

Primary literature

Fujishima H, Fukagawa K, Takano Y, et al. The Early Efficacy of Topical Levocabastine in Patients with Allergic Conjunctivitis. *Allergol Int.* 2006 Sep;55(3):301-3.

Study Objectives

To compare the efficacy of topical levocabastine and artificial tears in improving the clinical symptoms of allergic conjunctivitis.

Methods

Participants:

36 patients (10 men and 26 women; mean age 41.0 ± 15.4 years; range: 20-73 years) with allergic conjunctivitis.

Setting: Multi-site

Exclusion criteria: 1) Patients who had any ocular surface diseases other than allergic conjunctivitis 2) patients who had used systemic or topical medications (e.g. steroids, nonsteroidal anti-inflammatory drugs, anticholinergic, immunosuppressives, mast-cell stabilizers, antihistamines during the past week, 3) patients younger than 20 years 4) women who were pregnant or potentially pregnant, and 5) patients who wore contact lenses.

Diagnoses were based on clinical symptoms and slit-lamp examination. Patients were asked to grade their baseline symptoms of ocular itching, conjunctival redness, and foreign body sensation on a scale of 0 to 3 (0= none; 1= mild, 2=moderate, 3=severe). Patients who had pre-treatment symptom grades that differed by more than 1 between their eyes were excluded from the analysis to reduce the bias caused by differences in symptom severity. Objective bulbar conjunctival injection was graded on a scale of 0 to 3 (0= none, 1=mild, 2=moderate, 3=severe) based on slit-lamp examination.

Interventions:

All patients were treated with one drop of levocabastine (Livostin[®] Eye Drops 0.025%) in one eye and one drop of artificial tear (Soft Santear[®]) in the contralateral eye.

Follow-up: symptoms and signs were re-evaluated at 15 and 30 minutes after instillation

Blinding: double-blind (neither the patients nor examiners were notified of the laterality of the eye drops)

Outcome: degree of ocular itching, conjunctival redness, foreign body sensation.

Main results

Both levocabastine and artificial tears significantly reduced ocular itching compared with pre-treatment levels, at 15 and 30 minutes ($p < 0.001$), but levocabastine was significantly more effective than artificial tears ($p = 0.001$ at 15 minutes and $p < 0.001$ at 30 minutes)

Levocabastine reduced conjunctival redness at both 15 and 30 minutes ($p < 0.001$) compared with pretreatment levels, while artificial tears reduced conjunctival redness only at 30 minutes ($p = 0.023$). Levocabastine was also significantly more effective in reducing conjunctival redness than artificial tears ($p < 0.001$ at 15 and 30 minutes)

Levocabastine also significantly reduced foreign body sensation in the eye compared with pre-treatment levels at 15 ($p = 0.001$) and 30 minutes ($p < 0.001$). Levocabastine was clearly more effective than artificial tears in reducing foreign body sensation at both 15 ($p = 0.005$) and 30 minutes ($p = 0.001$).

Both levocabastine ($p < 0.001$) and artificial tears ($p = 0.017$) significantly reduced bulbar conjunctival injection at 30 minutes, but levocabastine was more effective than artificial tears ($p < 0.001$)

No adverse events were observed during this study.

Conclusions

Both artificial tears and levocabastine were effective in reducing acute symptoms of allergic conjunctivitis. However, levocabastine however was significantly more effective than artificial tears.

Comments/critical appraisal

In this study, neither the patients nor examiners were notified the laterality of the eye drops. This double-blind method excluded the most important potential sources of bias, which was bias arising from subjectivity of patients' evaluation of symptoms and responses to the drugs. The blinding method of the study was sufficient, but the sample size of the study was very small and the randomization process of treatment allocation was not clearly described. In addition, in the study, patients were asked to grade their baseline and post-treatment symptoms on a scale of 0 to 3. This symptom score method could negatively affect the objectivity of outcome assessment. Moreover, each patient in the study received one drop of artificial tears. Instillation of just one drop may not be sufficient considering that artificial tears work primarily by removing and diluting allergens that come into contact with the conjunctival surface. Lastly, This study somewhat lacked scientific merit since it did not include a placebo control group. Overall, the study addresses an important topic and it definitely adds to what is already known about the treatment of allergic conjunctivitis. Unfortunately, the internal validity and study design are rather weak.

The inclusion and exclusion criteria were appropriate and well-defined. The study was conducted in Japan and the study population consisted of entirely Japanese. Due to safety reasons, the study excluded people who were pregnant and patients who were younger than 20. Despite these restrictions and limitations, the efficacy findings of the study may still be applicable to the general adult population. The efficacy of artificial tears or topical levocabastine is unlikely affected by race or ethnicity.

