

## **1. Primary Source**

**Juniper EF, Guyatt GH, Ferrie PJ, King DR. Sodium cromoglycate eye drops: regular versus "as needed" use in the treatment of seasonal allergic conjunctivitis. J Allergy Clin Immunol. 1994 Jul;94(1):36-43.**

### **Study objectives**

To compare the efficacy and safety of sodium cromoglycate eye drops when used regularly versus prn for the treatment of seasonal allergic conjunctivitis

### **Methods**

#### **Design**

This was a randomized control trial with 2 parallel comparison groups. Patients were required to have a history of allergic conjunctivitis that required treatment or was associated with moderate to severe untreated symptoms during the previous 2 ragweed seasons. In addition, patients must have tested positive to skin prick test for ragweed pollen. Sixty-two patients who met entry criteria were randomly assigned to two groups. One group used sodium cromoglycate on a regular basis, the other were instructed to use sodium cromoglycate on PRN basis. The study was conducted during 6 weeks of ragweed pollen season in Hamilton, Ontario.

#### **Allocation**

In addition to ragweed pollen, patients also underwent skin prick test for *A. tenuis*, *Cladosporiumspecie*, and grass pollen. The 62 patients who met the entry criteria were paired up according to 5 criteria: 1) skin sensitivity to ragweed pollen; 2) severity of ragweed pollen-induced conjunctivitis; 3) skin sensitivity to fungal spores; 4) skin sensitivity to grass pollen; 5) gender.

For each pair of subjects, one patient was randomly assigned to the regular treatment group, the other to the prn treatment group.

#### **Blinding**

This was an unblinded study as all patients knew the name and direction of their assigned treatment.

#### **Follow-up period**

Follow-up period started 1 week before ragweed season on August 10. Participates were followed until the end of ragweed pollen season on September 21.

#### **Setting**

This study occurred in the community setting as patients used the treatments at home.

#### **Participants**

Sixty-two patients with sensitivity to ragweed pollen skin prick test were included in the study. Participants in the regular and prn treatment groups shared similar characteristics. The average age in both groups was 42 and both group had equal gender ratio of 17 male to 14 female. The number of participants in each severity category of conjunctivitis was similar as well.

#### **Intervention**

One group was instructed use sodium cromoglycate starting 1 week before ragweed pollen was expected in the air (August 10). Patients were told to instill 2 drops into each eye four times per day until the end of ragweed season (September 21).

The second group was instructed to use sodium cromoglycate when their symptoms became bothersome on an as needed basis. Patients were told to instill 2 drops into each eye when needed, for up to a maximum of 4 times per day. The second group was told to stop using the eye drops when the symptoms became controlled, but to restart again if symptoms returned.

If eye symptoms were uncontrolled with the maximum daily dose of sodium cromoglycate, all patients were instructed to take terfenadine 60mg when needed, and up to 120mg daily. Patients who required nasal symptom treatment were given beclomethasone dipropionate nasal spray, and were instructed to use 2 puffs in each nostril twice daily, and up to four times per day when needed. Patients were not allowed to use terfenadine for uncontrolled nasal symptoms. Patients with asthma were allowed to use salbutamol and beclomethasone dipropionate inhalers as prescribed by their physicians. All patients were instructed not to use any other hay fever medications.

### Outcomes

Between August 10 and September 21, participants were required to complete a symptoms diary each morning and evening to record the severity and duration of itching, soreness, watering, and swelling of the eye, and overall nasal symptoms. Severity scores ranged from 0=none, 1=mild, 2=moderate, 3=severe, and duration was evaluated as 0=none, 1=a few short episodes, 2=many episodes, 3=continuous. Each morning and evening patients also recorded the amount of sodium cromoglycate drops, nasal spray, and terfenadine, as well as any non-hay fever medications that were used within the past 24 hours.

In addition, participants also attended clinics after 1, 3, and 6 weeks of treatments. Patients filled out the Rhinoconjunctivitis Quality of Life Questionnaire and reported any adverse reactions.

Investigators compared scores from diaries and Rhinoconjunctivitis Quality of Life Questionnaire between the two treatment groups. Although only 58 patients completed the study, analysis included all available data with the intention to treat.

### Patient follow-up

Investigators checked patient diaries for accuracy after 1, 3 and 6 weeks of treatment and reviewed medication instructions to ensure adherence and correct administration.

### Main results

Fifty-eight out of 62 participants completed the study. All data were included in analysis up to the time of withdrawal. The regular treatment group used 3 times as much sodium cromoglycate eye drops as the prn group. On average, participants in the prn group used 2.3 drops per day.

There was no difference in the severity and duration of patient diary eye symptoms between the 2 groups, which included eye itchiness, soreness, wateriness, and swelling. Although the prn group used terfenadine more frequently, the difference was not statistically significant. There was no difference in diary nasal symptoms, and there was no significant difference between the two groups for use of beclomethasonate nasal spray.

Results of Rhinoconjunctivitis Quality of Life Questionnaire demonstrated that the regular treatment group had better quality of life. The treatment group had significantly less practical problems and activity limitations, and their overall quality of life score was significantly better.

