

Clinical efficacy of a Ginkgo biloba extract in the topical treatment of allergic conjunctivitis

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PURPOSE. *To investigate the clinical efficacy of a Ginkgo biloba extract associated with hyaluronic acid ophthalmic solution (GB-HA, Trium[®], SOOFT, Italy), compared to hyaluronic acid ophthalmic solution (HA) alone, in seasonal allergic conjunctivitis (AC).*

METHODS. *A total of 60 patients with symptomatic AC were enrolled and randomly assigned to the two treatment regimens. After a washout period of 15 days, the treatment with GB-HA eye-drops or HA ophthalmic solution alone was initiated and continued for 1 month. The clinical symptoms such as conjunctival hyperemia, conjunctival discharge, and chemosis, and subjective signs as itching, photophobia, stinging, and lacrimation, were evaluated before and after the treatment. A 0–4 score was used by an independent clinical observer to quantify the above parameters.*

RESULTS. *Patients treated with GB-HA, compared to patients treated with HA alone, showed a significant decrease in the appearance of conjunctival hyperemia, conjunctival discharge, and chemosis. Furthermore, all patients treated with GB-HA showed a significant improvement of subjective symptoms, compared to HA patients. Compared to their baseline values, patients treated with HA alone showed a small but not significant improvement in only some of the clinical and subjective symptoms.*

CONCLUSIONS. *The results suggest that Ginkgo biloba extract may exert therapeutic activity in the treatment of seasonal allergic conjunctivitis. Hyaluronic acid did not exert any valuable effect on this pathology. (Eur J Ophthalmol 2009; 19: 331-6)*

KEY WORDS. *Ginkgo biloba extract, Seasonal allergic conjunctivitis, Hyaluronic acid*

Accepted: September 28, 2008

INTRODUCTION

Seasonal allergic conjunctivitis (SAC) is an inflammation of the conjunctiva caused by allergens that trigger a hypersensitive type 1 reaction mediated by IgE and mast cells. The degranulation of mast cells involves the release of various chemical substances such as histamine and arachidonic acid derivatives such as prostaglandins and leukotrienes (1, 2). This process causes vascular dilation of the conjunctival tissue, with subsequent increment of

vascular permeation and leukocyte chemotaxis, stimulation of the nervous endings, and increment of glandular secretion causing conjunctival hyperemia, chemosis, conjunctival discharge with itching, and lacrimation (3, 4). The severity of the acute episodes is variable. They could be limited to ocular involvement with photophobia and visual acuity impairment or might be associated with other nonocular diseases such as rhinitis, bronchitis, or allergic dermatitis. The prevalence of seasonal allergic conjunctivitis is estimated at around 20% (5, 6).

Recently a new eyedrops preparation (Trium[®], SOOFT, Italy) has been proposed for the treatment of SAC. It contains an association of two synergic active molecules—Ginkgo biloba (GB, 0.05%) and synthetic hyaluronic acid (HA, 0.15%)—and an innovative preservative agent (N-hydroxymethylglycinate).

In the past 10 years, mainly in the United States, numerous studies have been conducted aimed at analyzing the pharmacodynamic properties of both the whole dried GB extract (EGb 761) and its single constituents and demonstrating the molecular mechanisms of action of each of the different substances. The combined mechanisms of action of the GB components, such as flavonoids (Quercetin, ginkgetin, kaempferol, isorhamnetin, procyanidin, prodelphinidin) and terpenoids (Ginkgolides A, B, C, J, M, and bilobalides) have antioxidant, anti-inflammatory, and neuroprotective properties (7-9). They seem to be able to re-establish normal tear secretion due to action on the sympathetic and parasympathetic innervations of the lacrimal gland, by re-establishing the normal level of nervous fibers stimulus and the adjustment of neurotransmitter release and degradation (9), reduce stinging (ginkgetin) due to inhibition of the synthesis of the proinflammatory prostaglandin (PGE₂) and modulation of the transcription of the genes involved in the inflammatory response (codified genes for COX1-2) (10), and operate antiapoptotic cytoprotective action and antioxidant action (terpenoid properties) (11, 12); furthermore, by blocking lipid peroxidation and the transformation of the lipid component of the cell membranes, they encourage stability and reduce the process of degranulation and perform a protective and trophic action on nerve cells (5).

