·Clinical Research·

Neuroprotective effects of erigeron breviscapus (vant.) hand-mazz on glaucoma—A multi-center clinical trial

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Abstract

• AIM: To evaluate the neuroprotective effects of a Chinese herbal drug, erigeron breviscapus (vant.) hand-mazz (EBHM), on glaucoma patients with controlled intraocular pressure (IOP) after surgical and/or medical therapies.

• METHODS: A total of 99 primary glaucoma patients (113 eyes) with medically or surgically controlled IOP were given orally either EBHM or placebo for 6 months and then evaluated in a multi-center, prospective, randomized and double masked clinical trial by quantifying the visual field changes using visual field defect scoring (VFDS).

• RESULTS: After 2, 4, 6 months of treatment, the VFDS in EBHM Group (66 eyes/55 patients) decreased by 0.44±1.60, 1.27 ±2.16 and 1.42 ±2.37 respectively, indicating a time-dependent improvement of visual field upon EBHM treatment, whereas the VFDS in Placebo Control Group (47 eyes/47 patients) decreased by -0.02 ±1.5, 0.68 ±1.73 and 0.40 ±1.57 respectively. Statistically, the differences of VFDS between the two groups were significant (P<0.05) at 2 and 4 months, and highly significant at 6 months of treatment (P= 0.007). The average IOP in both groups was 15mmHg (range 8-18mmHg) during the period of the study (P>0.05). No serious side effects were reported in glaucoma patients on EBHM.

• CONCLUSION: EBHM appeared to be safe and effective in neuroprotection for patients with glaucoma. More studies are needed to determine the safety and effectiveness of longer-term EBHM treatment.

• KEYWORDS: erigeron breviscapus (vant.) hand-mazz; glaucoma; neuroprotection

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INTRODUCTION

Glaucoma, as a blindness-causing disease, is an optic neuropathy characterized by optic nerve damage. Up to now, almost all glaucoma treatments are aimed at lowering intraocular pressure (IOP) by pharmacological or surgical approaches since elevated IOP is believed to be the major risk factor. However, progressive loss of visual field or blindness can still occur in glaucoma patients with controlled IOP. It is now recognized that this disease has its major detrimental effect upon the eye by killing retinal ganglion cells. Therefore, neuroprotection based therapies to protect neurons are the most important in its management.

Jiang *et al* [1-8] have focused on the development of erigeron breviscapus hand-mazz (EBHM), a traditional Chinese herb, which is capable of preserving and /or improving visual field in IOP controlled glaucoma. Being considered as a neuroprotective drug, EBHM, commercially named Meierui and manufactured by Hunan Xiangya Pharmaceutical Co., was approved by China State Drug Administration to be

Table 1 Demographics, diagnosis, courses, intraocular pressure, stages, medical therapy, visual acuity with corrections, C/D, mean defects of the sensitivity of visual field and visual field defects scores between EBHM treated croup and Control Group prior to study

Variable		EBHM (n =55)	Control(n =44)	t	P
Sex	M	23	29	χ^2=5.689	0.017
	F	32	15		
Age (a,$\bar{x}\pm s$)		52.09 ± 16.55	56.66 ± 14.59	1.437	0.154
Diagnosis	POAG	35	21	χ^2=0.766	0.382
	ACCG	31	26		
Courses(mo)		44.20 ± 53.74	48.94 ± 72.90	0.398	0.691
IOP(mmHg,$\bar{x}\pm s$)		14.55 ± 2.26	14.02 ± 2.84	1.090	0.278
Stage	Early	21	21	χ^2=5.042	0.080
	Middle	25	20		
	Late	20	6		
Medication	No	46	34	χ^2=2.338	0.311
	One	18	9		
	Two	2	4		
Visual acuity with correction	0.8	40	28	χ^2=0.012	0.912
	0.5-0.7	26	19		
C/D ($\bar{x}\pm s$)		0.704 ± 0.193	0.706 ± 0.196	0.058	0.954
MD ($\bar{x}\pm s$)		9.386 ± 7.102	6.986 ± 4.695	2.161	0.033
VFDS($\bar{x}\pm s$)		6.34 ± 5.82	4.39 ± 3.97	2.118	0.036

Values are expressed as mean ± standard deviation; IOP= intraocular pressure; C/D = cup disc ratio; MD= mean defect of visual sensitivity;VFDS= visual field defect score

used in clinical settings in 2001. In order to evaluate the effectiveness of this drug in glaucoma patients, a multi-center, prospective, randomized and double masked clinical trial was conducted in a group of patients with primary open angle glaucoma and angle-closure glaucoma.

