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The impact of saffron (*Crocus sativus*) supplementation on visual function in patients with dry age-related macular degeneration

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Abstract

The aim was to evaluate the impact of saffron supplementation on visual function in patients with dry age-related macular degeneration (ARMD).

Fifty-four participants, 23 male and 31 female, with dry ARMD were assigned to one of the following two groups. The treatment group (n=29) consumed 50 mg saffron daily during a 3-month period, while 25 subjects served as the control group. Visual acuity, contrast sensitivity, and retinal thickness were measured at the beginning and at the end of the study. Quality of life was evaluated using the Melbourne Low Vision Index (MLVI) before and after treatment.

Significant increases in visual acuity and contrast sensitivity were found in the saffron group but not in the control group. Changes in macular thickness were not statistically different between the two groups.

Short-term consumption of saffron may slow down the progression of disease and improve visual function, especially contrast sensitivity, in patients with dry ARMD.

Introduction

Age-related macular degeneration (ARMD) is the most common cause of vision loss among elderly people of both developed and developing countries.[1,2] Vision decreases in the initial stages of the disease and most patients have no other symptoms. Vision loss then gradually increases among non-neovascular ARMD patients through several years while neovascular ARMD shows severe and sudden vision loss due to sub-retinal hemorrhage and fluid accumulation. In the dry type, retinal changes include pigmentary changes, soft and hard exudates and geographic atrophies. These changes may cause wet and neovascular changes in later stages. Dry ARMD can be subdivided into several categories such as mild, moderate and severe.[3,4] Vascular endothelial growth factor (VEGF) has a significant effect in increasing the

rate of vision loss in patients with neovascular ARMD. Epidemiologically, risk factors for the disease include age, gender, smoking, high blood pressure, obesity, white race, genetics and diets low in antioxidant and zinc and high in fat. Aging increases the severity and incidence of the disease significantly.[2,3,5] The presence of Complement Factor H also increases ARMD incidence.[6] There is a correlation between cataract surgery and ARMD, but this relationship has not been reported in the Age-Related Eye Disease Study (AREDS) study.[1,7]

Hitherto, efficacy of *Crocus Sativus* (saffron) in the treatment of ocular diseases has been confirmed in many studies.[8-11] Saffron is rich in phytochemicals; however, its main components include crocin and crocetin. These carotenoid derivatives have anti-apoptotic properties. In addition, saffron has a neuroprotective role against oxidative damage.[12] Crocin may also be effective against neurodegenerative damage caused by oxidative stress. The antioxidant effects of saffron extract has been reported in several experimental studies.[8-10,13] In spite of numerous pharmacological studies on saffron, there is very little evidence of the beneficial effects of this medicinal plant in ARMD. In view of the lack of an effective treatment to control ARMD, the therapeutic effect of saffron in improving visual function of patients with ARMD was investigated in this study.

Materials and Methods

All participants were patients admitted to the ophthalmology clinic at Baqiyatollah Hospital.

Inclusion criteria

Participants over the age of 50 with dry type ARMD who were admitted to the ophthalmology clinic at the Baqiyatallah Hospital (Tehran, Iran) were included in this study. The reason for choosing to study dry ARMD was that patients with wet ARMD are usually under various treatments such as injection, photodynamic therapy or receiving anti-VEGF

and other medication. In addition, retinas of patients with wet ARMD may have hemorrhage, neovascularization and scars, which can cause severe vision loss, adding many confounding factors that would limit the study. As a result, we aimed to study the dry type disease that has much less confounding factors. All participants had signs and symptoms of mild to moderate dry ARMD. Cases with small drusen or a few medium-sized drusen were considered to be mild, cases with many medium or at least one big drusen or geographic atrophy without any sub-foveal involvement were designated as moderate and cases with geographic scars at the fovea were labeled as severe.

Exclusion criteria

The following cases were excluded from the study; wet and severe dry type ARMD and patients with systemic diseases such as hypertension, diabetes, or glaucoma, ARMD secondary to retinal diseases, and patients taking any other dietary supplements. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committee at the Baqiyatallah University of Medical Sciences. Participants were adequately informed and written consent was obtained from the participants or their attendants.