Synthetic hyaluronic acid (HA) is a naturally occurring mucopolysaccharide (glycosaminoglycan) of the extracellular matrix, composed of alternating N-acetyl-D-glucosamine and D-glucuronic acid moieties, that due to its mucoadhesive properties protects, moistens, and lubricates the ocular surface. It favors even distribution and adherence of eyedrops on the ocular surface and re-establishes stability of the tear film structure; it protects the ocular surface from environmental agents and it has water retentive properties, which improve ocular surface wettability (13). It determines an increase in the amount of lacrimal film and an increase in the stability of lacrimal film; in fact, it is used in the treatment of dry eyes because of its long ocular surface residence time (14). It also has indirect anti-inflammatory properties (13). Finally, hyaluronate has viscoelastic properties that can lubricate the ocular surface, reducing

friction during blinking and ocular movements (13).

The aim of this study was to evaluate the efficacy and the tolerability of the GB-HA association, administered as eyedrops preparation, in patients affected by SAC in its symptomatic phase. This treatment effect has been compared to that of a HA eyedrops preparation alone.

METHODS

At the Department of Ophthalmology of the University of Foggia between April 2007 and May 2007, 60 outpatients were recruited, both male (36) and female (24), with a mean age of 16.3±3.2 years and randomly assigned to the two treatment regimens: 30 patients were treated with GB-HA eyedrops (group GB-HA) and 30 patients with HA eye drops alone (group HA). The patients were randomized using an envelope method. In brief, 30 envelopes contained a card showing GB-HA group and 30 envelopes contained a card showing HA group. Within 24 hours after enrollment, an envelope was picked up and the inside card showed the way to treat the patient: GB-HA or HA. The patients were selected with a history of SAC in the past 2 years. The diagnosis was confirmed as the patients underwent allergologic tests (cutireaction, PRIST, RAST) and other specific ocular examinations (conjunctival scraping and cytologic examination of the lacrimal liquid).

Informed consent obtained from all patients and their parents was necessary. The study followed the Declaration of Helsinki and IRB approval was obtained. Patient information was collected regarding personal data, personal and family history, with particular emphasis to the presence of allergy, concomitant associated extraocular symptoms (rhinitis, bronchitis, dermatitis), other current therapies, and lifestyle. Before the patients' evaluation, the 15-days-long washout period was observed. In this time any topical or systemic therapy that could influence the evaluation was suspended and artificial tears drops were instilled three times a day. During the observational period GB-HA eyedrops preparation was administered at a dose of two drops in 30 patients and in each eye three times daily for 1 month, and no other topical, systemic corticosteroids, antihistamines, or nonsteroidal anti-inflammatory drugs were administered. Another 30 patients were treated with HA ophthalmic solution with a dose of two drops in each eye, three times daily for 1 month, and were evaluated after the treatment.

The study provided two visits for the clinical pre- and after

Fig. 1 - Comparison of the scores regarding clinical ocular signs (conjunctival hyperemia, discharge, and chemosis) after 1 month of treatment with GB-HA versus HA eyedrops (* $p < 0.05$).

