME include focal laser, intravitreal injections of antivascular endothelial growth factors, steroids and vitrectomy. These are effective, but have significant drawbacks in terms of cost and invasiveness.

Diabetics also can develop retinal oedema that does not impact vision because the centre of the macula is spared. This non-centred diabetic retinal oedema (NCDME) has been shown to progress to CDME in at least two important studies. The ETDRS reported that approximately 22% of subjects who demonstrated NCDME and assigned to deferral of laser photocoagulation progressed to CDME within 12 months.[1] Recently, the PKC-DMES group reported that about 33% of NCDME patients progressed to CDME in 1 year.[2] The current treatment for NCDME is observation. Since NCDME seemed a precursor to overt DME in a percentage of patients, NCDME appears to be a reasonable stage to test new therapeutic approaches to diabetic macular oedema (DME).

Our group reported that brief (4 min/day) treatment of diabetic animals with low-intensity far-red/near-infrared light, or photobiomodulation (PBM), inhibited lesions that contributed to diabetic retinopathy (DR).[3] This work also demonstrated that PBM was effective at inhibiting oxidative stress and local inflammatory changes that are believed to contribute to progression of DR.[3 4] In an effort to develop new therapies for DME, we investigated the ability of brief daily exposure of eyes to PBM to treat NCDME in diabetic patients.

METHODS

Study materials and patients

Study protocol and informed consent were approved by the IRB at the Stokes VA Hospital. Diabetic patients with NCDME were identified clinically and confirmed using spectral domain OCT (SD-OCT, Spectralis, Heidelberg). We defined NCDME as definite retinal oedema from DR within 3000 microns of the centre of the macula but not involving the centre determined by clinical exam and SD-OCT. Enrolled patients were required to have a central SD-OCT subfield of ≤225 microns. Minimal cut-offs for non-central SD-OCT subfield thickening were determined using the values from the DRCRnet Funpublished and published Protocol O data.[5]

Patients who received systemic or topical anti-inflammatory agents, intravitreal injections of steroids, antivascular endothelial growth factor/trap or focal laser within 3 months were excluded. Patients with vision <20/40, or inability to undergo the treatment, were also excluded. Demographic data was recorded. Eight eyes of four consecutive patients with NCDME were reported.

Photobiomodulation treatment

Patients were treated with PBM twice daily using light-weight, portable, battery-operated devices (Warp 10, Quantum Devices, Barneveld, WI/QBMI Photomedicine, Dodgeville, WI) (figure 1A and B). The devices were held an inch away from the closed treatment eye. After a duration of 80 s, the device automatically turned off. A delay timer prevented the device from being reactivated for several minutes. The device emitted a light of 670 nm, producing a dose of 25 Joules/cm^2 at 1 inch. The device itself does not produce any heat. Patients with two eligible eyes were randomly selected as to which was treated. Fellow eyes acted as controls. Treatment was applied for a minimum of 2 months with the patient having the option to continue for

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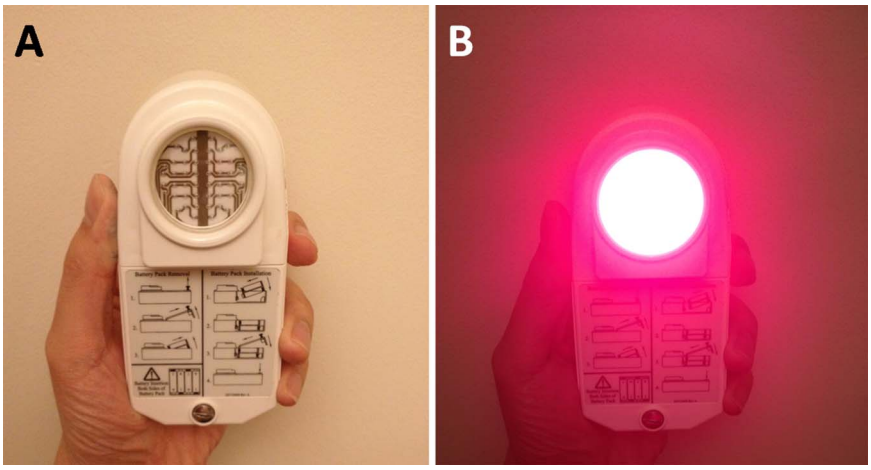

Figure 1 (A) Image of the device from the patient's viewpoint. Study participants were asked to hold the device an inch away from the closed study eye during use. The device was designed to shut off after 80 s. (B) Image of the device turned on and demonstrating that it was a lightweight, portable, battery-operated device that emits red coloured light of 670 nm. The device did not emit heat, and was completely cool to the touch.

up to 9 months. Three of the four patients elected to continue past 2 months.