MATERIALS AND METHODS

Patients This study, which was obtained from the Ethics Ethnic Committee of Xiangya Medical College, Central South University, China, was conducted from May 2002 to January 2003 in the following hospitals: Beijing Tongren Hospital, Beijing Union Hospital, Shanghai Eye and ENT Hospital of Fudan University, Hospital of Qingdao Medical College, Ruijin Hospital of the Second Shanghai Medical University, West China Hospital of Shichuan University, Eye Center of Beijing University and Xingtai Eye Hospital.

Patients were selected for this clinical trial based on the following inclusion criteria: ① aged from 18 to 70 years old with primary open angle glaucoma or chronic angle-closure glaucoma. Anti-glaucoma surgeries were performed at least 3 months ago with type I or type II filtering blebs developed. Mean IOP was 18mmHg or lower with or without medication at two measurements (10 am and 3 pm); ② clear ocular media and 6.0D or less with best-corrected visual acuity of 20/60 or better; ③ no evidence of retinal abnormalities that might influence the pattern of visual field loss, including diabetic retinopathy, macular degeneration, and retinal vascular occlusion; ④ patients had stopped taking medications that may help the recovery of visual functions, including ATP, inosine, red sage root, vitamins and other products. All the participants must sign the consent. Exclusion criteria: ① histories of serious systemic diseases, which would affect his/her ability to participate in this trial (e.g., primary hypertension, heart diseases, gastric ulcer and diabetes); ② inability or unwillingness to provide informed consent or abide by the study protocol; ③ IOP could not be reduced to 18mmHg or less by medications; ④ late or end stage in glaucoma incapable of being evaluated by automated static threshold perimetry or advanced visual field loss (RF>20%); ⑤ hypotony (IOP ≤7mmHg) with thin filtering cystic bleb or bleb leakage; ⑥ participants with noted side effects due to the drug based on physician's judgment.

Ninety-nine participants (113 eyes), as summarized in Table 1, were randomly recruited in this clinical trial, including 55 patients(66 eyes) in EBHM Group and 44 patients (47 eyes) in Placebo Control Group (Table 1).

Methods This is a prospective, randomized and double masked clinical trial. EBHM and placebo (both tablets look the same) were provided by Xiangya Pharmaceutical Co.. The participants were given orally either EBHM or placebo 2 tablets each time, three times a day for a period of 6 months. Patients were examined based on the following two criteria before and at 2, 4 and 6 months after treatment: ① effectiveness or ineffectiveness criteria including visual field (automated static threshold perimetry, threshold program 24-2); corrected visual acuity (the Snellen E Chart at 5m); IOP by Goldmann tonometer; fundus examination for

vertical C/D ratio by direct ophthalmoscope; blood pressure and pulse rate, and ② safety criteria including a complete physical examination, gastric side effects and other adverse effects of the drug.

The algorithms for visual field defect score (VFDS) [9], ranging from 0(no defect) to 20(end-stage), developed by the Advanced Glaucoma Intervention Study Investigators (AGIS, 1994)[10] was employed to evaluate the changes/defects in visual field over time in each treatment group.

Statistical Analysis SPSS for Windows Release 10.0 was used for statistical analysis. All results are expressed as the mean± SD. The data were processed for statistical analysis with student's *t*-test for differences between EBHM Group and Placebo Group, paired *t*-test for difference between pre-and post-treatment in the same group, and linear regression analysis for the relation between two variables. For all tests, $P<0.05$ was considered as statistical significance.

RESULTS

General Information In total 237 patients were recruited in the initial trial. Forty-three (18.1%) patients failed to complete the procedure for the following reasons: loss of follow-up(38 patients); development of diarrhea and swollen leg, not being related to the drug as verified(2 patients), body itch, tachycardia, dizziness and asthma (2 patients) as well as feeling "ineffectiveness" and stopped taking the drug on his own (1 patient). Among the remained 194 patients who completed the procedure, 70(36.1%) patients failed to meet the requirement of visual field test, 23 (11.9%) patients had uncontrolled IOP (>18mmHg) and 2 (1.0%) exhibited progressive cataract, leaving a total of 99 (51%) patients, including 55 patients (66 eyes) in EBHM Group and 44 patients (47 eyes) in Placebo Control Group, for analysis.

