A randomised controlled trial investigating the effect of lutein, zinc and antioxidant dietary supplementation on visual function in healthy eyes

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Abstract

Background and aims

It has been suggested that retinal lutein may improve visual acuity for images that are illuminated by white light. Our aim was to determine the effect of a lutein and antioxidant dietary supplement on visual function.

Methods

A prospective, nine- and eighteen-month, double-masked randomised controlled trial. For the nine-month trial, 46 healthy participants were randomised (using a random number generator) to placebo (n = 25) or active (n = 21) groups. Twenty-nine of these subjects went on to complete 18 months of supplementation, 15 from the placebo group, and 14 from the active group. The active group supplemented daily with 6 mg lutein combined with zinc and antioxidants. Outcome measures were distance and near visual acuity, contrast sensitivity, and photostress recovery time. The study had 80 % power at the 5 % significance level for each outcome measure. Data were collected at baseline, nine, and 18 months.

Results

There were no statistically significant differences between groups for any of the outcome measures over nine or 18 months.

Conclusion

There was no evidence of effect of nine or 18 months of daily supplementation with 6 mg lutein combined with zinc and antioxidants on visual function in this group of people with healthy eyes. ISRCTN78467674.

Keywords: lutein, visual function, randomised controlled trial, antioxidants

Introduction

The role of lutein supplementation in the improvement in visual function for patients with age-related macular degeneration (AMD) has been established via a randomised controlled trial [1]. It has been suggested that lutein and its isomers, zeaxanthin and meso-zeaxanthin play a similar role in humans as in plants, as antioxidants and screeners of high-energy blue light [2].

With respect to healthy eyes, the blue-light filter effect of lutein/zeaxanthin may reduce longitudinal chromatic aberration [3-5]. In addition, the acuity hypothesis states that these nutrients may improve visual acuity for images that are illuminated with white light by absorbing poorly focussed short wavelengths before this light is processed by the retina [6, 7]. In theory, if an emmetropic eye views a mid-wavelength object (approximately 550 nm) in blue-dominated sunlight, shorter wavelengths will focus in front of the retina, and longer wavelengths will focus behind such that there is a range of focus of approximately 1.20 dioptres [5]. The fact that images are not degraded may be explained in part by the pre-retinal filtering effect of the lutein/zeaxanthin. Lutein and its isomers are collectively known as macular pigment (MP) within the retina.

During the design of the trial, 6 mg daily intake of lutein from food had been reported to be associated with a reduced risk of AMD (57 % lower risk for the highest quintile of lutein intake, 6 mg per day, relative to the lowest quintile, 0.5 mg per day) [8]. The reasons for using a multi-ingredient formulation include the fact that AMD has a multifactorial aetiology, and so may be affected by more than one nutrient, and also that nutrients are thought to work synergistically together.

Despite a lack of empirical evidence, lutein/zeaxanthin supplements are being taken by the public in an attempt to improve retinal health and vision in the absence of disease [9].The aim of this RCT was to determine the effect of a lutein and antioxidant dietary on measures of visual function in healthy eyes.

Materials and methods

The study was approved by the Aston University Human Sciences Ethical Committee (code 02/M). The tenets of the Declaration of Helsinki were followed [10]. The trial was registered for an International Standard Randomised Controlled Trial Number (ISRCTN 78467674), and the method has been published [11]. Reporting of this RCT adheres to the guidelines set out in the revised CONSORT statement [12].

Recruitment

Recruitment methods included an editorial in the regional press and advertising throughout the Aston University Campus.

Research centres

The main research centre was Aston University, Birmingham. A secondary research centre was a UK optometric clinical practice. Data collection took place in standard consulting rooms at both centres. Investigators and participants were masked to group assignment.

