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EFFECTS OF ANTHOCYANOSIDE OLIGOMER ON MESOPIC CONTRAST SENSITIVITY IN MILD TO MODERATE MYOPIA

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Abstract

Purpose : We performed a randomized, double-blind, placebo-controlled trial in mild to moderate myopia patients to evaluate the benefit of taking a nutrient supplement containing anthocyanoside oligomers for improving nocturnal visiual function and/or clinical symptoms.

Methods: The subjects included have refractive error between -1D(Diopters) ~ -8D in both eyes, symptoms of decreased night vision and asthenopia based on the scoring result of a pre-structured questionnaire, and abnormal results of mesopic contrast sensitivity(MCS) screening test showing abnormal curve of contrast sensitivity in the middle and high frequency level, between 6.0 and 30.0 CPD(Cycles per degree) at mesopic condition(-2~0 log cd/m^2). Total 60 people who qualified the criteria above were enrolled and the subjects were instructed to take the investigational product (anthocyanoside or placebo) twice daily for a 4 week period. The enrolled subjects were investigated for nocturnal vision performance by MCS and clinical symptoms at their first visit and re-evaluated at post-intervention (4 weeks later). MCS was measured and improvement of contrast threshold level according to each CPD was calculated by subtracting initial values from final values. Age, refractive error, and MCS were compared between the placebo and anthocyanoside.

Results: After 4 weeks of drug administration 22 of the anthocyanoside group showed symptom improvement compared to 1 of the placebo group ($p=0.000$). Contrast sensitivity levels according to each CPD before and after drug treatment showed significant improvement in the anthocyanoside group but not in the placebo group. Mean MCS change of anthocyanoside group is 2.41±1.91 which showed significant improvement compared to -0.40±2.47 of the placebo group($p=0.000$). MCS changes of anthocyanoside group showed significant improvement compared to placebo group in all levels of CPD($p<0.05$). During our investigation none of the subjects complained of specific side effects related to anthocyanoside use.

Conclusion: Our results show that under careful selection of people with significant symptoms and

definite MCS abnormalities, anthocyanoside oligomers may improve the subjective symptoms and objective MCS results.

Keywords : anthocyanosides, anthocyanoside oligomer, bilberry, mesopic, contrast sensitivity, myopia

INTRODUCTION

Bilberry(Vaccinium myrtillus) is small deciduous shrublet that grows in wooden areas of central and northern Europe, northern Asia, and North America. Bilberry fruit has been used in traditional European medicine for nearly one thousand years[1]. During world war II, the British Royal Air Force noted reports from pilots that nighttime visual acuity was improved after consuming bilberries.

Bilberry fruit preparations have been investigated for their effects on vision acuity in dim light[4], on patients with pigmentary retinitis when taken with beta-carotene[5], on night vision in normal subjects[6], on patients with diabetic retinopathy when taken in combination with beta-carotene[7], on patients with significant hemeralopia[8], on patients with macular degeneration, diabetic retinopathy, retinal inflammation, or retinitis pigmentosa[9], and on patients with progressive myopia[10]. Later research investigated bilberry's microcirculatory function in patients with various retinopathies[11], myopia, glaucoma, or retinitis pigmentosa[12]. Additional studies also investigated bilberry's effects on the progression of cataract formation in patients with senile cortical cataracts when taken in combination with vitamin E [13].

Anthocyanosides are the pharmacologically active constituents of bilberries. Anthocyanoside molecules consist of a backbone known as anthocyanidin which is bound to one of three sugars: arabinose, glucose, or galactose.[2,3] Five different anthocyanidins in bilberry produce more than fifteen different anthocyanosides. Anthocyanoside oligomers, a more potent active ingredient than natural anthocyanosides have shown better pharmacological effects in a number of studies. The biochemical mechanism of anthocyanosides are not quite clear but some results suggests the inhibition effect on the cGMP phosphodiesterase (PDE) rod-photoreceptors of the retina, acceleration of rhodopsin resynthesis, protection of the blood vessel by increasing its resistance and decreasing the penetrability, enzyme inhibition activity (elastase, collagenase, peroxidase, trypsin and alpha-chymotrypsin and etc.) and also neutralizing the activity of oxygenated free radicals.

A randomized controlled study may be needed to determine reliably the clinical effect of anthocyanoside oligomer in people who have clinical symptoms of asthenopia and poor nocturnal vision. For the evaluation of nocturnal vision, we employed a new, computerized integrated tool

called as ACV(L2 Informatique, Paris, France), which was developed and validated by a group of aerospace military researchers in France. We have performed a randomized, double-blind, placebo-controlled trial in mild to moderate myopia patients to evaluate whether there is any benefit of taking a nutrient supplement containing anthocyanoside oligomers 100mg (Eyezone, Hanmi Pharmaceuticals, Seoul, Korea), twice daily, for improving poor nocturnal vision and/or clinical symptoms of asthenopia.

