Lightmasks that prevent dark adaptation for non-central diabetic macular oedema: the CLEOPATRA RCT

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Scientific summary

The CLEOPATRA RCT

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Scientific summary

Background

Centre-involving diabetic macular oedema (DMO) is the most common cause of moderate visual loss in people with diabetes mellitus. Participants may present with non-central DMO and remain asymptomatic until the disease progresses to involve the centre or the DMO may develop de novo as centre-involving DMO. Approximately 8% of people with diabetes mellitus have centre-involving DMO and a further 8% have non-central DMO. As non-centre-involving DMO is asymptomatic, visual acuity measurement is not a useful option to monitor disease progression. Optical coherence tomography (OCT) is now the standard diagnostic tool to objectively locate and quantify DMO and assess response to treatment. The standard treatment options for people with visual impairment caused by centre-involving DMO are invasive and include repeated intravitreal injections of antivascular endothelial growth factor (anti-VEGF) agents, steroids or laser. There is an unmet need for non-invasive preventative and treatment options for non-central DMO to prevent potential visual morbidity caused by disease progression. Hypoxia may contribute to the development of macular oedema and diabetic retinopathy and 100% oxygen inhalation has been shown to alleviate DMO in the short term.

During dark adaptation, rod photoreceptors in the retina consume nearly all the oxygen available to the eye. In diabetes mellitus, where the retinal oxygen supply is compromised, the hypoxic status during dark may exacerbate the microvascular changes. As people only dark-adapt at night during sleep, sleeping in an environment illuminated with 500- to 505-nm light to suppress the rods may prevent or reverse DMO. A proof-of-concept study on 12 participants who slept at night using a mask containing a chemiluminescent source that exposed one eye only to light for 3 months showed that the treatment had no safety issues, was acceptable to participants and both colour vision and microaneurysm count improved (Arden GB, Gündüz MK, Kurtenbach A, Völker M, Zrenner E, Gündüz SB, *et al.* A preliminary trial to determine whether prevention of dark adaptation affects the course of early diabetic retinopathy. *Eye* 2010;**24**:1149–55). A second study used light-emitting diodes to illuminate one eye with 505-nm light during sleep in 40 participants with bilateral DMO. A total of 34 participants completed the study. This study showed an improvement in retinal function and decrease in retinal thickness at 6 months (Arden GB, Jyothi S, Hogg CH, Lee YF, Sivaprasad S. Regression of early diabetic macular oedema is associated with prevention of dark adaptation. *Eye* 2011;**25**:1546–54). Based on these observations, the Noctura 400 Sleep Mask (Polyphotonix Medical Ltd, Durham, UK) was Conformite Européenne (CE)-approved for the treatment of diabetic retinopathy. Short-term studies of this lightmask in DMO have been reported. Acceptability and safety of these lightmasks have been evaluated on 60 participants and 27% withdrew by the end of 3 months. The long-term effectiveness, compliance and safety of lightmasks that suppress dark adaptation as a treatment option for DMO is not known. In this Phase III clinical trial, we investigated whether or not offering a Noctura 400 Sleep Mask to wear as lightmasks over closed eyelids during sleep at night for 24 months could treat and prevent the progression of non-centre-involving DMO.

Objectives

The specific research questions addressed in this trial in eyes with non-central DMO were as follows:

- Does offering the lightmasks to wear during sleep at night that are designed to decrease dark adapation to wear during sleep in participants with non-central diabetic oedema reduce the maximal retinal thickness in eyes with non-central DMO compared with those offered a non-lightmask at 24 months?

- Does offering the lightmask to wear during sleep at night decrease light adaptation during sleep at night prevent the progression of non-central DMO to centre-involving DMO compared with eyes in the non-lightmask arm at 24 months?
- What is the compliance of wearing the lightmasks over 24 months?
- What is the safety profile including sleep disturbance caused by these lightmasks?
- What are the effects of lightmasks on visual function in eyes with non-central DMO when compared with the effects of 100% oxygen inhalation?

Methods

Design

This multicentre, prospective, individually randomised, single-masked, clinical trial evaluated the clinical effectiveness and safety of offering the lightmask to wear during sleep at night to prevent dark adaptation versus the non-lightmask in eyes with non-central DMO by 24 months. A subset of the participants also took part in a mechanistic evaluation substudy.

Setting

The study was conducted in the ophthalmology departments of 15 NHS trusts.