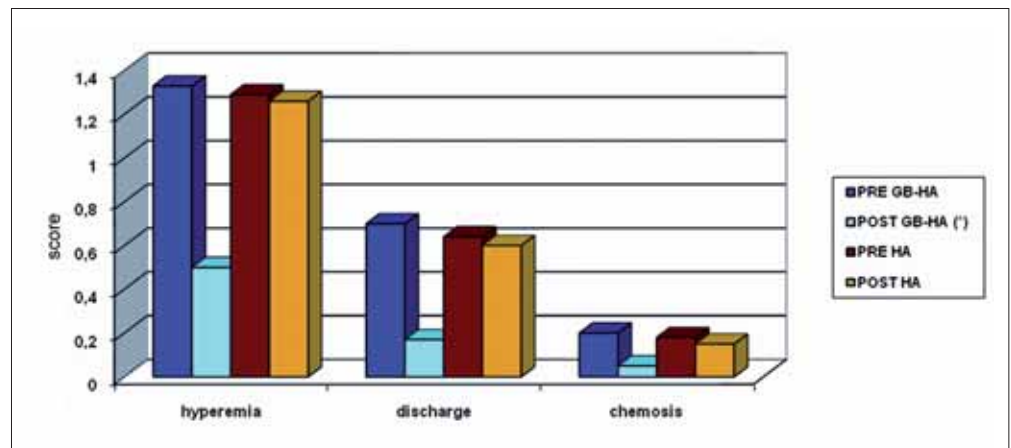
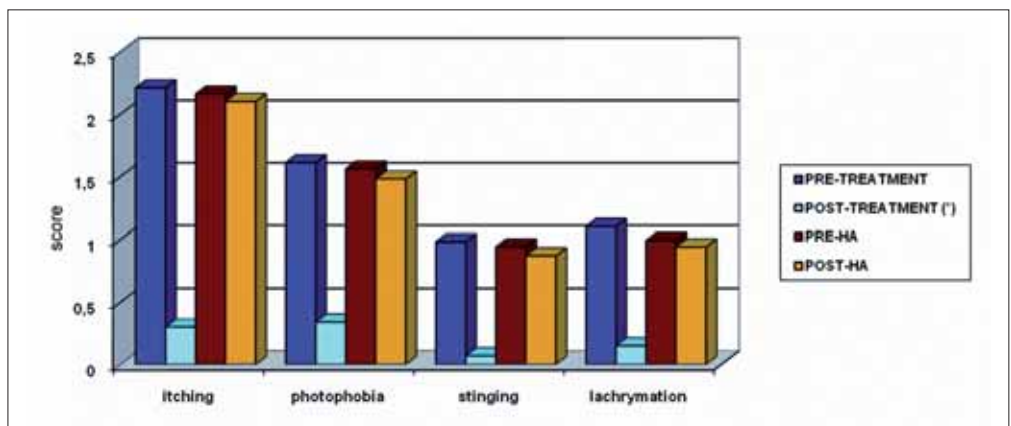


Fig. 2 - Comparison of the scores regarding subjective symptoms (itching, photophobia, stinging, and lacrimation) after 1 month of treatment with GB-HA eyedrops versus treatment with HA eyedrops (* $p < 0.001$).



1 month post-treatment evaluation of the patients: clinical signs and symptoms and any side effect associated with the treatment were registered.

The clinical signs such as conjunctival hyperemia, discharge, and chemosis and subjective symptoms such as itching, photophobia, stinging, and lacrimation were evaluated before and after 1 month of the treatment with GB-HA or HA eyedrops. The score 0–4 was used to classify the severity of the clinical signs.

Subjective symptoms were evaluated with score 0 to 3 according to the following classification: 0 = no symptom; 1 = occasional presence of symptom of mild or moderate intensity; 2 = daily presence of symptom of mild or moderate intensity or occasional presence of symptom of severe intensity; 3 = constant presence of symptom of any intensity or daily presence of symptom of severe intensity. The reduction time of the symptoms were measured according to a scale of 1 to 3 based on the patient report (1 = insufficient; 2 = good; 3 = excellent).

The clinical signs, the subjective symptoms, and all other

qualitative variables were expressed as an average with $\pm$ standard error. The statistical analysis was performed using the nonparametric Wilcoxon test and p value less than 0.05 was considered significant.

RESULTS

All the enrolled patients concluded the study successfully. The percentage of patients presenting the clinical signs and claiming the symptoms was dramatically reduced: at the control examination at 1 month, the results of the objective tests demonstrated a significant difference ($p < 0.05$) between the scores regarding clinical ocular signs of group GB-HA versus group HA (Fig. 1); after 30 days of treatment with GB-HA eyedrops all the patients also showed a significant difference ($p < 0.001$) in scores regarding subjective symptoms (Fig. 2).