Participants were initially referred to a retinal specialist for selection and confirmation of a definitive diagnosis. The patients then underwent complete ophthalmologic and optometric examinations. Optometric examinations included measurement of distance and near vision, contrast sensitivity and refraction both with an automatic refractometer and retinoscopy. If the patients did not have enough vision to see the chart at a distance of 6 meters, the chart was moved to a closer distance and vision examinations were completed. Contrast sensitivity was then tested using the Melbourne Edge test (MET). After the optometric examinations, Optical Coherent Tomography (OCT) (Spectralis) was performed without the need to dilate

the pupil.

All patients filled the questionnaire about quality of life and related activities of the Melbourne Low Vision Index (MLVI) before and after the examinations. If the patients' vision were not enough to read the questionnaire, their attendant would read it to them. The questionnaire (part B) consisted of nine questions, each question having five items. The sum of the scores was calculated as the final score. A score of 36 was the maximum score, which indicated that the patient has no problems with performance of daily activities. A lower score would indicate problems in performing routine tasks. The patient was then referred to the pharmacy to receive the capsules. The capsules were made of gelatin and contained 50 mg Saffron extract and 250 mg of starch. Placebo capsules contained only 300 mg of starch. Because the Saffron extract was dried, there was no need to add a preservative. The pharmacist did not have any information about the study or the vision of the patients. He was only aware that he was supplied with two kinds of capsules, A and B, saffron and Placebo respectively, and that he had to give the same type of capsule to each patient on subsequent visits. Patients were randomly assigned to the intervention or control groups. Subjects in each group were given 30 capsules and capsule data was recorded. Patients were advised to consume one capsule daily. Two phone calls were made to each subject during the first month to ensure that the capsules were taken correctly and that there were no adverse side effects. Each saffron capsule contained 50mg saffron stigma plus 150 mg pharmaceutical grade starch while the placebo capsules contained only 200 mg pharmaceutical grade starch. Once the patient had consumed the capsules for the first month, he was recalled to the clinic to receive the second round of 30 capsules. Two more follow up phone calls were made during in the second month and finally the patient returned to the clinic for the last batch of 30 capsules and took them as prescribed. The subjects then underwent full re-examination and completed the same questionnaire again in order to study the effects of any visual

changes on their daily activities. Finally, the data collected from all patients were analyzed using SPSS version 21 software. Continuous variables were presented as mean and standard deviation. Categorical variables were presented as absolute and relative frequencies. Independent t-test, Chi-square and Fisher exact test were used to compare the groups. All reported P-values were based on two-sided hypotheses.

Results

Sixthy-nine participants with ARMD and no other ocular diseases entered the study. Fifteen patients did not continue the study for various reasons. The main reasons were either the lack of satisfaction with the impact of the capsules during the first month or family and medical problems. A total of 29 patients in the saffron group and 25 patients in the placebo group (54 participants, 23 male and 31 female) completed the study. The mean age of the patients in the placebo and saffron groups were 68.9 ± 8.26 and 70.24±8.5 respectively with no statistically significant difference between the age of the groups (P = 0.66). Twenty-five patients did not have cataract surgery and 27 patients had a history of cataract surgery with no significant difference between the two groups in this regard (P = 0.502). In terms of education, 29 participants were illiterate, 22 had primary education and three had a college degree (Table 1). Again there was no statistically significant difference between the groups (P = 0.369). The patients' chief complaints were inability to read and write, watching TV, driving, face recognition, housework, and fear of falling down stairs.

The mean baseline corrected vision of the test and control groups were 0.46 ± 0.41 and 0.62 ± 0.55 Log MAR, respectively, before the tests and no statistically significant difference between the groups was found (P = 0.124). However, the mean corrected vision of the test and control groups at the end of study were 0.41 ± 0.41 and 0.65 ± 0.54 Log MAR, respectively, showing a statistically significant difference between the saffron and control

groups (P = 0.001) (Table 2).

The mean corrected visual acuity of the saffron group before and after the study were 0.46 ± 0.41 and 0.41 ± 0.41 Log MAR, respectively (P = 0.004). The mean corrected visual acuity of the control group before and after the study were 0.62 ± 0.55 and 0.65 ± 0.54 Log MAR, respectively, with no statistically significant difference (P = 0.094).

The mean baseline contrast sensitivity of the saffron and control groups were 16.31 ± 3.63 and 14.8 ± 4.91 dB, respectively, which indicated no statistically significant difference between the groups (P= 0.152). However, the mean contrast sensitivity of the saffron and control groups at the end of study were 18.18 ± 3.40 and 14.4 ± 4.53 dB, respectively, showing a statistically significant difference (P= 0.001) (Table 2).