### **Conclusions**

Although patient diary scores exhibited no difference in eye and nasal symptoms between the regular and prn groups, the regular treatment exhibited significant better Rhinoconjunctivitis Quality of Life Questionnaire. When cromoglycate sodium is used before allergy conjunctivitis symptoms began, it may be more effective in preventing deterioration in quality of life during pollen season than if the drops were used only when symptoms began.

### **Comments/Critical appraisal**

#### Internal validity

The internal validity of the study is poor because there were many extraneous factors which could have affected eye symptom scores. Patients were allowed to use terfenadine for severe eye symptoms that were not controlled with sodium cromoglycate. The use of oral terfenadine can lead to resolution of eye symptoms and thus the eye symptoms in the prn group may not be accurately reflected. In addition, beclomethasone nasal sprays were also allowed for nasal symptom treatment, but it may potentially help eye symptoms as well. With these additional medications, it is not clear if the control of eye symptoms was a direct result of sodium cromoglycate.

It is unknown if the Rhinoconjunctivitis Quality of Life Questionnaire developed by the researchers was a validated tool. In addition, internal validity also greatly depends on the accuracy of self reporting in patient diaries. Although the regular treatment group was instructed to use 2 drops per day throughout the study period, it's highly likely that there were adherence issues. Although the investigators did check diary after weeks 1, 3, and 6, the study provided no additional strategies to ensure adherence.

#### External validity

Participants in this study do reflect the patients with allergic conjunctivitis in the general population. The patients included in the study had different degrees of conjunctivitis to ragweed pollen, from mild to severe. There was almost an equal distribution of women and men, and majority of patients were also allergic to grass pollen. Although the external validity is good, the results of this study can only be selectively applied to the general population due to poor internal validity.

## **2. Primary Source**

Lindsay-Miller AC. Group comparative trial of 2% sodium cromoglycate (Opticrom) with placebo in the treatment of seasonal allergic conjunctivitis. Clin Allergy. 1979 May;9(3):271-5.

### **Study objectives**

To compare the efficacy of sodium cromoglycate with placebo for the treatment of seasonal allergic conjunctivitis.

### **Methods**

#### Design

This is a double-blind, randomized control trial comparing 2% Opticrom versus placebo. A total of 49 patients with past history of severe eye symptoms associated with hay fever were recruited. The trial

occurred over a period of four weeks. Patients were randomly assigned cromoglycate sodium or placebo eye drops.

#### Allocation

A total of 49 patients were recruited from "hay fever register" and all have past history of severe eye symptoms and hay fever rhinitis. Although allocation was random, the method was not stated. Six patients were excluded from analysis because they used the eye drops incorrectly. Of the remaining participants, 20 received sodium cromoglycate and 23 received placebo.

#### Blinding

The researchers stated in the abstract that this study was double blinded however the specific procedure was not mentioned in the actual article.

#### Follow-up period

Patients were followed up after 4 weeks of treatment.

#### Setting

This study occurred in the community setting as patients used the treatments at home.

#### Participants

All participants had a history of severe eye symptoms in addition to allergic rhinitis. Exclusion criteria included contact lense wearer, patients requiring topical steroids, or patients with additional eye diseases. The characteristics of treatment and placebo groups were similar. The average age was fairly young, 22 for sodium cromoglycate and 27 for placebo. Children were also included as the age range spans from 6-57. There was more female than male in both groups. From past history and clinical features, all patients were diagnosed with seasonal allergic conjunctivitis. All patients had a positive skin prick test to grass pollen.

#### Intervention

Participants were given diary cards before allergy season. They were instructed to start using the assigned eye drops as soon as symptoms developed. Participants were directed to use 2 drops four times per day. The frequency of eye drop and other medication use was recorded by each patient. Patients were instructed to contact clinic if there they felt no beneficial effects after 4 days of eye drop use and were given alternative therapy.

#### Outcomes

During the four weeks, patients evaluated their eye symptoms including itching, redness, watering, soreness, grittiness, and photophobia. Each parameter was rated from 0-4 (0=none, 1=mild, 2-moderate, 3=severe, 4=very severe). At the end of the trial, patients were asked to provide an opinion on whether or not the sodium cromoglycate was a success or failure. Clinicians also conducted this final assessment after reading through patient's diary cards.

#### Patient follow-up

An initial assessment was not performed. Patients were supplied with eye drops and diary cards before hay fever season before they have developed any eye symptoms. Final assessment occurred at a clinic. The patients brought in their dairy which was assessed by one clinician. Both the patients and clinicians gave their opinion on whether the treatment was effective or not.

### **Main results**

At the end of the trial, 90% of patients in sodium cromoglycate group rated the treatment as success only 52% of patients in placebo group felt the treatment was successful. The clinician opinion was similar, 85% success rate in sodium cromoglycate group and 43% in placebo group. There was a statistically significant difference for both patient and clinician ratings. From the patient diary, sodium cromoglycate had better relief of ocular symptoms than placebo, however this was not statistically significant.