Inclusion/exclusion criteria

For inclusion, participants had to 1) provide written informed consent, 2) be available to attend one of the research centres, 3) present with no ocular pathology in either eye. Absence of pathology was assessed through dilated pupils using slit lamp binocular indirect ophthalmoscopy. Exclusion criteria relate to the inclusion of zinc and vitamin E in the study formulation. The exclusion criteria included type I and II diabetes as diabetic retinopathy may confound the results. Those taking anti-platelet or anti-coagulant medication were excluded because of possible interaction with vitamin E, as were those who used nutritional supplements that potentially raised vitamin and mineral intake above the recommended safe limits. People with conditions that affect dietary absorption, such as Crohn's disease, were also excluded.

A dilated fundus examination was carried out prior to enrolment. Fundus photographs were taken using Topcon non-mydriatic TRC-NW5S retinal camera (Topcon House, Bone Lane, Kennet Side, Newbury, Berkshire RG14 2PX, UK) at baseline and at each subsequent visit.

Masking

The study formulation and placebo tablets were produced by Quest Vitamins Ltd, and were identical in external and internal appearance, and taste. The manufacturer allocated distinguishing symbols, μ and λ to the tablet containers. The trial was double-masked; and the manufacturer revealed the code only when all data had been collected and analysed. Throughout this manuscript, the letters P and A will be used to refer to the placebo and active formulation respectively.

Intervention

The study formulation contained the following:

Lutein	6mg
Vitamin A	750μg
Vitamin C	250mg
Vitamin E	34mg
Zinc	10mg
Copper	0.5mg

The placebo tablets contained cellulose and were identical in appearance to the active tablets.

Participants in both groups were instructed to take one tablet, at the same time every day, with food. They were encouraged not to alter their diets, or to change their current supplementation regime. A contact telephone number was provided.

Randomisation

Only one investigator was involved in the randomisation process, which employed the random-number generator in Microsoft Excel for Windows XP. Odd and even numbers indicated group.

Outcome measures

At the first visit, refractive error was neutralised with lenses for both eyes, and the eye with the best logMAR (minimum angle of resolution) score for visual acuity was included in the study. Only one eye of each participant was included. Refractive error was neutralised with lenses at each subsequent visit and the resulting trial lenses were used for all visual function tests. Distance visual acuity (DVA) was measured using Early-Treatment Diabetic Retinopathy Study (EDTRS) logMAR charts and near visual acuity (NVA) was measured using Bailey-Lovie reading cards.

Contrast sensitivity (CS) provides additional information about vision and was measured using a Pelli-Robson chart (Clement Clarke International, Edinburgh Way, Harlow, Essex, CM20 2TT, UK). The Pelli-Robson chart determines the contrast required to read large letters and is designed to test mid- to low-spatial frequencies [13].

The Eger Macular Stressometer (EMS) (Gulden Ophthalmics, Elkins Park, PA 19027) was used to measure photostress recovery time (PSRT). This is the time taken for the regeneration of photopigments in bleached photoreceptors to a level that allows resolution of, for example, a letter at near. The EMS has been found to be reliable to within ± 7 seconds [14]. The instrument is hand-held and consists of a flash bulb and a near reading chart. It houses a 40.6 cm length of string, which, when extended, maintains a constant working distance while the subject determines the smallest letter size that can be read on the integrated VA chart monocularly. The test types range from Snellen equivalents of 6/6 to 6/30, with letter size decreasing from the top to the bottom of the chart. The working distance is then reduced to 15.2 cm (measured using a marker on the string) and the patient is directed to look at the centre of the flash tube, situated just above the test type. A third button press simultaneously activates the flash and starts the timer. The device is then returned to 40.6 cm and the patient is asked to read the line of letters above the smallest line read before bleaching as soon as it becomes visible. A fourth button press stops the timer when the patient has recovered enough macular function to correctly

identify three from the five letters on the designated line. A note of this PSRT is made and a fifth press of the button resets the instrument.

Sample size calculation

Reliability data from previous studies was used to determine effect sizes for use in sample size calculations for visual acuity (± 0.1 logMAR) [15], CS (± 0.15 log units) [13], and PSRT (± 7 seconds) [14]. The largest group size required for 80% power at the 5% significance level was for DVA (n = 13), indicating that a total minimum of 26 participants was required for the study.