The mean contrast sensitivity of the saffron group before and after the study were 16.31 ± 3.63 and 18.18 ± 3.40 dB, respectively (P = 0.000), which was in favor of increased contrast sensitivity. The mean contrast sensitivity of the control group before and after the study were 14.8 ± 4.91 and 14.4 ± 4.53, respectively, which showed a significant deterioration (Table 3).

The mean baseline central macular thickness of the saffron and control group were 258.35 ± 47.55 and 256.18 ± 44.78, respectively, with no statistically significant difference between the groups (P= 0.86). The mean central macular thickness of the saffron and control groups at the end of study was 256.17 ± 43.61 and 264 ± 30.20, respectively. Again, there was no statistically significant difference between the groups at the end of study (P = 0.32) between the groups. The mean central macular thickness did not significantly differ during the course of study, neither in the saffron (P= 0.267) nor in the control (P= 0.119) group (Table 4).

Average baseline ratings of Quality of Life (QOL) of the saffron and control groups were 33.82 ± 3.91 and 29.48 ± 5.97, respectively, with a statistically significant difference (P = 0.002). Average rating quality of life of saffron and control groups at the end of study were 34.06 ± 3.7 and 30.56 ± 5.61, respectively, with a statistically significant difference (P =

0.008). There was no statistically significant difference within each group before and after the study (saffron group, P = 0.32;control group, P = 0.06) (Table 5).

Discussion

The results of this study showed improvement of visual function, especially contrast sensitivity, in patients with dry ARMD following supplementation with saffron. It is important to note that there is no specific and classic treatment for patients suffering from dry ARMD. Blue Mountain Eye Disease Study indicated that dietary zinc (more than 5/15 mg daily) decreases the occurrence of any ARMD and even the progress of ARMD after 5 or 10 years. Other studies have suggested that the intake of antioxidants can decrease the severity of ARMD.[14]

Saffron contains effective compounds including Crocetin, Crocin and Saffranal[15] which can improve retinal performance in various ways. Crocin, the active principle of saffron, can increase blood circulation in the retina and choroid. The ischemic pathological changes in ARMD mainly occur in the pigmented layer of the retina and photoreceptor blood supply is through the choroidal circulation. Improvement of choroidal blood circulation may therefore improve blood flow to the photoreceptors,[8] resulting in increased visual performance. Another reason that can justify improvements in visual function of ARMD patients is the role of beta-carotene present in saffron on the structure and function of photoreceptors, as has been reported in previous studies.[16] The role of beta-carotene and saffron extract in improving the visual function could be attributed to the maintaining of the shape and structure of the photoreceptor layer. Previous studies have also shown that crocin can protect photoreceptors and prevent their degeneration. Saffron is not only involved in the maintenance and operation of photoreceptors, but it can also enhance the connection of photoreceptors with other retinal cells such as bipolar cells. Most studies have used 20 or 30

mg doses of the extract and the results were almost the same in most cases. In the present study, a daily dose of 50 mg was used. It should be noted that a daily intake of 1.5 grams of saffron has been found to be harmless in human.[17] We found that a daily consumption of 50mg of Saffron improves visual acuity and contrast sensitivity of patients with the dry ARMD. This improvement may be due to the combined effects of the saffron ingredients on retinal function. Visual acuity has been reported to increase by about two lines in patients who were treated with a daily dose of 20 mg of saffron extract.[18] This improvement was found to be nearly one line in our study. Patients who were treated with 30 mg of Saffron for 3 and 6 months did not show a significant increase in visual acuity objectively, however, they did report an enhancement in vision subjectively.[19] Our study indicates that doses more than 30 mg will not result in a greater increase in visual acuity. A slight increase in visual acuity over 3 months indicates that the disease may be under control and further deterioration is prevented, since vision actually partially improves during this period while, on the other hand, a slight reduction of vision and contrast was observed in the control group during the same period. These findings demonstrate the positive effects of saffron consumption. Many studies have shown that improvement in contrast sensitivity may improve functional vision. Although there was a significant improvement in contrast sensitivity in the saffron group, it did not appear as a significant increase in functional vision. It is suggested that evaluation of functional vision by measuring the performance of tasks, may result in improved findings.

