Neuroprotective effects of wolfberry in normal tension glaucoma: abridged secondary publication

JSM Lai *, HHL Chan, JCH Chan, ACY Lo, JWY Lee, RCC Chang, KF So

KEY MESSAGES

1. Normal tension glaucoma can progress in the absence of high intraocular pressure.
2. Neuroprotection supplements the therapeutic effect of anti-glaucoma medications.
3. Daily oral wolfberry food supplement for 2 years does not show additional beneficial effect in the treatment of normal tension glaucoma.

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JSM Lai, HHL Chan, JCH Chan, ACY Lo, JWY Lee, RCC Chang, KF So

Department of Ophthalmology, The University of Hong Kong

* Principal applicant and corresponding author: smjlai@netvigator.com

Introduction

We conducted a prospective randomised control study to investigate the neuroprotective effect of wolfberry supplement in normal tension glaucoma (NTG), which is a progressive optic neuropathy that occurs under normal (<21 mmHg) intraocular pressure (IOP). Contributing factors may include nocturnal hypotension, increased blood viscosity, and genetic factors. NTG is associated with migraine headaches, Raynaud phenomenon, and diffuse cerebral ischaemia. Similar to other types of glaucoma, NTG results in progressive and irreversible retinal ganglion cell death that manifests as visual field loss and thinning of the retinal nerve fibre layer (RNFL). The progressive damage of the optic nerve is not caused by high IOP. Despite this, reduction of the IOP slows down the progression of the disease, but in many cases the disease still progresses despite a low IOP.

Wolfberry (*Lycium barbarum*) has been proven in rats to promote retinal ganglion cell survival against elevated IOP.[1,2] The neuroprotective effects of wolfberry are partly due to modulating the activation of the retinal microglia.[3] In animal studies, wolfberry protects neurons from ischaemic and toxic stresses to the brain.[4,5] This study aims to investigate the neuroprotective effects of oral wolfberry supplement in NTG.

Methods

This study was conducted in the eye clinic of the Grantham Hospital. Ethics approval was obtained prior to the commencement of the study. Informed consent was obtained from each participant. Patients with NTG who required anti-glaucoma treatment were invited to participate. NTG was defined as glaucomatous cupping that resulted in general or focal neuroretinal rim thinning, disc haemorrhage, or intereye cup/disc ratio asymmetry of >0.2, and visual field defects, with an IOP consistently <21 mmHg. Diagnosis of NTG was made based on the Goldmann tonometer for IOP, gonioscopy examination of the drainage angle, cup-disc ratio assessment, visual field test using the Humphrey Visual Field Analyzer, and optical coherence tomography of the RNFL thickness using the Heidelberg Spectralis system. For the visual field test, the 24-2 Swedish Interactive Thresholding Algorithm full-threshold Humphrey visual field was used. Medical records and IOP levels of eligible subjects were reviewed before commencement of ocular-hypotensive treatment. Only those with two consecutive pre-treatment IOP of <21mmHg were invited to participate.

Participants were assigned randomly to the control group (topical anti-glaucoma medications) or the wolfberry group (taking 20 wolfberry dry seeds per day) in addition to topical anti-glaucoma medications, which include prostaglandin analogue, carbonic anhydrase inhibitor, beta-blocker, and alpha-agonist. These drugs were used in the above sequence as monotherapy or in combination.

All participants were followed up every 4 months for 2 years. In each visit, they underwent ophthalmic tests including visual acuity test, IOP measurement, gonioscopic examination of the drainage angle, and cup-disc ratio assessment. They attended the eye clinic every 6 months for visual field test and RNFL thickness measurement.

The primary outcome measures were change in the mean RNFL thickness and change in the mean deviation (MD) in the visual field 24-2 tests. The visual field test result with fixation loss, false positive and negative values <20% for the test was considered reliable. For the RNFL measurement, images with signal strength <8 were discarded. The mean RNFL thickness in each of the superior, inferior, nasal, and temporal quadrants was calculated. The secondary outcome measures were the IOP and the cup-disc ratio.

Results

Between December 2014 and December 2016, 113 patients were recruited. Of them, 30 withdrew from the study and 83 (44 in treatment group, 39 in control group) completed the 2-year follow-up. The two groups were comparable in terms of the demographics and baseline clinical parameters (Table 1).

The rates of visual field loss were evaluated by the parameter MD over time through linear mixed models. The rates of RNFL loss over time were evaluated by the mean thickness of RNFL of four quadrants by linear mixed models, in which the average evolution of the outcome variable (ie, MD and RNFL thickness) is described using a linear function of time. Random intercepts and random slopes introduce subject and eye-specific deviations from this average evolution. The model can account for the fact that different eyes may have different rates of visual field loss over time, while also accommodating correlations between both eyes of the same individual. Slopes for individual eyes were estimated by best linear unbiased predictions. Covariates of age, baseline IOP, and baseline average cup-to-disc ratio were adjusted in the mixed linear models. Changes of both the MD and the RNFL thickness were not significant after controlling for age, laterality, baseline MD, baseline IOP, and average cup-disc ratio (Table 2).