Follow up

Data collection took place at baseline, nine, and 18 months. Recruitment started in December 2002 and ended in March 2004.

Statistical analysis

For each outcome measure the change between baseline, nine month, and 18-month values was calculated. Each data set was checked for normality of distribution using SPSS software (version 11) for Microsoft Windows XP. When the data set was normally distributed, a two-tailed independent samples t-test was used to determine whether the means of these values differed at the 5% significance level between the placebo and antioxidant formulation. When the data set was not normally distributed, the non-parametric Mann-Whitney U test was used. A mixed ANOVA was used to assess the effect of the between-subjects variable (group), and the within-subjects variable (time), on the outcome measures (dependent variable).

Enrolment, duration and compliance

Out of the 66 people that completed enrolment questionnaires, eight did not meet the inclusion criteria or decided not to enrol. The remaining 58 individuals were randomised to active or placebo groups: a breakdown is shown the Consort flowchart (figure 1).

Insert figure 1 about here.

Enrolment continued until nine months before the end of the data collection period, and this accounts for the difference in numbers between the nine- and 18-month cohorts. Of the 12 participants that were lost to follow up, one became pregnant, two moved out of the area, four had difficulty taking the tablets, and five developed illnesses unrelated to the project. These subjects were not included for analysis. Of the 46 participants who took part for nine months, 29 went on to take part for 18 months.

Statistical analysis was carried out on a per protocol basis. Compliance was assessed by counting remaining tablets at the follow-up visits, and averaged 92.3 %. The difference in compliance was not significant for either cohort.

Baseline data

Although it is not usually considered necessary to test for statistical differences between two randomly allocated groups, since any differences will have arisen by chance alone, we acknowledge that our small sample size could have resulted in some baseline differences between groups. The cohort ranged in age from 22 to 73 years (mean ± SD: 50.0 ± 15.9), and seventy-four percent were female. For the nine-month trial, twenty-five participants were randomised to the placebo (mean ± SD age: 50.1 ± 15.1 years) and 21 (mean ± SD age: 49.8 ± 16.4 years) to the active group. For the 18-month trial, 15 subjects were randomised to the placebo (mean ± SD age: 48.3 ± 15.8 years) and 14 to the active group (mean ± SD age: 46.7 ± 16.0). There was no significant difference in age or gender between groups for the nine-month comparison. For the 18-month comparison, the P group contained two males and 13 females and the A group contained seven males and seven females ($X^2 = 4.71$, $p = 0.03$); there was no significant difference in age.

All participants were White British. There was no significant difference in eye colour or baseline DVA, NVA, CS, or EMS scores between groups. A Student's t-test was used to assess differences between groups in age, smoking history (pack years), and years spent living abroad. Dietary intake of lutein, vitamins C and E, retinol equivalents, and zinc was assessed using food

frequency questionnaires and food diaries. Analysis of food diaries was carried out using FoodBase 2000 (Institute of Brain Chemistry and Human Nutrition, London) for Microsoft Windows XP. There was no significant difference between groups for any of these characteristics. In the A group, one person was taking thyroxine and one person was taking codeine. In the P group, one person was taking diazepam, one was taking thyroxine, and one was taking bendrofluazide. Participants were asked to provide details of additional nutritional supplementation. There was no difference in supplementation between groups (see table 1).

Insert table 1 about here.

The baseline characteristics are shown in table 2 for the nine-month group, and table 3 for the 18-month group.

Insert tables 2 and 3 about here

Assessment of change in characteristics

All participants were asked to fill out end-of-trial food diaries and food frequency questionnaires in order to assess any change in dietary habits over the trial period. Eighty percent were returned by the nine and 18-month P groups, 86 % by the nine month A group, and 79 % by the 18 month A group.

