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The Effect of Borage on Retinal Venous Pressure of Healthy Subjects with the Flammer Syndrome Running Title: Borage and Retinal Venous Pressure

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Abstract

Background: The purpose of this study was to measure retinal venous pressure (RVP) in eyes of healthy subjects who consumed borage tea for three weeks and to compare values to an untreated placebo group.

Methods: RVP was measured in two groups of healthy subjects at baseline and after three weeks. The intervention group (N=20) consumed borage tea (10 grams in a liter of water daily) for three weeks. The placebo group (N=20) followed a water regime (1liter a day) for the same period. In both groups a distinction was made between those with the Flammer Syndrome (FS+) and those without it (FS-) by means of anamnesis. RVP was measured bilaterally by means of ophthalmodynamometry which is done by applying increasing pressure on the eye via a contact lens. The minimum force required to induce a venous pulsation is called ophthalmodynamometric force (ODF). The RVP is defined as the sum of ODF and intraocular pressure (IOP).

Results: Baseline RVP values were significantly higher in FS+ subjects (36.93±9.06mmHg) than FS- subjects (26.03±2.07mmHg) (P<0.001). Consumption of borage for three weeks significantly reduced RVP from a mean value of 38.91±8.56 to 32.50±8.55 mmHg in FS+ subjects (p<0.001). There was trend towards a decrease in RVP from a mean of 26.39±2.45 to 22.44±2.79 in FS- subjects which did not reach clinical significance.

Conclusion: Consumption of borage tea for three weeks may decrease RVP. This effect seems to be stronger in people with FS and may be due to the calcium antagonising side-effects of this plant.

Keywords: Borage, Retinal venous pressure, Ophthalmodynamometry, Flammer syndrome

Abbreviations: IOP: Intraocular Pressure; RVP: Retinal Venous Pressure; ODF: Phthalmodynamometric Force; OPP: ocular perfusion pressure; FS: Flammer syndrome; FS+: those with the Flammer Syndrome; FS-: those without the Flammer Syndrome; PGE1: prostaglandin E-1; ET-1: endothelin- 1

Introduction

Borage (Boragio officinalis) [1] is a flowering herb native to Europe, North Africa and Asia. This plant is cultivated in several countries including Iran [2] which cultivates and exports thousands of tons of borage yearly to different markets. Boragio Officinalis has beautiful blue star-shaped flowers and brown nut-like shaped fruits (Figure 1). In contrast to Europeans who preferably drink coffee, Iranians prefer drinking tea [3,4] and actually have one of the highest rates of tea consumption in the world [5]. One treasured beverage, known for its medicinal properties [1] is borage tea. Throughout history borage has a long reputation for its various beneficial properties. Avicenna described the multiple effects of borage including "comfort to the pounding heart", The Roman naturalist Pliny believed that

borage "elevates a person's mood"; whereas Cleopatra used it as her "secret skin serum" [6].

Figure 1: Photograph of Boragio Officinalis with blue star-shaped flowers rich in polyphenols.

Today, these assumptions appear to hold some scientific truth. The flowers of borage show cardio depressant effects [7] mediated possibly though a calcium antagonising mechanism similar to Verapamil, and treatment with borage has been shown to reduce skin redness and roughness and improve skin hydration [8]. Besides these effects, one remarkable property is the ability of borage to reduce atherosclerosis [9] and exert both vasodilating [1,10] and bronchodilating [7] properties. These particular properties are due to the chemical constituents of borage.

Chemically, borage flowers are rich sources of vitamins A and C as well as carotenoids and polyphenols [1,2]. Polyphenolic compounds not only exert antioxidant properties [11,12], but in a series of studies have also shown to improve blood flow [13-17]. The seeds of borage are rich in gamma linolenic acid [2]. Gamma linolenic acid is an essential fatty acid that the body converts into prostaglandin E-1 (PGE1) [18, 19], in other words, it is an intermediate of PGE1 which, in turn, is an endogenous vasodilator which enhances blood flow [10].