Data analysis

Patients were analysed using SD-OCT, and thickness of the retina was displayed using Spectralis-generated colour thickness maps created by the Spectralis SD-OCT image analyser software (figure 2).The mean retinal volume per eye, generated by the Spectralis software, were not used in our analyses of NCDME, because those values represented average thicknesses across all SD-OCT subfields, whereas NCDME, when present, commonly accounted for only a tiny section of a particular subfield. Instead, the percent area of thickened retina across the macular region was determined by point-counting methods on the Spectralis-generated colour thickness map. A grid was overlaid on the SD-OCT colour map, and colour was determined at each of about 140 points across each macula. Each point was categorised as thickened (orange, orange-red, red) and not thickened (green, green-yellow). The percent of macular region that was thickened was determined for scan. Thicknesses pretreatment and post-treatment were compared.

Statistical methods

A paired sample t test analysis was run to assess changes from baseline in treated eyes. An α of $p<0.05$ was used to determine statistical significance.

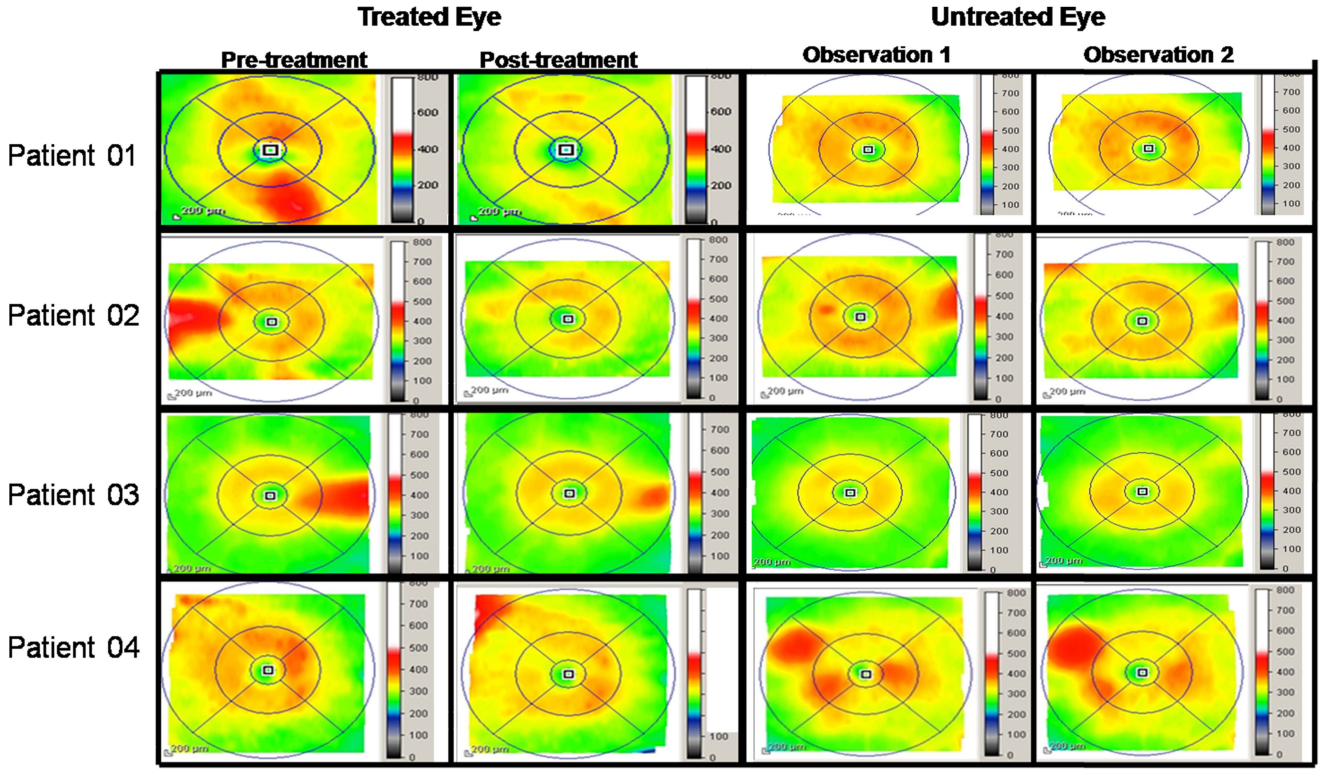

Figure 2 SD-OCT thickness colour map of each of our four study patients demonstrating pretreatment SD-OCT macular thickness and post-treatment macular thickness of the treated eye (first and second columns on the left, respectively). Fellow (untreated) eye data is demonstrated in the two columns on the right. Duration of PBM treatment of each of the patients at the time of these photos was 7, 7, 9 and 2 months, respectively.