The group GB-HA showed a significant decrease of signs and symptoms: conjunctival hyperemia, conjunctival dis-

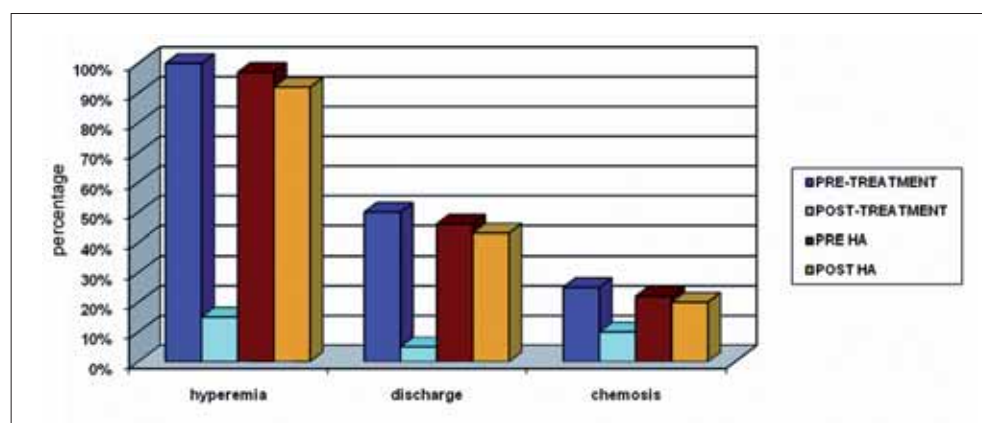


Fig. 3 - Percentage distribution signs of ocular inflammation before and after treatment with GB-HA eyedrops versus treatment with HA eyedrops (* $p < 0.05$).

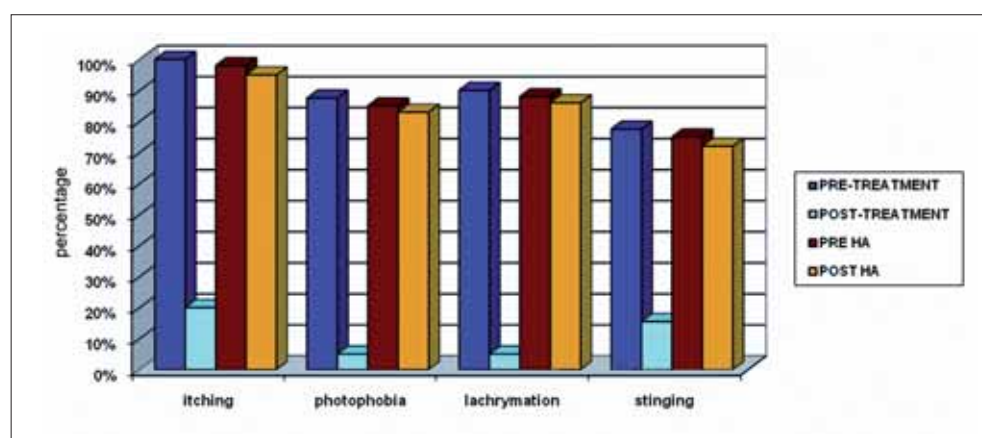


Fig. 4 - Percentage distribution of ocular symptoms (itching, photophobia, stinging, and lachrymation) before and after treatment with GB-HA eyedrops versus treatment with HA eyedrops (* $p < 0.001$).

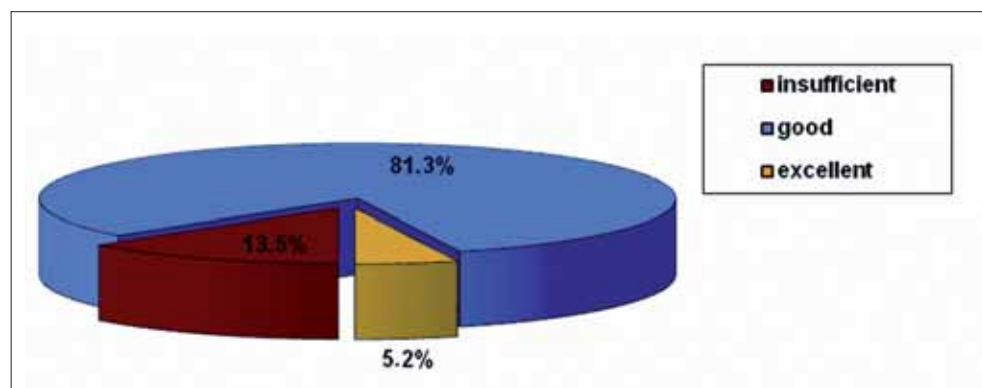


Fig. 5 - Evaluation of the rapidity of action of GB-HA eyedrops in reducing the ocular symptoms.

