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Research article

Effect of Korean Red Ginseng supplementation on dry eye syndrome in glaucoma patients – A randomized, double-blind, placebo-controlled study

Hyoung Won Bae [1], Ji Hyun Kim [2], Sangah Kim [1], Minkyo Kim [1], Naeun Lee [3], Samin Hong [1], Gong Je Seong [1], Chan Yun Kim [1,*]

[1] Department of Ophthalmology, Severance Hospital, Institute of Vision Research, Yonsei University College of Medicine, Seoul, Korea
[2] Siloam Eye Hospital, Seoul, Korea
[3] Department of Ophthalmology, Hallym Hospital, Incheon, Korea

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ABSTRACT

Background: Many patients with glaucoma have difficulty using antiglaucoma eye drops because of dry eye symptom. In this prospective, randomized, double-blind, placebo-controlled study, we evaluated the effect of Korean Red Ginseng on dry eye syndrome in patients with glaucoma treated with antiglaucoma eye drops.

Methods: Forty-nine participants were allocated to the Korean Red Ginseng (3 g/day; $n = 24$) or placebo ($n = 25$) groups for 8 weeks. Tear film stability, fluorescein corneal staining, conjunctival hyperemia, tear production, grade of meibomian gland dysfunction, and dry eye questionnaire (Ocular Surface Disease Index) were evaluated at baseline and on completion of the treatment.

Results: Almost all patients displayed dry eye symptoms and signs at baseline. After the 8-week intervention, Korean Red Ginseng supplementation significantly improved the tear film stability and total Ocular Surface Disease Index score, as compared to placebo ($p < 0.01$).

Conclusion: Korean Red Ginseng supplementation may provide an additional treatment option for dry eye and patients with glaucoma using antiglaucoma eye drops.

1. Introduction

Glaucoma is a chronic and progressive optic neuropathy characterized by visual field loss and is the second leading cause of global blindness after cataract [1]. The primary goal of glaucoma treatment is to reduce intraocular pressure (IOP) using antiglaucoma eye drops, laser treatment, or surgery [2,3]. Antiglaucoma eye-drop application is the most common therapy, and can significantly lower IOP and delay glaucoma progression [4,5]. However, patients with glaucoma who use antiglaucoma eye drops have been shown to have a higher prevalence of ocular surface disease than the normal population [6,7]. Irritation and conjunctival hyperemia induced by dry eyes are among the main problems when treating patients with glaucoma who require a lifetime management [8–10]. Dry-eye therapy has been solely symptomatic, mainly by the application of artificial tears. However, numerous recent studies have demonstrated that inflammation and apoptosis may play key roles in the development of dry eye syndrome (DES) [11–16].

Ginseng (the root of *Panax ginseng* Meyer) is a valuable folk medicine used in East Asian countries. The two kinds of ginseng, air-dried white ginseng and steamed red ginseng, harbor a variety of active components, including ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids, and its diverse pharmacological effects have been observed in the central nervous system and the cardiovascular, endocrine, and immune systems

* Corresponding author. Department of Ophthalmology, Severance Hospital, Institute of Vision Research, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemun-gu, Seoul 120-752, Korea.
E-mail address: kcyeye@yuhs.ac (C.Y. Kim).

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[17–25]. Korean Red Ginseng (KRG) is known to have more pharmacological effects than raw ginseng because of the change of its chemical components (such as Rg3 and Rh2) that are produced in the steaming process [26].

Because of chronic inflammation, conjunctival pathological changes, including squamous metaplasia and goblet cell loss, have been found on cytological analysis of dry eye disease and, thus, anti-inflammatory drugs, such as topical steroid and cyclosporine A, are effective agents for DES [27,28]. In an earlier study performed by the authors [29], participants stated that the discomfort caused by antiglaucoma eye drops was relieved by KRG intake. Furthermore, the symptoms and signs of dry eyes were improved in some of these patients.

In this randomized, double-blind, placebo-controlled study, we examined the effect of KRG supplementation on DES in patients with glaucoma.

2. Materials and methods

2.1. Ethical statement

This prospective, randomized, double-blind, placebo-controlled, parallel group study was performed at the glaucoma clinic of the Severance Hospital, Seoul, Korea. The study was conducted in accordance with the Declaration of Helsinki, and informed written consent was obtained from each participant. The Institutional Review Board of the Yonsei University Health System approved the study protocol.