Although our patients expressed better satisfaction with their quality of life in comparison to their pre-study condition, these changes were not significant statistically. In other studies, patients have also reported enhancement of their vision,[19] although the visual recovery was not quantifiable objectively. Patients who were treated with saffron for 15 months have significant improvements in their quality of life.[18] It appears that patients' statements about quality of life may not be reliable and that quality of life may not be easily determinable by a

questionnaire. For example, a slight reduction in contrast sensitivity in a normal person will reflect in a statement such as "I cannot see well," even though the patient may have a visual acuity of 20/20. Satisfaction as in improvement of quality of life may therefore be more closely correlated to improvements in contrast sensitivity rather than visual acuity. Furthermore, saffron has also been found to have anti-Alzheimer and antidepressant properties, which could justify why saffron consumption may result in reporting wellbeing. The impact of saffron consumption on the quality of life could be evaluated more accurately in a future study over a longer period of treatment. There was a significant correlation between visual acuity and contrast sensitivity between the placebo and saffron groups. Increased contrast sensitivity resulted in better visual acuity. This result is predictable, because improvements in photoreceptors function can improve vision.

In this study, no side effect of saffron was found. This finding has also been reported in other studies. It can therefore be concluded that saffron is safe and somewhat effective in the treatment of dry ARMD, at least in a short-term perspective.

Measurement of central macular thickness has shown that the thickness increased slightly in the saffron group and dropped slightly in the placebo group. These small changes were not statistically significant. In addition, other studies have shown that macular thickness decreases in both saffron and control groups, but these changes were not significant. It seems that saffron may have no significant effect on the macular thickness.

Conclusions

In conclusion, findings of the p-resent trial suggest that short-term consumption of saffron extract is safe and may slowdown the progression of dry AMD and improve visual function. Given the paucity of effective treatments for controlling the progression of dry AMD, the present results may find implication for the routine management of patients. However,

confirmation for the present results in future longer term studies is recommended. Finally, whether supplementation with purified crocin would lead to improved efficacy deserves additional investigations.

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Table 1. Characteristics of participants in the two groups (count and percentage).

Factors	Treatment group (n=29)	Placebo group (n=25)
Sex		
Male	15 (65.2%)	8 (34.8%)
Female	14 (45.2%)	17 (54.8%)
Level of schooling		
Illiterate	13 (44.8%)	16 (55.2%)
Primary education	14 (63.6%)	8 (36.4%)
College degrees	2 (66.7%)	1 (33.3%)
History of cataract surgery		
No cataract	15 (62.5%)	9 (37.5%)
Operated	11 (45.8%)	13 (54.2%)
Not operated	3 (50.0%)	3 (50.0%)

Table 2. Mean (STD) corrected vision differences between treatment *vs* control group.

Variables	Treatment group (n= 29)	Placebo group (n= 25)	P-value
Mean corrected vision (degree) (std):			
a-before the treatment:	0.46 (0.41)	0.62 (0.55)	0.517 (NS)*
b-after the treatment:	0.41 (0.41)	0.65 (0.54)	0.001 (S)**
P-value	0.004 (S)**	0.094 (NS)*	

*NS, not significant; **S, significant.

Table 3. Mean (STD) Contrast sensitivity differences between treatments *vs* control group.

Variables	Treatment group (n= 29)	Placebo group (n= 25)	P-value
Mean contrast sensitivity (degree) (std):			
a-before the treatment:	16.31 (3.63)	14.8 (4.91)	0.152 (NS)*
b-after the treatment:	18.18 (3.40)	14.4 (4.53)	0.001 (S)**
P-value	0.000 (S)** (Increase)	0.009 (S)** (Reduce)	

*NS, not significant; **S, significant.

Table 4. Mean (STD) OCT differences between treatments *vs* control group.

Variables	Treatment group (n= 29)	Placebo group (n= 25)	P-value
Mean OCT (degree) (std):			
a-before the treatment:	258 (47.55)	256.18 (44.76)	0.86 (NS)*
b-after the treatment:	256.17 (43.61)	264 (30.20)	0.32 (NS)**
P-value	0.267 (NS)*	0.119 (NS)*	

*NS, not significant; **S, significant.

Table 5. Mean (STD) quality of life (QOL) score between treatments *vs* control group.

Variables	Treatment group (n= 29)	Placebo group (n= 25)	P-value
Mean QOL score (degree) (std):			
a-before the treatment:	33.82(3.91)	29.48 (5.97)	0.002 (S)**
b-after the treatment:	34.06 (3.7)	30.56 (5.61)	0.008 (S)**
P-value	0.32 (NS)*	0.06 (NS)*	

*NS, not significant; **S, significant.