General information about the patients recruited in this study is summarized in Table 1, including case numbers in both EBHM and Control Group, gender, age, type of glaucoma, IOP, stages and courses of glaucoma, IOP reducing medication usage, corrected visual acuity, MD and VFDS values. There were no significant differences in all the parameters between the two groups, except for gender (female is more common in EBHM Group), MD and VFDS ($P<0.05$). The visual field defect was more predominant in EBHM Group than that in Placebo Group.

Intraocular Pressure The mean IOP was less than 15mmHg in both groups: 14.9±1.72 (range 8- 18)mmHg in EBHM Group and 14.68±2.08(range 8-18)mmHg in Placebo Group. The difference in IOP between the two groups was not significant at each time point (Table 2).

Table 2 The comparison of IOP before and after EBHM therapy

(mmHg, $\bar{x}\pm s$)

Month	EBHM (n =66 eyes)	Control (n =47 eyes)	t	P
0	14.55 ± 2.26	14.02 ± 2.84	1.090	0.278
2	14.52 ± 2.16	14.49 ± 2.59	0.068	0.946
4	15.09 ± 2.16	15.13 ± 2.14	0.092	0.927
6	15.48 ± 2.13	15.07 ± 2.23	0.980	0.329
Total	14.91 ± 1.72	14.68 ± 2.08	0.644	0.521

Visual Field Defect Score After 2, 4, 6 months of treatment, the VFDS in EBHM Group (66 eyes/55 patients) decreased by 0.44±1.60 (-5-6), 1.27±2.16 (-4-3) and 1.42± 2.37 (-5-6) respectively and the differences were statistically significant ($P<0.01$), indicating a time-dependent improvement of visual field upon EBHM treatment, whereas the VFDS in Placebo Control Group (47 eyes/44 patients) decreased by -0.02±1.5(-4-5), 0.68±1.73(-4-4) and 0.40±1.57 (-3-4) respectively and the differences were significant except for that at 4 months ($P<0.05$). The differences in VFDS between the two groups were statistically significant ($P<0.05$) at 2 and 4 months and highly significant at 6 months ($P<0.01$) (Table 3).

The VFDS in EBHM Group decreased time-dependently as shown by a linear correlation between VFDS and the duration of treatment ($r = 0.971$, $P = 0.029$). The linear regression equation is: $Y=0.019+ 0.255X$(X: treatment time/month; Y: VFDS). There was no linear correlation between VFDS and the duration of treatment in Placebo Group ($r = 0.727$, $P= 0.273$)(Figure 1).

Changes for visual field upon treatment were evaluated as follows: ① improved: VFDS decreased by 4 or greater; ② unchanged: VFDS increased or decreased by less than 4, and ③ regressed: VFDS increased by 4 or greater. With this criterion, our results of visual field scoring after treatment for 6 months showed the numbers of the improved, unchanged and regressed cases were 12, 54 and 0 respectively in EBHM Group; 0, 46 and 1 respectively in Placebo Group (Table 4). The improvement rates for EBHM Group and Placebo Group were 18.18% and 0% (χ^2 test, $P=0.005$).

Visual Acuity Changes for visual acuity upon treatment were evaluated by using Snellen Visual Acuity Chart as follows: ① improved: 2 or more lines improvement, and ② unchanged: none or just 1 line improvement or worse. With this criterion, the improvement rates of visual acuity after treatment for 6 months in EBHM and Placebo Group were 20.50% and 18.18% (χ^2 test, $P > 0.05$).