MATERIALS AND METHODS

More than 200 volunteered people, aged 8 to 65, visiting the Young Dong Severance hospital during the period of April to August 2000, were screened and people who met the inclusion criteria have been included in our study. All of the subjects had been fully explained of the procedures and informed consent were obtained before the study in accordance to the world medical association declaration of Helsinki(48^{th} General Assembly, Somerset West, Republic of South Africa, October 1996). The inclusion criteria are first refractive error must be between −1 D(Diopters) ~ -8D in both eyes, second the subject should have the symptom of decreased night vision and symptomatic asthenopia based on the scoring result of a pre-structured questionnaire, third the results of ACV screening test shows abnormal curve of contrast sensitivity in the middle and high frequency level (between 6.0 and 30.0 cpd) at mesopic condition(-2~0 log cd/m^2). If the subjects comes under any one of the following exclusion criteria they were excluded from the study : prior medical history of hypersensitivity to anthocyanocides or products containing anthocyanosides, ages more than 70, pregnancy or expecting a pregnancy, confirmed organic eye disease and/or previous eye operation history, medical history of disease which affects vision such as diabetes, and internal use of medicine or products which are known to affect the eye.

Nocturnal vision was measured by MCS(morphoscopic contrast sensitivity) at mesopic condition based on ACV(L2 Informatique, Paris, France) program. The lowest contrast level at a given target size was measured at mesopic condition, which provide the information on the patient's nocturnal vision performance. The person suffering from poor nocturnal visions usually show the abnormal curve of contrast sensitivity in the middle and high frequency level (between 6.0 and 30.0 cpd) at mesopic condition. Only the people showing such an abnormality in at least one of the two eyes at their first visit were included in our study. Total 60 people who have poor nocturnal vision and self-recognized symptoms of asthenopia were enrolled after signing in informed consent form and divided

randomly into two groups, 30 for Eyezone and the other 30 for Placebo group. The enrolled subjects were instructed to take the investigational product (Eyezone or Placebo) at twice daily for 4 week period.

The enrolled subjects were investigated for nocturnal vision performance and clinical symptom of asthenopia at their first visit and re-evaluated at post-intervention, 4 weeks after taking Eyezone or placebo. Both investigator and enrolled subjects were blinded with regard to grouping, to which intervention the patients are belonged.

The study subjects were subject to a planned questionnaire at their first visit and re-evaluated at post-intervention period. They answered for the 7 questions about the severity/frequency of the eye symptoms(Table 1). The questions were evaluated with 4 grades of score. Score 1 for no symptoms, score 2 for symptoms 1~2 times/week, 3 for symptoms 3~4 times/week, 4 for symptoms every day. It was determined as "Improved" if the person showed the score of 1 or 2 at the second visit, identifying mild or negligible suffering from the items having belonged to severe problem, the score of 3 or 4 at their first visit.

MCS measurements before and after treatment was compared with paired T-test in the placebo group and Eyezone group respectively. MCS measured with ACV and improvement of contrast threshold level according to each cycles per degree (CPD) was calculated by subtracting initial values from final values. Age, refractive error, and mesopic contrast sensitivity measured with ACV were compared between the placebo and Eyezone group with unpaired T-test and symptom scoring comparison between the two groups were analyzed with Chi-square test.

Table 1. Questions for severity/frequency of the eye symptoms

Questions
1. Frequent eye strain or pain at normal life?
2. Eye strain or pain at reading?
3. Dryness of eye or tearing at reading?
4. Eye strain at sudden bright lights?
5. Decreased vision in dark places?
7. General weariness when reading?

RESULTS

Among the 200 volunteers 60 people were qualified for our study. The mean age and refractive error between the placebo group and the Eyezone group were not significantly different(Table 2)($p>0.05$). After 4 weeks of drug administration Eyezone group showed more symptom improvement than the placebo group(Table 3)($p=0.000$). Contrast sensitivity levels according to each CPD before and after drug treatment showed significant improvement in the Eyezone group but not in the placebo group(Table 4,5). Mean MCS changes of Eyezone group showed significant improvement compared to placebo group in all levels of CPD(Fig1, $p<0.05$). During our investigation none of the subjects complained of specific side effects related to anthocyanoside use.

Table 2. Age, sex and refractive error in placebo and Eyezone group

	Placebo	Eyezone	P value
Age	36.0±12.6	41.1±13.1	0.133
Sex (M : F)	11 : 19	18 : 12	0.071
Refractive error	-4.04±1.76	-3.39±1.83	0.053

Table 3. Improvement of eye symptoms between placebo and Eyezone group

	Placebo	Eyezone
Not improved	29	8
Improved	1	22

p=0.000 (Chi-Square test)

DISCUSSION

Visual acuity has been and will probably continue to be the most often used clinical measure of visual function. But, in recent years, contrast sensitivity testing has been widely promoted as an important adjunct or even replacement for visual acuity testing.[14] Recent studies have demonstrated that contrast sensitivity is useful for understanding the difficulties in performing everyday visual tasks.[15] Contrast sensitivity are suggested as important factors in predicting mobility performance at mesopic conditions in people with low vision[21,22]. Additionally reduced mesopic vision are accompanied by increased risk of night-time traffic accidents[23]. Abnormalities of mesopic contrast sensitivity tests despite normal photopic visual acuity may limit the persons performance in low