Discussion

NTG can develop and progress even in the absence of a persistently elevated IOP. Unstable blood perfusion to the optic nerve may play a role in the pathogenesis. Patients with systemic hypotension, migraine, or obstructive sleep apnoea are at higher risk of developing NTG. Although NTG is IOP-independent, reduction of IOP is effective in slowing down progression of NTG in most cases. Factors that cause unstable blood perfusion to the optic nerve can hardly be altered. Neurologists aim to develop pharmacological agents to protect the nerve and brain tissues. Wolfberry (*Lycium barbarum*) has been proven in a rat model to promote retinal ganglion cell survival against elevated IOP.[1,2] Wolfberry modulates the activation of the retinal microglia to exert its neuroprotective effects.[3] However, this study failed to demonstrate an additional benefit of daily consumption of wolfberry for 2 years in terms of visual field MD and RNFL thickness.

There were limitations to this study. Failure to show a significant difference may be due to the short follow-up period, as glaucoma is a slow progressive disease and may take 5 to 10 years to see the therapeutic effect of the wolfberry supplement. In addition, the sample size may be underpowered. In sample size calculation, it was assumed that 20% of cases would have fast progression with visual field index change >3 dB/year. A more accurate sample size calculation should have been adopted, taking into account the percentage of fast progression in practice. Subjects often decided not to join the study once they knew they were randomised into the control group. This resulted in a relatively long enrollment period. The drop-out rate was high (26.5%), owing to compliance to the treatment protocol. Subjects in the treatment group might not adhere to the dosage of the prescribed oral wolfberry, and subjects in the control group might have taken self-purchased wolfberry. The initial design was to supply wolfberry tablets and placebo tablets. However, owing to the strict regulations for clinical trials, no commercial drug firm agreed to manufacture wolfberry tablets. Therefore, wolfberry dry seeds were used. In addition, dry seeds contained numerous fibres and the dosage was difficult to quantify. The quality of the seeds varies at different times of the year; this may influence their effect. A larger-scale double-blind randomised controlled study using quantified tablets that contain consistent ingredient concentration can increase the recruitment rate and minimise the dropout rate. A longer follow-up for at least 5 years is needed to show any neuroprotective effect of wolfberry.

TABLE 1. Demographic and clinical characteristics of study subjects

Characteristic	Control group (n=39)	Treatment group (n=44)	P value
Age, y	69	74	0.069
Right eye	36	41	
Left eye	31	41	
Visual field baseline	-8.63±7.72	-8.78±6.46	0.896
Visual field mean deviation change	-1.34±3.51	-0.56±2.46	0.136
Retinal nerve fibre layer thickness			
At baseline			
Superior	84.98±20.30	82.65±16.77	0.449
Nasal	65.71±10.82	64.62±10.00	0.529
Temporal	58.20±13.92	59.78±13.03	0.482
Inferior	74.22±19.61	75.41±17.34	0.698
Overall	70.78±12.16	70.61±10.28	0.930
Change			
Superior	-0.15±4.96	-0.14±5.55	0.984
Nasal	-0.43±5.54	0.04±5.83	0.623
Temporal	0.34±3.99	0.52±5.19	0.818
Inferior	0.19±7.94	-0.36±5.22	0.608
Overall	-0.01±4.06	0.01±3.43	0.969
Intraocular pressure at baseline, mmHg	13.69±2.99	13.21±2.58	0.311
Average cup-disc ratio at baseline	0.79±0.76	0.77±0.10	0.285
Vertical cup-disc ratio at baseline	0.79±0.08	0.77±0.10	0.252

* Data are presented as mean or mean±standard deviation

TABLE 2. Multivariable models assessing the changes of visual field in mean deviation between groups over time adjusting for age, laterality, baseline intraocular pressure, and baseline cup-disc ratio

Parameter	Visual field mean deviation change		Retinal nerve fibre layer thickness change	
	Coefficient (confidence interval)	P value	Coefficient (confidence interval)	P value
Groups	-0.66 (-2.2 to 0.91)	0.315	0.34 (-0.11 to 0.78)	0.14
Baseline intraocular pressure	-0.018 (-0.30 to 0.26)	0.84	-0.11 (-0.18 to -0.046)	0.001
Average cup-disc ratio	-2.4 (-11 to 5.9)	0.51	-5.26 (-8.1 to -2.4)	<0.001
Age	-0.029 (-0.081 to 0.023)	0.27	-0.21 (-0.42 to -0.00023)	0.048

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References

1. Chan HC, Chang RC, Ip KC, et al. Neuroprotective effects of Lycium barbarum Lynn on protecting retinal ganglion cells in an ocular hypertension model of glaucoma. Exp Neurol 2007;203:269-73.
2. Chiu K, Zhou Y, Yeung SC, et al. Up-regulation of crystallins is involved in the neuroprotective effect of wolfberry on survival of retinal ganglion cells in rat ocular hypertension model. J Cell Biochem 2010;110:311-20.
3. Chiu K, Chan HC, Yeung SC, et al. Modulation of microglia by Wolfberry on the survival of retinal ganglion cells in a rat ocular hypertension model. Ocul Biol Dis Infor 2009;2:127-36.
4. Yang D, Li SY, Yeung CM, et al. Lycium barbarum extracts protect the brain from blood-brain barrier disruption and cerebral edema in experimental stroke. PLoS One 2012;7:e33596.
5. Li SY, Yang D, Yeung CM, et al. Lycium barbarum polysaccharides reduce neuronal damage, blood-retinal barrier disruption and oxidative stress in retinal ischemia/reperfusion injury. PLoS One 2011;6:e16380.