2.2. Participants

Participants were enrolled prospectively between July 2013 and December 2013. Inclusion criteria were an age of 20–75 years, diagnosis of glaucoma, established topical hypotensive therapy using only travoprost, and presence of subjective dry eye symptoms, including a tear film breakup time (TBUT) < 10 seconds and a Schirmer I test < 15 mm in at least one eye. One eye of each patient was selected randomly when both eyes were eligible. Glaucomatous eyes were defined by a glaucoma specialist based on a glaucomatous visual field (VF) defect confirmed by two reliable VF tests and typical appearance of a glaucomatous optic nerve head including cup-to-disc ratio > 0.7, intereye cup asymmetry > 0.2, or neuroretinal rim notching, focal thinning, disc hemorrhage, or vertical elongation of the optic cup. Exclusion criteria included a history of any ocular surgery, evidence of acute or chronic infections, an inflammatory condition of the eye, a history of intolerance or hypersensitivity to any component of the study medications, women of childbearing age, and the presence of current punctal occlusion. Patients with media opacity or other diseases affecting the VF were also excluded. All participants were provided with the same artificial tears (1 mg sodium hyaluronate) to use as required during the study period, whereas individuals who were on medications for dry eye treatment other than artificial tears were excluded.

2.3. Study design

Participants were randomized to receive one of two treatment regimens for 8 weeks. The treatments were 1 g of KRG administered as two 500-mg powder capsules or placebo administered as two identically appearing capsules, taken three times daily in both groups. KRG powder was manufactured by the Korea Ginseng Corporation (Seoul, Republic of Korea) from roots of a 6-year-old KRG, *Panax ginseng*, harvested in the Republic of Korea. KRG was made by steaming fresh ginseng at 90–100°C for 3 hours and then drying at 50–80°C. KRG powder prepared from grinded red ginseng, and a capsule contained 500 mg of powder. KRG was analyzed by high-performance liquid chromatography. KRG extract contained major ginsenoside-Rb1: 5.61 mg/g, -Rb2: 2.03 mg/g, -Rc: 2.20 mg/g, -Rd: 0.39 mg/g, -Re: 1.88 mg/g, -Rf: 0.89 mg/g, -Rg1: 3.06 mg/g, -Rg2s: 0.15 mg/g, -Rg3s: 0.17 mg/g, -Rg3r: 0.08 mg/g, and other minor ginsenosides. Placebo capsules were also provided by the Korea Ginseng Corporation, and they were identical in size, weight, color, and taste. The participants were instructed to avoid taking other forms of KRG or any type of ginseng for the duration of the study.

Group assignment of the participants was determined prior to the initiation of the study. Block randomization, which was generated by our institutional biostatistics department using a computer-generated random sequence, was used to randomize the participants. Study investigators, participants, and their caregivers were blinded through the provision of the medication as identically appearing capsules in boxes, with neither the investigator providing the medication nor the participants aware of the allocated treatment.

We performed objective clinical measurements of all participants, including tear film stability (TBUT), ocular surface health (fluorescein ocular surface staining), conjunctival hyperemia, tear production (Schirmer I test), and the grade of meibomian gland dysfunction (MGD), at baseline and again 8 weeks after the daily oral administration of 3 g of KRG or placebo. Subjective assessment of DES using a questionnaire was also conducted at each visit.

2.4. Outcome measures

The TBUT was identified following the procedure reported by Lemp [30]. A fluorescein strip (Haag-Streit AG, Köniz, Switzerland) was moistened with a drop of saline solution, and placed on the inferior palpebral conjunctiva. The patients were asked to blink several times to mix the fluorescein with the tear film. They were instructed to open their eyes and not blink, and the time between eye opening and the appearance of the first dry spot was measured in seconds. This procedure was repeated three times, and the mean of the three measurements was recorded finally as TBUT.

After the measurement of the TBUT, fluorescein staining on the ocular surface was evaluated using the standardized methods recommended by the National Institutes of Health Symposium on Dry Eye [30]. Briefly, corneal staining was scored 3 minutes after fluorescein instillation by observing the cornea through a cobalt blue light. It was graded using a scale of 0–3 (absent to diffuse) and recorded for the five corneal sections (central, superior, temporal, nasal, and inferior.). The maximum score for each area was 3. The scores of the five areas were summed to obtain a total score for each eye, producing a maximum score of 15.

Conjunctival hyperemia was evaluated by the investigator based on a visual inspection. A standard five-point scoring system was used with the following descriptors based on photographic standards: 0 (none) = normal, bulbar conjunctival vessels easily observed; +0.5 (trace) = trace flush, reddish-pink color; +1 (mild) = mild flush, reddish color; +2 (moderate) = bright red color; and +3 (severe) = deep, bright, diffuse redness.

The Schirmer I test was performed under anesthesia. To obtain anesthetic conditions of all the ocular structures, more than three drops of topical anesthetic (proparacaine hydrochloride ophthalmic solution 0.5%) were applied to the conjunctiva and both lid margins. Then, Schirmer strip was placed on the lower lid 2 mm lateral to the lateral canthus. Patients sat in the dark with both eyes closed for 5 minutes. After the strip was removed, a length of the wet area of the strip was measured in millimeters.