Physical Examination There is no significant difference found in blood pressure (both diastolic and systolic blood

Table 3 The comparison of VFDS reduction at 2,4,6 months after treatment ($\bar{x} \pm s$)

Months	EBHM (n =66 eyes)			Control (n =47 eyes)			[b]t	[b]P
	VFDS reduction	[a]t	[a]P	VFDS reduction	[a]t	[a]P		
2	0.44 ± 1.60	2.268	0.027	-0.02 ± 1.5	0.103	0.918	1.550	0.124
4	1.27 ± 2.16	4.875	0.000	0.68 ± 1.73	2.893	0.006	1.555	0.123
6	1.42 ± 2.37	4.964	0.000	0.40 ± 1.57	1.893	0.065	2.748	0.007

[a] intra-group paired t-test between pre- and post-treatment; [b]comparison of VFDS reduction between two groups at the same time, t-test

Table 4 Comparison of the visual field after 6-month therapy

Group	eye(n)	Improve(%)	No change(%)	Worse(%)	χ^2	P
EBHM	66	12(18.18)	54(81.82)	0(0.0)	10.749	0.005
Control	47	0(0.0)	46(97.87)	1(2.13)		

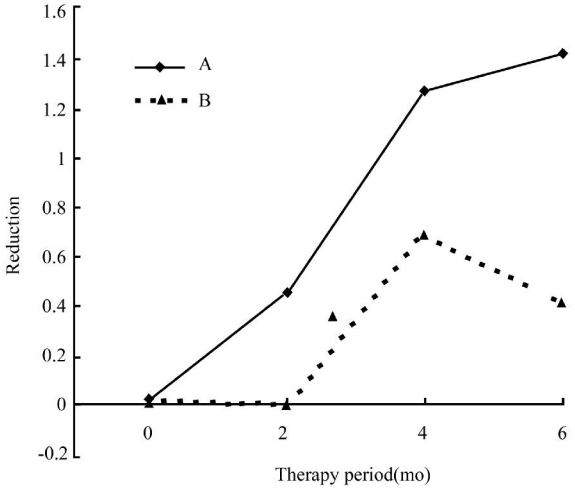

Figure 1 VFDS reduction curves in two groups A:EBHM Group;B:Control Group

Table 5 The percentage of visual acuity improvement after 6-month therapy

Group	eyes (n)	Improve (%)	No change (%)	χ^2	P
EBHM	66	10(20.59)	56(79.41)	0.129	0.720
Control	47	6(18.18)	41(81.82)		

ANOVA test

pressure) or pulse rate between the two groups, either before or after treatment.

DISCUSSION

EBHM, a whole dry herbal plant, is classified as a Chinese herbal medicine. Its main components include 4'-hydroscutellarein,4'-hydrobaicalein-7-β-D-plamyagin,4'-hydrosutellarein-7-β-D-glycuron methyl ester, pyromeconic acid and several kinds of flavones. Previous pharmacological studies demonstrated that EBHM is able to dilate the blood vessels, reduce blood vessel resistance, increase blood flow, improve microcirculation and inhibit thrombosis. Works from Jiang *et al*[3-6, 8] showed that EBHM is capable of ① improving the activity of cytochrome oxidase in retinal ganglion cells and optic nerve axoplasmic transport of rat models with acute elevated IOP; ② stimulating the recovery of axoplasmic transport of injured or dying RGC in calibrated crush injury of rat optic nerve, and③ protecting, at least partly, RGC in rats against N-Methyl-D-aspartate(NMDA)-induced damage. Clinically, a retrospective study [1] showed that the visual field improvement rate was 22.8% (Esterman grids) in glaucoma patients treated with EBHM for 2-6 months. A prospective, double-masked, randomized clinical trial[2] of 51 IOP controlled glaucoma patients demonstrated that the visual field improvement rate was 93.10% upon EBHM treatment. Another prospective randomized clinical study [7] of 45 glaucoma patients treated with EBHM for 6 months exhibited that the mean sensitivity(MS) increased by 1.42dB in EBHM Group, and decreased by 0.95dB in Control Group. The improvement rates of visual field in EBHM and Control Group were 56.52% and 4.55% respectively. These clinical trials indicated that EBHM is effective in preservation and improvement of visual field in IOP controlled glaucoma patients even at middle or late stages.

The AGIS investigators[10] reported a retrospective study of 49 patients (73 eyes). The IOP dropped to 16.7mmHg at 1 year, and remained in this range(14.7mmHg) throughout a 10-year follow-up after conventional filtration surgery. The probability of progression to blindness was 46% at 10 years after surgery. Eyes going blind had postoperative IOP equal to or lower than those not becoming blind. Eyes going blind had more advanced field loss at the time of surgery, with scotomas above and below the horizontal axis, than those not going blind which had scotomas in only one hemifield. The

results indicated that the patients with more advanced field loss at the time of surgery appeared to have worse prognosis in visual function.