Textbook

2. Friesen, A. Conjunctivitis. In: Canadian Pharmacists Association. Patient Self-Care, 2nd ed. Ottawa, ON: Canadian Pharmacist Association, 2010

Source Description

Patient self-care, 2nd edition (2010) is a peer-reviewed Canadian reference manual based on best available evidence on treatment options for minor ailments. It is published by the Canadian Pharmacist Association (CPhA). A rigorous review process is employed to ensure that the information is accurate and unbiased. The content of the manual is extensively reviewed by CPhA pharmacist editors and two reviewers who are recognized experts in the particular clinical area. New and controversial statements are referenced within the text.

Summary

Electrolyte irrigation solutions such as balanced salt solution and ocular lubricants such as polyvinyl alcohol and hypromellose and polyvinyl alcohol are considered the first line treatment of seasonal allergic conjunctivitis. The expected clinical benefits of lubricants and irrigation solutions include allergen dilution and decrease in allergen-conjunctiva contact time. They usually have to be applied several times a day and refrigeration of the products may improve soothing effect. In addition, ocular lubricants that contain benzalkonium chloride as preservative may irritate eyes, especially if used ≥ 4 times per day. If there is no improvement within 72 hours, patients may be referred to physician or eye care practitioner.

Critical appraisal

In terms of internal validity, the major limitation of this manual is that although it is based on the best available evidence, it also contains selected information representing the opinions based on experience and opinions of individual authors. Furthermore, the external validity of this manual is very good since it does not only contain information for adult population, but it includes information for special populations such as pregnant and lactating women, infants, children, elderly, and patients with renal insufficiency.

Narrative Review

3. Bielory, BP, O'Brien T, Bielory L. Management of seasonal allergic conjunctivitis: guide to therapy. *Acta Ophthalmol.* 2011 Nov 8 doi: 10.1111/j.1755-3768.2011.02272.x. [Epub ahead of print]

Source description

Management of seasonal allergic conjunctivitis: guide to therapy is a review article published in the November 2011 issue of *Acta Ophthalmologica*, an English-language peer-reviewed medical journal published by Willey-Blackwell Publishing Inc. This review article is co-authored by Dr. Leonard Bielory, an international expert in inflammatory disorders of the anterior portion of the eye, especially various forms of ocular allergy and is a regional expert on pollen and climate change.

Summary

The initial treatment options for seasonal allergy conjunctivitis are saline solution or artificial tears. They work primarily by minimizing conjunctiva-allergen contact time through dilution and removal of the allergens from the ocular surface. If tear substitutes fail to provide adequate relief, ointments or time-released tear replacements may be used at night to provide moisture to the ocular surface while the patient sleeps. These agents only provide temporary relief and do not treat the underlying allergic reaction or modify the activity of inflammatory mediators. The use of these agents is limited to mild seasonal allergic conjunctivitis.

Critical appraisal/comments

There is limited scientific evidence supporting the use of lubricating agents for the treatment of allergic conjunctivitis. The recommendations discussed in the review are mostly based on theoretical rationale and expert opinions. This approach is inexpensive, but there is a huge potential for bias. In terms of external validity, the authors do not provide information for special populations such as pediatric and pregnant or lactating women. Thus the recommendations provided in the review are only applicable to the general adult population.

Clinical Practice Guideline

American Academy of Ophthalmology. Preferred Practice Pattern. Conjunctivitis. San Francisco, CA: American Academy of Ophthalmology 2011. http://one.aao.org/CE/PracticeGuidelines/PPP_Content.aspx?cid=9d9650fb-39a3-439c-9225-5fbb013cf472. Accessed May 27, 2012

Study objectives

The objective of this guideline is to develop a set of recommendations for the initial evaluation of a patient with conjunctivitis and treatment recommendations for each type of conjunctivitis

Scope

The patient population includes individuals of all ages who present with symptoms and signs suggestive of conjunctivitis, such as red eye or discharge. No information was provided regarding study intervention, outcomes and duration.

Methods

The guideline is developed without any external financial support by a panel of ophthalmologists with expertise in conjunctivitis and a methodologist. Furthermore, it is externally reviewed by experts and stakeholders before publications.

In 2007, a literature search of articles in the English was conducted in PubMed and the Cochrane Library on the subject of conjunctivitis for the years 2002 to 2007. To complete this limited revision, PubMed and the Cochrane Library were searched on February 10, 11, and 14, 2011 on the subject of conjunctivitis, limited to English and publication date of 2008 to the date of the search. The results were reviewed by the Cornea/External Disease Panel and used to prepare the recommendations, which they rated in two ways.