charge, and conjunctival chemosis were reduced respectively to 85.2%, 45.3%, and 15.7% (Fig. 3); itching, photophobia, lachrymation, and stinging were reduced respectively to 80.4%, 82.5%, 85.6%, and 62.3% (Fig. 4). Instead, the group GB-HA did not show a significant improvement of signs and symptoms, with decrease of conjunctival hyperemia to 5%, conjunctival discharge to 3%, and conjunctival chemosis to 2.4%. Itching, photophobia,

lachrymation, and stinging were reduced respectively to 3.4%, 2.3%, 2.2%, and 3.2%.

A side effect was registered only in one case: the patient reported stinging during instillation of the GB-HA eyedrops. However, this did not hinder completion of the 30 days of treatment.

Reduction in time of symptoms in group GB-HA was judged as "good" by 81.3% of patients (Fig. 5).

DISCUSSION

Allergic conjunctivitis is a condition that occurs seasonally or perennially in response to environmental allergens. Ocular itching is the hallmark symptom of allergic conjunctivitis and is often the most troublesome for the patient. Other symptoms and signs of allergic conjunctivitis include ocular redness, tearing, mucus production, foreign body sensation, chemosis, and lid edema. In its mildest form, the signs and symptoms may be self-limiting. However, often the signs and symptoms of allergic conjunctivitis are recurrent, waxing and waning, and may be accompanied by other allergic manifestations, such as allergic rhinitis (15).

The ophthalmic therapies available for preventing and treating these allergic diseases are somewhat limited (6). Most of the drugs available are membrane stabilizers intended to inhibit the degranulation process of the mast cells and the release of inflammation mediators (16); antihistaminic drugs, that more or less selectively inhibit H₁ receptors, are considered to exert excellent clinical effects, but cause a wide range of side effects (17, 18).

The use of topical nonsteroidal anti-inflammatory drugs, which inhibit the release of inflammation substances such as prostaglandins, demonstrate efficacy in reducing inflammation without any side effects (19). However, not all forms of allergic conjunctivitis are sufficiently controlled by these drugs. Furthermore, while the efficacy of steroids in the treatment of acute inflammation is unquestionable, their use must be limited in time and kept under medical supervision. In fact, these substances are active on the cellular components of inflammation and the release of inflammatory agents, thus effectively and rapidly controlling the inflammation, but on the other hand, if used for long periods, they can provoke side effects as cataract and glaucoma (20).

In our study, the analysis of the data collected before and after the treatment demonstrated a statistically significant reduction (Wilcoxon test, $p < 0.001$ and $p < 0.05$) of the signs and symptoms associated with SAC. Since no other antiallergic drugs were administered during the investigation period, it could be suggested that the pharmacologic action of GB-HA eyedrops demonstrated efficacy in reducing all the symptoms and most of the signs that characterize allergic conjunctivitis. It might confirm the favorable role of Egb 761 and hyaluronic acid (8).

Itching, the principal and most annoying symptom of this disease, received the most relief from the treatment. However, the important reduction of photophobia, stinging, and lacrimation were also registered.

No adverse effects, whether topical or systemic, associated with the administration of the collyrium were registered, demonstrating safety of its use. The presence of hyaluronic acid, with its mucomimetic and lubricating properties, gives immediate relief, increases retention of the solution, without affecting sight quality, and contributes to the reduction of inflammation (13).

The data reported allow us to affirm that hyaluronic acid is useful in eliminating the feeling of dry eye and burning in all of the patients' aspecific inflammation of the conjunctiva.

The efficacy of GB-HA eyedrops is therefore comparable to that of all other pharmacologic classes, and can be advised as a solution for the control and reduction of ocular symptoms in the acute phase of allergic conjunctivitis. In particular, Trium® eyedrops represents a valid choice in long-term therapy, since it is devoid of side effects and is well tolerated also in young patients.

ACKNOWLEDGEMENTS

These experiments were supported by the International PhD Program School in Neuropharmacology, University of Catania Medical School, Italy.

The authors received no financial support and have no proprietary interest.

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