There was no change in dietary lutein, vitamin C, vitamin, E, or vitamin A for any of the groups (9P, 9A, 18P, or 18A). The normal nine month P group, however, had a significant change in mean zinc intake from (mean ± SD) 6.82 ± 2.15 mg to 10.26 ± 4.39 mg ($t = -3.54$, $df = 24$, $p = 0.002$). There was no significant change in dietary zinc over time for any other group. There were no changes in ocular health or smoking habits, and no participants developed AMD-related ocular changes.

Adverse effects

There were no reported adverse events or side effects from any of the study participants.

Results

Masking success

An end of trial, assessment was made of masking success by asking participants if they thought they knew which tablet they were taking, and if so, which one. Out of those participants taking the placebo tablet, 12 % correctly guessed which tablet they were taking, and 10 % incorrectly guessed. Out of those taking the nutritional supplement, 9 % guessed correctly which tablet they were taking, and 11% incorrectly guessed. The remaining participants were not prepared to make a guess indicating masking success.

Outcomes: between groups

There was no significant difference between groups at nine or 18 months for any of the outcome measures. Results are shown in tables 4 and 5, where the p value refers to the analysis of the difference in the amount of change between active and placebo groups for each outcome measure.

Insert tables 4 and 5 about here.

Outcomes: within groups

In order to assess the effect of time on the outcome measures over nine months, paired samples t-tests were carried out for DVA, NVA, CS, and EMS score. There were significant improvements over nine months in DVA ($p = 0.047$, eta squared = 0.15), and NVA ($p = 0.007$, eta squared = 0.27) in the P group. Eta squared describes the effect size and the following guidelines can be used for interpretation: 0.01 = small effect, 0.06 = moderate effect, 0.14 = large effect. Although the eta squared values for DVA and NVA suggest a large effect these changes are not clinically significant, [15].

For those participants who attended two follow-up visits, a mixed between-within subjects ANOVA was carried out to determine whether there was a change in each outcome measure

over time (main effect for time), if there was a difference in the effect on each outcome measure between the two interventions (main effect for group), and also whether there is the same change in scores over time for the two groups (interaction effect). The ANOVA results are shown in table 6 and the change in outcome measures over 18 months are shown graphically in figures 2 to 5.

Insert table 6 and figures 2 to 5 about here.

There was a significant change in CS and EMS score over time, but there was no difference between the P and A groups, and no difference in the change in these outcome measures over time between the two groups. The effect size for the change over time was moderate for CS (Eta squared = 0.119) and large for the EMS (Eta squared = 0.149). In the A group, the changes were not clinically significant for CS (less than ± 0.15 log units) [13] or EMS (less than ± 7 seconds) [14]. In the P group, the change in EMS was not clinically significant but the change in CS of + 0.15 log units is the limit for clinical significance. Apart from chance, the only explanation for this change in CS is that the scores did in fact improve in the P group over time.

Discussion

This clinical trial was designed to evaluate the effect of a nutritional supplement containing 6mg lutein, 750 µg vitamin A, 250 mg vitamin C, 34 mg vitamin E, 10 mg zinc, and 0.5 mg copper on clinical measures of visual function. The study demonstrated that this nutritional supplement had no effect on clinical visual outcome measures over nine or 18 months in healthy eyes. The same formulation was assessed in a randomised control trial of people with age-related maculopathy, which was powered for CS as an outcome measure [16]. The formulation had no significant effect in this group either. Other combined-nutrient formulations have been effective in improving visual function for people with age-related macular disease, including those used in the Age-Related Eye Disease Study (AREDS) [17] and the Lutein Antioxidant Supplementation trial (LAST) [1]. A full review of randomised controlled trials investigating the effect of nutritional supplementation on age-related macular disease has been published by the authors [18].