Each recommendation was rated by the panel according to its importance to the care process, which represents care that the panel thought would improve the quality of the patient's care in a meaningful way. The ratings of importance are divided into three levels:

- Level A, defined as most important
- Level B, defined as moderately important
- Level C, defined as relevant but not critical

The panel also evaluated each recommendation on the strength of evidence in the available literature. The “ratings of strength of evidence” also are divided into three levels:

- Level I includes evidence obtained from at least one properly conducted, well-designed, randomized, controlled trial. It could include meta-analyses of randomized controlled trials.
- Level II includes evidence obtained from the following:
 - Well-designed controlled trials without randomization
 - Well-designed cohort or case-control analytic studies, preferably from more than one center
 - Multiple-time series with or without the intervention
- Level III includes evidence obtained from one of the following:
 - Descriptive studies
 - Case reports
 - Reports of expert committees/organizations (e.g., PPP panel consensus with external peer review)

Results

Treatments of mild allergic conjunctivitis include over the counter antihistamine/vasoconstrictor agent or the more effective second-generation topical histamine H₁-receptor antagonists. Mast-cell stabilizers can be used if the condition is frequently recurrent or persistent (Level A-I evidence). Low-potency topical corticosteroid can be added to the regimen if the symptoms are not adequately controlled (Level A-III evidence). Additional measures such as artificial tears, cool compresses, oral antihistamines, and allergen avoidance, frequent clothes washing, showering before bedtime may be useful (Level B-III evidence).

Comments/critical appraisal

The internal validity of the recommendations made in this guideline is quite good since each recommendation is given an explicit rating that shows the strength of evidence that supports the recommendation and reflects the best scientific evidence available. In addition, there is no conflict of interest identified since all of the authors and reviewers are volunteers and do not receive any compensation for their contribution. Furthermore, according to the guideline, the level of evidence for the use of ocular lubricant in allergic conjunctivitis is quite weak. The recommendation was based on either descriptive studies, case reports, or panel consensus. In terms of external validity, this guideline is applicable to general population since it is developed for individuals of all ages who present with symptoms and signs suggestive of conjunctivitis. The guideline does not have exclusion criteria, thus it is not clear whether this guideline is applicable to pregnant and lactating women or people with co-morbidities.

5. Website

Terrie, YC, Bowling, EL. Update on the OTC Treatment of Allergies: Focus on Allergic Conjunctivitis. Pharmacy Times Office of Continuing Professional Education. <https://secure.pharmacytimes.com/lessons/200903-02.asp>. Accessed May 28, 2012.

Source description

The information was extracted from Pharmacy Times Office of Continuing Professional Education, which is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Summary

The use of artificial tear solutions is recommended for the initial therapy of mild-to moderate cases of allergic conjunctivitis. It works by diluting or washing away the offending allergen from the ocular area and lubricating the eye. Ocular lubricants that are formulated as artificial tear solutions contain preservatives and inorganic electrolytes to achieve tonicity and sustain pH, as well as water-soluble polymeric systems. These products typically contain enhancing agents, such as carboxymethylcellulose, glycerin, hydroxyethyl cellulose, hydroxypropyl methylcellulose, methylcellulose, polycarbophil, polyethylene glycol 400, polysorbate 80, or polyvinyl alcohol. Administration 2 to 4 times daily as needed is recommended. Artificial tear products that contain preservatives may cause allergic reactions and should be discontinued if a reaction occurs. Artificial tear products can be refrigerated to provide additional soothing and comfort upon instillation. They are considered very safe and can be used as often as needed. If the use of artificial product has not been successful, topical antihistamine solutions or antihistamine-decongestant combinations may be used.

Critical appraisal

In terms of external validity, the authors do not provide information for special populations such as pediatric and pregnant or lactating women. Thus the recommendations provided in the review are only applicable to the general adult population. In terms of internal validity, the author uses secondary and tertiary sources, which summarize and consolidate the source materials into an overview and may present subjective commentary and analysis.