Table 4. Contrast sensitivity before and after placebo treatment

CPD	Before	After	P value
0.6	30.61±3.96	31.26±3.14	0.244
1	29.52±4.16	29.46±3.75	0.918
1.5	29.55±4.25	28.98±4.00	0.307
3	26.65±3.93	26.10±4.97	0.333
6	21.50±7.48	19.64±6.91	0.003
7.5	18.67±7.86	17.38±7.89	0.033
9.5	15.55±8.06	14.70±7.59	0.240
12	10.14±7.51	10.10±6.79	0.936
15	6.73±6.19	6.47±5.61	0.673
19	0.89±2.74	0.70±1.83	0.475
24	0.70±1.79	0.77±2.01	0.816
30	0.49±1.65	0.60±1.91	0.644

Table 5. Contrast sensitivity before and after Eyezone treatment

CPD	Before	After	p value
0.6	31.44±3.81	33.45±2.73	0.000
1	30.68±4.20	32.54±2.66	0.000
1.5	30.29±4.45	31.97±3.35	0.001
3	27.92±30.67	30.67±4.11	0.000
6	22.75±6.41	25.04±7.05	0.000
7.5	20.63±8.11	22.77±7.89	0.000
9.5	16.72±8.56	19.61±8.19	0.000
12	11.46±8.06	14.03±9.05	0.000
15	8.01±7.07	10.9±8.79	0.000
19	1.51±3.88	5.31±6.67	0.001
24	2.00±3.25	4.32±5.70	0.003
30	1.12±2.43	2.84±4.44	0.000

illuminated conditions.

Previous publications of anthocyanoside effects on improvement of nocturnal vision have suggested controversial results. Earlier publications reported improvement of nocturnal visual functions in normal individuals after multiple dose of anthocyanosides[16,17,18] but recent reports demonstrates no significant effect of anthocyanosides in single[19] or multiple oral dose[20, 24] on night

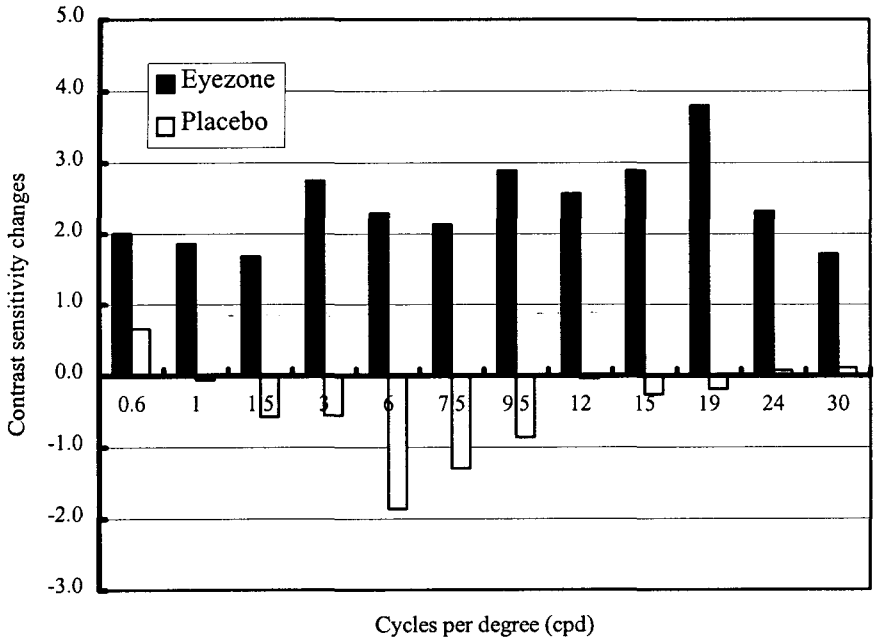

Fig 1. Mean mesopic contrast sensivity changes before and after drug treatment

vision. Our reports shows improvement in mesopic contrast sensitivity and symptoms. The reason of conflicting results may be differences in subjects, method of evaluating night vision, concentration and dose of drug administration. Previous studies with normal subjects[19,20,24] couldn't prove the effect of anthocyanosides but in myopia and night blindness subjects it proved to be effective[18]. We selected a new method called ACV to access MCS with a computerized method, which may have enhanced the sensitivity of detecting MCS changes. The study to evaluate reliability of ACV is under way in our institution and preliminary data shows that it is quite reliable. The dose and duration of anthocyanosides we used were greater than previous reports of single oral dose of maximum 36mg[19], multiple oral dose of 24mg, given twice daily for 4 days[20],and 160mg (25% bilberry extract) for 21days[24]. We gave 100mg, twice daily for 4 weeks and this also may have been a factor for the improvement in MCS results.

The interpretation of the effects of anthocyanosides on night vision should consider the subjects, method of evaluation, dose and duration of treatment for accurate conclusion. Our results show that under careful selection of people with significant symptoms and definite MCS abnormalities, anthocyanoside oligomers may improve the subjective symptoms and objective MCS results. This suggests the necessity of future studies to provide the indications for anthocyanoside use and optimal

dose and duration of treatment.

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