A branch of the AREDS looked at the effect of antioxidant and zinc supplementation on visual loss in people with age-related cataract and found no significant effect [19]. Conversely, in another randomised controlled trial, supplementation with 15 mg of lutein three times per week for two years was associated with improvements in visual acuity and glare sensitivity in patients with age-related cataract. However, no effect was found using 100 mg alpha-tocopherol supplementation three times weekly [20].

In a healthy group of 27 subjects aged between 60 and 84 years, those with higher levels of MP did not have significantly different visual sensitivity than a group of younger subjects aged between 24 and 36 years, whereas subjects in the older group with lower levels of MP did differ from the younger group [21]. This suggests that retinal lutein levels may effect visual function.

The specific uptake of lutein and zeaxanthin at the macula has been investigated with respect to the potential functional role of these carotenoids in normal visual function. The macula is specialized for high spatial resolution and also for colour vision and it has been hypothesised that lutein and zeaxanthin play a part in these processes. With any optical system defects in the

formation of the image occur and these aberrations can be classified as chromatic or monochromatic. In the human eye longitudinal chromatic aberration results from the dispersion characteristics of the ocular media, and a dioptric interval of around 0.9 D between the paraxial foci for 656.3 nm red light and 486.1 nm blue light has been reported [22]. Transverse chromatic aberration results in long-wavelength light being deviated less than short-wavelength light, which has the effect of producing a red blur around the edge of an image. When viewing white light, the combined effect of transverse and longitudinal chromatic aberration would be to create a purple penumbra, or shadow, to the image.

Short-wavelength light is scattered more than long-wavelength light by air molecules and larger atmospheric molecules. This scattering effect results in the blue coloration of the sky, as well as the blue haze seen around objects viewed in the distance. Wooten and Hammond [7] hypothesize that MP may increase visibility by reducing the luminance of the background with respect to the object itself. This means that the contrast of the object is increased. A person with a macular pigment optical density (MPOD, the amount of lutein or its isomers at any point in the retina) of 0.0 would only be able to see an object at 10 km that a person with an MPOD of 0.5 would be able to see at 11.9 km.

In 1866 it was proposed that MP might reduce longitudinal chromatic aberration through absorption of short-wavelength light [23]. It has been since been shown that a filter covering a similar spectral range to MP can reduce the radiance of the short-wavelength blur circle to a sub-threshold value [24]. The hypothesis that MP reduces short-wavelength chromatic blur and therefore enhances spatial vision (often termed the acuity hypothesis) [7] has been tested under different illumination conditions. One condition consisted of mid-wavelength yellow light that is not absorbed by MP, and the other consisted of a white light that was subject to chromatic aberration because the blue portion would be absorbed by MP [25]. No relationship between MP and resolution acuity or between MP and hyperacuity in either illumination condition was found. However, a marginal improvement in red-green discrimination with increased MPOD has been

reported, supporting the theory that increasing MP levels improves human chromatic discrimination sensitivity [26].

Macular pigment is also thought to improve visual performance by reducing the strength of the rod signals that are subject to large spatial summation and therefore more sluggish responses [27]. Absorption of blue light by MP may extend high-acuity cone-mediated vision at low light levels. Supplementation with 10 or 20 mg daily lutein or zeaxanthin over six months was reported to lower contrast acuity thresholds in the mesopic range in a recent conference abstract [27]. Similarly, a significant downward trend in contrast acuity thresholds was found with 10 mg or 20 mg daily lutein and zeaxanthin supplementation in a larger cohort, although MPOD was not significantly correlated with either the amount of forward light scatter in the eye, or contrast acuity thresholds [28].

Conflict in the literature may be explained by the acuity hypothesis. Although the MP filters the out-of-focus short wavelength light, there is an associated reduction in luminance that may effect acuity [29]. In other words, any improvement in visual acuity may be countered by luminance reduction.

Studies investigating retinal response (as opposed to serum response) to lutein supplementation have found a range of responses, including no retinal response in three out of 11 people over 14 weeks [30], and no retinal response overall in a cohort of 12 young and 17 elderly subjects following 5 weeks of supplementation [31]. .Increases in MPOD of 15 – 23 % have been found in some studies [32-34], while increases of around 40 % have been reported in others [1, 35-37].