Therapeutic Option	Mechanism of Action	Onset of Effect/Duration of Treatment	Adverse Effects	Contraindications	Drug or other Interactions	Risk Level for Drug Interactions	Convenience/ Cost
<p>Ocular surface lubricating agents (including saline/artificial tears (e.g., polyvinyl alcohol and hypromellose), ointments and time-release tear replacements)</p>	<p>Physically irrigate, dilute, and remove allergens from the ocular surface¹; reduce allergen-conjunctiva contact time; Treat co-existing tear deficiency</p> <p>no direct effects on the mediators of inflammation; only provide temporary relief;for moderate and severe forms of SAC¹</p>	<p>Onset: 5-15 minutes</p>	<p><i>Common:</i> burning, dry eye, eye irritation, redness <i>Uncommon:</i> eyelid edema, epiphora, eyelid erythema, eye pain, eye discharge.</p> <p>Chronic and frequent use (≥ 4 times a day) may result in problems such as irritation and redness because of effect of the preservative. Detergent preservative such as benzalkonium chloride is known to be toxic to the corneal epithelium. Signs of preservative toxicity include stinging upon instillation and conjunctival inflammation</p>	<p>Safe use during pregnancy and lactation has not been established.</p> <p>Hypersensitivity to any of the ingredients.</p> <p>Should not be used in infants and small children under 3 years³.</p>	<p>No known significant interaction</p> <p>Concomitant ocular medication should be administered 15 minutes prior to the installation of these products</p>	<p>Low</p>	<p>OTC products \$5-10/15 mL</p>

Place in therapy

Most literature on allergic conjunctivitis is in agreement that ocular lubricating agents such as saline solution or artificial tears are useful for the initial treatment options for **mild** seasonal allergic conjunctivitis (SAC) (1). They work primarily by physically irrigating, diluting, and removing allergens that may come into contact with the conjunctival surface. (1) They can also moisten the eyes, which often become dry when irritated [1]. These agents only provide temporary relief and neither treat the underlying allergic reaction nor modify the inflammatory mediators (1). If tear substitutes are inadequate, ointments or time-released tear replacements may be used at night to provide moisture to the ocular surface (1). The recommendations on the use of ocular lubricating agents for the treatment of mild SAC are mostly based on theoretical rationale and expert opinions since there is limited scientific evidence. There is only one primary literature that investigates the effectiveness and safety of ocular lubricants. One study showed that a single instillation of one drop of topical antihistamine, levocabastine, was more effective than that of artificial tears in controlling acute symptoms of allergic conjunctivitis (2). The efficacy and safety of lubricating agents in special populations such as infants, children, pregnant and lactating women have not been demonstrated. The product monograph indicates that the use of artificial tears is contraindicated in children under 3 years old (3).

Patient counseling tips

Ocular lubricating agents typically must be applied several times (2-6 times) daily in order to be effective. It is recommended to refrigerate these agents prior to their use because they could cause vasoconstriction and provide additional relief when applied immediately in a cold state (4). Furthermore, it is important for patients to wash their hands and remove any eye contacts before using lubricating agents. Concomitant ocular medication should be administered 15 minutes prior to the installation of lubricating agents (3). In order to avoid contamination, the dropper bottle must be kept tightly closed and the dropper tip must not touch any surface or have direct contact with the eye. Eye drops should not be used more than 30 days after first opening (3). Chronic or frequent use of preservatives such as benzalkonium chloride may cause eye irritation, especially if used ≥ 4 times a day (5). Thus, patients who require frequent applications for long periods of time should use a preservative-free product to prevent toxicity (5).

Product examples:

1. **Visine® Tears® Dry Eye Relief (ingredients: glycerin 0.2%, hypromellose 0.2%, polyethylene glycol 400 1%)**
 2. **Refresh Tears Lubricating Eye Drops (ingredients: carboxymethylcellulose sodium 5 mg/mL)**
- Directions: Unless otherwise prescribed, instill 1 drop in the affected eye(s) 4 times a day or as needed.

References:

1. Bielory, BP, O'Brien T, Bielory L. Management of seasonal allergic conjunctivitis: guide to therapy. *Acta Ophthalmol*. 2011 Nov 8 doi: 10.1111/j.1755-3768.2011.02272.x. [Epub ahead of print]
2. Fujishima H, Fukagawa K, Takano Y, et al. The Early Efficacy of Topical Levocabastine in Patients with Allergic Conjunctivitis. *Allergol Int*. 2006 Sep;55(3):301-3.
3. Refresh Tears Lubricating Eye Drops product monograph. <http://home.intekom.com/pharm/allergan/refre-tr.html#CONTRA-INDICATIONS>. Accessed June 21, 2012
4. Terrie, YC, Bowling, EL. Update on the OTC Treatment of Allergies: Focus on Allergic Conjunctivitis. Pharmacy Times Office of Continuing Professional Education. <https://secure.pharmacytimes.com/lessons/200903-02.asp>. Accessed May 28, 2012.
5. Friesen, A. Conjunctivitis. In: Canadian Pharmacists Association. Patient Self-Care, 2nd ed. Ottawa, ON: Canadian Pharmacist Association, 2010