Table 1 Demographics, visual acuity, HbA1c% and study duration

Patient	Age	Gender	HbA1c%	Eye	Pre-BCVA	Post-BCVA	Retinopathy	Treatment duration
1	42	M	7.4	OD	20/20	20/20	Severe NPDR	7 mo
2	69	M	6.5	OU	20/20;20/20	20/20;20/20	Severe NPDR	7.5 mo
3	71	M	7.4	OS	20/20	20/20	Mild NPDR	9 mo
4	63	M	7.1	OS	20/30	20/80	PDR	2 mo

HbA1c%, hemoglobin A1c; BCVA, best corrected visual acuity; M, male; mo, months; NPDR, nonproliferative diabetic retinopathy; OD, right eye; OS, left eye; PDR, proliferative diabetic retinopathy.

RESULTS

Demographic data is summarised in table 1. All patients were male, aged 42–71 years. No changes in treatment of the patient's systemic disease occurred. Average haemoglobin A1c% was 7.1, and did not vary significantly during study. Patient 4 had proliferative diabetic retinopathy treated with pan-retinal photocoagulation 4 years prior to study, and CDME treated 3 years prior to study with focal laser.

All patients demonstrated NCDME. PBM resulted in a significant reduction in macular thickening (figure 2, column 1 vs 2). Regions corresponding to thickened areas on SD-OCT were reduced by a mean of 20.0%±11.7% in all treated eyes. As a group, untreated fellow eyes showed no such improvement in retinal thickness with a mean change of −3.0%±8.0%, indicating a worsening effect.

During the study, Patient 4 developed sectoral optic nerve hyperaemia and oedema in the treated eye, consistent with non-arteritic ischaemic optic neuropathy (NAION). Laboratory work-up was negative, but even before our study, he had risk factors for NAION including diabetes, hypertension, and a small cup-to-disc ratio. His acuity decreased to 20/80 with trace-afferent pupillary defect, which returned to baseline with observation. Despite this, the patient demonstrated a significant reduction in NCDME in the PBM-treated eye. There was no such reduction in the untreated eye (figure 2, columns 3 and 4). No other adverse events were noted during the study.

CONCLUSIONS

The results of this series suggest that only 160 s per day of PBM caused a significant decrease in NCDME. Patients with NCDME, by definition, do not have oedema along the foveal centre, but evidence has indicated that a significant portion of patients with NCDME will progress to CDME within 1 year. Thus, successful reversal of NCDME likely will inhibit progression to more visually threatening CDME. One patient developed NAION, but we speculate that it was not related to PBM treatment. Additional patients will need to be studied to clarify this.

Our previous work demonstrated that PBM modulates pathways that might contribute to DME, including oxidative stress and inflammation.[3] Thus, PBM appears to have promise as an adjunct to inhibit retinal oedema. Additional benefits are that it requires only minutes per day, is cost effective and non-invasive. Future research along with a larger clinical trial is warranted on more patients to further explore the clinical usefulness of PBM therapy in DME and other lesions of DR.

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Competing interests None.

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REFERENCES

1 Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol* 1985;103:1796–806.
2 PKC-DMES Study Group. Effect of ruboxistaurin in patients with diabetic macular edema: thirty-month results of the randomized PKC-DMES clinical trial. *Arch Ophthalmol* 2007;125:318–24.
3 Tang J, Du Y, Lee CA, *et al*. Low-intensity far-red light inhibits early lesions that contribute to diabetic retinopathy: in vivo and in vitro. *Invest Ophthalmol Vis Sci* 2013;54:3681–90.
4 Tang J, Kern TS. Inflammation in diabetic retinopathy. *Prog Retin Eye Res* 2011;30:343–58.
5 Diabetic Retinopathy Clinical Research Network. Reproducibility of macular thickness and volume using Zeiss optical coherence tomography in patients with diabetic macular edema. *Ophthalmol* 2007;114:1520–5.

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