The eye is one of the best-perfused organs in the body. One factor influencing this process is the ocular perfusion pressure (OPP) [20]. Traditionally, OPP is calculated as the difference between systemic blood pressure (measured in the upper arm) and intraocular pressure (IOP), in the assumption that retinal venous pressure is equal to IOP. In other words, a spontaneous venous pulsation is physiological. This assumption, however, is neither always correct for those with a disease (e.g. glaucoma) [21-23] nor for healthy subjects [22,24]. In particular, healthy people who suffer from a dysregulation of blood flow in the context of the Flammer Syndrome, [25] have higher retinal venous pressures [22,26].

On one particular clinical occasion, we observed by chance that the retinal venous pressure of an Iranian woman who suffered from the Flammer Syndrome [25] was reduced significantly after she had drunk borage for a month period to improve her skin complexion. The woman was young and healthy. Taking the above information into account we wondered whether borage tea would actually have an effect on the RVP of healthy people with the Flammer Syndrome and thus performed this investigation.

Materials and Methods

Participants

Participants were invited by an ophthalmologist (VZ) of the Farabi Eye Hospital in Teheran to participate in this study on a volunteer basis and received a routine ophthalmological check-up in return. The study was approved by the local ethical committee of Teheran University of medical sciences and all participants gave their consent to participate in the study. Also, this study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Included were 40 healthy subjects. Subjects were randomly assigned to one of equal two groups by picking out a "borage" or "water regime" card out of a stack of cards. Those for the borage regime were given 21 packs of each 10 grams of borage tea along with instructions for borage tea preparation. Excluded were subjects under local or systemic medication as well as subjects with a history of eye or general disease. None of the participants had any pathological findings (other than increased retinal venous pressure) in their routine ophthalmological examination. A distinction was made between subjects with (FS +) and those without (FS-) the Flammer Syndrome as follows.

The flammer syndrome

FS was defined as being present if it was detected in the patient history. FS was defined as present (FS+) in the patient history if the subjects answered five or more of the following six questions with "Yes", and as absent (FS-) if the subjects answered less than five questions with "Yes":

1) Do you suffer from cold hands or feet even in summer [27]?;

2) Do you have trouble falling asleep, especially when you are cold [28]?;

3) Are you seldom thirsty, and do you have to remind yourself to drink enough [29]?;

4) Do you suffer from migraine attacks [30]?,

5) Do you have low blood pressure [27]?,

6) Do you identify smells better than others [31]?

Borage tea brewing instructions

- Place ten grams of borage flowers in a tea pot.
- Add ¼ of a tea spoon of saffron dissolved in 4 large table spoons of boiling water to the tea pot.

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- Add three tea spoons of fresh lemon juice.
- Add 1 Liter of boiling water to the tea pot and allow the mixture to brew for 20 minutes.
- Remove the tea leaves and drink with a piece of rock candy or sugar depending on your taste.

Ophthalmodynamometric measurement of retinal venous pressure

Retinal venous pressure (RVP) was measured in both eyes of all participants in a sitting position by means of an ophthalmodynamometer (Meditron GmbH, Völklingen, Germany). All measurements were performed by the same ophthalmologist (VZ) who was blinded as to whether the subject was in the borage or the placebo group. This device consists of a conventional Goldmann contact lens fitted with a pressure sensor at its outer margin where the Goldmann contact lens is usually held during an ophthalmoscopic examination. The device is connected to an LCD screen.

Ophthalmodynamometry was conducted by applying increasing pressure to the eye via the contact lens. This applied pressure can be read as an IOP increase on the attached LCD screen based on a calibration curve. The IOP increase that is required to induce a venous pulsation is called the ophthalmodynamometric force (ODF). If a spontaneous venous pulsation is present, ODF is said to be 0, if not present, increasing pressure is applied. The RVP is defined and calculated as the sum of the ODF and IOP [RVP = ODF + IOP].

Statistical analysis

Statistical analysis was performed using SPSS 16.0 software (SPSS Inc, Chicago, Illinois, USA). The mean of RVP and IOP values in right and left eyes were calculated and used for analysis. Because of the small sample number in each group, nonparametric tests were used to analyse the data; Mann–Whitney U test for comparing the quantitative variables between two different groups (unpaired data) and Wilcoxon signed-rank test for before-after analyses (paired data). A p-value <0.05 was considered statistically significant.