### **Conclusions**

Based on patient and clinician opinion, sodium cromoglycate 2% was found to be significantly more effective than placebo. Ratings from patient diary however showed no significant difference between the 2 groups for relief of ocular symptoms, including itching, redness, watering, soreness, grittiness, and photophobia.

### **Comments/Critical appraisal**

Since this study was published in 1978, the randomization, allocation, and blinding methods were not fully specified in detail. Analysis was not performed with the intention to treat, as results from 6 patients were excluded because they were improperly using the eye drops. There was no initial assessment of patients or follow-up during the trial, therefore monitoring of patient adherence was unknown. The final evaluation of treatment success was opinion based. The author did not include criteria for "success" or "failure" for both clinician and patient opinions. The mean age of the 43 patients is mid-twenties and the oldest participate was only 57 years old. The study occurred in Ireland and it is likely all participants were Caucasian. Due to poor internal and external validity, it is difficult to apply the result to the general population.

## **3. Tertiary Source**

**Bielory, L. Ocular allergy guidelines. Ocular allergy guidelines: a practical treatment algorithm. *Drugs*. 2002;62(11):1611-34.**

### **Study objectives**

This guideline examines available therapies for ocular allergies including seasonal allergic conjunctivitis. Two algorithms are provided in the study outlining the primary and secondary approach using both non-pharmacological and pharmacological agents. In addition, the author provides an overview of primary evidence for each individual medication or drug class.

### **Scope/ Method**

This guideline did not specifically analyze the primary studies for sodium cromoglycate. The author provided a brief summary of several trials involving sodium cromoglycate and provided an overview of its efficacy and safety.

### **Main results**

The author listed mast-cell stabilising agents within the secondary treatment algorithm for acute and chronic forms of ocular allergy. However, the place in therapy was not clearly identified for sodium cromoglycate as the author did not specify treatment order of 3 other medication classes including antihistamine, antihistamine/decongestants, and dual-action agents.

Looking at sodium cromoglycate evidence, the author summarized that sodium cromoglycate has a relatively small benefit over placebo and the efficacy was shown to be dose-dependent. This topical eye drop has long safety profile. Although mast cell stabilizers are mostly indicated for treatment of corneal involvement in several ocular allergies, sodium cromoglycate is commonly used in acute seasonal allergic conjunctivitis in clinical practice.

#### Conclusions / Comments/Critical appraisal

This guideline provides a brief overview of sodium cromoglycate. Although the author does cite primary references, the specific findings are not examined and only a short summary is provided. After reading this guideline, it's not clear when sodium cromoglycate should be used when compared to other non-prescription medications.

#### **4. Tertiary Source**

**Friesen, AM. Chapter 15: Eye Care – Conjunctivitis. Patient Self Care 2<sup>nd</sup> ed. Canadian Pharmacist Association, 2010. Pg 121-126.**

#### Source description

Patient Self Care is a textbook that guide clinicians with OTC recommendations in variety of self care topics, including seasonal conjunctivitis media. Each chapter is written by expert authors and edited by staff at the Canadian Pharmacist Association before publication. The textbook contains information regarding patient assessment, goals of therapy, lifestyle management, prevention strategies selection of non-prescription medications, and follow-up monitoring.

#### Summary

Sodium cromoglycate is recommended as second line therapy for the treatment of mild to moderate seasonal allergic conjunctivitis by Patient Self Care. The maximal effect can be achieved up to 10 days of therapy. This medication can also be used for prevention of symptoms, but it must be initiated before allergy season. The author included decongestants and topical antihistamines/decongestant combination as second line therapy too.

#### Comments/Critical appraisal

The non-prescription summary chart does provide a good overview of the place in therapy for sodium cromoglycate. However, this textbook did not provide primary references for efficacy and safety of sodium cromoglycate. The recommendations are likely based on expert opinion and clinical experience rather than evidence.

#### **5. Tertiary Source**

**Doughty, M. Management options for UK optometrist: general eye irritation and allergic conjunctivitis. Optometry Today: Continuing education and training, 2010.**

**<http://www.optometry.co.uk/uploads/articles/articlepdf%2015th%20oct.pdf>**

#### Source description

Optometry Today is a UK optometry association that provides continuing education to optometrist. In this continuing education and training module, an expert author provides the treatment strategy for patients with seasonal and perennial allergic conjunctivitis. The article differentiates between difference drug classes and provides a summary of the available over the counter and prescription medications.

### Summary

In the article, the author recommends sodium cromoglycate to be used regularly and continuously for the duration of allergy season to increase patient's tolerance to allergens. Since the onset of sodium cromoglycate can take up to over a week, patients may require additional treatments such as antihistamine or decongestant for initial management of symptoms. Sodium cromoglycate is not known to cause significant adverse events and there's no contraindication other than allergy to the active ingredient or the preservative benzalkonium chloride.

### Comments/Critical appraisal

This continuing education article provides practical information on the mechanism, efficacy, safety, and duration of treatment for sodium cromoglycate. Within the mast cell stabilizer section, the author cites some primary references; however, his recommendation that sodium cromoglycate should be continuous administered was not referenced and likely came from clinical experience and expert opinion. The module was very in-depth as it was intended for optometrist audience who would receive continuing education credits.