A putative lutein-binding protein which binds with high affinity and specificity to lutein and other xanthophylls has been discovered in the retinae of human eyes [38], It has been suggested that people who are less responsive to lutein supplementation may be so because of genetic differences that result in reduced or less efficient binding proteins [39]. It is possible that this factor

may have had an effect on our results but we believe it is unlikely that all participants would have been non-responders.

The fact that MPOD was not measured in this study means that we do not know how responsive the participants were to the lutein supplementation. It would also have been interesting to track MP levels over the nine and eighteen month intervention periods. Unfortunately we did not have access to an MPOD measurement device at the start of the trial.

Studies have been carried out to investigate differences in bioavailability between pure and esterified lutein. One study reported no significant difference in serum lutein response between 6 mg lutein from spinach, 6 mg pure lutein, and 10.23 mg lutein esters [40]. In another study, serum response was greater from lutein esters than pure lutein [41]. Although these studies suggest that the use of lutein esters in our formulation should not have hindered bioavailability, it is important to note that they recorded serum response rather than retinal response. Although the retinal response is related to serum response, and dietary modification affects both, there is some variability in retinal response between subjects [30, 32, 42].

The use of a mixed antioxidant and mineral formulation does not permit assessment of the effect of specific nutrients on visual function. The rationale for using a mixed formulation is that nutrients are thought to work synergistically together. A relevant example of this synergism is the facilitation of vitamin A transport from the liver by zinc [43]. Although serum concentrations of lutein, zeaxanthin and antioxidants have been found to be responsive to dietary modifications [30, 36], they were not measured during this trial. Non-invasive compliance assessment was undertaken as blood analysis was considered likely to hinder recruitment.

At baseline the nine-month P group consumed significantly more dietary vitamin C than the A group. End of trial dietary analysis was carried out on at least 75 % of the participants in each group. There was no change with time in dietary lutein, vitamins C and E, and retinol equivalents in any of the groups. A mean increase in dietary zinc intake was shown in the nine

month P group. These differences could confound the results, although this would be of greater concern if a significant difference in improvement of any of the outcome measures had been found between the P and A groups in the nine-month cohort.

The results of this study add to the debate within the literature. Nutritional supplementation that includes 10 mg lutein daily has been associated with improved visual function in people with AMD [1] and supplementation with 15 mg of lutein three times per week for two years was associated with improvements in visual acuity and glare sensitivity in patients with age-related cataract [20]. A significant trend for improvement in CS was found with 10 mg or 20 mg daily lutein and zeaxanthin supplementation in people with healthy eyes [28]. The results of this study suggest that daily supplementation with 6 mg lutein combined with zinc and antioxidants is not sufficient to effect a change in visual function. The results of other studies suggest that daily supplementation with at least 10 mg of lutein may result an improvement in visual function in people with age-related macular disease, age-related cataract, or healthy eyes. Lutein dosage may be an important factor in the effectiveness of ocular nutritional supplements.

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Both authors contributed to the design of the trial, statistical analyses, and preparation of the manuscript. Hannah Bartlett collected the data. Both authors read and approved the final manuscript. The authors declare no competing interests.

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Figure legends

Figure 1: CONSORT flow diagram

Figure 2: Mean distance visual acuity (DVA) recorded for the 18 month cohort at baseline, nine, and eighteen months. Error bars represent standard deviation.

Figure 3: Mean near visual acuity (NVA) recorded for the 18 month cohort at baseline, nine, and eighteen months. Error bars represent standard deviation.

Figure 4: Mean contrast sensitivity (CS) recorded for the 18 month cohort at baseline, nine, and eighteen months. Error bars represent standard deviation.

Figure 5: Mean Eger macular stressometer (EMS) score recorded for the 18 month cohort at baseline, nine, and eighteen months. Error bars represent standard deviation.