Results

Forty individuals were assigned in the study. Half of them drank borage tea for three weeks. Flammer Syndrome (FS+) was present in twenty-one individuals. Mean ± SD of age in FS+ and FS- groups was 47.43±10.14 and 41.63±9.45 years, respectively (p=0.047, marginally significant). There was no difference in age in borage treated and untreated individuals. Baseline RVP values were significantly higher in FS+ subjects with a mean RVP of 36.93±9.06 than in FS- subjects with a mean RVP of 26.03±2.07 mmHg (P<0.001). Borage consumption significantly reduced RVP from 38.91±8.56 to 32.50±8.55 mmHg (p=0.003) in FS+ patients, without a significant change in IOP (Table 1, Figure 2). There was trend towards a decrease in RVP from a mean of 26.39±2.45 to 22.44±2.79 in FS- subjects which did not reach clinical significance (Table 2). No significant changes in IOP or RVP were accounted for in the placebo group (Figure 3).

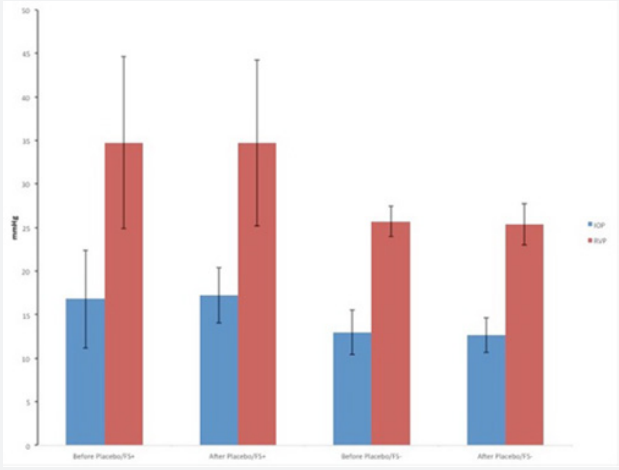

Figure 2: Box plot of the intraocular pressure (IOP) and retinal venous pressure (RVP) values in individuals with the Flammer Syndrome (FS+) and individuals without the Flammer Syndrome (FS-) before and after consumption of borage tea.

Table 1: Intraocular pressure and retinal venous pressure values of Flammer Syndrome (FS+) individuals in borage treated and untreated groups.

Borage treated individuals (n=11)			
	Before	After	p-value*
RVP (mean±SD)	38.91±8.56	32.50±8.55	0.003
IOP (mean±SD)	14.00±2.91	14.68±2.03	n.s
Placebo individuals (n=10)			
	Before	After	p-value*
RVP (mean±SD)	34.75±9.54	34.70±9.30	n.s
IOP (mean±SD)	16.80±4.54	17.20±2.66	n.s

*Wilcoxon Signed Rank test

RVP= retinal venous pressure, IOP=intraocular pressure, SD=standard deviation, FS += Individuals with the Flammer- Syndrome, n.s= not significant.

Table 2: Intraocular pressure and retinal venous pressure values of FS- individuals in borage treated and untreated groups.

Borage treated individuals (n=9)			
	Before	**After**	**p-value***
RVP (mean±SD)	26.39±2.45	22.44±2.79	n.s
IOP (mean±SD)	14.70±2.35	14.89±2.67	n.s
Placebo individuals (n=10)			
	Before	After	p-value*
RVP (mean±SD)	25.79±1.74	24.40±2.45	n.s
IOP (mean±SD)	13.00±2.48	12.65±1.81	n.s

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*Wilcoxon Signed Rank test

RVP= retinal venous pressure, IOP=intraocular pressure, SD=standard deviation, FS-= Individuals without the Flammer Syndrome, n.s=not significant.