Participants

Adults with non-centre-involving DMO (defined as retinal thickening not involving the central 1000 µm of the macula, and characterised by presence of microaneurysm, exudates or oedema) and OCT evidence of increased retinal thickness in at least one non-central Early Treatment Diabetic Retinopathy Study (ETDRS) zone of $\geq$ 320 µm with best corrected visual acuity (BCVA) in the study eye better than 55 ETDRS letters (Snellen visual acuity 6/24) were included in the study.

Eyes with clinical evidence of centre-involving macular oedema (central subfield on OCT of > 300 µm), other causes of macular oedema or history of treatment for DMO at any time in the past 4 months (e.g. focal/grid macular photocoagulation, intravitreal or peribulbar corticosteroids, anti-VEGF drugs or any other treatment) in the study eye were excluded.

Interventions

Participants were individually randomised to the lightmask or non-lightmask in a 1 : 1 allocation ratio. The Noctura 400 lightmask was manufactured by Polyphotonix Medical Ltd. This CE-approved device is designed to deliver 500- to 505-nm light to a user's retina through closed eyelids. The lightmask is a fabric mask with a light-emitting unit containing two organic light-emitting diodes, powered by two 3-V (CR2450) batteries. It was offered to be worn over both eyes at night during sleep. The lightmasks have a lifetime of 83 days and so a replacement lightmask was resupplied every 83 days for 24 months. The lightmask also contained capacitive sensors that can sense when the masks are being worn. These compliance data are logged and stored within the lightmask and then downloaded when the mask is returned, using 'contactless' radio frequency identification technology for data analysis by the manufacturer. Participants were advised to use the lightmasks every night during sleep for 24 months and they were reviewed every 4 months for clinical assessments and monitoring of safety and compliance, and for resupply of the masks. The trial also included a mechanistic substudy of 28 participants who underwent retinal oximetry at baseline and 12 months to explore the effect of lightmasks on hypoxia compared with 100% oxygen inhalation.

Follow-up

The participants were followed up for 24 months.

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Clinical outcomes and analysis

Between 10 April 2014 and 15 June 2015, 308 participants were randomly assigned to the lightmask (n = 155) or non-lightmask (n = 153) arm. The primary outcome was the mean change in adjusted maximal retinal thickness at 24 months estimated from a linear mixed-effects model that took into account the all reported outcome data at the 4-monthly time points, including at 12 and 24 months. The primary outcome was analysed in both the intention-to-treat (ITT) and per-protocol populations. A total of 277 participants (lightmask arm, n = 144; non-lightmask arm, n = 133) contributed to the ITT analysis model, and all participants contributed to the ITT sensitivity analysis. No significant difference in change in maximal retinal thickness from baseline was observed between the arms at 24 months {–9.2 µm [standard error (SE) 2.5 µm] for lightmask vs. –12.9 µm [SE 2.9 µm] for non-lightmask; adjusted mean difference between arms –0.65 µm, 95% confidence interval [CI] –6.90 to 5.59 µm; p = 0.84}. Other outcomes at 24 months included differences in BCVA and time to centre-involving DMO and they did not indicate any differences between arms. Compliance with wearing the lightmasks decreased over time. The complier average causal effect estimate of the treatment effect for compliers defined by 70% compliance was –4.2 (95% CI –44.6 to 36.1), by 60% compliance this was –3.1 (95% CI –32.4 to 26.3) and by 50% compliance this was –2.5 (95% CI –26.7 to 21.7). Across these three definitions of compliers, the results were consistent in estimating a small non-significant intervention effect, which was not close to the detectable effect of 15 µm retinal thickness.

Mechanistic results

The mechanistic study involving 28 participants was part of the main prospective randomised clinical trial but was conducted in a single centre only. Willing participants were consented to have additional tests including retinal oximetry, multifocal electroretinography (mfERG) and scotopic microperimetry with and without 100% oxygen therapy at baseline and at 12 months. The outcomes were changes in retinal arteriovenous oximetry differences, mean changes in P1 and N1 amplitudes and peak time on mfERG and mean retinal sensitivity on scotopic microperimetry with and without oxygen inhalation and with and without lightmasks at 12 months.

The study showed that retinal arteriovenous oximetry differences, mean change in P1 and N1 amplitude and peak times on mfERG and scotopic retinal sensitivity did not change significantly with 100% oxygen inhalation at baseline or with the lightmasks at 12 months.

Conclusions

To our knowledge, this is the first randomised controlled trial that evaluated the effect of using a lightmask as a treatment or preventative option for non-central DMO. The study did not support the use of the lightmask for this condition. Compliance with the lightmasks reduced over time and the mechanistic study did not support the role of hypoxia in non-central DMO.

Trial registration

This trial is registered as ISRCTN85596558.

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This report

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