The current multi-center, prospective, randomized and clinical trial showed that the VFDS in EBHM Group decreased by 1.42, whereas the VFDS in Placebo Control Group only decreased by 0.40. Interestingly, VFDS decreased by 2.21 in glaucomatous eyes at the middle and late stages in EBHM Group, which suggested that EBHM appeared to be more effective in protection and/or recovery of the seriously injured RGC. It is also possible that the method for visual field screening used in this study is less sensitive for glaucomatous eyes at early stage compared to middle or late stages. In addition, qualitative analysis for the changes in morphology of visual field defect, other than quantitative analysis for different stages of visual field defects categorized according to the retinal sensitivity, was used in most previous studies. Further studies are needed to elucidate the mechanisms of the differences in effectiveness of EBHM at different stages of visual field loss.

It is well known that elevated IOP is the most important factor for glaucomatous optic neuropathy and, as a result, lowering IOP is the most effective and commonly used therapeutic approach in glaucoma treatment. Our results demonstrated that the mean IOP in the two groups was less than 15mmHg (EBHM Group: 14.91mmHg; Placebo Group: 14.68mmHg) and there was no statistically significant difference in IOP between the two groups during follow-up (every 2 months, till the end of the 6th month). We therefore concluded that EBHM is effective in rescuing glaucomatous optic neuropathy while the IOP is controlled to normal or below.

Wheeler *et al*[11] suggested that the treatment course of neuroprotective reagent used for IOP controlled glaucoma should be long enough before any evaluation regarding its effectiveness can be made conclusively. Even with limited resources of both participants and the supply of the pharmaceutics, our 6-month study has indicated a neuroprotective effect of EBHM on glaucomatous neuropathy. However, it should be noted that, as a first-time multi- center clinical trial, we were short of experiences needed for this type of study. Furthermore, there were obstacles in cooperation and communication between the examiners and patients, especially when a psycophysical examination was conducted, as evidenced by the high rate of loss of follow-up and excluded cases.

Up to date, there is no "golden standard" available for the estimation of glaucomatous visual field loss. Hills and Johnson [12] elucidated that *t*-test was very sensitive to small changes of the entire visual field. However, *t*- test was unable to reliably detect small and moderate scotoma. These findings suggest that *t*-test has limited clinical practicability for objective detection of glaucomatous visual field loss that is not characterized by the changes of the entire visual field. The tendency of visual field changes during a certain amount of time (5 times of examination at least) could be depicted by linear regression analysis. Its application is still limited, based on the reasons described above. Heijl [13] postulated that the correct evaluation of the progressive rate of glaucomatous visual field is determined by "the status of tested point (defect or normal)", eccentricity, and the status of the entire visual field. It is more important to detect the new defect in an area that is previously normal than the changes in the defected area, for the threshold at the defected spot is more fluctuated. Our study used the VFDS for not only the quantitative analysis of the defected areas but also the qualitative analysis of characterized glaucomatous visual field loss, therefore being able to objectively evaluate the visual field changes.

Consistent with the previous observation by Jia *et al* [2], no serious side effects in cardiovascular or other systems were observed during the 6-month clinical trial, which suggested that EBHM can be safely used in preserving and enhancing survival of RGC of IOP controlled primary open angle glaucoma and angle-closure glaucoma.

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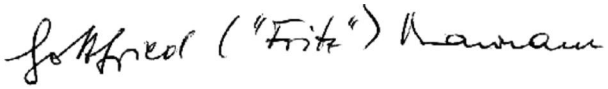
A letter from Prof. G O H Naumann, MD (Immediate Past–President of ICO/IFOS)

Dear Professor Xiu–Wen Hu!
Dear Colleague!

Thank you so much for your kindness in sending me the latest issue of your "International Journal of Ophthalmology".
Your most generous book review summarizes our attempts to stress the foundation of ophthalmic microsurgery by focusing on ophthalmic pathology.
You clearly describe my intentions and I am grateful for you making young ophthalmologists aware of our work.
Judging from the pictures and the English summary I am most impressed about the positive development of the Journal that you edit.
Looking forward to seeing you at the next occasion on one of our ophthalmological meetings around the world, I remain.

Sincerely Yours



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