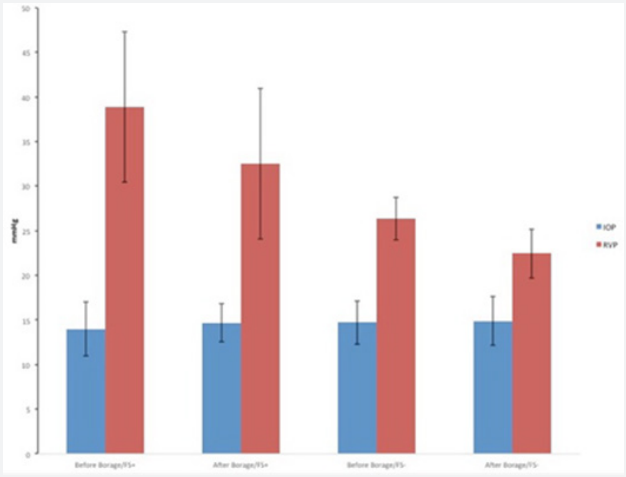

Figure 3: Box plot of the intraocular pressure (IOP) and retinal venous pressure (RVP) values in individuals with the Flammer Syndrome (FS+) and individuals without the Flammer Syndrome (FS-) before and after consumption of drinking water (placebo).

Discussion

Firstly, the study provides evidence that consumption of borage tea for three weeks reduces RVP. At this time we cannot fully explain why the components in borage may exert an RVP reducing effect. We can only hypothesize that it may be due to the calcium antagonizing side-effect of this plant [32]. Such an effect of borage has previously been demonstrated using isolated tissue preparations [7]. In this particular investigation borage leaves produced a concentration dependent relaxation of spontaneous and K+-induced contractions similar to the calcium channel blocker Verapamil. This explains the traditional use of Boragio Officinalis for its antispasmodic, vasodilator and cardio-depressant activities [7,33]. Secondly, the study confirms previous observations that subjects with FS have higher RVP than subjects without FS [22] The RVP reducing effect of borage seems to be stronger in the group with FS than in the group without FS. This effect is again most likely due to the calcium antagonizing side-effect of this plant [7]. People with the FS often respond much stronger to certain classes of drugs. In clinical settings we often observe that when treated e.g. systemically with calcium channel blockers these people often feel sick and have more side- effects than expected with regular dosages of systemic medications such as calcium channel blockers or beta blockers. If however, the same drugs are given to a much lower dosage the desired effect can still be observed but without or with much less side effects. This difference of sensitivity to drugs in subjects with FS can be explained by a different expression of ABC-transport proteins [34]. These are proteins that are involved in the transmembrane transport of drugs. This may explain why subjects with FS reacted stronger to the effects of borage than those without FS.

Despite the anatomically normal appearance of their vessels, people with FS have a disturbed autoregulation of their blood blow [35] and higher levels of systemic oxidative stress [36]. Increased levels of systemic oxidative stress, in turn, increase the synthesis of endothelin- 1 (ET-1) [37]. Endothelin-1, diffuses from the circulatory blood or is produced in the neural tissue of the retina [11] causing a local vasoconstriction of the vessels [38, 39] and leading to dysregulation of blood flow. Endothelin-1 values in people who suffer from FS are generally higher compared to healthy controls [40-42]. Borage exerts strong antioxidant activities linked to its diverse polyphenolic content [43] which improve blood flow [13-17]. Moreover, borage appears to decrease ET-1 levels, an effect most likely due to its calcium antagonizing side-effects. Calcium channel blockers can lead to vasodilation or relief from vasospasm [44, 45] and can partially block the effect of ET-1 [46].

Nutritional studies are usually difficult to perform and thus findings of this study should be interpreted with caution. This study has various limitations. Net hydration of the subject at the point of RVP measurement, blood pressure or the long-term fluctuation of RVP were not evaluated. Another problem that needs to be faced is one of standardization: Not each borage leaf may have the same quantity of antioxidants, not all subjects may be following their borage or water regimes as accurately as possible and finally there is little interest on the part of industries to invest in nutritional studies as they cannot patent for the natural herb itself and thus do not make as much money.

Conclusion

In conclusion, consumption of borage tea may decrease RVP. We assume this effect may be due to the calcium antagonizing side-effects of this plant. Further long-term research on the effect of borage on RVP is warranted.

Ethics Approval and Consent to Participate

The study was approved by the local ethical committee of Teheran University of medical sciences and all participants gave their consent to participate in the study. Also, this study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

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